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Ref: Docket No. 00N-1484, CDER 199665. Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule

Abbott Laboratories (Abbott) is very pleased to have 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.

We commend the Agency on their effort towards global harmonization and to improve the overall quality of safety reports. However, Abbott believes that dialogue with stakeholders and the practicality on the implementation of certain requirements described in the proposed rule should be taken into consideration before the rule is finalized, so as to achieve the best results through an effective approach to serve the public health.

Abbott endorses the Pharmaceutical Research and Manufacturers of America's (PhRMA) response to the Agency on this proposed rule, and thanks the Agency for their consideration of our attached comments. Should you have any questions, please contact Ivone Takenaka, Ph.D. at (847)-935-9011 or by FAX at (847) 938-3346.

Sincerely,

Doug Sporn / jmt

Douglas L. Sporn

Abbott

October 13, 2003

Comments on Part II
Safety Reporting Requirements For
Human Drug and Biological Products; Proposed Rule

Docket No. 00N-1484

The following comments on the above-mentioned document are submitted on behalf of Abbott Laboratories.

GENERAL COMMENTS

Abbott shares the FDA's objective to improve patient safety by streamlining the domestic drug safety reporting requirements and harmonizing them with ICH and CIOMS. However, Abbott is concerned that the proposed reporting requirements are very complex, time consuming and do not appear to improve the signal evaluation, despite the harmonization to ICH and intended effect to further worldwide consistency in the collection of safety information and submission of safety reports, increase report quality, and expedite FDA's review of critical safety information.

This approach appears to contradict other FDA's "science-based" and "risk-based" approaches to regulatory compliance (e.g., good manufacturing practices). Implementation of this rule, as proposed, will necessitate enormous burden on system validations, compliance measures to address the plethora of reporting processes, workload restructuring and resource shifting. Abbott recommends that the FDA consider a pilot study program to evaluate the impact of the regulations and whether the desired ends have been achieved.

Implementation of these proposed regulations within 180 days poses a significant workload burden to industry. The costs associated with implementation and the estimated increase in reporting volume for both clinical and postmarketing, are not adequately accounted for and are underestimated in Sections V and VI of this proposed rule.

Abbott endorses FDA's proposal of prohibiting the use of Suspected Adverse Drug Reaction (SADR) reports the Agency receives in product liability actions. Abbott also endorses: the use of MedDRA as the preferred coding dictionary for medical terms in adverse event reporting, the proposed harmonization with ICH E2A, and the proposal of revoking the requirement of submission of safety reports in NDA/BLA annual reports to avoid duplicative reporting.

SPECIFIC COMMENTS

III. DESCRIPTION OF THE PROPOSED RULE

III.A. Definitions

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

In the term 'SADR' – the word "reaction" implies causality by ICH definition of "reaction." This change in terminology suggests more of an association between reported events than may exist in the reporter's view since "reaction" is applied regardless of the reporter's assessment of relationship. Historically, the Agency's reviewing divisions have requested that for certain issues, informal reports and/or line lists be provided to them on a periodic basis. Abbott believes this process effectively meets the needs of providing information to the Agency as a supplement to established reporting requirements.

The ICH E2A definition regarding causality assessment of SADRs for clinical trials includes a statement that "reasonable possibility" means "a relationship cannot be ruled out." This statement is contradictory because "reasonable possibility" means "it is likely that a relationship exists", while "a relationship cannot be ruled out" means that "there is no possibility that a relationship exists." The US legal interpretation of "reasonable possibility" under the proposed rule will be significantly different from the practical implementation of the ICH E2A definition. It should also be noted that the EU Clinical Trials Directive (2001/20/EC), due to come into effect on 01 May 2004, is consistent with the ICH E2A definition; therefore the proposed definition in the FDA Rule would be inconsistent with that already adopted by other ICH regions. Thus, causality assessments for clinical reports will become obsolete because a company would submit to the FDA almost everything "serious and unexpected" under this proposed definition, and could report clinical cases to the FDA which are not expeditable to other agencies.

The following is Abbott's impact analysis of considering all "serious, unexpected events" where a causal relationship between the drug and the events could not be ruled out with certainty as "associated" for the purpose of expedited reporting.

- Under this proposal, Abbott estimates that the volume of clinical trial safety reports that the FDA receives on an expedited basis will substantially increase. For example, with respect to serious unexpected events, only the following cases would not be considered "not related": where patients were not on the drug product; where it is impossible, either temporally or biochemically, for the drug product to cause the event; and elective procedures for pre-existing conditions. Furthermore, if "probably not" cases are considered "associated", the number of expedited reports would rise nearly four times, increasing the burden to industry and to the Agency, with little added value. Since the information on these events is currently provided to the Agency reviewers annually, it would be helpful to know of documented situations whereby receiving these types of cases sooner could have changed the assessment of an investigational product's safety. Based on the review of 2002 clinical cases in the Abbott database, our analysis of "probably not" cases, which would be considered "associated" under this rule, would result in an increase of expedited reports by 400%.

- This rule as proposed will cause an increase in the volume of expedited clinical safety reports leading to an associated increase in the volume of expedited postmarketing safety reports for the subset of products that have an approved NDA, as such products will require duplicate reporting to both the IND and NDA.

- Under the current reporting system, Abbott will send over 100,000 investigator letters for the year 2003. Under the proposed rule, we estimate a four-fold increase in the volume of letters sent to investigators informing them of expedited reports that very likely will unnecessarily alert them of SADRs that have little probability of being related to the drug. This will increase the workload and associated costs for investigators in that they will need to further report these "unlikely drug related" expedited reports to their IRB.

- This rule as proposed will also increase the workload and associated costs for the IRBs who will be receiving and reviewing these additional expedited reports. Abbott, as a sponsor, has recently received requests from several IRBs to submit to them summary safety information instead of multiple individual expedited reports. Therefore, we believe it is highly unlikely that this increased volume of reports will be acceptable to IRBs.

- This proposal will create a discrepancy between what is considered "associated" in expedited reports versus other global submissions (e.g., clinical study summaries, PSURs, etc.) where "associated events" are separated out in listings from non-associated events due to the difference in approach between the FDA proposed rule and the ICH guidance documents.

