



BASF Pharma

September 18, 2000

0165 TO SEP 19 A9:23

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

Re: Docket No. 00D-1306

Comments on FDA draft guidance: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics.

Dear Sirs,

This document has been much needed for a number of years. We support this proposed guidance and we welcome the opportunity to comment on it.

General comments

In our view, this guidance should not be limited only to the AE section of the labeling. It should be broadened to include any section of the package circular that relates to AEs or the potential for AEs. For example, AEs are discussed in Contraindications, Warnings, and Precautions. The only comments the Agency makes is that the AE section should properly reference the other sections. These sections are not, however, really separate, as they all address AEs in humans, and, as such, should be integrated in format and in objectives.

The agency should also discuss in this document how the sponsor should address significant toxicology, reproductive toxicology, carcinogenicity and mutagenicity findings that have not appeared in clinical testing in man, but which do not appear to be species specific, or do not occur at multiples of doses that could reasonably be expected to be seen in humans.

Drugs for chronic therapy are typically studied in an open manner to gain information regarding long term usage, since placebo control is simply not practical for possibly many years in phase 3. The difficulty is that the percentage of AEs will be higher the longer a patient is exposed to a drug. For drugs used chronically, the Agency should specifically allow for expressing AEs as events per 100(0) patient years of exposure as well as percentages.

Section II, B, 1, page 2

The Agency suggests as standard wording, the paragraph beginning: "Because clinical trials are conducted under widely varying conditions,..."

In our view, there is a great deal of similarity between trials conducted throughout industry, and therefore, the Agency should be more flexible in allowing comparative statements, as long as they are appropriately qualified.

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Section III, first bullet, page 7, "Pooling data"

In our view, pooling of adverse reaction rates for labeling should be consistent with the approach used in the NDA. The FDA draft reviewer guidance 'Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review' (Nov. 1996) is a little more specific as follows:

'Finally, if a decision is made to pool data for several studies, some consideration should be given to how the pooling is accomplished. It is probably most common to simply combine the numerator events and the denominators for the selected studies. Other more formal weighting methods are available, e.g. weighting studies on the basis of study size or inversely to their variance, and the reviewer should address the issue of how the pooling was accomplished and the rationale for selecting the method used for pooling'

Based on this approach, which we believe to be reasonable, we would suggest an addition (shown in bold) to the text in Section III:

*"If there are not major study- to-study differences in rates, an overall pooling is probably the most clinically useful representation of a drug's adverse reaction profile. **Appropriate consideration should be given to whether simple pooling is sufficient or whether a more complex form of weighting (e.g. weighting studies according to their variance) is more appropriate.**"*

Section III, last bullet, page 8, "Significance testing"

The Agency advises that including the results of significance testing is generally not appropriate. We agree with this, but as the purpose of the labeling is to characterise a profile to aid prescribing decisions, we would advocate the use of confidence intervals. Most likely these would be associated with a measure of relative risk.

We appreciate the opportunity to comment on this draft guidance. Please contact the undersigned at 973/426-6022, if you have any questions or comments regarding this response.

Sincerely,



Robert J. Mandetta
Associate Director, Regulatory Affairs

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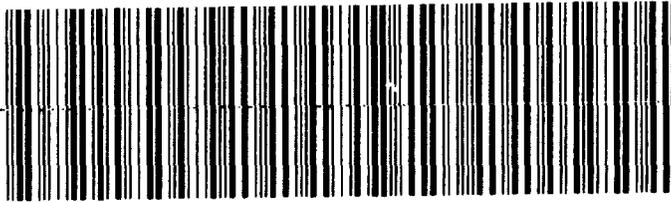
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