PHARMACIA

Kathleen J. Day
Senior Director
Global Regulatory Affairs
Promotion & Labeling

Pharmacia Corporation
7000 Portage Road
Kalamazoo, Michigan 49001

telephone: (616) 833-8301
facsimile: (616) 833-8632
kathleen.j.day@pharmacia.com

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

Re: Docket No. 00N-1269 – Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements of Prescription Drug Product Labels (65 Federal Register 81082 - 81131; December 22, 2000)

Sir/Madam:

PHARMACIA Corporation submits the following comments on the "Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements of Prescription Drug Product Labels; Proposed Rule". Our comments are provided in accordance with the request as stated in the Federal Register (FR) (Vol. 65. No. 247 of December 22, 2000) and the FR of March 30, 2001 that extended the comment period to June 22, 2001.

PHARMACIA is in general agreement with the comments sent to FDA by the Pharmaceutical Research and Manufacturers of America (PhRMA). We are providing comments on the proposed rule to emphasize those issues of significant importance to PHARMACIA.

Our comments are provided in order and are identified by the outline system presented for the information contained the FR notice. For example, a comment pertaining B,1,f" of Section III would refer to the following:

B = Revised Content and Format Applicable to Newer Drugs
1 = Highlights Section
f = Indications and Usage

The outline system designations are used whenever possible to identify specific sections and appear in parentheses before the comment. In addition, and for simplicity, the outline identifiers for the broader topics are followed by key words describing the part of the proposed labeling the comments address.

FDA requested comments on 15 specific issues. The issues, and our responses, are contained in a table provided as an Attachment to this letter. Many of the responses to the specific issues refer to the comments cited below to avoid duplication of text within the table.

00N-1269

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DETAILED COMMENTS REGARDING THE PROPOSED RULE

Section III - Description of the Proposed Labeling Requirements

B,1 - "Highlights of Prescribing Information"

Pharmacia does not support the inclusion of a "Highlights" section in the labeling for the following reasons:

- Health care practitioners will more often than not, particularly when limited by time constraints, read only the "Highlights" section, or portions of it, and not read the comprehensive information in the body of the labeling. We are concerned that the appropriate selection of a medication may be compromised by a prescriber's reliance on a Highlights" section. Thus, the "safe and effective use of prescription drug products" would not be enhanced by the addition of a "Highlights" section, rather, it would be diminished.

- The importance of a particular piece of safety information can vary greatly depending on the individual circumstances of the potential patient. Deciding what safety information merits inclusion in a "Highlights" section could require a company to hypothesize a "typical patient" and assess the relative importance of each piece of safety information in terms of that hypothesis. That approach would not be medically appropriate. We note that the prototype labeling for Capoten Tablets in the proposed rule contains information in the Comprehensive Prescribing Information, Warnings/Precautions section on patients with valvular stenosis which is frequently seen in patients using Capoten. The statement in Warnings/Precautions suggests that products in this class should be used cautiously in patients with valvular stenosis since they may be at particular risk of decreased coronary perfusion. However, there is no mention in the "Highlights" section that patients with this condition may be at greater risk.

- The inclusion of a "Highlights" section in the prescribing information would create a new avenue for products liability lawsuits against manufacturers that has not previously existed. This avenue would be created as a result of the decision manufacturers would be required to make as to information to include in the "Highlights" section and, just as importantly, information not to include. Even if that decision is effectively endorsed by the Agency through the approval of the prescribing information, absent preemption (which the proposed rule does not address), the Agency's approval is no shield to the products liability lawsuits that will be based on the "Highlights" section.