- Labeling that includes tables or listings of associated adverse events will present higher rates of events than currently shown, which generally use events of possible, probable or unknown relationship to study drug. These factors may result in a biased presentation of the drug safety profile, and may cause considerable confusion when a new indication is added with artificially high SADR numbers to an already established product insert with lower original AE numbers.

Abbott agrees that serious, unexpected SADRs that occur in studies not being conducted under an IND must be submitted as expedited reports to an IND (if one exists). Abbott would like this provision formalized in the regulations. This proposal is consistent with the overall intent of the proposed rule to increase reporting of previously unidentified drug toxicities by including reports from studies not conducted under the IND. The FDA should clarify whether for post-NDA approval, serious, unexpected SADR cases from IND-exempt studies must be submitted to both the IND and the NDA or just to the NDA. Abbott suggests that these reports be submitted only to the NDA.

Abbott supports the use of special reporting exemptions as discussed (e.g., study endpoints, known consequences of the underlying disease).

Clarification of "spontaneously" reported events versus those that are abstracted from the narrative descriptions is requested. General practice for conservative postmarketing reporting often results in collecting events from labs and history sections, and/or including events mentioned by the reporter in the course of adverse event investigation. This occurs even if the events were not the original intent of the report or if the reporter states they were not related to the drug. Abbott proposes that the events that should be reported are those that are the focus of the reporter's initial call; Abbott would appreciate FDA comment on this matter.

III.A.2. A Life-threatening SADR

Life-threatening category: "FDA is proposing to amend this definition by adding the phrase "or sponsor" after the word "investigator." Thus, reports of life-threatening SADRs would be based on the opinion of either the investigator or sponsor.

Abbott appreciates the primary intention of FDA's proposal to be the harmonization with ICH E2A. However, clarification is needed as to the ultimate purpose and/or use of the sponsor's assessment of causality. While this proposal allows the sponsor to offer an opinion of whether an event is life threatening, Abbott believes an adequately trained investigator is best positioned to make this assessment.

Alternatively, Abbott proposes that the determination of "life-threatening" should be made by the reporter who is in direct contact with the patient, or by the trained healthcare provider that obtained the direct information and is able to make that decision. Sponsors currently have the alternative of exercising medical and scientific judgment in deciding whether expedited reporting is appropriate in other situations for events that are considered medically important.

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

Abbott understands and shares FDA's interest in unexpected SADRs. However, Abbott believes that submission of SADRs with unknown outcome, despite the sponsor's efforts, will not result in meaningful reports. Reports in which no outcome could be ascertained usually provide little additional information beyond the adverse event term. FDA's proposal to require direct contact (active query) between reporters and health care professionals should improve the quality of reports, therefore, rendering this unnecessary. Additionally, there is already a mechanism in place, defined by ICH, by which reports of medical significance may be submitted in the absence of a reporter-provided serious

outcome. Abbott routinely utilizes this avenue to report cases in which no serious criteria were provided.

We recommend that the Agency provide some support for their assertion that reports without serious outcomes are not being sent appropriately. Before changing the requirements, Abbott recommends that the impact of these changes on the current system already in place be taken into consideration. Abbott believes the implementation of this significant burden is unnecessary and likely to be uninformative.

The proposed third classification (serious, nonserious, unknown outcome) creates difficulty when assessing data from a worldwide view. For the purposes of other regulatory authorities, those with unknown outcome will generally be nonserious and cited as such in appropriate sections of PSURs. Subsequently, it would be difficult to reconcile the overlap between those listings and the additional appendices that FDA proposes for the PSUR.

III.A.4. Contractors

The proposed definition of "Contractor" is very broad, as anyone with a licensing agreement would be interpreted as a contractor. The regulatory requirement for a 5-day notification represents an onerous burden on the manufactures, distributors, packers and all other related business entities for all reports, not just life-threatening or death reports.

Furthermore, the proposed requirement to exchange all adverse event reports within 5 calendar days with all the contractors specified, including for cases which do not meet the minimum required data set, will be inordinately complex and burdensome with no perceived added value in promoting patient safety. It is fairly certain that the short turnaround proposed for exchange will result in poor quality reports, since it will only allow sufficient time for forwarding raw source data, with no time for active query or translation.

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

The definition of a "full data set" is unclear. "Completion of applicable elements of MedWatch 3500A or CIOMS I forms" may be interpreted in various ways by different reviewers. It is understood that a minimum data set requires information on four data fields. In contrast, a full data set may mean that all available information for remaining data collection fields will be filled in "as appropriate." In some cases, all data fields may not be filled in on the MedWatch 3500A form, either because such information does not exist, is not provided, or cannot be obtained on follow-up.

III.A.6. Active Query

The proposal states that "any individual with some form of health care training" would have responsibility for active query. Abbott proposes that this include nurses, pharmacists, and allied health field personnel. Abbott also proposes that customer advocates that have received training on adverse event/pharmacovigilance and package insert in addition to a medical terminology course, should be included as individuals able to handle consumer-only calls or otherwise anonymous reports.

The Agency proposes "in person, by telephone, videoconference, etc." as direct verbal contact means to obtain SADR or medication error information. In some instances, the reporter requests a letter or form to be completed at his/her convenience. The feasibility of using this mechanism of contact for less developed countries in which a sponsor may market their products is very challenging. Alternatively, the Agency should consider and provide the appropriate requirements in regards to acquiring this information via electronic mail (e-mail).

In addition, Abbott requests that the Agency address how reports originating outside the US should be handled with respect to the requirement for direct telephone contact. In some countries, due to cultural differences or established reporting schemes, company affiliates receive adverse event reports from their regulatory agencies, often by letter. Additionally, there are many co-marketer systems in place among companies that would require sensitivity to these ex-US differences and reporting schemes. Active query, as suggested, does not recognize or consider ex-US requirements.

The requirement to submit copies of hospital discharge summaries, autopsy reports and death certificates is not realistic for spontaneously reported events as they are rarely made available even when requested for clinical study patients. The Agency should consider the workload burden, privacy initiatives/accessibility to documents, and the impact of electronic reporting (E2B) that would eliminate hardcopy submissions. The privacy rules such as HIPAA, EU Privacy Directive and other privacy initiatives, including state regulations, may impede such activities.

