Novartis Pharmaceuticals

Comments on FDA Proposed Rule: Safety Reporting Requirements for Human Drug and Biological Products
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Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ about 78,200 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals Corporation researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

As one of the world's largest pharmaceutical manufacturers, Novartis has committed extensive resources to the handling of safety information for its investigational and marketed products. The proposals outlined in the FDA Proposed Rule will significantly impact our safety handling operations and we appreciate the opportunity to offer comments on these proposals.

I. General Comments:

FDA states in the Summary of the Proposed Rule that it "is taking this action to strengthen its ability to monitor the safety of human drugs and biological products. The intended effect of these changes is to further worldwide consistency in the collection of safety information and submission of safety reports, increase the quality of safety reports, expedite FDA's review of critical safety information, and enable the agency to protect and promote the public health." FDA further states in Section V.C. Benefits that "the benefits of the proposed rule would result from both the public health gains ..... and the economic savings attributable to the more efficient use of industry and regulatory resources."

Novartis agrees with FDA stated goals and appreciates FDA's efforts to clarify definitions and requirements, streamline and reduce redundancy in reporting, and improve the overall quality of safety reports. However, we believe that the increased number and complexity of new requirements being proposed will severely compromise rather than facilitate FDA's objectives, both for industry and the agency. In addition, FDA has not provided any evidence that the new requirements will in fact improve its ability to monitor the safety of human drugs and biological products over the existing requirements.

While FDA has made some welcome attempts in this Proposed Rule to bring its regulations into worldwide harmonization, many of the changes proposed are not in concert with ICH guidelines, CIOMS proposals, and industry practice. Proposed definitions and activities that are specific to the US, and especially those that are in conflict with ICH guidances, create an additional workload burden for global companies and increase the potential for confusion and non-compliance. Moreover, the costs and resources involved in implementing these new requirements will far outweigh any savings realized through efficiency gains and redundant reporting.

It is not clear whether FDA has consulted non-industry stakeholders in the development of the proposed rule. The proposed requirements for active query, supporting documentation, and SADR reporting will have significant impact on healthcare providers, hospitals, investigators, and IRBs and an assessment of the impact on these stakeholders has not been provided in the proposed rule.

The requirements being proposed by FDA are extensive and will require significant re-programming of adverse event database software and changes to existing procedures in order meet the proposed regulations. The proposed 6-month timeline for implementation is an unrealistic expectation. Novartis believes it will take a minimum of 1 year to implement these requirements.

II. Summary:

Issues of particular concern to Novartis include the following:

a. Suspected Adverse Reaction (SADR). FDA's re-interpretation of the definition, as well as coinage of a new term, are not consistent with the agreed-upon ICH2A guidance. Implementation of this new definition will create a scenario whereby almost all AEs are automatically considered suspect because "the relationship cannot be ruled out." The result will be a significant increase in the number of serious, unexpected, suspected cases that will require unblinding, reporting to health authorities, and notification to investigators and IRBs. This situation will add considerably to the AERS database "noise," potentially compromising signal detection efforts. There is also the potential for impacting study integrity if large numbers of study patients require unblinding. The adoption of a different interpretation of "reasonable possibility" will also create a situation where cases are handled differently between the US and rest of the world during the conduct of a global clinical trial. This will have a significant impact on the preparation and analysis of safety data tables for inclusion the Common Technical Document. In the postmarketing arena, the new term and definition may result in potential litigation issues.

b. SADR with Unknown Outcome. This new category of reports is not consistent with ICH and CIOMS recommendations. We agree that there should be intensive efforts to obtain this information using active query, if possible. However, creation of a third category of report requires additional programming and work processes to accommodate a requirement that is specific only to the US. It will also create discrepancies between PSURs submitted to the FDA and those submitted to regulators outside the US.

c. Active Query. The proposal to require direct verbal contact between a health professional at the company and the reporter for all serious adverse events, always expedited reports, and medication errors is an enormous and unnecessary resource burden for companies and may ultimately be a disincentive for physicians to report. Detailed, focused questionnaires sent by mail or e-mail will facilitate the collection of quality, detailed information and will achieve the same purpose in most instances. A risk-based approach to obtaining follow-up information, such as that recommended by CIOMS is consistent with FDA goals and enables companies to utilize its resources for maximum value. In addition, it is not appropriate that FDA specify the qualifications of company personnel, but only to state that they must have adequate training, experience, and/or education to perform the required activities.

d . PSUR Additional Requirements. FDA's proposals for special appendices and additional reports (i.e. IPSR) that are specific only to the US do not meet the stated objective of harmonizing safety reporting requirements and in fact, serve to undermine this effort. In fact, FDA even acknowledges in II.B.1 Rationale for This Proposal: International Standards that "harmonization of the format and content, as well as the reporting frequency, of these reports by al countries in the three 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 number and complexity of additional requirements will require the addition of significantly more resources and complicate the establishment of a global PSUR system.

e. Medication Errors. While we recognize the importance of monitoring, understanding, and preventing medication errors, the addition of medication errors with their unique definition and required expedited handling only adds to the increasing complexity of scenarios for safety reporting. This proposal does not take into account the other stakeholders involved in this issue, who play a considerably larger role than the pharmaceutical industry. Requiring expedited handling of reports where there is no adverse event involved is unnecessary and will not serve to meet FDA's stated objectives.

e. Follow-up. The proposed follow-up scheme adds additional complexity, utilization of resources, and administrative burden for no perceived public health benefit. Documentation of due diligence efforts is already required and available on request.

f. Supporting Documentation. The requirement for supporting documentation for all expedited reports of death and hospitalization is unrealistic, burdensome, and does not take into consideration cultural, legal, and privacy law differences around the world. The necessity of translating these documents in advance is costly and will exceed the specified timeline for providing these documents to FDA.

