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Date: June 20, 2001

The Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, MD 20857

RE: IMMUNEX CORPORATION COMMENTS ON FOOD AND DRUG ADMINISTRATION'S PROPOSED RULE –

21 CFR Part 201 [Docket No. 00N-1269] Posted in the Federal Register / Vol. 65, No. 247/Friday, December 22, 2000

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels; Proposed Rule

Dear Sir/Madame:

Please find attached comments and responses to the proposed rule on labeling [Docket No. 00N-1269] from Immunex Corporation. If you have questions regarding our responses, please contact Karen McLeod, Manager, Regulatory Operations at telephone number (206)-381-6211 or email mcleodk@immunex.com.

Sincerely,

Dawn Viveash, MD

Vice President, Professional and Regulatory Affairs

Cc: File 100, 901.587

00N-1269

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Immunex Corporation
51 University Street, Seattle, Washington 98101-2936
t. 206.587.0430 f. 206.587.0606 www.immunex.com

GENERAL COMMENTS

Immunex Corporation is a leading biopharmaceutical company dedicated to improving lives through immune system science innovations.

Immunex applauds the efforts of the FDA to improve pharmaceutical product labeling by making it more useful to health care practitioners. Our response to the proposed rule is focused on the 15 specific questions posted for comment in the Federal Register with the proposed rule. In general, Immunex agrees with the proposed new format for the COMPREHENSIVE PRESCRIBING INFORMATION that puts most often used sections first and adds a numbered COMPREHENSIVE PRESCRIBING INFORMATION INDEX. These two changes will improve ease of navigating to specific headings and are an excellent precursor to the electronic label.

Immunex supports the Food and Drug Administration's efforts to move toward electronic labels as described by Janet Woodcock in the CDER Live presentation on April 26, 2001. The best solution to easy access and navigation of the growing number of complex and rapidly changing labels will be use of computer and worldwide web technologies to replace printed paper labeling inserts. This is supported by high volume of Internet users accessing healthcare information sites today.

Immunex agrees that labeling changes should be identified when labeling is revised, but would not support revisions solely because changes are no longer "recent". Users could be advised of headings or subheadings containing new or revised text by preceding a heading with an asterisk (*) in the COMPREHENSIVE PRESCRIBING INFORMATION INDEX. We do not support inclusion of the HIGHLIGHTS section because it poses significant liability, increased review cycle time, and cost concerns to the manufacturer.

QUESTIONS 1 AND 2 – THE HIGHLIGHTS SECTION AND PRODUCT LIABILITY CONCERNS

(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;

(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: (a) Titling this section ''highlights'' rather than ''summary,''; and (b) including the following statement, in bold, at the end of the highlights section: ''These highlights do not include all the information needed to prescribe (name of drug) safely and effectively. See (name of drug)'s comprehensive prescribing information provided below.'' If these are not sufficient, 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.

Including a **Highlights** section in prescription drug labeling poses a significant products liability risk to pharmaceutical manufacturers. FDA states in its Proposed Rule that manufacturers would be responsible for proposing language for the **Highlights** section, subject to FDA review and approval. This will put manufacturers in the difficult position of attempting to determine which information within the lengthy and complex prescribing information is most important for physicians to know. The principle underlying the Learned Intermediary defense available to manufacturers in products liability litigation is that manufacturers provide physicians as much information as possible about a drug. An individual physician then determines which information is important in making a prescribing decision for an individual patient. Requiring manufacturers to guess which information will be most important most of the time runs counter to the well-established legal roles of manufacturers and physicians.

As manufacturers juggle these competing concerns, inconsistencies among drugs in a class are likely to result, as well as internal inconsistencies between the **Highlights** section and the more comprehensive sections of an individual package insert. These inconsistencies could possibly be exploited by plaintiffs in products liability actions and, more importantly, will hinder the usefulness of the **Highlights** section to physicians.

It is a laudable goal to make package inserts easier for physicians to use in an efficient manner. Including an Index section at the beginning of the insert, as FDA has proposed, will permit physicians to navigate the insert quickly and have ready access to the comprehensive information that they need. Immunex supports the inclusion of an Index and believes that it accomplishes more effectively the objective of making package inserts more user-friendly.

QUESTION 3

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

If the Highlights section of the labeling is retained, the entire boxed warning should be included within it. The boxed warning may itself be a summary of key warning information that is discussed at greater length elsewhere in the insert. To require that information to be summarized first in the boxed warning and secondly in the Highlights/boxed warning synopsis risks paring down the information to the point that it looses its usefulness. Requiring repeated summarizing of the key safety information for a product will also pose a products liability risk to manufacturers, as plaintiffs argue that the information was inconsistently or too sparingly presented.

QUESTION 4

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

The proposed exclamation point character (!) is an acceptable icon for a boxed WARNING entry in the **Comprehensive Prescribing Information Index** section. Since a boxed WARNINGS section is not always present in product labeling, the use of an icon or special character facilitates the consistent use of the number "1" for the **INDICATIONS AND USAGE** section with or without a boxed **WARNING**. The single line warning box is sufficient for the boxed **WARNINGS**' text in the **Highlights** and **Comprehensive Prescribing Information** sections and is familiar to physicians. Any specialized symbols should be avoided for compatibility with current word processing and production printing systems.