In response to the Agency's request for comments on whether "written requests for follow-up information would be appropriate", Abbott believes for the following situations a written follow-up would be appropriate:

1. After attempts by the sponsor to contact reporter by phone have been unsuccessful
2. At the reporter's request
3. Only for serious unexpected or unknown outcome reports

Abbott supports the proposal to limit active queries for nonserious cases with a full data set.

III.A.7. Spontaneous Reports

Under the proposed rule, the definition of "spontaneous report" has been amended as "only unsolicited safety information from an individual, such as healthcare professional or consumer, to a company or regulatory authority would be considered a spontaneous report." Abbott believes programs such as Patient Named Basis (PNB) or registries are somewhat of a hybrid between spontaneous reporting and true clinical trials. However, they are closer to spontaneous reports than to clinical trials, because they are generally significantly larger to simulate usual case experience. In addition, the reporters are not investigators, but are usually physicians in practice, not necessarily familiar with clinical trial reporting regulations, and details may not be monitored in the same manner as in clinical trials. Thus, to obtain full signaling value from such cases, it would be prudent to handle these cases as spontaneous cases where all serious, unexpected events would qualify as expedited reports.

Furthermore, FDA states that "serious and unexpected", "unexpected SADRs with unknown outcome", "always expedited events", and "medication error" reports would be subject to reporting from such "studies." This section is confusing as it seems to require that such "studies" (e.g., registries, etc.) should be handled as clinical study cases, and yet it requires expedited reporting of types of cases that are being proposed for spontaneous reporting in prior sections. As such, this proposed change does not appear to enhance the value of the information, and would require changes in the current processes and re-training.

FDA needs to clarify whether legal cases (individual plaintiffs) would be included in the provisions for "class-action" lawsuits. The separation of lawsuits in reporting format will require many significant system and process changes, and subsequent re-training for a very small percentage of reports. This is not cost effective.

Clarification is needed in regards to how the sponsor should identify the newly defined "non-spontaneous" reports on the MedWatch 3500A form. According to the proposed rule, they would not be considered "studies." Please clarify whether "other" should be chosen in section B2 of the MedWatch 3500A form.

III.A.8. Medication Errors

Abbott endorses PhRMA's response on FDA's proposed requirement on medication errors and reiterates that this should be a responsibility of a wide range of healthcare sectors, and the pharmaceutical industry must not be singled out. As reported in the Institute of Medicine (IOM) Report and by the Institute of Safe Medication Practices (ISMP), the majority of medication errors are primarily related to medical practice and the dispensing of medications, and not related to pharmaceutical industry. In addition, the majority of medication errors do not result in adverse events.

Abbott agrees with FDA that understanding the root cause of medication errors is fundamental to implementation of corrective and preventive actions. While it may be reasonable to report medication errors associated with AEs (or even name confusion), industry is not in the appropriate position to evaluate health delivery systems for root causes.

The proposed rule defines "Potential Medication Error" as "an individual case safety report of information or complaint about product name, labeling or packaging similarities that does not involve a patient." This broad definition may produce a huge volume of reports of limited or no interest for product safety. FDA should clarify the relationship between this reporting requirement and product complaints, specifically as it relates to the definition of "potential medication error."

Medication errors might be more appropriately classified into different subcategories to reflect relevant medical issues. If such categorization were to be introduced, it would be necessary to create appropriate coding conventions, presumably within MedDRA, so as to be able to process and manage the data efficiently and consistently.

Abbott agrees that FDA should be informed of reports of medication errors received by manufacturers, but questions the rationale and value of requiring this information on an expedited basis in all cases, especially for those cases where the error is not a result of packaging or dosing information confusion.

Abbott suggests the following modifications:

1. Expedited reports should be required if the reason for the reported medication error was a misunderstanding of the product name or the labeling/package instructions.
2. Expedited reporting should be required if the medication error resulted in a serious unexpected SADR.
3. Medication error reports received by the applicant that do not require expedited reports under current suspected ADR rules (serious unlabeled), be reported and discussed in aggregate in the next scheduled PSUR.

III.A.9. Company Core Data Sheet, Company Core Safety Information (CCSI), Listed SADR, Unlisted SADR, and Unexpected SADR

Abbott believes the implementation of a single CCSI for an active product (and irrespective of formulation) poses concerns, as formulation specific or dosage specific information may be lost/missed. In addition, this proposal is inconsistent with the CIOMS V guideline recommendations on the use of CCSI that is in force at data lock.

III.B. IND Safety Reports

III.B.1. Review of Safety Information

Traditionally, adverse events with unknown outcome have been triaged as non-serious. Under the proposed rule, these are automatically treated as expedited reports and a chronology of all efforts to secure outcome information is required to be submitted. Abbott questions that this will contribute valuable safety information since without outcome the case is difficult to assess. While sponsors should document a chronology of efforts to get outcome information, that information should be appropriately filed and reviewed during routine or non-routine FDA inspections. Compliance with requirements to seek additional information by the sponsor should be assessed by auditing. This documentation would not add meaningfully to the FDA safety reviewer's assessment of the adverse drug reaction. Alternatively, the sponsor could submit this information upon request on a case-by-case basis if deemed necessary by the FDA safety reviewer.

As mentioned in this section, "the current IND safety reporting, §312.32(b), requires sponsors to promptly review all information relevant to the safety of the drug under investigation obtained or received by the sponsor from any source, foreign or domestic". Abbott suggests that the Agency clarify what should be submitted to the US-IND from ex-US clinical studies not under an IND (e.g., Phase I-III, including Phase IV postmarketing studies), both before and after a U.S. NDA is approved.

III.B.2.b. Serious and Unexpected SADRs

In regard to causality assessment, the proposed amendment may be interpreted as that both investigators and the sponsor will make determinations of seriousness, expectedness and causality. Expectedness is a regulatory definition that would be difficult for an investigator to apply in a consistent fashion.

In order to submit meaningful reports, the patient would have to be unblinded. Abbott believes this may seriously jeopardize our ability to conduct pivotal studies that must remain blinded to their completion. In addition to unblinding those reports that need to be submitted, for a study that randomization is in small blocks, the remaining patients in a randomization block may automatically be unblinded.