III. Specific Comments:

Due to the presentation of the same issues in several places in the document, specific comments are organized by topic rather than by numbered sections in the Federal Register to more efficiently address the concepts and objectives underlying the proposals.

A. Suspected Adverse Drug Reaction (SADR)

This new acronym and definition is not consistent with the accepted ICH acronyms/definitions of adverse drug event and adverse drug reaction. Since the ICH E2A document was published in 1995, the ICH terminology has been well integrated into everyday industry jargon and practice, as well as by regulatory bodies. As intended, it has enabled a more harmonized approach to global safety reporting. Creating a new acronym with a different definition specific to the US will create confusion and fractionate the handling of global reports. Furthermore, SADR is easy to confuse with SAE, which has become a well-recognized abbreviation for serious adverse event.

The interpretation that "reasonable possibility" means that "the relationship cannot be ruled out," while technically consistent with ICH E2A, is not consistent with the associated concepts of this definition as stated in both the ICH document and the EU Clinical Trials Directive. Both of these documents include the concept that "reasonable causal relationship" conveys that there are facts (evidence) or arguments to suggest a causal relationship.[1] Such facts, evidence or arguments include temporal relationship between the adverse event and the suspect drug, pharmacological plausibility, positive dechallenge and/or rechallenge, and existence of confounding factors such as concurrent illness, concomitant medications, or relevant medical history. The FDA definition of SADR does not include these concepts as part of the definition or accompanying explanation and in fact, reinterprets "reasonable possibility" to mean "the relationship cannot be ruled out."

Experience has shown that in both the clinical trial and postmarketing settings, it is extremely rare that an investigator or health care provider has enough information, or that the circumstances are so clear-cut, to rule out a reasonable possibility of association. Therefore, by implementing this new definition, FDA will be creating a scenario whereby almost all AEs are automatically considered suspect. The result will be a significant increase in the number of serious, unexpected, suspected cases that will require unblinding, reporting to health authorities, and notification to investigators and IRBs. This

[1] Guideline for Industry. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. ICH E2A, March 1995.

situation will add considerably to the AERS database "noise," potentially compromising signal detection efforts. There is also the potential for impacting study integrity if large numbers of study patients require unblinding.

FDA's suggestion to negotiate exclusion of specific AEs (e.g. disease progression for oncology trials) will not necessarily resolve these concerns. Prospectively defining the AEs for exclusion in every program is complex and may lead to differences in reporting among trials and programs. Moreover, if companies negotiate specific exclusions with FDA for every trial/program in order to address the above concerns, the FDA's objective of receiving every serious, unexpected AE (causality will no longer be a factor) for internal assessment, may ultimately be compromised, as well as create a huge administrative burden for both the industry and the agency.

The adoption of a different interpretation of "reasonable possibility" will also create a situation where cases are handled differently between the US and rest of the world during the conduct of a global clinical trial, affecting not only companies sponsoring trials but also clinical investigators who will require major re-training on the new definition. There will also be a significant impact on the preparation and analysis of safety data tables for inclusion the Core Technical Document. How would a company perform an analysis of those cases that are Reasonably Possible when the assessment of reasonably possible differs between geographical regions in a global clinical program? Furthermore, for consistency and in order to not appear to be withholding important information, companies may feel obligated to submit all of these cases to other regulatory agencies, even if not specifically required.

In the postmarketing setting, the new interpretation of reasonable possibility suggests that spontaneous reports of SADRs which are found to be definitely not related do not have to be reported. This appears to be inconsistent with the presumption that spontaneous reports are by default considered "possibly related." Furthermore, the distinction between spontaneous reports and solicited reports will be eliminated since causality assessment currently required for solicited reports would effectively default to "cannot be ruled out." The result will be the required reporting of a much larger volume of solicited reports that currently exists.

From a litigation perspective, basing the definition of a reportable postmarketing event on whether there is a "reasonable possibility" of a relationship between the drug and event, and defining "reasonable possibility" as the situation where a "relationship cannot be ruled out," is a potentially explosive change in reporting definitions, at least in terms of litigation. The proposed rule clarifies that "[f]or spontaneous reports, the applicant must always assume for safety reporting purposes under the section, that there is at least a reasonable possibility in the opinion of the initial reporter that the drug product caused the spontaneously recorded event." Thus, under the FDA proposed rule, a drug company assumes, for regulatory reporting purposes, that a relationship between a drug and a noxious and unintended response could not be ruled out by the initial reporter of the event to the company.

