Bayer HealthCare
Pharmaceuticals

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Mary E. Taylor, MPH
Vice President
Regulatory Affairs
North America

October 2, 2003

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

Re: Docket Number 00N-1484
Safety Reporting Requirements for Human Drug and Biological Products Proposed Rule

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Phone 203 812-2789
Fax 203 812-5364
mary.taylor.b@bayer.com

Dear Sir or Madam:

Bayer Pharmaceuticals Corporation has reviewed the FDA's proposed rule on Safety Reporting Requirements for Human Drug and Biological Products noted above. At this time we are providing our comments to this draft guidance.

If you have any questions please contact me at (203) 812-2789.

Sincerely,

Mary E. Taylor, MPH

cc: R. Celesk, PhD
F. Monteagudo, MD

00N-1484

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III.A. Definitions

The *Proposed Rule* suggests a new definition for the phrase "a reasonable possibility" (of relatedness to the event). Under the new rule "reasonable possibility" would effectively mean "a relationship cannot be ruled out."

BAYER COMMENT:
Bayer disagrees with this suggestion for the following reasons:

a) The proposed definition is incompatible with the existing understanding in other countries. This incompatibility would lead to different assessments in different countries with potentially difficult-to-solve reporting and investigator information conflicts in multinational studies.

b) The proposed definition would classify most events in clinical studies as associated, because it is very difficult to prove that any event is definitely not associated with study drug administration. In blinded studies this will result in unblinding of a considerable number of patients, jeopardizing the chance to obtain a meaningful result. Consequently, this proposal will mandate inclusion of a significantly higher number of patients in blinded clinical studies, which exposes more patients to an investigational new drug than necessary.

Bayer suggests keeping the original definition. Alternatively, provided that the Agency wishes to receive an increased number of adverse event reports from clinical studies, we suggest changing the guidance for 15-day submissions from clinical studies to "all serious, unexpected adverse events," dropping the assessment of association. In this approach it should not be required to unblind cases before submission. On the contrary, unblinding should be required only if this information is necessary to treat the patient (medical reason) or if the information is necessary to decide whether a study should be continued (statistical, general population under study reason).

III.A.6. Active Query

The *Proposed Rule* defines the term "Active query" as: *"Direct verbal contact (i.e., in person or by telephone or other interactive means such as a videoconference) with the initial reporter of suspected adverse drug reaction or medication error by a health care professional representing the manufacturer."*

The draft further explains that, in many cases, use of active query during initial contact with the reporters will provide manufacturers with adequate safety information and could eliminate or decrease follow up time. The Agency does not believe that it is sufficient for manufacturers and applicants just to send a letter to reporters requesting further information.

BAYER COMMENT:

Bayer disagrees with this assessment. While we agree that an energetic follow up is necessary to collect adequate safety information, our experience shows that some reporters consider efforts by manufacturers to pursue direct contact to be an unacceptable imposition on their time; they may misunderstand such contact as an another marketing tool.

The requirement for direct verbal contact has several disadvantages compared to our current practice (depending on the reporter and nature of the event, to follow up in writing or verbally, or both):

a) Documentation
A required verbal contact makes documentation more difficult:
"Reported terms" may be misinterpreted by the interviewer as there may be no other written documentation other than minutes from the telephone conversation.

b) A required verbal contact may discourage health care providers from reporting.
In current practice, the reporter may choose to ignore the requests for follow-up information, leaving the manufacturer with scant, confusing case details. While this is an unsatisfying situation, it does at least improve the determination of reporting frequency of possible adverse events and may help in identifying changes in quality of the product or changes of prescribing patterns. A required verbal contact may discourage such "lazy" reporters from reporting at all because they may feel that reporting a SADR is associated with unpleasant ramifications and increased work load.

c) The quality of the information would suffer:
In current practice, the reporter can answer questions in his/her own time, and has the opportunity to consult the patient's chart when responding. If direct verbal communication is required, the reporter will answer the questions either immediately, from memory, or later, after consulting the chart, answering questions without the benefit of having a written questionnaire. In both cases, the information will likely be incomplete and imprecise.

Bayer suggests maintaining the current practice that permits the company to use its discretion in determining the most useful means of obtaining follow-up information.

III.A.8. Medication Error

In section III.A.8 of the *Proposed Rule*, FDA defines Medication Error as: *"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: Prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."*

BAYER COMMENT:

While FDA has excluded deliberate overdose by a patient from being considered a Medication Error, it has not addressed intentional off-label use by medical practitioners. Potentially, such practice could be considered as constituting a Medication Error that the *Proposed Rule* would require companies to report. Company efforts to pursue information regarding off-label use might be construed by physicians as an effort to regulate medical practice.