This rule as proposed will potentially compromise the statistical validity of studies since more blind breaks will need to occur to determine if these additional serious, unexpected, associated cases need to be reported in an expedited manner. Since blinded cases are not normally submitted, there is no way to prevent the increase in the number of patients who will be unblinded due to this requirement. Sending in blinded reports would not help with signal detection.

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

This section, in general refers to IND safety reports, and within this context the terms "product administration changes" or "product" as well as "administration" may have different interpretations. Also, the terms "benefit-risk" or "lack of efficacy" are not applicable as efficacy has not yet been proven, and lack of efficacy reports in contrast to postmarketing safety reports seem incongruous with the concept of a clinical trial.

Under this section, FDA proposes that "... sponsor submit information no later than 15 calendar days after determination by the sponsor that the information qualifies for reporting under this paragraph." Abbott proposes that in line with ICH E2D guidance, that the day any sponsor receives the report that fulfills minimum criteria as well as meets the criteria for expedited reporting be considered "Day 0."

Abbott appreciates certain proposed changes in the rule are intended to increase consistency with ICH E2A guidance. It is mentioned as one of the examples in the ICH E2A to include "a. For an expected, serious ADR, an increase in the rate of occurrence which is judged to be clinically important." We recommend that the Agency provide guidance on what would be deemed a "clinically important" increased rate of reports.

Moreover, the proposed rule states "Although the increased frequency reports final rule pertains to postmarketing expedited safety reporting, FDA has decided to apply this increased frequency rule to its requirements for premarketing expedited safety reports because of the limited reliability of increased frequency reports (ref: 62 FR 34166)." Abbott would like the Agency to discuss in more detail what would be the added value of incorporating such requirement to the premarketing expedited safety reporting, vis-à-vis prior experience and an FDA regulation change revoking increased frequency reporting (62 FR 34166; June 25, 1997) and stating this activity has "proved of little value in identifying increased incidences of serious, labeled experiences."

III.B.5. Investigator Reporting

Clarification is needed regarding what is meant by "immediately" and what is meant by "promptly" in the following statement "an investigator must report to the sponsor only serious SADR immediately and any other SADR promptly . . ."

III.C. Postmarketing

III.C.2. Review of Safety Information

Further clarification is needed regarding the kind of *in vitro* studies that would fall into this category. *In vitro* studies may be exploratory and unvalidated; hence, the clinical

relevance cannot be adequately assessed from these studies and "appropriate medical judgment" may not be applicable to the findings.

The requirement may deter sponsors from seeking/conducting innovative tests that could, in the future, reduce the need for certain animal studies or provide more information regarding drug actions. It is the nature of exploratory work that findings may be unanticipated, but these findings may not have clinical relevance. The IND safety report is not the appropriate forum for presentation of findings from exploratory tests.

FDA is proposing to replace the phrase "adverse drug experiences (ADE)" with the phrase "postmarketing safety information". The replacement of "ADE" with the more generic "Postmarketing Safety Information" poses some concerns as it expands the concepts of adverse drug experiences.

Several changes in terms and definitions are being proposed. Please provide the rationale for these changes. To maintain consistency and avoid confounding of the terms, a careful review of all the proposed term changes including those mentioned above, and their impact to the current system should be conducted prior to their implementation, e.g., MedWatch 3500A form.

III.C.3. Reporting Requirements

Semiannual submissions appear to be based upon the US approval date. This presents a possible conflict with the timing of the PSUR based upon the international birth date. The submission of semiannual line lists and individual case reports based upon US approval dates may not be consistent with PSUR case listings resulting in different numbers of reports in each submission. Please confirm the intent and the correct dates upon which to base such reports. Further, clarification is also needed as to whether foreign serious expected reports are to be submitted in the semiannual submissions, although they are not required in the current periodic reports (i.e., TPSRs).

Regarding Table 6 and 7 proposed timeframe, it is not clear whether 30-day and 45-day follow-up clocks are triggered by the submission date or the initial received date. Industry already has a requirement to follow-up any clinically significant adverse event report. The requirement for the 45-day follow-up will complicate compliance requirements and add unnecessary time and cost burdens. Abbott recommends exclusion of this proposal (including the 45-day follow-up) based on its low relative value and high time and cost burden.

Abbott further requests confirmation that FDA will implement mechanisms to identify and reconcile any possible duplicate reports.

The following shows Abbott's estimation of the increase in the number of reports based on the proposed.

- Individual case safety reports (ICSR) – semiannual submission:
  - Estimate of burden (time, cost, validation) of producing Individual Case Safety Reports every six months:

    Abbott is currently processing 61 yearly periodic reports, 9 quarterly periodic reports and 1 monthly periodic report. Under the proposed rule, Abbott would have to submit at least 124 ICSRs during a 12-month period. As the number of reports doubles, the full time staff producing these reports would most likely need to be doubled. The format of the report will need to be changed to meet the new requirements. The new report will require a validation process.

- Estimate of system changes needed to accommodate the new proposed requirements:
  - System changes will include but may not be limited to the following:
    - New report type (30-day follow-up reports)
    - Possible change to MedWatch 3500A form to show new report type
    - Changes to Periodic Index to include new report type
    - Possible changes to E2B code lists to handle the new report type.

- In addition, these changes will significantly increase the volume of expedited reports, since these reports would need to be resubmitted with an explanation as to why no new information is available.

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

Abbott requests that the Agency clarify the following concerns:

- For global companies, direct verbal contact may be challenging. Abbott requests that the Agency address in the proposed rule whether the same requirements apply to foreign reports, as this is not feasible in centralized pharmacovigilance structures and taking into consideration other cultures and the ex-US methods of obtaining information.

- The FDA proposes that "applicants report all contact attempts made to obtain the information." Abbott recommends that the FDA focus inspection efforts on companies that do not exercise due diligence. Abbott proposes that contact

attempts be excluded from the adverse event report, but kept as documentation on file made available upon FDA's request; as is currently the practice.

- Moreover, the Agency should consider that Privacy Laws may cause hurdles in obtaining as well as reporting this type of information (e.g., HIPAA and EU Privacy Directive).