This provides a regulatory safe harbor for a drug company, but probably does not avoid the mischief this would undoubtedly create in litigation. A drug company defending a product liability suit may need to point out, depending on the circumstances of the particular litigation, that the FDA regulations require the company to assume that a there is "reasonable possibility" of a relationship between the drug and an event, for purposes of reporting to FDA. Currently, drug companies are required to report ADEs to FDA without regard to a reasonable possibility of a relationship, except in cases of ADEs observed in clinical trials or postmarketing studies. The proposed rules, however, imply an expanded scope of reporting for spontaneous reports for reasons that do not seem entirely clear, let alone warranted. But in litigation, these fine regulatory distinctions may be difficult for a court and jury to keep in mind. It is likely that plaintiffs will seek to reinforce the notion that

an SADR, though it is nothing more than a spontaneous report in most cases, has a relationship with a drug company's product that "cannot be ruled out."

Recommendation:
Novartis strongly urges FDA to reconsider its proposal and to keep its regulatory definitions, interpretations, and acronyms consistent with those agreed to by ICH and accepted practices. We believe that imposing such a drastic change in safety reporting requirements with the resulting complexity, complications, workload burden, and potential compliance issues is not necessary for all products, and has no demonstrated public health value.

If FDA has a specific concern in either the clinical trial or postmarketing setting, we recommend that FDA adopt a risk-based approach and require increased reporting on an as-needed basis. The development of risk management programs requiring review and approval by the FDA will also assist in meeting FDA's objective to ensure adequate safety reporting standards as part of its efforts to minimize the risk of drugs. In the postmarketing setting, FDA should not adopt a new postmarketing reporting standard based on a "reasonable possibility" of a relationship between the drug and event because it is confusing and potentially misleading, especially in a litigation situation.

B. SADR with Unknown Outcome

This new category of reports is not consistent with ICH and CIOMS recommendations. We agree that there should be intensive efforts to obtain unknown outcome information using active query, if possible. However, creation of a third category of report requires additional programming and work processes to accommodate a requirement specific only to the US. It will also create discrepancies between PSURs submitted to the FDA and those submitted to regulators outside the US. FDA has provided no evidence that potential public health benefit outweighs the increased burden on industry. Novartis believes that resources could be better utilized in trying to obtain this information and recommends that the current categories of "serious" and "non-serious" remain as the two major categories of reports, consistent with ICH guidelines.

The meaning of the word "outcome" is not clear throughout the document. In most instances it appears to refer to the regulatory categorization of reports into "serious", "non-serious", and "unknown outcome." However, at times it is unclear whether the FDA is referring to medical outcome or regulatory outcome. Novartis recommends that FDA give consideration to using different terminology so that the intended meaning can be easily distinguished. One suggestion is to replace the word "outcome" with "regulatory classification," where this is the intended meaning and utilize the word "outcome" to mean "medical outcome" which is commonly used in clinical trial data collection and universally understood.

C. Active Query

Novartis supports FDA's desire to improve the quality of reports on marketed products. We agree that a focused line of questioning would help facilitate the collection of detailed, relevant clinical information. However we do not believe that this has to be performed only by direct verbal contact. Detailed, focused questionnaires sent by mail or utilizing e-mail could achieve the same purpose in many instances.

While in theory obtaining as much information by telephone as possible eliminates or minimizes the need for further follow-up, in practice written information is often more accurate. Physicians often do not have the patient's medical records at hand and provide information by recollection, which is later discovered to be inconsistent with the medical records. Many physicians prefer to provide information in writing since completion of forms is an activity that can be delegated to a staff member. Furthermore, repeated interruptions by industry to obtain follow-up information may ultimately be a deterrent to report adverse events in the future.

The proposal to require active query for all serious AEs, always expedited AEs, and medication errors will significantly increase the workload and necessary resources to perform this activity. It is not clear from the proposal whether FDA's intent is for companies to implement active query globally or only in the US. Implementing this requirement outside the US will be a challenge, especially in small countries which operate with limited resources. In addition, direct contact of physician reporters is not permitted in some countries (e.g. Italy) due to cultural and legal constraints.

FDA estimates that implementing the active query requirement would cost companies one hour each for a health care professional and regulatory affairs professional to complete all of the activities involved. We believe this is a gross underestimation of time. It may take an average of one hour to generate the appropriate questions, make the contact, and document the information, however, this estimate does not consider the additional time required to track and process the responses. For Novartis, this would amount to greater than 40,000 hours required just to conduct active query on serious adverse event reports and does not include the time spent by the reporter answering the questions, or additional tracking and processing of the responses.

Novartis disagrees that active query should be conducted only by a health care professional. Many of the professionals in industry drug safety departments or individual country offices hold advanced scientific degrees, e.g. PhD, and have been adequately trained in the handling of safety information. Rather than define specific qualifications of individuals, we encourage FDA to use language similar to that stated in 21 CFR 211.25:

> Each person engaged in the .....shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions.

