

ATTACHMENT 1

Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format

The following comments provided are intended to further clarify the content of this guidance. We appreciate the opportunity to comment on the Food and Drug Administration draft *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* issued January 18, 2006.

Specific Comments:

Lines 49-70, *Adverse Reactions and Information to Include:*

The format of this section with the bullets and “**IF**” and “**OR**” on separate lines makes this section difficult to read; thus, recommend omitting the “if” and including the “or’s” as indicated below:

The adverse reaction is serious (see glossary for definition of serious adverse reaction);

or

The adverse reaction does not meet the definition of serious adverse reaction, but is still considered clinically significant (*otherwise clinically significant*)...

Adverse reactions that significantly affect patient compliance; **or**

The product interferes with a laboratory test.

For readability, apply this same format (ie, include conjunctions on same lines) to II.A.2, III.A.1, III.A.2, and IV.A.

Lines 177-179, *Information to Provide:*

If the source of the reporting is from ‘foreign experience’ with the drug, it may be beneficial to point out the ADR may have been associated with a different formulation, dose, or route of administration.

Lines 228-229, *When to Contraindicate:*

Use of the term “must” seems incorrect here. FDA may want to consider changing this to “can” so that the sentence reads, “Only known hazards, and not theoretical possibilities, can be listed.”

Lines 250-252, *Expected Adverse Reactions:*

For consistency with other sections, make the following sentence into a bullet:

The risk of the adverse reaction in the clinical situation to which the contraindication will apply...

Line 307, *Text Emphasis:*

Make header for III.C.3 (“Text Emphasis”) consistent with II.C.3 (“Emphasis in Text”).

Line 318, *When to Use a Boxed Warning*:

Because 21 CFR 201.57 states “The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data,” we suggest the Agency include examples or guidance as to when animal toxicity may warrant inclusion in a boxed warning.

ATTACHMENT 2

Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements issued for comment on January 18, 2006.

The following comments provided are intended to further clarify the content of this guidance. We appreciate the opportunity to comment on the Food and Drug Administration draft *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements* issued for comment on January 18, 2006.

Specific Comments:

Lines 299-381, *Recent Major Changes:*

For the initial conversion of approved labeling to the new format it would be helpful to indicate that only text changes to the relevant sections that occurred within one year of submission of reformatted labeling need to be identified. Also any changes to the text in these sections exclusively resulting from the initial reformatting process do not need to be identified

Lines 445-448, *Adverse Reactions:*

For clarity, the sentence, “This listing may include adverse reactions that are important for reasons other than frequency . . .” should be under a different subheading than “Most frequently occurring adverse reactions” since it refers to including adverse reactions not based on frequency.

Lines 459-466, *Adverse reaction reporting contact information:*

Reference is made to the "manufacturers" contact information. Please clarify if both manufacturer and/or marketer contact information should be required especially in those situations where the product is manufactured by one and marketed by another company. Also can the Agency provide guidance on the appropriate contact information for products that are co-marketed?

Lines 503-507, *Drug Interactions:*

The draft guidance indicates that if drugs are associated with a large number of clinically significant drug interactions, since it may not be possible to summarize all the critical information in Highlights, FDA recommends including a statement under the Drug Interactions heading to refer to the FPI. We suggest the FDA provide standardized language or examples of such a statement to assure consistency across products.

Lines 572-575, *Approved and Pending Applications:*

This section indicates that if an application is pending when the rule becomes effective, FDA will approve labeling in the old format and then the applicant would submit a labeling supplement. Can the agency provide guidance on how an applicant may resubmit the labeling in the new format for a pending application and any impact this may have on the review timeline?

Lines 578-581, *Approved and Pending Applications*:

“After labeling is approved in the new format, any subsequent changes to Highlights, other than identified minor exceptions, require submission of a prior approval supplement. . .” Can the agency provide any guidance on the review timelines for labeling with safety changes to Highlights?

Lines 649-652, *Mandated Statements*:

While the Agency will consider, on a case-by-case basis the formatting of certain mandated labeling statements we believe it would be very helpful to industry for the Agency to identify in this guidance the mechanism it will use to broadly communicate these decisions to industry. The Agency may consider providing specific guidance for 21CFR 201.24(a) since the new format could significantly impact the location of this mandated text.

Lines 698-699, *Formatting*:

FDA recommends a two-column format for the display of text in Highlights and Contents sections to enhance effective communication. As this may significantly impact the FPI layout we suggest the agency provide support for the statement that this formatting enhances communication.

Line 926, *Appendix E Table*:

To improve clarity, we suggest explanation or rewording the statement “FDA-approved patient labeling that is not for distribution to patients”.