- The FDA should clarify whether nonserious reports with a minimal data set from a consumer who declines to provide the health care provider's name, would still require follow up in light of the inability of the company to contact the healthcare professional (HCP). Abbott recommends that for any report where all reporters have identified that no further information is available, that no further follow-up attempts should be required.

- Clarification is also needed in regard to whether follow up reports are only required for HCP confirmed reports.

III.C.6. Spontaneous Reports and Reports from Clinical Trials

Abbott supports the proposal that either the sponsor or the investigator should base determination of causality on the most conservative assessment.

III.C.7. Lack of Efficacy Reports

Please clarify the requirement to compare lack of effect data in the postmarketing and pre-marketing settings. It is recognized that no drug is 100% efficacious, even in well-controlled trials. Due to the differences between clinical development and post-approval use of products with respect to different indications, populations not studied, and in obtaining/availability of laboratory cultures, it is unclear whether comparing the lack of effect data would be useful.

Abbott requests that the Agency provide more direction as to how to perform the frequency comparison to clinical trial incidence data, since a direct comparison is not possible, given that one would be a reporting rate and the other a true incidence.

III.D. Postmarketing Expedited Reports

III.D.2. Information Sufficient to Consider Product Administration Changes

The new requirement that an expedited safety report be submitted for "Information sufficient to consider product administration changes" is not consistent with current processes. The sponsor's standard process is to review the data for a given product in the aggregate whether that is several events of a serious nature or multiple events of a non-

serious nature. When the medical decision is made that product administration changes (labeling changes) should be made, a supplement is submitted to the FDA therapeutic reviewing division with the post-marketing data as support for the change. Since implementation of labeling changes cannot occur without the submission of a labeling supplement it is unclear what value would be added by submitting a single expedited report to the FDA safety assessors.

III.D.4. Always expedited reports

The submission of SADRs, regardless of seriousness or expectedness as "always expedited reports" will not necessarily enhance signal detection, and has the potential to dilute and obscure potentially newly identified signals. For example, for a product with a well-established adverse event profile and an adequate label, implementation of this proposal would result in an increase in expedited adverse event reports that will not contribute to the understanding of the safety of the product. These events are available in the PSUR or other periodic reports.

In addition, the classification of these events as expedited without reference to expectedness or causality is not consistent with ICH E2A and, thus leads to different reporting standards worldwide making PSUR reporting problematic. Such reports will not appear in the PSUR list of "serious, unexpected." Such is also the situation with classifying medication errors as expedited reports. FDA and other regulatory agencies worldwide would not be receiving the same information.

Abbott recommends the Agency carefully reassess the proposed changes as they could create confounding reporting, especially when global reporting system have already been in place. The process as proposed will become so complex in practice, that it will be difficult to comply with in terms of initial and follow-up reporting timelines, and requires institution of more detailed tracking mechanisms.

The requirement of submission of certain events as "always expedited" may lead to useful information only if there is clear definition of how broadly or narrowly the interpretation of the proposed Medically Significant SADR Listed Events are. Specific MedDRA terms should be provided by the agency for each adverse event appearing on the list. While we understand that FDA reserves the right to add events to the list, it is doubtful that events would ever be deleted from the list. Therefore, it may be possible to reach a state where the majority of all SADRs are required to be submitted in expedited fashion. This will eventually lead to a tremendous volume of information impeding appropriate handling and analysis of the data.

There are many other terms synonymous to those on the "Medically Significant SADR List" and clarification is needed as to whether those terms should be reported as such. Furthermore, specifying a list of SADRs may create confusion as a non-listed other

medically significant event may be identified in future, and companies would have to rely on FDA's notification of their expectation as to whether these reports should be submitted as expedited reports or in any other manner.

The terms in the listed "medically important SADR" should be carefully evaluated and defined according to the international standards in order to avoid confounding of terms in relation to the reporting requirements. For example, FDA should clarify:

- Whether terms such "anaphylaxis" should be determined as a reporter term or the CIOMS definition;

- The term "sclerosing syndromes" should be defined;

- Requiring seizures to be reported as expedited cases will cause confusion when seizure is the indication for use, or when there is a history of seizures being treated and a product for an intercurrent illness is administered;

- It is unclear as to what is intended by "suspected transmission of an infectious agent" and whether this would be limited to those reports in which the reporter suspects/proves transmission;

- The minimal criteria for endotoxin shock in the absence of a reporter term of such (e.g., confirm whether the FDA would permit a company not to report a case of Staphylococcal sepsis as possible endotoxin shock);

- Whether an adverse event must be designated as a congenital anomaly by the reporter, or if one should refer to supplemental definitions, such as that provided by the CDC. For a product that is a known teratogen with a well-documented profile, reporting cases as always expedited will not generate a new signal;

- If toxic epidermal necrolyis is on the list, cases of Stevens-Johnson Syndrome would not be expedited reports. A list of always expedited reports need to be verbatim terms or it would be difficult to maintain compliance.

III.D.6. Follow-up reports

Abbott agrees with the idea of a minimum data set. However, the proposed follow-up timeline in multiple timeframes complicates reporting requirements, does not account for the reporter and adverse event outcome/resolution-driven timeframes, and creates increased complexities for monitoring, making it difficult to assure compliance.

In a case where no new information has been obtained in attempted follow-up on a 30-day report, a submission of a report stating that no new information is available should not be required since it does not really provide any significant additional/medically

relevant information. Abbott proposes to continue with the current state of keeping this information on file and available for review during an inspection.

Clarification is needed as to when the 15-Day clock would start for follow-up reports following submission of a 30-day follow-up report. In addition, considerations should be made as to whether there will be a mechanism in place to link "new" 15 day reports as follow-up reports to the initially submitted nonserious or serious expected report, when the initial report (via PSUR or TPSR, or semiannual submission) may not have been submitted to the FDA at the time FDA receives the follow-up 15 day report. This mechanism should be in place by the time this rule becomes effective.

Abbott endorses PhRMA's opinion regarding the proposed requirements under this section, and reiterate that overall, the documentation of attempts to gain further information is regulatorily burdensome and does not add medical understanding to the safety database.