FDA also proposes in III.B.2.b that a chronological history of all active query efforts be documented in detail in the case narrative. We believe that including this information in the narrative adds no medical value and may lead to potential legal risk in the event of litigation. In addition, when companies move to electronic transmission of ICSRs, this additional documentation may force companies to restrict the medical narrative so not to exceed the 20,000 character limit. Records of due diligence have always been maintained in the case record and available on request and should continue to be handled in this manner.

Recommendation:
We propose that this activity be recommended, not required, and only for those potentially "higher risk" cases, such as serious, unexpected AEs and AEs of special interest. E-mail contact should be also considered a valid form of active query. For non "high-risk" cases, written follow-up should be sufficient in most instances and the use of detailed, focused questionnaires would be useful to gather complete information in these cases. We agree with the risk-based approach to obtaining follow-up information offered by CIOMS V. Records of active query efforts should continue to be maintained as part of the case file and available on request.

D. Periodic Safety Update Reports

FDA's proposal for Periodic Safety Update Reports (PSURs) is not consistent with the format and content described in ICH E2C and E2C Addendum. FDA's proposed extensive additional US-only requirements are in conflict with the primary objective of the ICH process, which was to harmonize the preparation of reports and enable a single report to be prepared and sent to all health authorities. Novartis strongly urges FDA to reconsider these additional requirements and follow the agreed-upon ICH documents.

ICH E2C Addendum. The bridging and addendum documents described in ICH E2C Addendum are not addressed in the FDA proposal. Is it FDA's intent to implement these documents?

TPSRs versus PSURs. FDA's proposal for TPSRs adds considerable new requirements and therefore, the benefit in preparing a TPSR versus a PSUR is questionable. Novartis has several products marketed only in the US which have been on the market for more than 15 years with no change in indication or intended population. We believe that preparing a full PSUR for products such as these with a well known safety profile does not improve public safety and utilizes considerable company resources. Novartis recommends that for products greater than 15 years old, companies be given the option of preparing the current US Periodic Report.

Worldwide Marketing Status. The requirements for worldwide marketing status are more extensive than that described in ICH E2C. This information is not always available, especially for older products. Novartis proposes that the words "when known" be added to the "dates of market launches," and that lack of approval should only be presented if it occurred for safety reasons, in accordance with ICH guidelines. In addition, we recommend that the list of indications be deleted from this section since it is already provided in the accompanying Company core Data Sheet.

Changes to the Company Core Data Sheet. FDA's proposal to use the CCSI at the beginning of the reporting period is often impractical and not in line with the various options provided in ICH E2C Addendum. Due to the large volume of cases continually being processed, the Novartis practice is to assess listedness at the time of data entry, using the CCSI which is current at that point in time. We recommend that applicants be permitted to use this approach with appropriate explanations provided in the PSUR. All versions of the CCSI used during the period will be provided.

Line Listings. While FDA has stated that line listings will be permitted, Novartis proposes that these should be accepted in lieu of semi-annual line listings in either paper or electronic format, in accordance with ICH recommendations.

Summary tabulations. Summary tabulations as proposed contain too many breakdowns by category. We believe that aggregate totals are more valuable for seeing the entire picture, rather than broken down in so many segments.

The request for cumulative data for all SADRs that are serious and unlisted is burdensome and requires clarification. Are cumulative counts required for each term in the case and do the counts include previous reports of that term which may not have been categorized as serious and unlisted? For example, if a rash is associated with a serious, unlisted case SADR, does this mean that cumulative numbers are required for all reports of rash with that product? For products which have numerous events reported for each case, this could represent almost the entire database for the product. Novartis believes that it is more medically meaningful to evaluate cumulative data by the case, and not by the term. We recommend that cumulative data be required only for cases discussed in the individual case histories, and that this be presented in a format similar to that used for IND Safety Reports.

Case Reports from Class Action Lawsuits. The proposed requirement to evaluate overall drug safety based on allegations made in class action lawsuits is concerning. The requirement clearly deviates from a science-based approach to safety assessment in favor of a tabulation and an assessment of allegations filed in litigation, which may not have any scientific basis whatsoever. FDA is ill-equipped to appropriately evaluate the allegations made in class action lawsuits or any other litigation. These tabulations and discussions that FDA would require drug companies to prepare have the potential to be a virtual playground

for the plaintiff's bar. The discussion and analysis that FDA is proposing may well become key evidence in product liability litigation. Moreover, there is a significant danger that such tabulations and discussions might intrude into both the attorney client privilege and attorney work product privilege otherwise available to the drug company seeking to defend itself against baseless litigation filed with respect to its FDA-approved products. Therefore, Novartis recommends that FDA consider excluding the reporting of litigation cases altogether unless they contain medically confirmed information.

For medically confirmed cases involving litigation, we recommend that the proposal to include in the PSUR be extended to any report of a "legal" origin since not all multiple plaintiff lawsuits are officially classified as "class action." In addition, we propose that a discussion of these cases be included in the Overall Safety Evaluation section of the PSUR, and not addressed as a separate section. If a specific issue is involved, it can be addressed in Section 6 of the PSUR.

