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April 20, 2006

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

**RE: Docket No. 2005D-0011, January 24, 2006 (71 FR, 3998-3999)**

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the FDA's two draft Guidances for Industry entitled, "Warnings and Precautions, Contraindications, and Boxed Warning Sections of the Labeling for Human Prescription Drug and Biological Products – Content and Format" and "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements."

Wyeth is one of the largest research based pharmaceutical and healthcare products companies and is a leading developer, manufacturer, and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications. Wyeth appreciates the opportunity to comment on the above mentioned draft guidances; our comments are provided below.

**I. WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, AND BOXED WARNING SECTIONS OF THE LABELING**

**A. Warnings and Precautions – Clarification of "Clinically Significant"**

Clarification is requested regarding the meaning of "clinically significant" in the WARNINGS AND PRECAUTIONS section of the draft guidance (Section II, p. 2). The use of the term "clinically significant" to identify adverse reactions that do not meet the definition of "serious" but are still considered clinically significant (*otherwise clinically significant*) is broad and open to interpretation (e.g., Lines 53, 61-68). Although several examples of adverse reactions that are "*otherwise clinically significant*" are provided (Lines 64-68), the examples are not all-inclusive and could still result in broad interpretation by both the sponsor and FDA.

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In addition, the examples in the draft guideline suggest that a clinically significant adverse reaction could be included based on an individual case. However, a single case may not be representative of the seriousness of the overall experience with cases of that adverse reaction in the general population receiving the drug (also refer to the WARNINGS AND PRECAUTIONS – Application of definition of “Serious” comment below).

*We recommend that the bullet point examples be limited to those provided (i.e., remove “could include”) in Line 63 and also revise each example in Lines 64-68 to add “generally” (e.g. “Adverse reactions that generally require discontinuation, dosage, or regimen...”).*

## **B. Warnings and Precautions – Clarification of “Serious”**

Clarification is requested regarding use of the term “serious adverse reaction” in the WARNINGS AND PRECAUTIONS section and the Glossary of the draft guidance. This term is used to provide the industry with specific criteria for the selection of adverse reactions that should be included in this section (e.g., Lines 58-59) and while the Glossary provides a definition of “serious adverse reaction”, it appears to be the same as the definition of “serious” described in the ICH guideline<sup>1</sup> E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.” However, the ICH definition of “serious” is specific for the review and interpretation of individual case reports. Applying this ICH definition to the WARNINGS AND PRECAUTIONS section implies that an adverse reaction should be included based on the evaluation of an individual case, even if the particular adverse reaction does not meet the definition of “serious” in the vast majority of cases reported.

*We recommend that the application of the definition of “serious adverse reaction” for purposes of determining what should be included in the WARNINGS AND PRECAUTIONS section be revised to clarify that it should not be based on an individual case. The determination to include a Warning/Precaution should take into account factors such as the likelihood of occurrence, the likelihood that the adverse reaction could reasonably result in one of the serious outcomes listed, and clarify that the criteria are distinct from the ICH use of “serious” for purposes of evaluating an individual case report. We therefore recommend that the Glossary definition (Lines 387-394) be revised to “For purposes of this guidance, the term serious adverse reaction refers to any reaction at any dose where there is a reasonably likelihood that the adverse reaction will result in any of the following outcomes....”*

<sup>1</sup> Reference is also made to E2B “Data Elements for Transmission of Individual Case Safety Reports” which includes the same definition for “serious.”

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## C. Warnings and Precautions – Consistency of Information to Provide

The elements described in the “Information to Provide in the WARNINGS AND PRECAUTIONS” section (Lines 155-184) are more expansive than the requirements stated in the Final Labeling Rule. This potentially could result in unnecessary redundancy and significantly increase the amount of information to include in this section<sup>2</sup>.

The Final Labeling Rule includes specific examples of information to provide such as limitations in use imposed by the adverse reaction (e.g., avoiding certain concomitant therapy) and steps that should be taken if the adverse reaction occurs (e.g., dosage modification). However, the draft guidance requests much more detailed information than is required by the Final Rule such as repeating information already presented in the Adverse Reactions Section (e.g., a discussion of known risk factors), and/or requests information that would dilute the importance of the information contained in this section (e.g., the source of the information about the adverse reaction). Of specific concern is the recommendation to include “a discussion of how to treat, or otherwise manage, an adverse reaction that has occurred”. In deciding how to treat or manage an adverse reaction, a physician must make an individualized medical judgment that takes into account the specific patient and the circumstances under which the patient is being treated. The manufacturer’s responsibility is to provide the physician with information necessary for safe and effective use of the drug, not to provide treatment advice. Therefore, it is beyond the scope of physician labeling to ask the manufacturer to provide generalized patient treatment recommendations.

We believe the recommendations to include a description of the adverse reaction and outcome (Line 158-159) and a discussion of the steps to take to reduce the risk of, decrease the likelihood, shorten the duration of, or minimize the severity, etc. (Lines 163-168) are appropriate and are consistent with the requirements defined in the Final Rule. However, the points recommended in the draft guidance expand upon the requirements of the Final Rule, adding a level of detail that could make the overall length of the labeling unwieldy.

*We recommend a cross-reference to the Adverse Reactions section<sup>1</sup>, or other appropriate sections, where applicable and deleting the following from the draft guidance:*

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<sup>2</sup> While still in draft, the Guidance for the Industry entitled *Labeling for Human Prescription and Biological Products – Implementing the New Content and Format Requirements* emphasizes the need to avoid redundancy (Section III, B. 2.); the guidance provided herein seems contrary to this general principle.