III.D.7. Supporting Documentation

The requirement to submit copies of hospital discharge summaries, autopsy reports and death certificates is not realistic for spontaneously reported events as they are rarely made available even when requested for clinical study patients. The current privacy regulations (i.e., HIPAA, EU Data Protection Directive and other state and local laws), will impede compliance with the proposed rule requirement. If safety reporting, more specifically, postmarketing adverse event reporting investigation is exempt from HIPAA, FDA should clearly inform the public that there is not a legal liability in obtaining this type of information (e.g., requirement for consent forms and confidentiality releases).

These requirements will cause an excess workload burden in providing supporting documentation and attachments to reports. The implementation of electronic reporting systems (E2B) eliminates the requirement for hardcopy submissions. If supporting hardcopy documentation is required, there would be additional burden to the Agency to reconcile the electronic and hardcopy documents received. There would be additional cost and time expenditure to the company to identify and implement a validated system that could incorporate electronic/manual submission requirements simultaneously.

Please clarify whether the requirement for a narrative list of other relevant information can be interpreted to mean that all data known to the sponsor, if deemed not pertinent, does not need to be included on MedWatch 3500A form.

III.D.9. Contractors and Shared Manufacturers

See comments under section III.A.4.

III.D.11. Class Action Lawsuit reports

Please clarify whether class action lawsuit cases need to meet minimum data set requirements. Frequently, specific adverse events are not identified in these legal cases, rather they say "patient was harmed" without any specifics.

III.E. Postmarketing Periodic Safety Reports

Abbott agrees that the most significant safety information on a product is usually generated in the first several years after its launch. It is unclear as to why the FDA is proposing new TPSR requirements for the older products, since the 1998 AERS data showed that approximately 75% of the postmarketing periodic safety reports included 10 or fewer reports accounting for only about five percent of all reports submitted with the postmarketing periodic safety reports. Abbott proposes keeping the current periodic safety reports for products approved prior to 1998, and sending the FDA MedWatch forms for all reports (including foreign nonserious and serious labeled) when the periodic report is due. IPSRs and TPSRs would not be adding new safety information beyond what the proposed PSUR schedule would find. In addition, the proposed reporting on SADR will require system changes, reprogramming and revalidating of all safety reports on the database.

This is Abbott's estimated impact of the proposed change on the number of reports and time spent per report.

- Each separate type of periodic report (TPSR, PSUR, IPSR) would require extensive re-programming of the safety database system to be performed by the vendor. In doing so, vendor would need a clear consensus from all of their clients as to the report requirements. Vendor's assessment for changes of this nature often requires at least one year to complete. Once completed by the vendor, the company would have to install the system in their controlled environment, test, validate, and train staff.

- As with the current PSUR in the system, multiple run-time parameters and administrator settings must be determined. The significant increase in the number of reports due to the semi-annual submission requirement is one of the highest concerns.

III.E.1. Traditional Periodic Safety Reports (TPSRs)
III.E.1.c. Increased frequency reports

The FDA revoked increased frequency requirements for expedited reporting because of its inability to detect safety signals using this type of information (62 FR 34166 and "Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations of

Aug 11, 1997). Therefore, the value of including this requirement in this proposed rule is questionable. Prior to reinstating this requirement for safety reporting, the FDA should scientifically evaluate the data available and provide guidance as to how to calculate and what would constitute a meaningful increase in frequency.

III.E.1.h. Contact person

Abbott recommends that a single person from Regulatory Affairs who can identify the appropriate medical/other personnel to address questions should be the contact for a company, rather than customizing every CIOMS and /or MedWatch form. Furthermore, there are legal implications for inclusion of a designated licensed physician on the MedWatch 3500A form. This public availability of the physician's name could place him/her in jeopardy of being named in individual lawsuits or in lawsuits involving another company, since his/her name would be available through another company when adverse events are forwarded by regulation to that company. Some companies have already established a system for all agency contact to be done through the Regulatory Affairs Department to ensure appropriate documentation. Abbott recommends that the proposed requirement is deleted.

Abbott also proposes that the responsibility for reviewing reports be extended to trained and qualified RNs and RPhs.

In addition, the proposed rule suggests that the FDA is shifting communications from a written format to verbal exchanges. Abbott recommends this proposal is removed and that initial contact continues via a written format.

III.E.2. Periodic Safety Update Reports (PSURs)

Abbott supports FDA's proposal to accept PSURs as defined by the ICH criteria. However, the lengthy list of FDA-specific appendices serves to make it highly unlikely that the same report can be used globally, thus disrupting harmonization efforts. For consistency, ICH E2C recommendations should be adopted as part of this proposed rule. It should be emphasized that many recommendations in the ICH E2C are interim steps until regulatory authorities uniformly accept the PSUR schedule based upon the international birth date. In aligning ICH E2C with the proposed rule, we recommend the following:

- The addendum reports introduced in ICH-E2C Addendum (section *1.4.4.3 Addendum Reports*) resemble in purpose that of the proposed interim periodic safety report (IPSR) and should take the place of the IPSR, if required.

- The recommendations in the ICH E2C section "*1.4.4.5 Time Interval between the Data Lock Point and the Submission*" are very valuable and should be considered

by the FDA due to the following: 1) the need for sponsors to receive comments (if they are to be submitted) from regulatory authorities prior to the next data lock point for comments to be considered for the subsequent PSUR and; 2) the option for the sponsor to negotiate additional time for PSUR submissions in exceptional circumstances.

III.E.2.b. Worldwide Marketing Status

The wording in this Section should be aligned with ICH E2C, which includes "treatment indications and special populations covered by the market authorization, when relevant." The proposed rule does not use the wording "when relevant." This most often is not relevant in practice.

III.E.2.d. Changes to Company Core Safety Information (CCSI)

The proposed rule states, "A copy of any modified section of the CCSI would be included." Abbott recommends harmonization with ICH E2C, and this requirement is eliminated. If the CCSI at the beginning of the reporting period is included in the PSUR and the changes are "clearly described, with presentation of the modified sections" (as outlined in ICH E2C but not in the proposed rule), the same result can be obtained and harmonization achieved.

Clarification is needed in regard to the use of the CCSI that was in effect at the beginning of the period under review.

Abbott also requests clarifications on what would be the potential for variations in expectedness/listedness between PSURs that companies may elect to submit for products approved prior to the 1998 cutoff, and for products for which PSURs will now be required, since they are based on different reference documents.

