ABBOTT LABORATORIES
Regulatory Affairs
Global Pharmaceutical Research and Development

Douglas L. Sporn
Divisional Vice President
Regulatory Affairs
Global Pharmaceutical Research and Development
D-R44R, AP30-1

200 Abbott Park Road
Abbott Park, Illinois 60064-6157
Telephone: (847) 937-7986
Facsimile: (847) 938-3346
E-mail: doug.sporn@abbott.com

May 5, 2003

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

Ref: Docket No. 02N-0528 - CDER/CBER Risk Management: Concept Paper on PREMARKETING RISK ASSESSMENT

Abbott Laboratories is pleased to provide the attached comments on the CDER/CBER's concept paper, Premarketing Risk Assessment for drugs and biologics, published in the Federal Register on March 6, 2003.

Should you have any questions, please contact Ivone Takenaka, Ph.D. at (847)-935-9011 or by FAX at (847) 938-3346.

Sincerely,

Douglas L. Sporn

Abbott

May 5, 2003

Comments on Concept Paper
PREMARKETING RISK ASSESSMENT

Docket No. 02N-0528

GENERAL COMMENTS

Abbott concurs with the Agency that all efforts must be made to detect and assess the safety of a drug as early as possible. However, the timely introduction of products that offer therapeutic benefits and improved quality of life should be fairly balanced with risk.

The recommendations outlined in this concept paper tend to take a "one size fits all" approach. The design of clinical trials for the assessment of safety and efficacy should be approached on a case-by-case basis. If common applications are sought, they may preferably be approached via specific Agency guidance per therapeutic indication and/or patient population. Nonetheless, the following comments are offered on the proposals in this paper in its current form.

It is unclear throughout the concept paper as to whether the proposed recommendations apply to all new drugs in development or only to drugs in class known to cause certain types of adverse events. A decision tree would be useful in determining which drugs may warrant application of the recommendations.

SPECIFIC COMMENTS

III. IMPORTANT CONSIDERATIONS IN GENERATING RISK INFORMATION DURING CLINICAL TRIALS

A. What is the appropriate size of the premarketing safety database?

For long-term exposure drugs, ICH guidelines allow the inclusion of all exposures in the 1500 subject safety database. The Agency's recommendation to limit the safety database to subjects with at least 4-week exposure will necessitate evaluation of a significantly larger number of patients. This raises several concerns. First, the value of these larger numbers is unclear because pivotal studies, when combined into integrated summaries of safety, currently provide adequate power to detect common adverse events in the 4-6 week window. Second, larger numbers of patients will extend the duration of clinical trials, thus delaying the final efficacy analysis, NDA filing, and availability of the new product to those in need, while very likely yielding few, if any, insights into risk assessment. Third, important safety information may become apparent at shorter durations of exposure. It is not clear how this safety information would be analyzed if it may not be included in the 1500 subject database.

The Agency is urged to reconsider the proposed recommendations on the detection of rare events in Phase III trials. The width of the confidence intervals around adverse event (AE) rates will not appreciably change with this increase in sample size and the

probability of observing rare events will remain low. Larger numbers of patients will extend the duration of the clinical trials as described above.

It is of concern that dose ranging is being proposed in Phase III. Such exploration places great burdens at the Phase III stage, with increased recruitment, extended duration of trials, and possible confounding of endpoint analysis. Typically the proposed dose is established during Phase II. Further examination of dose ranging may be better addressed by performing dose titration to effect in open long-term studies.

The suggestion to study doses above the highest proposed dose is also of concern and may not be ethical. It would be challenging scientifically and ethically to justify to IRBs the formal study of doses that have been already established in Phase II as not tolerated/unsafe or as not providing sufficient additional efficacy to justify the higher dose.

Abbott supports the Agency's interest in appropriate sample sizes for short-term treatment, particularly in the area of acute infections.

Lines 101, 110, 116 and 123-126, 134, 136.

In general, any new drug could probably be made to meet at least one of the broad conditions for which more than 1500 subjects could be requested in the safety database, thus making the need for more than 1500 subjects commonplace. Further, the recommendations as noted in these lines suggest that they apply to any drug. Please clarify whether these recommendations apply only to drugs in classes that are already known to cause serious spontaneous AEs.