- In the regulatory arena, the labeling functions to provide the prescriber with a summary of the essential scientific information needed for the safe and effective use of the product. Warnings serve an additional function in the legal arena, that of obtaining an informed consent from the patient. These two models often become confused in product liability/drug litigation. The adequacy of the labeling becomes tested by an inquiry into whether the information provided was sufficient to enable the prescriber to not only safely prescribe but also to obtain a satisfactory informed consent. Inevitably, the "Highlights section," particularly the sections devoted to warnings and precautions and to adverse reactions, would become a template for a satisfactory informed consent. As the Agency acknowledges, it is highly unlikely that all pertinent information could be included in a "Highlights" section to enable the safe use of a given product. As such, lawyers will always be able to creatively argue that there was some "disconnect" between the "Highlights" section and the safety information provided in the comprehensive prescribing information. For example, lawyers might contend that an adverse reaction not appearing in the "Highlights" wasn't conveyed by the prescriber because it wasn't listed in that

location and, if the patients had been advised, he/she would have refused the therapy. For that reason alone, the "Highlights" section should not be required. As noted elsewhere in this document, use of a thorough index, along with the logical reordering of the comprehensive labeling, can aid health care practitioners in locating pertinent information within the labeling.

- Another liability concern with the "Highlights" section is that newer drugs would have a "Highlights" section and older products would not have such a section. Lawyers may attempt to argue that the new format is "better", and therefore, that the old format should be considered "inadequate." The proposed regulation should make it clear that utilization of the prior format is mandatory for drugs not qualifying for the revised format and that this cannot be argued in legal cases.

- A "Highlights" section would be duplicative of the "Index" section, increasing the length and complexity of the label. Simplicity better serves the FDA's stated objective of "mak[ing] it easier for health care practitioners to access/read, and use information in prescription drug labeling..."

In the event that the requirement for a "Highlights" section is not eliminated in the final rule, the following specific comments apply:

- FDA should mandate the contents of the "Highlights" section by specifying precisely the information that must be included. These specifications should be drug-specific and apply equally to branded, or NDA, and generic, or ANDA, versions of the drug product.

- The half-page limitation (i.e., a half-page of text on 8 1/2 x 11 inch paper) would not be feasible for many products, in particular products with lengthy and complex labeling (e.g., antivirals, antineoplastic agents, histamine receptor antagonists). Also, extending beyond the half-page limitation would decrease the perceived value of including a "Highlights" section. Additional comments on the "size" of labeling appears below under "B,4 – Format."

- ***(B,1,a)*** **Product name(s):** The trademark and established name(s) of the drug should appear first and foremost, above the "Highlights" section title.

- ***(B,1,b)*** **Inverted black triangle:** Although this symbol is used on prescription labeling in the UK to bring attention to new molecular entities (NMEs) and to help health care practitioners determine an appropriate reporting route for adverse reactions, it is not a generally recognized symbol in the US. Without specific explanation, the symbol adds little value and would likely cause confusion. Training of healthcare care practitioners would be necessary if this symbol is adopted because, unlike in the UK, the mechanism for reporting adverse drug reactions (ADRs) in the US does not differ between NMEs and more established products. In addition, varying perception of the meaning of the term "new" (e.g., Newly approved by FDA? New to the prescriber? New to other health care practitioners?) negates the value of the message. Also, a symbol such as an inverted black triangle is not prescribing information and is therefore misplaced in a section identified as "Highlights of Prescribing Information".

- ***(B,1,d)*** **Boxed Warning:** There is no need for duplication of a full boxed warning/contraindication in the "Highlights" section if it already appears prominently at the beginning of the comprehensive portion of the labeling. In addition, for an extensive boxed warning/contraindication (>20 lines), summarization is not desirable or appropriate. A referral statement, i.e., "See Boxed Warning in the Comprehensive Prescribing Information section", placed in a box in the "Highlights" section, would be a reasonable option.

- ***(B,1,e)*** **Recent Labeling Changes:** Sections of the prescribing information changed since the last revision should be identified. However, the heading should be changed to "Labeling Changes" because many older products do not undergo frequent revision and the word "recent" would not be applicable. The date of revision could be added to the cited sections as a means of notifying the health care practitioner of the time the section was revised.

- ***(B,1,f)*** **Indications and Usage:** Abbreviation of the indications in the "Highlights" section would potentially lead to confusion. The indications should be listed verbatim from the comprehensive prescribing information or, for indication statements that may be amenable, they could be presented with bullet points and cross-referenced to the comprehensive prescribing information. Lastly, some indication statements include explanatory notes and thus are very long. In the latter case, reference could be provided to the full text in the comprehensive prescribing information.

