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NOVARTIS

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Via United Parcel Services
Drug Information Branch (HFD-210)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Re: FDA Docket No. 01D-0056
Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines

Dear Sir or Madam:

Novartis Pharmaceuticals Corporation is a leader in the discovery, development, manufacturing and marketing of prescription medicines. We are committed to improving health and well-being through innovative products and services. Novartis would like to take this opportunity to comment on FDA's Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines.

General Comments

At the outset, Novartis believes that many of the recommendations in the Draft Guidance are useful in terms of clarifying existing regulations. At the same time, however, some of the recommendations will require reprogramming and subsequent re-validation of the safety database. In many cases, the company's internal procedures and workflows will have to be revised to assure full compliance. In addition, where the recommendations are not aligned with ICH and EMEA regulatons and policies, companies will have to implement measures to ensure that local procedures and workflows are consistent with the new recommendations, while maintaining other global procedures consistent with regulations in foreign countries. The recommendations may also require additional staffing so that companies can fulfill the direct verbal contact recommendations relating to follow-up reports. These changes will require time to implement and will likely be associated with new learning curves. Companies would accordingly appreciate receiving sufficient time for implementation of procedures consistent with the recommendations.

01D-0056 C18

Identifiable Patient (lines 326-331)

The Draft Guidance provides information on assessing whether there is an identifiable patient. It provides that a report stating that "an elderly woman had anaphylaxis" or "a young man experienced anaphylaxis" should be included because there is enough information to suspect that specific patients were involved. We would welcome even more clarification on the minimum descriptor required as a threshhold for an "identifiable patient". In addition, if, for example, "12 patients of Dr. Smith's" fulfills the FDA's expectations for an identifiable patient, we would appreciate clarification as to whether that information should be submitted as one adverse experience report, or as multiple reports. This additional clarification will also assist companies in assessing the reportability of adverse events that may be received from Internet sites.

Direct Verbal Contact With the Reporter (lines 317-320)

The Draft Guidance provides that an applicant seeking information on an adverse experience should use direct verbal contact with the initial reporter of the adverse experience (e.g., in person, by telephone or other interactive means such as a videoconference.) While direct verbal contact may well yield more comprehensive information in some situations, we do not agree that verbal contact will always yield the most comprehensive follow-up information. For example, it seems reasonable to assume that some physicians may prefer not to be interrupted during busy office hours with telephone calls or face-to-face meetings. Similarly, they may prefer that their staff not be interrupted so that they can focus on their daily responsibilities in the office. In those situations, companies are probably more likely to receive follow-up information by sending the physician a form for completion, with a return, self-addressed stamped envelope. The physician or office assistant can then complete the form when it is convenient to do so.

There may also be situations where consumers who report adverse experiences to a company will provide more information in writing than in a telephone conference. For example, if the patient attempts to elicit medical advice during the conversation and is told by the company representative that medical advice must come from their own doctor, the consumer may be reluctant to provide adverse event information. In addition, written information received from consumers may be more credible than statements made on the telephone because there is documentation confirming the information reported (e.g., responses to questions about prior medical history or similar events that occurred before the drug treatment was initiated). The patient could simply deny that he/she had a positive medical history on the telephone.

Finally, and as discussed in the section of this letter relating to Internet issues, companies do not always receive a telephone number from the reporter. This presumably would be the case in some situations where the adverse experience is reported via the Internet. Accordingly, in light of these difficulties, if the FDA does include the direct verbal contact recommendation in its final guidance, we are hopeful that there will be some qualifying language which allows sponsors to make appropriate, reasonable decisions with regard to follow-up methods.

Incarceration (lines 260-263)

We believe that the guidance document should not include incarceration as an example of a *significant or persistent disability* under the definition of seriousness. Incarceration is a societal response to unlawful behavior, not a medical diagnosis or outcome. While we believe the *underlying behavior* leading to incarceration is certainly one factor to consider in assessing seriousness, the outcome of that behavior--incarceration--is heavily dependent on many non-medical variables, such as whether the police were called to the scene, whether there were any witnesses to the behavior, and whether the individual was able to escape. Given the differences in the criminal justice systems in the fifty states and in foreign countries, it is impossible to consider the outcome of incarceration as a measure of the seriousness of an adverse event. Doing so would likely lead to inconsistent reporting since two patients who experienced the same level of a rage reaction could be assessed differently if only one was caught and put in jail. We therefore believe the assessment of seriousness for conditions such as rage reactions should relate to the medical events and behaviors (e.g, extreme anger lasting 10 hours, extreme aggression), rather than whether the patient was incarcerated.