Study Reports. FDA proposes that copies of full clinical and non-clinical study reports be appended if new safety issues are raised or confirmed. Since these are already submitted at the end of the studies, resubmitting them with the PSUR is duplicative and unnecessary. Summaries are already provided in the PSUR. Novartis recommends that additional copies of study reports should be provided only upon request by FDA.

Appendices:

Core Company Data Sheet – Providing the CCDS for the next reporting period is not practical. If recommendations emerge from the PSUR, the next version of the CCDS may not yet be finalized in time to submit it with the PSUR. We recommend that only copies of CCDS's used during the PSUR report period be provided.

Consumer reports. A separate summary tabulation for consumer reports should not be required if these are already submitted within the body of the PSUR.

Lack of efficacy. Lack of efficacy is already discussed in another section of the PSUR. It should not be necessary to repeat this information in a summary tabulation.

Interim Reports. FDA's proposal for interim PSURs is a departure from the periodicity and format recommended in ICH E2C and E2C Addendum. These reports pose a large burden on companies both in format and cut-off dates. Cut-off dates for PSURs are typically set on an annual basis. The 6-month cut-off for the 7.5 and 12.5 year interim reports requires a different cut off date which is specific only to the US for these particular reports, with no added public safety value. Since the EU is in the process of considering a 3-year PSUR to replace the current 5-year PSUR, Novartis urges FDA come to agreement on the required periodicity with the other ICH regulatory partners and institute a harmonized timeframe and format.

Combination Products. If the applicant chooses to produce a separate PSUR for combination products, we believe the international birth date should be based on the approval date of the combination product and not on approval dates of the individual components, as proposed.

E. Semi-annual Submission of ICSRs

The request for this data outside of the periodic report schedule is not consistent with ICH recommendations and creates additional submissions (and the accompanying extra work) for companies. Electronic submission will facilitate compliance with this requirement; however, until the implementation of electronic submission, Novartis recommends that FDA continue to accept paper submissions at the time of the TPSR or line listings with the PSUR. We also request clarification if it is FDA's intent that the cases presented in the

PSUR or TPSR will not match the cases sent by semi-annual submission due to the differences in time period between the semi-annual submission and the PSUR.

F. Medication Errors

While we recognize the public health importance of this issue, the FDA proposal focuses on the pharmaceutical industry and does not include the other stakeholders involved in the healthcare system, who clearly play a larger role than pharmaceutical companies in the occurrence of medication errors. Medication errors are primarily related to the practice and dispensing of medicines, and not to the inherent safety of a drug nor errors involving the pharmaceutical industry.

The collection and reporting of medication errors is a new requirement specific to US reports. As such, it is not in keeping with efforts to harmonize safety reporting in the ICH regions and creates an additional burden for companies which must implement new procedures and software to accommodate this requirement for one country. This is especially true for reports of "potential" medication errors, which is likely to produce many reports of no product safety interest.

Industry compliance with the FDA proposal will require revision of the existing FDA MedWatch data collection form, which does not contain all the necessary data fields to accurately capture information related to medication errors. The same holds true for the current adverse event databases. Considerable re-programming of AE databases will be required to accommodate these reports, since the minimum data set and criteria for expediting are not consistent with those of adverse event reports.

While FDA has stated publicly that medication error reporting is intended only for domestic postmarketing reports, it is not explicitly clear in the Proposed Rule. Particularly for trade name confusion, required reports should be limited to the US given the complexity of global language and pronunciation differences.

Clarification is requested on the definition of "in the course of professional practice." If interpreted broadly, physician-prescribed overdoses or off-label use could be included in this definition. We recommend the definition explicitly exclude these. For reports of actual or potential confusion between two products, we recommend that a copy of the report be required to be sent to the other company.

Clarification is also requested on the appropriate reporting of reports of medication error which results in a suspected adverse reaction.

Novartis believes that the timely assessment of medication error information could be achieved without the added burden of sending all reports in an expedited manner, especially for those cases where the error does not result in an adverse event. We propose that FDA consider requiring expedited reporting only for those medication errors that result in serious, unexpected adverse events and that the PSUR or TPSR serve as the vehicle for reporting and discussing all other medication error reports.

G. Always Expedited Reports

Novartis supports the concept of designating specific adverse events as important medical events. However, we question the value of requiring expedited reports for expected adverse events which are already described in the labeling and request that FDA consider exempting expected adverse events from this requirement. One suggestion is to rename these events as "medically important" or "always serious" events, which would ensure that these would always be expedited to FDA if they were also unexpected.

Some of the terms on this list are quite broad and subject to interpretation, e.g. liver necrosis, sclerosing syndromes, acute renal failure, anaphylaxis. Novartis recommends

that all terms on this list be translated into MedDRA terms by FDA. If newer versions of MedDRA alter the terms, FDA should be responsible for providing the new terms that define these events.