The FDA should define the appropriate age ranges to be included in exposure data for groups, such as neonates, infants, children, and adolescents. It should be taken into consideration that exposure data may not be obtainable.

III.E.2.e. Worldwide Patient Exposure

ICH E2C states, "When possible and relevant, data broken down by sex and age (especially pediatric vs. adult) should be provided." The proposed rule does not use the wording "when relevant" and this is not consistent with ICH E2C. The proposed rule also states "if these data are not available, an explanation for the lack of such information would be included". It should be left to the discretion of the MAH to provide pediatric exposure data when it is medically appropriate and should not be required for every PSUR.

III.E.2.f. Individual Case Safety Reports
III.E.2.f.ii. Summary Tabulations

The requirements of additional appendices such as medication errors, class action lawsuits, etc., are certainly FDA specific and most likely will create a burden since separate documents for the same PSURs will have to be generated for different countries.

Setting up the tabulations would require changes in the system, in the process, and in training of staff. In addition, this will require the establishment of new validated tabulations, validation test strategy, and validation testing. Ongoing, the increased burden of increased time spent for each PSURs includes running tabulations, and validation queries.

III.E.2.g. Safety Studies

The proposed rule states "copies of full reports for these studies should be appended only if new safety issues are raised or confirmed." The wording should be made consistent with ICH E2C, that is, "copies ... should be appended only if deemed appropriate."

III.E.2.h. Other Information

The lack of efficacy requirement is addressed in this section, and separately in III.E.2.k.vi Lack of Efficacy reports (appendix) and under III.E.2.k.vii Information on Resistance to Antimicrobial Drug Products. For consistency and simplicity, it should be addressed once under the Other Information section to be consistent with ICH.

III.E.2.k. Appendices
III.E.2.k.iii. Spontaneous reports submitted to the applicant by an individual other than a health care professional

The FDA should clarify what is meant by reports received from individuals other than a health care professional (i.e., SADR reports from consumers).

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

Class action lawsuit lists would overlap with consumer cases resulting in the potential for apparent "over counting". Based on the same rationale described in section III.A.7 Spontaneous report, that "FDA believes that the vast majority of SADR information from class action lawsuits is duplicative..." and "in many cases, information in addition to the minimum data set is not available for these SADR reports and follow-up is unlikely to result in acquisition of new information..." this requirement should be eliminated from inclusion in all periodic reports as well. There is little perceived value, it goes against

harmonization since it is not required by ICH E2C, and efforts spent in collecting this information could be better devoted to signal generation and evaluation.

III.E.2.k.vi. Lack of Efficacy reports

Under this section, it is stated, "This appendix would contain 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..." This is of questionable value given the differences in quantifiable patient exposure between clinical trials and spontaneous reports as well as the differences in definitions of lack of efficacy between clinical studies and spontaneous reports.

III.E.2.k.vii. Information on resistance to antimicrobial drug products

Resistance information: The best approach to this requirement would be if FDA maintained a central resource for the US resistance data, such that companies manufacturing various antibiotics can utilize the same reference information.

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

See comments under III.E.1.h.

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

The IPSR format is confusing, and the timeline is based on the US approval. The addition of the report every six months on all products would require an extensive new burden. Rather than creating a new IPSR or TPSR report, Abbott proposes the following: to maintain the current periodic reports in place of TPSRs for older products, accompanied by a complete line listing of cases (including foreign serious labeled and foreign nonserious) or MedWatch forms; and PSURs for newer products, which could be accompanied by all MedWatch forms. Abbott proposes that these should not take effect until FDA is prepared to accept electronic reporting.

III.E.5. Reporting Requirements

As mentioned in the comments under Section III.A.6, it is unclear how these changes will impact E2B submission initiatives. The implementation of these proposed requirements is regulatorily burdensome if hard copy attachments are required, even though reports may be submitted electronically. Abbott recommends submission of hardcopies should be eliminated or this requirement should become effective after the electronic submission is fully implemented.

IPSRs are based upon US approval dates but they are supposed to be reported between PSURs, which are based on international birth dates. Harmonization with PSUR requirement is strongly recommended.

Under the proposed revised Part 312.32 (c)(1)(iii) Submission of Written Reports (pg 12476), the proposed rule states "Foreign SADR may be submitted either on an FDA MedWatch 3500A form or, if preferred, on a CIOMS I form. Please clarify whether FDA would accept domestic SADRs reports on CIOMS I forms, or must a MedWatch 3500A be submitted.

III.F. Reporting Format

III.F.1. Forms Versus Narrative Format

The types of reports (TPSRs, PSURs, and IPSRs) and their periodicity are complicated. This combination of reports with different timelines is of questionable value. In line with FDA's goal of achieving global harmonization, Abbott recommends that the proposed periodicity of PSURs remain the same (every six months for 2 years; annually for 3 years; then every five years) together with the semi-annual listings that FDA has proposed. Further alignment with ICH is a must.

Abbott applauds FDA's acceptance of the international birth date and the adoption of the same PSUR frequency used internationally (i.e., six months for 2 years; annually for 3 years; then every 5 years). However, using U.S. approval dates for these reports goes against the global harmonization. The proposed rule states in "II.B. Rationale for This Proposal" that "...harmonization of the format and content, as well as the reporting frequency, of these reports [postmarketing periodic safety reports] by all countries in the three [ICH] regions is essential to eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products and not on the different reporting requirements of different regions." The utilization of a reporting frequency based first on one ICH region and then on a second ICH regional approval works against the concept of harmonization described in the proposed rule. The true acceptance of harmonization should be the first approval of the drug product in any country worldwide followed by acceptance that the most important safety findings will occur within the first several years regardless of the ICH region of first approval.

If any additional types of reports would be implemented, the addendum report described in the Addendum to ICH E2C would be a better choice to promote harmonization. Furthermore, if the TPSRs and IPSRs remain in the U.S. regulations and the addendum report of the Addendum to ICH E2C is adopted, there will be confusion because the intents of these reports are similar.

