Aventis Pharmaceuticals

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June 20, 2001

Via fax and UPS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 00N-1269
Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels; 65 Fed Reg, P 81081-81131 (Dec. 22, 2000)

Dear Sir/Madam:

Aventis Pharmaceuticals is pleased to provide the following comments on the above-referenced proposed rule entitled, "Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels." The proposal would revise current regulations to require that the labeling of new and recently approved products include a section containing highlights of prescribing information and a section containing an index to prescribing information, reorder currently required information and make minor changes to its content, and establish minimum graphical requirements.

While Aventis Pharmaceuticals supports reasonable changes that simplify and improve the package insert, we have some issues with certain sections of the FDA proposed rule and offer the following comments:

General Comments

The proposed rule does not include information on how implementation of the prior draft guidance on adverse reactions[1] and other labeling initiatives (e.g., pregnancy[2]) will be coordinated with this proposed rule. It would have been more helpful had this rather comprehensive proposed rule on labeling content and format incorporated those other guidances.

[1] Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics, May 2000
[2] Evaluation of Human Pregnancy Outcome Data, June 1999

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II. B. Physician Survey (p. 81084, column 1)

"(1) The labeling sections physicians read most often and perceive as most important are: Dosage and Administration, Contraindications, Warnings, Adverse Reactions, and Precautions;"

Aventis agrees that the highlighted sections are the most important and should be placed up front in the PI. We would also include the *Indications* section in this list, as one of the sections physicians will seek.

III. A. Description of the Proposed Labeling Requirements (p. 81085, column 2, paragraph 1)

"...The proposed rule would revise current Secs. 201.56 and 201.57 to incorporate these format elements as requirements for new and more recently approved drugs. Older drugs would remain subject to the format requirements in current Sec. 201.57, which would be redesignated as Sec. 201.80".

Aventis supports applying the proposed rule prospectively but does not believe it should be applied retrospectively. However, the sponsor should have the flexibility to apply the rule to older drugs.

Specific Comments on the questions posed by the Agency

"(1) Whether, and under what circumstances, it may be inappropriate to include the proposed 'Highlights of Prescribing Information' section in the labeling of a particular drug or drug class."

Aventis opposes the addition of a "Highlights of Prescribing Information" section for the following reasons:

- Providing a "Highlights of Prescribing Information" section could lead to healthcare professionals reading only the highlights section instead of the "Comprehensive Prescribing Information."
- The addition of at least half a page (and potentially more) to the current labeling of certain already lengthy texts, particularly those with accompanying patient package inserts or medication guides, to become so large as to present difficulties for production line equipment to accommodate and fold such very large documents.

Instead, we suggest that the agency consider evaluating the effectiveness of reordering the PI information (i.e. placing the more "important" information first) on the prescriber's awareness, before requiring the addition of an index or highlights section.

"(2) Does the inclusion of a highlights section have a significant effect on manufacturers' product liability concerns and, if so, is this concern adequately addressed by.... could the agency take different or additional measures to alleviate product liability concerns without eliminating the highlights section altogether or lengthening it to an extent that it would no longer serve its intended purpose."

Aventis feels strongly that this section could create additional liability for the company because certain sections should not be abbreviated (e.g., boxed warning, indications, and safety information). Aventis supports the position taken by PhRMA in its comment letter to FDA with respect to these and other product liability concerns, including but not limited to the needs for express pre-emption and FDA-mandated content requirements should the FDA adopt a highlights section.

"(3) Whether the full text of any boxed warnings should be included in the proposed 'Highlights of Prescribing Information' section, regardless of length."

Although Aventis opposes the proposed highlights section, if it is adopted Aventis recommends that the full text of any boxed warning, regardless of length, be included in both the highlights section and at the beginning of the "Comprehensive Prescribing Information" section.

"(4) What different types of icons could be used to signal a boxed warning and what are their costs and benefits?"

The box itself has a very high profile and is familiar to U.S. healthcare professionals. Adding icons is unnecessary and could be confusing.

"(5) Whether there should be a time limit by which the 'Recent Labeling Changes' section must be removed."