Bayer proposes that only those problems resultant from product characteristics (e.g. labeling) that are within the control of a company, be reportable as Medication Errors. Adverse events resulting from intentional off-label use, or other product uses that are not within the control of a company, should not be treated as Medication Errors.

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

The proposed rule suggests amending § 312.32 (c)(1)(i) by replacing the phrase "*any adverse experience associated with the use of the drug that is both serious and unexpected*" with the phrase "*any SADR that, based on the opinion of the investigator or sponsor, is both serious and unexpected.*"

BAYER COMMENT:

We believe that the original suggestion could be misunderstood in the sense that it is interpreted to mean that both the sponsor and the investigator should assess whether a SADR is expected. We believe that this was not intended and would not be desirable. The investigator should assess an association between study drug administration and an event and should be able to apply seriousness criteria. The investigator should not be held responsible for the assessment of listedness.

Bayer suggests replacing the above-mentioned phrase with the phrase "any SADR that is serious based on the opinion of the investigator or sponsor and unexpected".

II.B.3.b. UNEXPECTED SADRs with UNKNOWN OUTCOME.

The *Proposed Rule* would require "*...companies subject to the agency's postmarketing safety reporting regulations submit to FDA in an expedited report SADRs that are unexpected and for which a determination of serious or non-serious cannot be made (i.e., SADR with unknown outcome)...*" This section further states "*...A company that receives a report of an adverse drug experience is able, in most cases, to determine if it is serious or non-serious...*"

BAYER COMMENT:

Bayer disagrees with this proposed change for the following reasons:

a) The proposed change would introduce a vaguely defined class of uncertain adverse events that is incongruous with the rigid definitions outlined by the ICH.
b) Bayer's experience has been that a substantial portion of the spontaneous reports received, particularly with regard to those arising from consumer complaints, provide event terms that are not readily translated into a medical context. These same reports often cannot be confirmed by a healthcare professional (who may be unaware of a consumer complaint), leaving the complaint uncharacterized as to seriousness and outcome, regardless of the success of follow-up attempts.

Bayer endorses the continuation of current practices that provide for vigorous follow-up for all potentially serious adverse event reports, and the assignment of serious designation to those cases where legitimate doubt exists regarding outcome. The uniform characterization of all events with uncertain outcome as serious and expeditable would be counter-productive, clouding the interpretation of more robust safety information. Therefore, Bayer recommends maintaining the current industry practice for interpreting the seriousness of events with unknown outcome.

III.D.4. ALWAYS EXPEDITED REPORTS

The *Proposed Rule* would require "*The following medically significant SADRs, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, would be subject to an always expedited report...*" *(LIST)*

BAYER COMMENT:

Bayer disagrees with this proposal. Existing regulations in the U.S. as well as in ex-U.S., ICH-adherent countries provide rigid and clear seriousness criteria. Appending the *Ad Hoc* list of diagnoses provided in the *Proposed Rule*, to the expeditable criteria, decreases the clarity currently integral in reporting regulations. In the worst case, expedited reporting might be driven by the multiple synonyms found in medical textbooks for the diagnoses listed in the *Proposed Rule*, which may actually confuse the process of risk management.

Bayer recommends that the list of "Always Expedited Reports" NOT be adopted. However, in the event that the Agency is unwilling to forgo this change, Bayer proposes that ALL events regarded as serious should be expedited, so as to avoid the inevitable confusion in the interpretation of this rule.

II.B.2, III.E.1.h, III.E.2.K.xi, and III.F.4 "Licensed Physician"

Sections II.B.2, III.E.1.h, III.E.2.K.xi, and III.F.4 of the *Proposed Rule* refer to the requirement that a "Licensed Physician" must review SADR/Medication Error reports and serve as a contact person to be listed in Section G. of the MedWatch report form.

BAYER COMMENT:

FDA has provided no guidance as to what constitutes licensure, or what licensing jurisdiction/agency should issue such credentials.

Bayer suggests that a medical doctor's degree from an accredited medical school (for example, WHO list of accredited medical schools) should meet the proposed requirement. Should this suggestion be unacceptable because the Agency believes that the physician should have attained credentials to practice medicine issued by a governmental body, Bayer suggests that credentials issued by ex-United States countries be considered equally acceptable to those issued in the United States.