- ***(B,1,k)*** **Contacts for ADR reporting (both the "Highlights" section and "Warnings/Precautions" subsection of the comprehensive prescribing information):**

  1. A statement providing contact information is not prescribing information and thus is misplaced within the sections identified as "Highlights of Prescribing Information" or as "Comprehensive Prescribing Information".

  2. The value of stating the contact information is questionable. The Agency has offered no substantial evidence that this will facilitate ADR reporting by health care practitioners.

  3. The term "suspected" ADR may be confusing to practitioners. First, "suspected ADRs" may be a redundant term since the inherent definition of an ADR implies that the drug is reasonably associated - thus "suspected" - with the problem, or it would not be a 'reaction'. Second, the term "suspected" may be misinterpreted as "expected", misleading practitioners to predominantly report labeled adverse reactions rather than those which are unexpected (i.e., those reactions not recognized during the drug development process). This misinterpretation may be further reinforced by the required placement of the directions to report suspected ADRs immediately following the listing of the 'expected' adverse reactions in the "Warnings/Precautions" and "Adverse Reactions" subsections of the "Highlights" section. Furthermore, health care practitioners may mistakenly assume that because the condition experienced by their patient is not listed in the "Highlights" section, then it is not a reaction.

  4. If an ADR contact reporting statement is included in the prescribing information, it should appear in the logical location near the name and address of the manufacturer at the end of the labeling.

- ***(B,1,o)*** **Highlights reminder:** The limitation statement, "...these highlights do not include..." should appear at the beginning of the Highlights section, directly beneath the product name, to adequately inform the physician that the information in this section is insufficient for making prescribing decisions. Additional limiting language should be included such as; "...these highlights do not include all of the potential safety hazards that a practitioner might convey to the patient before obtaining an informed consent to therapy. For complete safety information, the label should be reviewed in its entirety."

- Further clarification is needed on how the addition of the "Highlights" (and "Comprehensive Prescribing Information: Index") sections may impact the content and format of Brief Summaries of Prescribing Information used for journal advertisements.

B,2 - Comprehensive Prescribing Information: Index

Pharmacia is in agreement that there is utility for a standardized index section, especially for electronic retrieval/location of information. However, the Index will significantly lengthen the prescribing information, and for some inserts, this may be particularly problematic (additional comments on the "size" of labeling appear below). Pharmacia notes that an electronic labeling initiative is currently under discussion. The Index would have the greatest value when labeling is available and used electronically. We suggest that this component of the labeling be coordinated with the probable availability of electronic labeling in the future.

(Prototype/model labeling) Boxed Warning icon: An icon consisting of an exclamation point (!) to signal that the labeling contains a boxed warning is confusing and could be mistaken for the numeral "1". If an icon or symbol is deemed necessary or desirable, it should be selected in consideration of avoiding confusion and the ability to be maintained in that form when the labeling is subjected to electronic transmission and printing.

B,3 - Comprehensive Prescribing Information

Pharmacia is in general agreement with the organization of sections and the section headings. However, flexibility on subheadings is required to accommodate the extremely varied product information.

Comments on specific subsections of the Comprehensive Prescribing Information follow.

- ***(B,3,a)*** **Boxed Warning:** See comments above on 1) the lack of need for duplication in both the Highlights and Comprehensive Prescribing Information, and 2) the unacceptability of the exclamation point icon.

- ***(B,3,e)*** **Warnings and Precautions:** Combining the Warnings and Precautions sections is desirable and would likely lead to less confusion by health care practitioners. The lack of standardized headings would not be problematic since appropriate headings would be used by the sponsor to add clarity to their labeling as is the current industry practice.

- ***(B,3,h)*** **Adverse Reactions:** Pharmacia is not in agreement with the change in definition of adverse reactions and believes that adverse experience data should be derived from events rather than reactions. This position was also stated in our 18 September 2000 response to Docket No. 00D-1306- Comments of the Draft Guidance for Industry on Content and Format of the Adverse Reactions Section of Labeling. A change from events to reactions would be particularly problematic, and in some cases not feasible, for older products whose labeling may be revised to comply with new content and format requirements. A change in the Adverse Reactions section for a currently marketed product would result in confusion by users of the labeling, raise serious liability concerns, and present a major burden on the pharmaceutical industry to create and on the FDA to review and approve.

