AstraZeneca

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Date APR 28 2003

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

Re: Docket Number 02N-0528
Response to FDA Call for Comments
Draft Concept Paper – Premarketing Risk Assessment

Dear Sir or Madam:

Reference is made to the March 7, 2003 Federal Register notice (Vol. 68, No. 45, Page 11120) announcing the availability of Draft Concept Paper – Premarketing Risk Assessment.

AstraZeneca has reviewed this draft concept paper and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Debra Shiozawa, Associate Director, at (302) 886-3137.

Sincerely,

Gary Horowitz
Executive Director
Regulatory Affairs
(302) 885-1008
(302) 886-2822 (fax)

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Enclosure

02N-0528 C4

US Regulatory Affairs
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Comments from AstraZeneca on the
FDA Draft Concept Paper - Premarketing Risk Assessment

General Comments

- The concept paper is quite comprehensive. However it has always been recognized that in spite of having large numbers of patients in Phase III, and even when pooling, the previous phases, there is always a random occurrence of an event that ultimately is shown during post-marketing period surveillance to be drug related.

- Care should be taken in ensuring that terminology is consistent between the concept papers and other draft rules under review (e.g. consistent use of the term suspected adverse drug reaction and adverse event report).

Comments from AstraZeneca on the FDA Draft Concept Paper – Premarketing Risk Assessment		
Section	**Line Number**	**Comment or proposed replacement text**
III.B.2.	159	A diverse safety database • Inclusion of a diverse population would require large numbers. This is ideal but lengthens the clinical trial process, may delay approval of needed medicines, and puts undo burden and expense on the sponsor. • Broadening inclusion criteria in the studies may enhance the sponsor's ability to generalize the findings to the population likely to use the product in the post-marketing period but generalized findings may not be useful. Suggest separate studies for the very elderly, patients with concomitant disease who would most likely use the medication.
III.C.	183	How can unanticipated interactions be detected as part of a safety assessment? • Certainly in a diverse inclusion study one would be likely to see unanticipated interactions. • For pharmacologically predictable interactions, an investigator would likely be prepared to react and treat appropriately. What about those biologic products where reactions may be unpredictable. Population PK

		studies would be of great ability just to see if there is a PK contribution or not. • For some interactions, rescue therapy may be needed, perhaps in advance of having sufficient knowledge to do so.
III.D.	228	When would comparative safety data be useful? • Using an arm that is a well-characterized agent, in addition to the test product would not yield background AE rates (D.1). Background rates are obtained from untreated populations.
IV.A.	364	How can adverse events be described to best ensure that safety signals are identified? • It is not practical to group AE terms and develop case definitions within the FDA. • MedDRA already includes the ability for special search criteria. The key is to have a process in place to search at multiple levels. It is clear that medically qualified people, who have experience recognizing that disease and the nuances of disease presentation, may utilize various approaches when searching this database
IV.G.	510	How can the analyses of missing data be most informative? • FDA comment solicited 1. How does this issue affect risk management and/or 2. Effective methods that could be used to address the challenge that missing data presents • Suggestions: Additional studies or other Phase IV comments may be added to clarify risk.