H. Follow-up Reports

The additional timelines and documentation being proposed are confusing and not in line with ICH timelines. Furthermore, the central tracking of follow-up attempts globally in order to provide the requested documentation on a case report is particularly burdensome as not all follow-attempts at the local country offices are done electronically. Standard practice has always included the submission of significant new information upon receipt and maintenance of the information and due diligence efforts in the case file. Requiring additional reports to reiterate what is already required and available on request is not an effective use of resources for industry as well as the agency.

We recommend that FDA retain the current requirement for 15-Day Reports and require that any new information obtained through active query or other methods continue to be sent in this time frame. In addition, we urge the Agency to reconsider the proposal to send documentation of follow up attempts as part of an individual case report. This requirement is burdensome, will require significant re-programming of the software that generates MedWatch forms to include this information, and does not improve the quality of the medical information. Attempts to obtain follow up information should continue to be maintained by the applicant and available upon request at any time. Specific concerns by the Agency as to whether the application holder is performing appropriate due diligence should be addressed directly with the application holder.

I. Supporting Documentation

Novartis agrees that autopsy reports and hospital discharge summaries sometimes contain valuable information that confirms or adds to existing case information. However, we disagree that these be requested on a routine basis. Autopsies are not routinely performed in many countries and therefore will not be available for many reports of death. Local privacy laws often inhibit the ability of company personnel to obtain these documents in a timely manner, if at all. Once obtained, the time required to perform translation of these documents often exceeds the 15-day time frame for submission. Translation services can be quite costly and not easy to obtain, especially in less developed countries. Novartis recommends that companies be permitted to use judgment in requesting this documentation, or on request by FDA.

Providing available medical documents to the FDA within 5 days of request is costly and difficult to implement in non-English speaking countries. In many large companies, the central processing site either receives an electronically entered case or a completed form. Source documents are not always sent to the central processing site, but are maintained and roughly translated by the local country personnel at the time of data entry or completion of a data collection form. In order to maintain readiness to meet a possible request by FDA, all source documents (and not just autopsy reports and hospital discharge summaries) would be required to be translated upon receipt by the local site, or risk not being able to meet the time requirements of an ad hoc FDA request. As this is a huge cost and resource burden for companies, we recommend that companies only be required to provide such detailed documentation, including translation, when it is in support of an identified safety signal and negotiate an achievable timeframe for transfer of the information.

We agree that if supporting documentation is not able to be obtained, that the manufacturer or applicant should maintain records of attempts to obtain this information at the company. As stated earlier, we believe that this policy should be in effect for all attempts to obtain follow up information and the records available to FDA on request.

J. **Contractor Reports**

The FDA definition of contractor is quite broad and could be interpreted to include wholesalers, PBMs, or hospitals that have business arrangements with a company. We recommend that FDA consider a narrower definition of contractor, which would include license or business alliance partners and paid vendors such as CROs.

Novartis agrees that prompt data exchange between contractual partners is necessary and important, however the 5-day timeframe proposed by FDA will be extremely difficult to meet in many types of arrangements. For example, this short time frame does not allow time for proper translation and would force companies to exchange raw data and not a completed CIOMS/Medwatch form, the result being that at any given time the partners would hold potentially different information on their respective databases, including different narratives and possibly coding. Thus, different authorities around the world would receive different versions of the same report, which is clearly unacceptable. On the other hand, when completed forms are exchanged this facilitates more rapid and consistent processing of the case using the same AE terms and narratives.

For co-marketing and independent sponsorship situations, Novartis recommends that the proposed rule state that the parties must agree on a timeframe for exchange but not later than 10-15 days (to be determined in the agreement) from receipt by the first party . The regulatory reporting clock start for the second company when it receives the information and the time frame for regulatory submission should be no longer than 15 days from receipt by the second company. This allows the case to be processed through the first company's case management process according to internal procedures and exchanged with the partner no later than 15 calendar days by way of a completed CIOMS/Medwatch form. This would allow the second company to enter the same information promptly into their own database, eliminating the potential for discrepancies, allowing more rapid and efficient handling, and permitting submission to the authorities as appropriate.

K. **Lack of Efficacy Reports**

The term lack of efficacy requires further clarification and clear definition from the FDA. For clinical trial reports, the term "lack of efficacy" is rarely used in this setting and usually refers to a non-responder or cases of disease progression. Please provide clarification if a clinical trial report should be classified as a lack of efficacy only when the term is specifically used, or should it also be used to indicate a non-responder or disease progression? Novartis believes that due to the difficulty in judging a true lack of effect by the investigator and/or sponsor, the term lack of efficacy should be reserved only for those instances when the investigator has specifically determined that a lack of efficacy situation has occurred.

The determination of an increased frequency of lack of effect is exceedingly difficult when comparing clinical trial and postmarketing information. The term lack of efficacy may be used differently in these situations, e.g. non-responder versus potential quality issue. In addition, numerator and denominator data are often difficult to obtain or estimate. We request that FDA provide guidance on appropriate methodology to calculate increased frequency.

The use of the term lack of efficacy is not consistent throughout the Proposed Rule and requires clarification. In the definition of serious (p.12425, III.B.2.c), a lack of efficacy refers to a single report with a drug product used in a life-threatening or serious disease and is considered as "information sufficient to consider product administration changes." In the section on PSURs (p. 12441, III.E.2.k.vi) the requirement is for an assessment of whether an increased frequency of lack of efficacy reports has occurred compared to that predicted by clinical trial data.

