ABBOTT LABORATORIES
GLOBAL PHARMACEUTICAL RESEARCH & DEVELOPMENT

DOUGLAS L. SPORN
Divisional Vice President
GPRD Regulatory Affairs
D-R44R, AP6C-1
Telephone: (847) 937-7986

100 Abbott Park Road
Abbott Park, IL 60064-6091
Facsimile: (847) 938-3106
e-mail: doug.sporn@abbott.com

March 21, 2003

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

Ref: Docket No. 02N-0528. Concept Paper on Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

Abbott Laboratories commends the Agency on their efforts to provide guidance to industry on Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, published in the Federal Register on March 7, 2003.

We are very pleased to have the opportunity to comment on this concept paper and thank the Agency for your 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) 938-3106.

Sincerely,

for:
Douglas L. Sporn

Abbott

March 21, 2003

Comment on the Concept Paper
Risk Assessment of Observational Data:
Good Pharmacovigilance Practices and
Pharmacoepidemiologic Assessment

Docket No. 02N-0528

The following comments are submitted on behalf of Abbott Laboratories.

III. A. What are the characteristics of a good case report?

Lines 87-88 and Footnote #2

The paper states – "The most aggressive follow-up efforts would be directed towards validating serious, unexpected adverse event reports that lack details deemed important for case assessment.[2]"

Comment

Please clarify whether by referencing the Council of International Organizations of Medical Science (CIOMS) Working Group V - Geneva 2001 Report, the Agency recommends sponsors to use the report guidelines when adverse event reports lack details deemed important for case assessment.

III. B. How are case series developed?

Lines 122-127. The paper states: "... the development of a case series through the identification of additional clinically relevant cases depends on thorough database search strategies based on Medical Dictionary for Regulatory Activities (MedDRA) terminology. Generally, case definitions would be developed to provide consistent characterization of the adverse events...."

Comment

The Maintenance and Support Service Organization (MSSO) has been a process for standardization of MedDRA medical terms and concepts. We would like to know what is the extent of the FDA's participation in this process so that standardization throughout industry, as well as, regulatory authorities can be reached.

IV. A. When and why are pharmacoepidemiologic studies recommended?

Comment

In this section, FDA recommends sponsors to perform epidemiologic studies and suggests these studies may be conducted using automated claim databases (e.g. HMO or Medicaid) that allow retrieval of records of product exposure and patient

outcomes. The Agency, however, is not taking into consideration the coming into operation April 14, 2003 Health Insurance Portability and Accountability Act and the Individual Identifiable Health Information (HIPAA-IIHI Act), which will impede sponsors' access to this type of information. Abbott recommends that the Agency address this issue in the guidance and define a process that allows sponsors to have access to this information.

Lines 172-173. The paper lists "Item 1. Demographic characteristics of patients enrolled in the health plan(s) (e.g. age and geographic location)".

Comment

We recommend that the database preferably be population-based and the data resource should be representative of the population at large.

IV. B. When and why would registries be established?

Line 205.

We recommend adding the following item:

(4) Assessment of a comparative population

Line 207.

We recommend adding the word "consistency" as noted:

...data quality, integrity *and consistency*

V. A. Calculating incidence rate and reporting rates: what is the magnitude of the safety signal?

Line 288-289. The paper states: ..."it is helpful to have an estimate of the background rate for the event being evaluated..."

Comment

We would like the Agency to make publicly available a bibliography of references for background incidence rates, so that companies with similar products would use consistent background information. Sponsors who supply such references in a risk management program could be the source of the original information, but it would be helpful to know what the FDA considers to be an appropriate background comparator rate.

V. B. Understanding the safety signal: who is at risk and when?

Line 317. "Item 7. Analyses of the effects of lot-to-lot variation and differences in product formulation ... and the risk of the event being evaluated."

Comment

Analysis of lot-to-lot variation could be limited due to the infrequent acquisition of such data.

V. C. Assessing causality: what factors would be considered?

Line 347-356. The paper states: "...it may be possible to assess the degree of causality between use of a product and an adverse event when the sponsor gathers and evaluates all available safety data..."

Comment

The degree of causality between the use of a product and an adverse event may be assessed on aggregate data, however, causality assessment on each reported specific case prior to single generation is problematic.

Furthermore, the suggested compilation of data and information described in points 1-5 is appropriate if the event is characterized by a signal with strong indication of a true association between the drug and the event. Multiple lower-level "signals" may be found in the pharmacovigilance process, and as a good practice, each of these signals is monitored and followed-up with a rigor appropriate to the level of medical concern. It is necessary to recognize, however, that the degree of response to some signals warrants a larger, swifter reaction than others.

V. D. How would safety signals be reported to FDA?

Line 374. The paper states: "When safety signals are identified, FDA would expect sponsors to: ...

Comment

We appreciate the process laid out by the Agency in this section, however, it is necessary to recognize that this is a series of events that happens over several steps followed by scientific analyses for a good understanding of the safety signals. As written, the Agency implies that the sponsor would initiate all actions simultaneously. A logical temporal fashion of reporting should be considered.

VI. HOW CAN SAFETY SIGNALS BE MONITORED THROUGH ENHANCED PHARMACOVIGILANCE EFFORTS?

Line 428. Regarding the suggested commitment: "Item 1. Submit adverse event reports in an expedited manner (i.e., as 15-day reports)"

Comment

If the process for filing events that fit the regulatory criterion for non-15 day reports is changed such that certain group of reports needs to be filed within 15 days will create confusion and breakdown of the process. For a company having multiple drugs, variable requirements for 15-day reporting on each drug will become technically difficult and could jeopardize the compliance and efficiency of reporting. A standardized criterion for 15-day submission is the most efficient process and it should be retained.

Line 452-456. The paper states: "While additional information is being developed....interim regulatory actions to communicate information about safety signals via labeling..."

Comment

There is a certain time span between the recognition of the signal and completion of pharmacoepidemiologic study to evaluate that signal. This paragraph indicates that the Agency may decide to take interim regulatory actions, such as a labeling change, to communicate the event. However, if the safety event is not confirmed upon the completion of the pharmacoepidemiology study, a reversal of the labeling change would be required. Therefore, we strongly recommend that labeling changes be done only after the event is confirmed. We recommend that interim communication be performed via other means and that "other means" be defined in the final guidance.

VII. QUESTIONS TO BE ADDRESSED AT THE PUBLIC WORKSHOP.

Line 462. Question 1. How can the quality of spontaneously reported case reports be improved?

Comment

We suggest the following: 1) the use of sample questionnaires designed to elicit key information elements pertinent to a specific adverse event, 2) education of health care practitioners and other reporters (e.g. patients) about the importance of quality safety reporting, and 3) improvement of the instructions for filling out MedWatch forms.

Line 468. Question 3. What are possible advantages or disadvantages of performing causality assessments at the individual case level?

Comment

Disadvantage: Individual case level causality assessment may create false signals. If the report contains multiple events, then all events would be grouped at the same level of causality. The event of interest may be linked inappropriately to the drug. This would have regulatory, time commitment and standardization implications.