QUESTION 5

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

It is not practical to generate a label revision just to delete "Recent Labeling Changes". A better solution is to specify sections and subsections with recent labeling changes made at a specific revision date. This could be done by placing an asterisk (*) in front of the heading and subheading in the **COMPREHENSIVE PRESCRIBING INFORMATION INDEX**. At the

end of the index the asterisk would be followed by, "Contains a recent change with this revision issued mm/yyyy." The term "recent" should be defined in the final rule as either 0 to 6 months or 0 to 12 months for consistent use in all labels. See example index below:

COMPREHENSIVE PRESCRIBING INFORMATION INDEX

1 ***INDICATIONS AND USAGE**

1.1 Hypertension

1.2 Heart Failure

1.3 Left Ventricular Dysfunction after Myocardial Infarction

1.4 *Diabetic Neuropathy

2 DOSAGE AND ADMINISTRATION

3 HOW SUPPLIED/STORAGE AND HANDLING

...

P PATIENT COUNSELING INFORMATION

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*Contains a recent change with this revision issued mm/yy

QUESTION 6

(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;

If the proposed **HIGHLIGHTS OF PRESCRIBING INFORMATION** section is used, then the manufacturer should have flexibility in how to present information in the Indications and Usage subsection. Circumstances may vary for each product and there may be valid reasons for either repeating verbatim all information from the COMPREHENSIVE PRESCRIBING INFORMATION, Indications and Usage subsection or to provide a bulleted list of the comprehensive information.

QUESTION 7

(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?);

The use of the Index section is justified provided that manufacturers have the flexibility to choose level of headings in the index to maintain a reasonable size for the package insert. Some labeling would print major headings only, and others may include all subheadings. The proposed COMPREHENSIVE PRESCRIBING INFORMATION INDEX would be a positive addition to product labeling and improve ability to locate specific information in the label. When electronic labeling is implemented, the index can provide hypertext linking for easy navigation to comprehensive section with information of interest.

QUESTION 8

(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;

Immunex believes that it is appropriate to not include standardized headings in the "Warnings/Precautions" section. While headings and sub-headings are useful to organize and locate information, the wording of these headings should be individualized for each specific drug or biological product.

QUESTION 9

(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;

While it is useful to provide a contact number for reporting adverse events in an easily accessible region of the package insert, it would be repetitive to include this information in both the Highlights section and Comprehensive Prescribing Information section. We feel that retaining this contact number in the Highlights section alone is appropriate. If the Highlights section is not retained, then including a contact number in the Comprehensive Prescribing Information would be appropriate.

QUESTION 10

(10) Whether the potential impact of the proposed rule on small entities has been accurately estimated by the agency, and whether small business concerns have been adequately addressed;

Immunex does not believe the full cost for implementing all elements of the proposed rule have been considered by the agency's cost estimate. Estimates have been made that inserts will actually increase by 50 to 100% in size. This will likely increase carton sizes, shipping costs, material usage, and storage space needs. Many products require refrigeration, and the necessity for larger cartons would increase refrigeration capacity requirements and energy costs for pharmacies and distribution centers.

QUESTION 11

(11) Whether the proposed requirement to bold certain information in proposed § 201.57(d)(5) will serve its intended purpose of ensuring the visual prominence of the bolded information or whether different highlighting methods may be more effective;

Bolding is appropriate for ensuring visual prominence. Other current formatting, including italics and underlining, are also effective. Flexibility should be maintained to allow use of new word processing and printing techniques and technologies that may develop.

QUESTION 12

(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.

If the Highlights section of the labeling is retained, there should not be an artificial limit on its size. Drugs have varying levels of complexity and a "one size fits all" approach is not appropriate. If manufacturers will be required to choose which information is most important for practitioners, they must be permitted the flexibility to include all of the information that they deem appropriate under the general guidance provided by FDA.

QUESTION 13

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

The use of the vertical line would be problematic for printing and confusing for physicians. Allowing space for vertical lines in margins would be using valuable insert space with not much benefit. Immunex proposes using the Comprehensive Prescribing Information Index to indicate changed sections and subsections by preceding the section title with an asterisk.

QUESTION 14

(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;

Immunex agrees in principle that 10-point minimum font size would make documents easier to read, but the insert size increase that could result with even an 8-point minimum font size would have far reaching impact on cost and therefore would greatly outweigh the benefit.

The costs to implement the proposed labeling changes will be significant and lengthy in implementation. The larger package inserts, will in many cases, require complete retooling of all packaging components, including individual boxes, shippers and pallet configuration and retooling of automated packaging lines. These larger individual cartons will cause a ripple effect throughout the supply chain that will be costly to the manufacturer, the distributor, the pharmacist and the patient in both time and money. The larger end product will cost more to ship, consume greater space on the shelf and require changes to ordering patterns. This ultimately will result in less product being carried at all levels of the supply chain due to storage constraints and increased potential for product stock outs.

QUESTION 15

(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 revised format and content should not be applied to drug products with an NDA, BLA, or efficacy supplement pending. Once the final rule is published there should be a two-year delay until the rule is effective. The prioritization of implementation outlined in the proposal is acceptable to Immunex if the effective date is two years after publication of the final rule.

From: KELLY A. SCHOENECKER (206)587-0430
IMMUNEX CORPORATION
51 UNIVERSITY STREET

SEATTLE, WA, 98101

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