Assuming FDA does decide to include a "Recent Labeling Changes" section, Aventis believes that instead of placing a time restriction on information included in this section, new information should include an "effective date" regarding the most recent label changes. This information could be removed after a minimum of at least one year or at the next update to the label (assuming the update to the label is after one year).

"(6) Whether the information required under the 'Indications and Usage' subsection in the proposed 'Highlights of Prescribing Information' section should be presented verbatim from the comprehensive labeling section or summarized in a bulleted format."

Although Aventis opposes the proposed highlights section, if it is adopted it should repeat the "Indications and Usage" section verbatim as it appears in the "Comprehensive Prescribing Information" section. Aventis believes that not using the "Indications and Usage" section verbatim could be confusing and misleading.

"(7) Whether it is necessary to include the proposed requirement for an index section given the proposed requirement for a highlights section (i.e., do the additional purposes served by the index justify its inclusion?)"

Aventis supports the inclusion of a standardized index section, which would make navigation through the comprehensive section more user-friendly for healthcare providers and further negate the need for a highlights section.

"(8) Whether not including standardized headings in the 'Warnings/Precautions' section is appropriate. If it is believed that specific standardized headings should be included, FDA requests comment about what they should be."

Although Aventis opposes the proposed "Highlights of Prescribing Information" section, if it is adopted Aventis believes that the subsection headings in the "Warnings/Precautions" section should be individualized for each specific product and not be standardized. "(9) Whether it is necessary to include a contact number for reporting suspected serious adverse drug reactions in the proposed 'Comprehensive Prescribing Information' section as well as the proposed 'Highlights of Prescribing Information' section."

Should the FDA adopt a highlights section, Aventis agrees with the FDA's position to include the contact numbers in both locations; however, we would propose the deletion of the word "serious" before the term "adverse drug reactions." We feel that all adverse drug reactions should be reported. We feel that healthcare professionals should be encouraged to report all possible adverse reactions, in addition to those that may be serious.

"(11) Whether the proposed requirement to bold certain information in proposed Sec. 201.57(d)(5) will serve its intended purpose of ensuring the visual prominence of the bolded information."

Aventis agrees with the FDA's position that bolding serves the purpose of ensuring adequate prominence of the bolded information. A requirement to print PIs with such features as highlighting or colored text would raise costs dramatically and not add to the prominence of text or data.

"(12) Whether the proposed one-half page limit on the 'Highlights of Prescribing Information' section (not including boxed warning(s) or contraindication(s)) is adequate or whether there are alternatives that would be more appropriate and under what circumstances such alternatives should be considered;"

While Aventis opposes the inclusion of a highlights section, should the FDA adopt it there must be flexibility in exempting certain products that may need to exceed the proposed half-page limit. It would not be acceptable to abbreviate a "boxed" warning simply due to an arbitrary page limitation.

"(13) What means (other than the vertical line proposed in Sec. 201.57(d)(9)) could be used to facilitate access to, and identification of, new labeling information in the proposed comprehensive prescribing information section."

Aventis believes a vertical line is adequate to identify new labeling information.

"(14) Whether the proposed minimum 8-point font size for labeling is sufficient or whether a minimum 10-point font size would be more appropriate."

Aventis considers a 6-point font size adequate to assure readability of the label.

"(15) Whether the revised format and content requirements should be applied to drug products with an NDA, BLA, or efficacy supplement that is pending at the effective date of the final rule, submitted on or after the effective date of the final rule, or that has been approved from 0 up to and including 5 years prior to the effective date of the final rule, or whether alternative application criteria should be used."

The new rule should only apply prospectively to products product applications submitted on or after the effective date of the final rule.

Specific Comments on the Labeling Proposal

III B. Revised Format and Content Requirements Applicable to Newer Drugs:

1. Highlights of Prescribing Information

p. 81087, column 2

"...Inclusion of only a limited amount of information in the highlights section would not affect any of the regulations related to prescription drug promotion. Manufacturers still would be responsible for ensuring that claims in promotional labeling and advertisements are consistent with the comprehensive prescribing information. .... This responsibility is described in the introductory paragraph of proposed Sec. 201.57(a) which provides that, in order to comply with Secs. 202.1(e) and 201.100(d)(1), statements made in promotional labeling and advertisements must be consistent with all information included in labeling under proposed Sec. 201.57(c) (i.e., the comprehensive prescribing information)".