L. Report Identification

The Proposed Rule specifies several additional report types in addition to the existing categories. Preparing separate identification for each report type is considerable work when there is a high volume of expedited reports sent each day. In addition, these report types are not specified in an E2b file, so FDA would only be receiving reports with the new report categories for manually submitted cases. Since companies sending reports via electronic transmission have no mechanism to comply with this request, Novartis recommends implementing this requirement only when it can be properly coordinated between manual and electronic submission.

M. Spontaneous Report vs. Solicited Report

Novartis appreciates FDA's effort to eliminate the ambiguity between solicited and unsolicited information. However, as discussed above under the section on SADRs, these distinctions will become moot if all serious and unexpected adverse events must be reported because "they cannot be ruled out." Novartis questions of purpose of FDA's efforts to specifically detail the handling of spontaneous, study, and solicited reports if ultimately they will all be assessed as suspect according the FDA proposed definition.

One circumstance not specifically addressed in the proposal is the handling of adverse events received through toll-free information services associated with disease management programs, particularly in the situation where a patient contacts the company by virtue of being enrolled in the program. While not necessary to deal with this level of specificity in the proposed rule, it would be helpful if FDA would address this situation in the accompanying guidance document.

N. Contact Person for Postmarketing Safety Reports

Novartis believes that it is not necessary and inconsistent with other FDA regulations to define the qualifications of the contact person. FDA should state clearly the expectations of the signatory and that the person must have the education, experience, and training to perform this function. As stated previously under the section on Active Query, rather than define specific qualifications of individuals, we encourage FDA to use language similar to that stated in 21 CFR 211.25: Below is an example of possible suggested wording:

> The person engaged in the signing of expedited reports, TPSRs/PSURs agrees to assume responsibility for the medical content and shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions.

This proposal as written also requires clarification. Does the licensed physician require an active license or just documentation of a license at some point, even if currently inactive. Does the license have to be from the US or can it be from any country?

O. Information Sufficient to Consider Product Administration Changes

As some *in vitro* studies are exploratory and not validated, it may be difficult to assess clinical relevance. Novartis requests clarification as to the types of *in vitro* studies that would be subject to this requirement.

P. Investigator Reports

FDA's proposed wording for CFR 312.32(a) states that "an investigator must report to the sponsor .... any other SADR...promptly unless the investigator's brochure specifies a different timetable..." Please provide clarification on the definition of "promptly."

Q. Pediatric Use Supplements

Novartis questions the value of a separate report for a pediatric use supplement. Pediatric use is already discussed in the PSUR in the Overall Safety Assessment and any information specific to the Supplement can be discussed here. A required separate report

consumes additional resources and duplicates reporting of this information. In addition, if the approval of a Pediatric Supplement restarts the 6-month PSUR cycle for product, the periodicity of submission will enable timely review of this information by FDA.

R. NDA/BLA Annual Reports

Novartis appreciates and agrees with FDA's proposal to eliminate duplication of information between the Annual Report and the TPSR/PSUR.

S. Liability Disclaimer

Novartis believes that FDA can take additional measures to promote submissions of SADR reports to the Agency and guard against their misuse. Our recommendation is that FDA provide specifically in the Proposed Rule that SADR reports are inappropriate, unreliable, and irrelevant for establishing a definitive causal relationship between a drug and an event, and that such reports are neither intended by FDA for use in civil litigation nor should they be used for that purpose under any circumstance. In support of this, FDA should rely on its statutory authority under the FDC Act of 1938, as amended, to establish specific requirements for record keeping and reporting by drug manufacturers. FDA should also specify that the policy reason for why SADR reports should not be used in civil litigation is to promote reporting of all events reasonably within the scope of the record keeping and reporting requirements established by FDA under the authority Congress has delegated to the Agency.

T. Location of Safety Records

Company safety records may be maintained in multiple locations, including multiple countries and off-site archives. Novartis recommends that only the corporate address and company contact person be provided to FDA. The company contact person will ensure that FDA receives the information requested in a timely manner, facilitate access to individuals and sites, resolve any issues that may arise during the visit, and otherwise assist the Agency so that the outcome of the Agency visit is maximized.

U. MedDRA

Novartis, as with many other pharmaceutical manufacturers, has already made a substantial investment in MedDRA and fully supports FDA's proposal to use MedDRA as the official standardized medical terminology, in accordance with ICH M1.

In litigation, the establishment of a standard terminology opens up the risk that MedDRA will be misunderstood or misused. Plaintiffs might use the MedDRA definitions and specific events captured under certain MedDRA categories to characterize, both quantitatively and qualitatively, to attempt to establish a causal link to drug products. Novartis recognizes that this is not a new issue for litigation (the same was true for COSTART), but the Proposed Rule presents an opportunity for the Agency to clarify that the use of the MedDRA terminology is not determinative of the specific medical character or definition of a particular reported event.

