sanofi aventis

Because health matters

21 April 2006

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Via fax and UPS

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

Re: Docket No. 2005D-0011

Draft Guidance for Industry on the "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format."

Dear Sir/Madam:

Sanofi-aventis U.S. Inc, a member of the sanofi-aventis Group, appreciates the opportunity to comment on the above-referenced Draft Guidance entitled *"Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format."*

This draft guidance provides important information regarding the inclusion of information in the appropriate sections of the labeling as well as recommendations regarding the format of the information. Comments regarding the draft guidance are provided below.

II: Warnings and Precautions Section

General Comments:

According to the New Content and Format Requirements issued in January 2006, the Warnings section and Precautions section of the labeling have been combined into a new section, entitled Warnings and Precautions. As these were previously in two separate sections, is there a need to provide a clear definition of what would be considered a warning or a precaution within the section?

Consideration should be given to provide a more precise definition of a warning and precaution, even though they are in the same section.

Specific Comments:

Section A: Adverse Reactions and Information to Include, Lines 129 - 137

Bullet #4: Adverse Reactions Associated with Unapproved Uses

"FDA may require a specific warning relating to an unapproved use if the drug is

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commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard (§ 201.57(c)(6)(i)). Clinically significant adverse reactions that appear to be linked primarily to an unapproved use of a drug (e.g., use for a disease, condition, or population not included in the INDICATIONS AND USE section, use of an unapproved dose or regimen) should be identified and discussed in the WARNINGS AND PRECAUTIONS section. The discussion should include a statement indicating that safety and effectiveness have not been established in that setting and that the use is not approved by FDA."

This section includes clear information about unapproved uses of the drug and clinically significant adverse reactions that appear to be linked mainly to these uses.

Consideration should be given to stating that the adverse event appears to be specific to the unapproved use of the drug.

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Section B. Information to Provide, Lines 176 - 179

- "A discussion of the mechanism of the adverse reaction"
- "The source of information about the adverse reaction (e.g., it may be informative to know whether the information is from clinical trials or postmarketing reports, or whether an adverse reaction was seen only in foreign experience with the drug)."

This section explains what types of information should be included in the description of serious adverse reactions. It includes references to the mechanism of the adverse reaction and the source of the adverse reaction. In some cases the mechanism may not be known for the adverse reaction. Is there a benefit to the reader of mentioning that the adverse reaction was only observed with foreign experience?

Consideration should be given to:

- Clarification of the statement regarding "mechanism of the adverse reaction, " to include "***if known.***"
- Deletion of the statement " was seen only in foreign experience with the drug."

III. Contraindications Section

A. When to Contraindicate, Lines 227 - 230

"A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities must be listed. If there are no known contraindications for a drug, this section must state "None."

In this section it is mentioned that only known hazards, and not theoretical possibilities, must be listed. In some cases, even if the adverse event had not been observed with the drug, it may be important to describe the theoretical risk.

Consideration should be given to rewording the sentence regarding theoretical possibilities.

Sanofi-aventis appreciates the opportunity to comment on the Draft Guidance for Industry on the "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" and are much obliged for your consideration.

Sincerely,

Mark W Moyer

Mark W. Moyer

Vice President, Head US Regulatory Affairs