In addition, there are several inconsistencies between the proposed rule and the draft guidance mentioned above that suggest these two initiatives have not been fully coordinated and may result in confusion. A few examples are as follows. The draft guidance describes an overview; it is not clear if this overview is the same as the adverse reactions section in the "Highlights" section or if the overview is in addition to the highlights. Another source of potential confusion is the proposed rule discussion about categorizing adverse reactions by severity, while the draft guidance provides a lengthy discussion on ordering adverse reactions by frequency. As a final example, the proposed rule states "The approximate frequency of each adverse reaction must be expressed in rough estimates or orders of magnitude..." (e.g., frequent, less frequent, rarely). However, the draft guidance makes the point of avoiding characterization of adverse reactions: "Use of the terms rare, infrequent, and frequent should generally be avoided."

Pharmacia suggests further review and discussion of the adverse reactions section in the proposed rule. We advocate that important points regarding adverse reactions be discussed in both the proposed rule and the guidance for industry, with the extensive detail provided in the guidance document.

- ***(B,3,o)*** **Patient counseling information:** This section of the labeling proposes to include information that the practitioner should convey to the patient (like the current Information for Patients subsection of the Precautions section). This is to be followed by the text of approved printed patient information or Medication Guide, should one of these exist. The option of presenting the printed patient information or Medication Guide as a section following a perforation, to allow for removal for the purpose of providing to the patient, should be allowed. Printing the approved patient labeling/Medication Guide in a manner that allows for removal will conserve document space and is an efficient and customary manner of providing the labeling to the pharmacist for subsequent forwarding to the patient.

- The name and place of business must be included at the end of the comprehensive prescribing information.

B,4 – Format

Prescribing information - "Size" due to larger font: The standard against which the proposed FDA format requirements are gauged (8.5"x11", single-spaced, 2 column, 8-point font, with 0.5" margins) may be appropriate in reference to prescribing information in electronic form or published in some manner. However, labeling distributed with product utilizes paper sized to accommodate the text which is then folded for inclusion in or on the product package. Pharmacia has determined that labeling revised using 8-point font, employing the 2 square "em's" of space for setting apart the index numbers, and using other format requirements of the proposed rule would double the size of a paper containing the prescribing information (commonly referred to as the package insert). The following represents some downstream issues as a result of following the proposed format requirements, which would significantly increase costs:

- Products with outserts (labeling adhered to the outside of the container) would be forced to use cartons to hold both product and prescribing information due to exceeding outsert limitations.

- New or modified automated packaging lines would be required to accommodate the larger package insert. This could include change parts for inserters but in many cases could require new cartoners. Many packaging lines currently equipped to outsert do not currently have cartoners in the line. Some of the inserts Pharmacia has reviewed would become so large that

it would no longer be possible to outsert them. The bottles and inserts would have to be placed in cartons simply to keep them together during distribution. Addition of cartoners is estimated to cost approximately $600,00 per packaging line. In addition to this expense for the pharmaceutical industry, printers who supply inserts could also be expected to invest significant capital. Some of these printers have equipment limitations for the size of paper sheets that can be folded. New folders are estimated to cost approximately $250,000 each.

- Increased use of paper and other packaging material resulting in a negative impact on the environment.

- To facilitate understanding of a given product, prescribing information frequently requires the use of data displays (e.g., tables, graphs, figures). These require careful placement within the labeling to avoid confusion. They also require considerable space thus adding significantly to the length of the prescribing information (see comments under Prescribing Information - "Size" due to larger font above). It is noted that the prototype labeling for Capoten Tablets in the proposed rule is a simplistic example, lacking displays of data or tables of adverse reactions which are very common in labeling. It is further noted that this prototype does not employ the proposed minimum 8-point font size.