Including Information About Follow-Up Attempts in the Narrative Section of Form 3500A (lines 377-383)

The Draft Guidance provides that an applicant should exercise due diligence to acquire all the information for an individual case safety report immediately upon receipt of a suspected serious, unexpected adverse experience. It also provides that the applicant should maintain records of its efforts to obtain follow-up information and should include in the narrative section of FDA Form 3500A a chronological description of these efforts if there is a delay in obtaining such information. We disagree with the FDA's suggestion to include information about follow-up attempts in the narrative. Doing so would be inconsistent with regulations in other countries, and would result in significant workflow and procedural changes for global compliance. In addition, this information is already stored elsewhere in companies, and is available upon request. This recommendation also appears to be inconsistent with other parts of the Draft Guidance, which direct companies to prepare concise narrative sections that contain only important medical information. In addition, the Draft Guidance is unclear as to whether a follow-up report would then have to be submitted even if no relevant follow-up medical information were received, simply to comply with the recommendation of describing follow-up attempts in the narrative section.

Supporting Documentation (lines 397-407)

The Draft Guidance provides that for individual case safety reports of serious, unexpected adverse experiences, the FDA encourages applicants to include relevant hospital discharge summaries and autopsy reports/death certificates. The Draft Guidance also provides that applicants should include a list of other relevant documents (e.g., medical records, relevant laboratory data, electrocardiograms, and other concise critical clinical data) maintained in their corporate drug or biological product safety files. We disagree with the FDA's recommendation to include supporting documentation with its follow-up submissions. There is no similar requirement from any other health authority, and the information is already on file with the company and fully available to the FDA upon request.

Periodic Reports (lines 455-545)

The Draft Guidance provides a number of new recommendations relating to periodic reports. These recommendations include a revised ordering of the sections of the report, a new recommendation for tabulation of reports, and additional requirements regarding foreign label changes. These new recommendations will require significant changes to workflows and procedures in the U.S., and include many requirements which differ from requirements for PSUR reporting outside of the U.S. Based upon the FDA's reported intention to transition to the PSUR format in forthcoming guidance documents, we would like to know whether the FDA recognizes that the current recommendations will require significant revisions of procedures and workflows for short term use, pending the adoption of the PSUR format in the near future. Companies would have to make significant revisions to their periodic reporting procedures and workflow, and then, once implemented, make significant changes a second time. We believe it will be difficult for companies to make all of these changes twice without some adverse impact on operations.

Internet Receipt of Adverse Experience Reports (lines 846-855)

The Draft Guidance provides that adverse experience information submitted to an applicant via the Internet (e.g., e-mail) should be reported to the FDA if the applicant has knowledge of the four basic elements for an individual case safety report. Applicants should review any Internet sites sponsored by them for adverse experience information. We believe it would be hepful to provide additional guidance on what constitutes an identifiable patient and an identifiable reporter for adverse events encountered via Internet sites. Many people use nicknames or invented names on the Internet. Would such names and the website address, without more, constitute an identifiable reporter? If other methods of contact are not provided in the e-mail message, how many responses to the e-mail should the company make if they do not receive follow-up information from the first response? In addition, and as noted in the direct verbal contact discussion above, companies will be unable to comply with the proposed verbal follow-up recommendations if they do not receive a telephone number from the reporter.

Death Cases (815-821)

Consistent with existing regulations, the Draft Guidance confirms that death is always a serious outcome. Thus, if death is associated with an unexpected adverse experience, or if death is associated with an expected adverse experience but the labeling does not specifically state that the adverse experience may be associated with a fatal outcome, a 15-day report should be submitted.

The Draft Guidance does not provide recommendations regarding how to handle an adverse experience when the only information received is "outcome-death". In the 1992 Guidance Document, the FDA recommends that domestic death-only cases be reported in the periodic report. Since that recommendation is absent from the Draft Guidance, we are unsure whether that recommendation remains in place. We would welcome recommendations from the FDA on how to handle death-only cases.

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In closing, Novartis appreciates the opportunity to comment on this important new Draft Guidance and looks forward to the FDA's response to our comments and those that are being submitted by other companies.

Sincerely,

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U.S. Head, Clinical Safety & Epidemiology
Novartis Pharmaceuticals Corporation