The FDA notes that the new rule would not obviate manufacturers' responsibility to provide a brief summary of prescribing information in advertisements. The proposed rule does not delineate the form the brief summary would need to have to be consistent with the new labeling requirements; however, according to section 202.1(e), it would seem that the new brief summary would need to include the following sections of the "Comprehensive Prescribing Information": bolded Warnings, Contraindications, Warnings/ Precautions, Adverse Reactions and Indications. Aventis requests some clarification on this issue, as well as direction on what headings would be required. Perhaps the FDA would entertain the idea that, if adopted, the "Highlights of Prescribing Information" could serve as an alternative brief summary. The FDA itself has noted in comments to the proposed rule that the Highlights section would include the most important information regarding drug-related risks. Furthermore, the FDA is proposing to require a bolded disclaimer at the bottom of the highlights section reminding practitioners that the highlights section is not

meant to be all-inclusive. This would alert practitioners to the fact that they still need to consult the full labeling, which is how they should already be using the brief summary in its current form.

p. 81087, column 3; p. P81088, column 1

"...It is unrealistic to expect practitioners to read every word of product labeling each time they reference it, regardless of how desirable it may be for them to do so. Therefore, FDA is proposing to add the highlights section to prescription drug labeling to draw attention to those sections of the labeling that are most important, and to do so in a way that readily facilitates and encourages more detailed follow-up....Nevertheless, the highlights section is not intended to act as a substitute for the comprehensive prescribing information, and it is extremely important for practitioners to be aware of this and to review all relevant sections of the comprehensive prescribing information before making prescribing decisions"

Providing a highlights section to physicians offers a means to avoid reading the "Comprehensive Prescribing Information," which is not FDA's goal or the objectives of this section. The FDA states it is unrealistic to expect practitioners to read the "Comprehensive Prescribing Information" every time they prescribe the product. However, Aventis disagrees with this statement because we believe that it is very important and essential for physicians to read the comprehensive text each time they refer to the package insert. If they are consulting the package insert for a particular adverse event, it is important that they read the comprehensive text and not rely only on a highlights section. The highlights section could encourage such shortcuts. In addition, if FDA provides an extra step (highlights section) that the physician will need to read before reading the comprehensive text, this would further exacerbate the already existing problem. Physicians should read the comprehensive text of the package insert. FDA and industry should work together in trying to optimally communicate the necessary safety and efficacy information in the "Comprehensive Prescribing Information." The proposed "Table of Contents," reformatting, and actual wording of the text in the various sections of the package insert should help achieve this goal. Adding a "Highlights of Prescribing Information" section is not the solution to this problem.

p. 81087, column 3

"...The agency recognizes that prescription drug labeling may be used as evidence in product liability cases and other types of civil actions to determine, among other things, whether a manufacturer has adequately disclosed information about risks associated with its drug. However, the agency believes that it is highly speculative to assert that, because certain risk information has been summarized in or omitted from the highlights section of prescription drug labeling (but included in its entirety in the comprehensive prescribing information), a manufacturer may be found liable in a product liability action based on a theory that the warning is "buried."

Due to busy and hectic schedules, some physicians either will not read the package insert and its updates or only skim over the package insert and selectively read certain sections. FDA will be reinforcing this behavior by providing physicians with a highlights section. FDA may not believe that this could be used or be substantiated in a product liability case or other types of civil actions, but Aventis feels differently. The labeling is a key component and represents a company's diligence in properly conveying all safety and efficacy information about its drug. The proposed highlights section will introduce an additional complexity to the legal situation, which could be used against companies if all relevant safety information is not included in this section. It is not the FDA's position to determine what will or will not influence the outcome of a product liability case. However, the question arises as to why industry or the FDA would want to provide a mechanism of information that could be misused or misinterpreted by lawyers or physicians. If companies were to act more conservatively and add to the highlights section all relevant safety information, this would not fulfill the objective of the highlights section, and would only add to the complexity and length of the labeling and further discourage physicians from reading the comprehensive text. Some "Warnings" sections are already half a page long or more.