- Using one product as an example, Pharmacia prepared a prototype package insert consistent with the proposed rule format. The insert essentially doubled in size and thus the size of the paper required to contain the text became too large as a single sheet to allow for folding by the insert vendor. In order to prepare the insert in a manner that would allow for folding, the text would have to appear on both sides of two separate sheets of paper. The two sheets would then require binding together, e.g., gluing or securing the pages in some manner and possibly enclosing the sheets in an envelope or plastic sleeve. The resulting bound insert would be too large to adhere with glue to bottles of product, which then would require the addition of a carton to the presentation. Cartoning with the larger bound insert would result in an increased cost of $.265 per bottle for just one package presentation of this product. These increased costs would persist for the life of the product.

Graphic elements: Various graphic elements are proposed and comments follow:

- Horizontal line separating 3 major sections: Not essential but reasonable to break the text in a logical manner.

- Headings bolded and centered: Bolding is useful and is consistent with current practices for labeling. Centering of headings should be optional with an alternative of placing them flush left, which is a current common practice for prescribing information.

- Bullet points: Useful when properly utilized.

- Color: The use of color must be optional. Color significantly increases the cost of a printed item. In addition, color would normally be eliminated on an electronically printed or photocopied version.

- 8 point font and 2 square "em's": Results in a significant loss of printable space. Refer to comments above under "Size".

- Use of one-half page for "Highlights" section: See Section III, part B,1 – "Highlights" section.

- Vertical lines to show revisions: The use of this element to show changed areas of the labeling is not feasible since the printed labeling accompanying the product is in a multi-columned (e.g., 4 columns across a page) format. Thus, a vertical line would not discriminate which column of text is affected and be confusing to the reader.

C - Revisions to Labeling for older drugs

Pharmacia does not agree with the elimination of in vitro data, particularly for antiinfective products unless a waiver is obtained from the Agency. In vitro data are useful and potentially critical in aiding decisions by health care practitioners. Similarly, mechanism of action information based on in vitro data is also useful.

Pharmacia strongly opposes the proposal to eliminate approved labeling text from older products. Approved labeling text was carefully negotiated between the FDA and the sponsor and should not be subject to standards that were not in effect at the time the text was deemed acceptable. Sponsors should not be expected to continually demonstrate appropriateness of data that met the standards for approval in the past.

Prescribers and patients benefit when all relevant information regarding safety and effectiveness is available to them. To remove information that has been available to prescribers and patients for years (and that FDA had at one time considered appropriate in labeling) will be confusing and may pose liability concerns.

FDA's rationale for the removal of some information from the labeling is not sound. First, the removal of this information would not make the labeling for older products consistent with the proposed regulations for the labeling of new products, as the format and content of the rest of the labeling will still be significantly different for older versus newer products. Second, health care practitioners fully understand that the approved uses and dosing regimens for a product are listed in the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections, and that data discussed elsewhere in the insert are presented for information purposes.

Regarding the section for Information for Patients in the labeling for older products, please see Pharmacia's comments for Point ***B, 3, o*** for newer products.

Section IV - Proposed Implementation Plan

A - General Implementation Scheme for the Revised Format and Content Requirements

Currently approved labeling should be "grandfathered". Implementation of the new labeling format should only be done prospectively, from the effective date of the final rule, for new chemical entities (NCEs) within a new drug class or for a novel compound within an existing class. NCEs within an existing, well-established class (e.g., triptans, antidepressants) should be exempt from the new format and be modeled after previously approved products within the same class. The existence of two dissimilar prescribing information formats for products within the same well-established class could lead to the presentation of different, possibly conflicting, information, thus increasing the chance for prescribing errors. Furthermore, labeling in dissimilar format within a well-established class would place a company manufacturing such a drug product at a competitive disadvantage.

The implementation of this final rule should be coordinated with that of the revision to the Adverse Reactions section, as well as the other ongoing and future labeling initiatives by FDA, so as to improve the clarity and minimize the learning curve for the reader and also to limit the burden on both FDA and industry resources.

To further maximize the potential of a new indexed format, as well as reduce the burden on FDA and industry, implementation of this final rule should be coordinated with the FDA initiative for complete electronic labeling.