The proposed reporting for PSURs would require extensive modification and validation of the electronic systems since SADR definitions are not ICH consistent and multiple new line listings are requested. The new criteria for "not associated" would need to be built into the clinical study line listings. This would require a change in system vendor products. Abbott's estimate of implementing this proposed requirement is a minimum of one year for the development of the new system, and the additional time for testing and validation. There are multiple steps involved in making software changes in a controlled environment. After a vendor makes changes, sometimes taking up to one year, the company must go through controlled process, including testing the system, and training staff on changes. Companies using the same vendor would have to agree upon with the new system.

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

Abbott strongly supports the recommendation of using MedDRA terminology for all pre- and postmarketing safety reporting. MedDRA has been internationally accepted and implemented for postmarketing safety reporting by industry. Even though we agree with the adoption of MedDRA for pre-marketing safety reporting, implementation of MedDRA for clinical trials as proposed for one year from the publication of the final rule is an extremely aggressive timeline and may not be realistic. Conversion programs into MedDRA terms may not exist for currently used clinical coding systems. Special consideration should be given for clinical development programs that are partially complete using some other coding system and that have an application planned for after the implementation date.

III.F.4. Contact Person

Every CIOMS I and/or MedWatch forms would have to be customized if the physician responsible for the content and analysis of a given form is required. (See previous comments under section III.E.1.h.). For consistency, Abbott recommends that a single contact person from Regulatory Affairs be identified within the company, who can then identify the appropriate safety person to address the Agency question.

III.I. Abbreviated New Drug Application (ANDA) Products

Abbott agrees with the waiver for periodic reports of ANDA products. Abbott also agrees with the agencies to tie the international birthdays together for innovator plus generics and have them submitted on the same schedule. This would provide the FDA a more comprehensive picture.

III.K. Safety Reporting for In Vivo Bioavailability and Bioequivalence Studies

In this section, FDA proposes the use of the U.S. label for the reference document because "studies that are not subject to an IND are unlikely to have an investigator brochure for use as a reference document." In extrapolating from this sentence, if a drug has an NDA approved, and an SAE occurs in a study that is not being conducted under an IND, clarification is needed as to whether the reference document for that study's SAEs should be the U.S. label, irrespective of the phase of the study.

V. ANALYSIS OF IMPACT

Abbott supports the FDA's efforts towards harmonization of the safety reporting requirements with ICH and CIOMS recommendations, including the adoption of MedDRA, for pre- and postmarketing reporting, and the PSUR. Further harmonization effort is necessary on the definitions of terms/medical terminology, reporting formats and timeframes, etc.

Despite those efforts, the proposed rule seems to create inconsistencies in all areas of safety reporting, especially due to the creation of new types of reports. There has been no demonstration that submitting all these additional reports in 15 days will enhance public health, but rather debilitate an already overburdened paper-based system. FDA states that the increase in timeliness will reduce hospitalizations due to SADRs. Abbott would appreciate any objective evidence or studies published that will support this finding.

Compliance may be adversely impacted due to the confusion and complexity of this proposed system.

The arguments under the section regarding Market Failure do not seem to support invoking a system so different from ICH.

V.C. Benefits

Most SADR reports are related to new drugs less than three years of age, which certainly is recognized as the most important additional efficacy and safety learning experience, thus, scrutiny on safety reporting is acceptable and understandable for these drugs. However, these stringent new requirements proposed in the rule, are applicable to all drugs including those with well established profiles. We recommend that the FDA conduct an assessment of these requirements on the benefits of public health because not all SADRs are preventable.

V.D. Costs of Compliance

V.D.1. Costs of New Record Keeping and Reporting Requirements

The analysis shown appears to be based on the 1998 data. The costs regarding dealing with legacy data, versioning processes and system validation have not been addressed. The FDA should make available a 2002 data report for review. Abbott has experienced an increase in adverse event report numbers during this timeframe even though foreign serious labeled and nonserious reports are not being submitted.

Abbott's estimation of increase in burden is as follows:

Cost and workload estimates of predicted number of future SADR reports expected to be included as revised expedited and new semiannual submissions:

- It is estimated that there will be at least 30 percent increase in the number of expedited report submissions. Semiannual submissions will require an increase in staffing. Record retention will increase, and so, will cost in retaining and managing these documents.

- In calculating the cost of compliance, the FDA should take into account system changes for the adoption of new definitions, extra reports, different types of reports, different timeframes, change in process, multiple and country specific reports with the same information, process validations, training multiple groups, and the implementation of different types of communication with different countries and people involved, including patients, customers and health care professionals.

Table 13. Number of Affected Reports by Regulatory Status

The following concerns should be addressed in regard to the information in this table:

- This table does not reflect the increased number of expedited reports that will be sent to the IND because of the expansion of the associated category to include categories of "probably not, unlikely, etc." There will be a substantial increase in the number of reports submitted.

- Previous sections stated that certain types of "studies" such as patient named programs, registries, etc., should be handled as clinical trial cases and not spontaneous reports. With such studies, cases of "always expedited", "medication errors", etc., were stated as requiring expedited reporting. Yet in Table 13, there is no listing for reporting of "always expedited" or "medication errors", etc., to the IND. Clarification is needed as to how FDA would like such "special study" expedited reports to be submitted, and whether such studies should be handled as clinical trial cases, but submitted only to the NDA.

V.D.1.b. New Time Burden
V.D.1.b.iv. IND and Bioavailability/Bioequivalence Safety Reports

In this section, the impact of the expansion of the "associated" classification to include cases where causal relationship cannot be 100% ruled out should be included. This will have a substantial impact on the number of cases submitted as an expedited report.

Table 14. Estimated New Burden for Expedited and Semi-Annual Reports

The FDA should clarify the listing of "individual case safety reports – semi-annual submission" under IND Safety as an IND safety reporting requirement, which was not described in the preamble. Based on Abbott's processes, the total number of hours listed for IND Safety reporting should be 30 hours not 20 hours.

List of Subjects

Part 312. Investigational New Drug Application
Section 312.32 IND Safety Reports

(c)(1)(iii). This section states that written reports may be submitted on FDA Form MedWatch 3500A or in a narrative format. It also states that foreign SADRs may be submitted on a CIOMS I form or MedWatch 3500A. Conversely, a CIOMS I form should be approved for use for domestic SADRs to decrease workload burden, enhance timeliness compliance, and integrate globally accepted formats. Abbott strongly recommends that CIOMS I form be also acceptable for domestic SADRs.