B. What are some characteristics of an ideal safety database?

Lines 147-150. It is unclear if the Agency is recommending that a) all long-term safety assessments be performed in trials with placebo or active comparators or b) a dedicated trial using placebo or active comparator should be conducted if there is a specific safety issue/endpoint to examine. Long-term comparative trials raise some substantial issues:

- Overall safety database sample sizes will probably increase significantly if it is necessary to power for small safety differences.
- The patient population willing to participate in comparator trials may substantially differ from that in an open label trial. Recruitment will be slower if one arm of the trial is perceived to be less desirable than the other.

- If the comparator trial is blinded, recruitment will be very slow/nonexistent (placebo) to just slow (active control) and the dropout rate will increase.
- If the comparator trial is open, results will be open to criticisms of potential bias.

The Agency should provide justification as to why single-arm, long-term studies are deemed inadequate for safety assessment.

Line 163-168. The concept paper recommends the inclusion of a demographic group commonly excluded from clinical trials in the past, such as the very elderly. The Agency should provide recommendations on choosing these important demographic groups. Since safety is a primary objective in clinical studies, the guidance should address how a sponsor would assure the subjects of their safety if the inclusion criteria is broadened (even if the "obvious contraindications" are excluded).

Lines 174-175. The Agency should take into consideration that dose-ranging for safety is more appropriately established in Phase II studies. A Phase III parallel group dose ranging study could be very large due to the power needed to detect relatively small differences. A dose ranging study with placebo and 3 dosages could easily require 600-800 subjects. If this study were in the context of a 6-12 month exposure, sample sizes would need to accommodate dropout rates and consequently missing data. Such accommodations place great burdens at the Phase III stage with resultant delays in drug development time. Perhaps allowing dose titration to effect in open label long-term studies may address some of these issues.

C. How can unanticipated interactions be detected as a part of a safety assessment?

Lines 186-226. Certain drugs are prescribed for acute diseases or symptoms that may not be population-specific, e.g., headache, acute self-limiting infections, etc. The Agency should provide guidance as to how the sponsor would select or prioritize the innumerable populations in which to test unanticipated interactions.

Lines 210-226. The concept paper states that unexpected relationships can be detected by incorporating pharmacokinetic assessments in clinical trials, including safety trials. These pharmacokinetics studies would most likely require the inclusion of multiple time points for specimen collection in large clinical trial settings, and still not guarantee that infrequent safety events would be detected.

D. When would comparative safety data be useful?

Lines 230-251. It is unclear as to whether these recommendations would necessitate increasing the safety database for all drugs. The term "could be useful", as noted in the paper, does not imply that such trials will be necessary. Such trials could result in considerable burden on a development program, as showing a "comparatively benign" safety profile would probably require very large sample sizes.

E. What are some special considerations for optimal risk assessment during drug development?

Lines 261-263 and 265-267.
It is not clear what benefits to risk management would be realized with the exploration of maintenance doses during Phase III trials.

Lines 269-272. The paper states: "If appropriate, an assessment would be performed of less obvious adverse effects that might not be detected or readily reported..." Please clarify as to whether adverse event occurrence from the sponsor's own studies would be sufficient for assessment, or whether additional sources, such as reports on related chemical compounds, should be evaluated. Furthermore, these recommendations could be interpreted as to necessitate a larger safety database for all drugs. We are not aware of measures that have been validated for the proposed populations, nor are we aware of anyone having defined the smallest change in such scales that is clinically important.

Lines 300-309. The number of specimens retained could be overwhelmingly enormous, considering the number of different clinical trials a sponsor performs. The Agency should clarify whether specific samples, e.g., certain investigational cases, or all samples collected and analyzed in a clinical trial, should be retained, and how long they should be retained, e.g., as long as the CRFs are kept or indefinitely, considering the stringency of HIPAA requirements in USA, as well as privacy requirements in other countries, such as EU. Practical limitations exist with regard to storage capacity, security, and the breadth of informed consent. Specimen management should be handled by the sponsor on a case-by-case basis. Sponsors should be encouraged to outline intended testing and specimen retention, as appropriate, in study protocols and informed consents. Samples should be retained for clearly defined purposes.

Abbott notes that the Agency intends to publish draft guidance in the area of pharmacogenomics later this year. However, several references to pharmacogenomic testing are provided in this concept paper. This seems premature. Such references should not precede the issuance of the forthcoming pharmacogenomic guidances. Abbott recommends that pharmacogenomic references be excluded from subsequent Risk Management draft guidances until the draft guidance on pharmacogenomics is issued and full public commentary is received.