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- *A discussion of known risk factors (Lines 161-162)*
- *A discussion of how to treat or otherwise manage an adverse reaction that has occurred (Lines 169-170)*
- *Commentary provided in Lines 171-174 regarding the mention of issues in this section although they may be discussed elsewhere in the labeling*
- *The mechanism of action of the adverse reaction (Line 176)*
- *The source of the information about the adverse reaction (Lines 177-179)*

## **D. Contraindications – General Comment: Expected Adverse Reactions Section**

The guidance presents a necessary clarification of the Final Labeling Rule with regard to reasons to contraindicate. The Final Labeling Rule states that contraindications should be based on “known hazards and not theoretical possibilities (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication).” This example in the Final Rule could be interpreted to require that the specific adverse reaction would have to be documented in order to contraindicate. However, Section III. A. 2. of the draft guidance provides the additional details necessary to clarify this example when considering adverse reactions to contraindicate that are highly likely to occur based on “what is known about the pharmacology, chemistry, or class of the drug” (Lines 254-255). We support the recommendations provided in the draft guidance and believe this additional detail is critical to identifying circumstances in which use of the drug should be contraindicated.

## **E. Boxed Warning – Clarification of Specific Criteria**

Clarification is requested regarding examples provided in the ‘When to Use a Boxed Warning’ section (Section IV. A). The draft guidance includes specific examples to provide guidance on criteria for a Boxed Warning, however, two points recommended in the draft guidance seem to expand upon the requirements of the Final Labeling Rule and could potentially add to the overall length of the labeling. Specifically:

- The use of ‘for example’ (Line 324) as stated in, “There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction)...”. We believe that limiting the examples to “a fatal, life-threatening or permanently disabling adverse reaction” appropriately represents the criteria to be considered and is consistent with the intent of Final Labeling Rule.

*We recommend that the term “e.g.” be revised to “i.e.” and Lines 323-325 be revised to, “There is an adverse reaction so serious in proportion to the*

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*potential benefit from the drug (i.e., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug.*

- The draft guidance provides additional examples of “other situations to highlight warning information” (Lines 336-346). However, identifying these other situations as observed or expected “adverse reactions” (Lines 341-342) without a qualifier of “serious” seems to expand upon the requirements in the Final Labeling Rule. Adding the term “serious” would create consistency with the Final Labeling Rule which characterizes a Boxed Warning as “certain contraindications or serious warnings...”, and would provide clear guidance for “other situations to highlight warning information that is especially important to the prescriber”.

*We recommend the term “serious” be added to “adverse reactions” such that Lines 341-342 be revised to, “Boxed warnings are more likely to be based on observed serious adverse reactions, but there are instances when a boxed warning based on an expected serious adverse reaction would be appropriate.”*

## **II. LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS – IMPLEMENTING THE NEW CONTENT AND FORMAT REQUIREMENTS**

### **A. Information in Highlights – Request for a Clarifying Example for Initial U.S. Approval**

Section IV. B. 1, Lines 280-282, ‘Initial U.S. Approval’ states that the initial approval date should be listed for products with multiple formulations approved or licensed in different years. However, the guidance does not include an example to illustrate how this would be implemented, for example, for a product with multiple formulations presented in the same prescribing information (PI) or for a product with multiple formulations presented in separate PIs.

*We recommend that an example(s) be included in Lines 280-282 to illustrate how the approval date should be listed for products with multiple formulations approved or licensed in different years.*

### **B. Information in Highlights –Consistency of Class Labeling Boxed Warnings**

Section IV.B.2 ‘Information in Highlights’ provides guidance on providing a concise summary of the information in the Boxed Warning, however the

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guidance does not include specific recommendations on how to summarize this type of important safety information. In addition, the document does not include commentary on how the Agency proposes to create and communicate consistency for multiple products with the same class labeling boxed warning. It is possible that the Agency could receive multiple submissions with recommendations for the same class labeling boxed warning Highlights. Depending on the timing to update the labeling, other Sponsors may be affected by the same labeling negotiations.

*We recommend that guidance be included on how best to summarize boxed warnings for the Highlights section. In addition, we recommend that the Agency make publicly available any approved class labeling boxed warning statements for the Highlights section and that Sponsors affected by an initial submission of a proposed class boxed warning have the opportunity to provide comments before the wording is finalized.*

### **C. Procedural Information – General Comment**

Consistent with the final rule, Section V. A. 2, Lines 578-581 state that revision of the Highlights (other than minor exceptions) require a prior approval supplement (PAS). As per § 314.70(c) (6)(iii), a changes-being-effected (CBE) supplement allows for a labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) add or strengthens a statement about drug abuse or dependence. We are concerned about the inconsistency that could be created as a result of lag time between the Sponsor revising this type of information in the comprehensive prescribing information section via a CBE and the timing for the review and approval of the revision to the Highlights section via a PAS.

*We recommend that the Agency treat these types of prior approval supplements with a high priority to ensure the timely revision of the Highlights.*

We are submitting the above comments in duplicate. Wyeth appreciates the opportunity to comment on the above mentioned draft guidance and trusts that the Agency will take these comments into consideration.

Sincerely,



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Regulatory Policy and Operations  
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