FDA has requested comment on the possible use of SNOMED in its notice of August 28, 2003. Novartis feels strongly that a harmonized approach to coding medical terms between companies and regulators is critical to the ability to jointly evaluate and communicate about safety information. Adding another terminology at this time will fractionate existing efforts toward global harmonization. We agree with FDA statements in II.B.1. Rationale for This Proposal: International Standards that "internationally, communication is impaired between regulatory authorities because of delays and distortions caused by the translation of data from one terminology to another" and that "the difficulty of analyzing data comprehensively may be compounded by use of incompatible terminologies and could lead to delays in recognizing potential public health problems." Novartis urges FDA to follow through on its stated intent to use MedDRA as the official standardized terminology.

V. Proposed Implementation Scheme

The proposed FDA-specific requirements will pose a considerable resource burden on global companies and require a substantial effort to implement requirements specific only to one country. The 6-month implementation time to implement the Final Rule is unrealistic. Extensive re-programming of adverse event database software and changes to existing procedures will be required to meet the proposed requirements. It is possible that implementation could be accomplished in 6 months if FDA eliminates the requirements for US-specific definitions and PSUR appendices and harmonizes with ICH guidelines, since global companies have already implemented these as part of EU compliance.

Novartis again urges FDA to harmonize its regulations with the agreed-upon ICH guidelines. If FDA moves to implement the new requirements as described in the Proposed Rule document, we recommend that FDA grant an implementation time of at least 1 year for implementation.

IV. Issues Not Covered in the Proposed Rule

While the following topics are not specifically addressed in the Proposed Rule, Novartis believes that pharmacovigilance and safety reporting process could be streamlined and enable the industry and FDA to spend more time focusing on important safety issues.

A. Investigator Notifications

The current requirement for companies to send copies of expedited reports from clinical trials to investigators concurrently with regulatory agencies frequently results in large numbers of single reports which must be tracked, analyzed, interpreted, and forwarded to IRBs who repeat this process. This is especially burdensome for centers involved in large numbers of clinical trials, as well as for companies who must track these reports in addition to the health authority reports.

Novartis requests that FDA consider adopting the proposals described in the EU Clinical Trial Directive and the upcoming CIOMS VI document (on which the Office of Drug Safety participates) which propose periodic notification (e.g. quarterly) of investigators and IRBs with an accompanying summary of the evolving safety profile of the investigational product. Periodic notification is more meaningful for investigators and relieves all parties of the continual burden of tracking individual reports. Expedited reporting to FDA and processes for updating the Investigator Brochure would remain unchanged.

B. Coding Incidental Findings from ICSRs

This topic is relevant to section II.B.2. (Quality of Post-marketing Safety Reports) in the preamble of the Proposed Rule.

During the course of follow-up data collection for spontaneously reported adverse events, medical concepts beyond the reporter's original, verbatim adverse experience term(s) are often introduced as part of the patient's clinical course or medical history. These concepts, which are not the focus of the reporter's reason for contacting the Company and for which no causal association with the use of the product is stated or implied, have been described in the CIOMS V report as "incidental findings".

CIOMS V defines incidental findings as follows:

An incidental event, adverse or otherwise, is one that satisfies the following criteria: although it occurs in reasonable clinical temporal association with the use of a drug product, it is not the intended subject of a spontaneous report (i.e., it did not prompt the contact with the pharmaceutical company or the regulator) and there is no implicit or explicit expression of possible drug causality by the reporter, other parties cited in the medical record, or the company's safety review staff.

Companies are increasingly being asked by FDA to code all clinical events, including incidental findings, that are abstracted from medical records, discharge summaries, etc., which occur at any point after a patient receives the suspect drug. This is not only impractical and burdensome as in the case of volumes of medical records describing a patient's lifetime medical history received as part of a case in litigation, but more importantly, this practice decreases the ability to identify the reporter's focus of the report to the Company and increases the "noise" in the spontaneous reporting system.

Miscellaneous events learned through follow-up are not necessarily "reported" by the initial reporter in the usual sense; therefore, there is no reason to presume that the reporter considered them related to the drug product. Not every event that happens to patients after they take a drug should by default be considered an adverse drug reaction.

Novartis recommends that the FDA incorporate the CIOMS V definition of incidental findings in the Final Rule. We propose to specifically exclude a requirement for coding unreported "incidental" adverse experiences obtained in response to a request for follow-up information. This information can be presented in the narrative section of the MedWatch or CIOMS form so that an evaluator can clearly discern the reporter's description of the adverse events versus incidental findings.

C. **"Double Reporting" to the NDA and IND**

FDA requires the reporting of the same information to both the IND and NDA for a marketed product under investigation. For products marketed and being studied globally, it is often confusing to decide on the appropriate route of reporting given the different licensed status for products in various countries, different indications being investigated, etc. Novartis recommends that to the extent possible, FDA should centralize the reporting of information to FDA, who would assume the responsibility for its appropriate filing (NDA, IND) and distribution. Companies can provide FDA with the desired number of copies, but delivered to only one address. This would eliminate the confusion of which applications must be referenced.