b. Inverted black triangle (p. 81088, column 2)

The proposed inverted black triangle is meant to identify a newly marketed product, suggesting that the safety profile of the product is not yet well established. The criteria for use of the black triangle should be very objective (i.e. related only to time on the market, not to patient exposure or to potential safety concerns the agency may have with the product). The other proposed criteria (i.e. indicated for a new population, administered by a new route, use of a novel drug delivery system, etc.) should be rejected as unnecessary, otherwise a product with many line extensions may have a black triangle throughout its marketed life, while the safety profile may have been well established years before. Aventis believes that the inverted triangle is unnecessary, since the vertical line (proposed Sec. 201.57(d)(9)) is sufficient and already addresses this issue.

3. Comprehensive Prescribing Information

b. Proposed Sec. 201.57(c)(2)—indications and usage (p. 81092, column 1)

"...Proposed Sec. 201.57(c)(2)(iv)(D) would modify the current section to permit the agency to require a statement that there is a lack of evidence that a drug is safe for a use or condition when the preponderance of the evidence shows that the therapeutic benefits of the product do not generally outweigh its risks. The agency believes that the current language is too limiting in that it only addresses products that are shown to be ineffective for a particular use or condition. This fails to address products that may be effective, but pose an unacceptable safety risk for the condition or use".

Aventis requests further clarification (examples) from the FDA on this proposal.

g. Proposed Sec. 201.57(c)(8)—use in specific populations (p. 81093, column 2)

Aventis agrees with the establishment of the new section entitled "Use in specific populations." By separating this information from other types of information currently required to appear under the "Precautions" section, such information would be easier to find and use.

k. Proposed Sec. 201.57(c)(13)--clinical pharmacology (p. 81095, column 1)

"... The proposal also would revise current Sec. 201.57(b)(2) such that in vitro data related to the activity or efficacy for all drugs, including anti-infective drugs, could be included only if a waiver is granted under Sec. 201.58 or 314.126(c). Since issuing the current regulations, extensive in vitro data has been included for nearly all anti-infective drugs. The agency believes that, despite the disclaimer concerning their lack of clinical relevance, inclusion of these data in approved product labeling creates the misleading impression that a product's in vitro action represents sufficient information to treat infections with the listed pathogens in humans".

The FDA is proposing that *in vitro* data related to the activity or efficacy of the drug that have not been shown to be pertinent to clinical use be included in the "Clinical Pharmacology" section only if a waiver is granted. By imposing this requirement, the FDA would be negating the validity of information that the agency itself has previously approved for inclusion in the labeling. The FDA should not be asking manufacturers to prove that their information has clinical validity; rather, the FDA should have to show manufacturers why the agency believes the information should not be included. The FDA already asks manufacturers to include statements in labeling that note the fact that *in vitro* data may not reflect clinical results. FDA has always been in favor of providing more information, not less, in product labeling, and providing *in vitro* data is simply one more way for manufacturers to provide as complete a picture of a product's activity as they can.

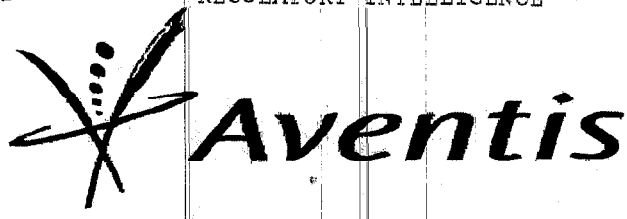
Comments Re: Docket No. 00N-1269 **June 20, 2001**

Aventis Pharmaceuticals appreciates the opportunity to comment on this proposed rule and thanks you for your consideration.

Sincerely,

James Boyd

James Boyd, Ph.D., MBA
N.A. Regulatory Center Head
Global Drug Regulatory Affairs



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REMARKS: ☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please comment

Re: Docket No. 00N-1269
Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels; 65 Fed Reg, P 81081-81131 (Dec. 22, 2000)

To Whom It May Concern:

Aventis Pharmaceuticals is pleased to comment on the above mentioned Draft Guidance.

We will also be sending a signed copy by UPS.

Regards,
Patti Stasiulaitis