C - Implementation Plan for Newer and Older Drug Products

As stated above under Section III, part C, we are not in agreement with the deletion of in vitro data particularly for antiinfective drug products or for information related to the mechanism of action. Thus, we have no comment on the submission mechanism (Changes Being Effected Supplement") or the submission timing (1 year after the effective date of the regulation) for these topics.

F - Relationship to Other Initiatives

Coordination of the various labeling initiatives (e.g., new regulations concerning pregnancy labeling and new Guidance documents for specific labeling sections) should be strongly considered to minimize confusion by health care providers and others who use product labeling and in consideration of the limited resources at FDA and within the pharmaceutical industry.

Section IV - LABELS

Pharmacia advocates the retention of the dispensing container instructions (e.g., dispense in a light resistant container) on the immediate container labeling. This information should be readily available to the pharmacist via the carton or bottle label to preclude the need to look for it in the prescribing information.

We appreciate the opportunity to provide comments on this proposed rule, and we would be pleased to discuss these comments with the Agency, at your request.

Sincerely,

Kathleen J. Day

Kathleen J. Day
Senior Director
Global Promotion and Labeling
Pharmacia Corporation

ATTACHMENT

This table contains the specific issues that FDA requested comment on as stated in the Proposed Rule (65 FR 81082 – 81131, December 22, 2000). The issues are listed in the FR on page 81086. Pharmacia's response to most of the 15 issues is contained in the accompanying letter and reference to that is noted.

FDA Specific Issues	Pharmacia Response
(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.	A "Highlights" section of the prescribing information is not appropriate under any circumstances and should be eliminated. Refer to comments under Section III, part B,1 – "Highlights Section" in the letter. In the event that this section is retained in the final rule, comments are also offered.
(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.	Refer to Section III, part B,1 – "Highlights" Section" for full comments. Brief comments follow: The proposed section presents very significant liability concerns and neither alternative a) or b) adequately address those concerns. In addition, liability concerns cannot be alleviated with any shortened version of the prescribing information that is additive to the full prescribing information.
(3) Whether the full text of any boxed warnings should be included in the proposed ''Highlights of Prescribing Information'' section, regardless of length.	If a "Highlights" section is retained in the final rule, any boxed warning should appear in the "Highlights" regardless of length. A boxed warning statement is by nature as brief as possible, it is carefully prepared, usually as collaborative effort between the drug sponsor and the FDA, and shortening it would not be appropriate or reasonable. One alternative if space is a critical issue is to retain the box in the "Highlights" section and include a statement such as the following within the box : "See Boxed Warning in the Comprehensive Prescribing Information".

FDA Specific Issues	Pharmacia Response
(4) What different types of icons could be used to signal a boxed warning and what are their costs and benefits.	Refer to Section III, part B,2 – (Prototype/model labeling Boxed Warning icon). Icons are not necessary to signal a boxed warning. The box itself, and the bold type within the box, are well recognized to represent critical safety information on the use of the drug product.
(5) Whether there should be a time limit by which the "Recent Labeling Changes" section must be removed.	Refer to Section III, part B,1,e – Recent Labeling Changes The title of this section should be changed to "Labeling Changes" and sections changed since the last revision should be identified. For older products in particular, changes do not occur frequently thus the noted changes may not be recent. The revision date could follow the cited section which would identify when a revision took place.
(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.	Refer to Section III, part B,1,f – Indications and Usage Indications should only be presented verbatim or, if the product indications are amenable to bullet points, be presented as bullet points with reference to the full text in the comprehensive prescribing information.
(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?).	Refer to Section III, part B,2 – Comprehensive Prescribing Information: Index An Index is not necessary in view of the indexing and ordering of the comprehensive prescribing information and would be redundant if the "Highlights" section is retained in the final rule. However, the Index may aid a reader slightly. Its greatest value would be associated with hyperlinking when prescribing information text becomes more widely available electronically.
(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.	Refer to Section III, part B,3,e – Warnings/Precautions Standardized subsection headings should not be stipulated because the information in this section is too variable.

FDA Specific Issues	Pharmacia Response
(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.	Refer to Section III, part B,1,k – ADR Reporting Statement A contact number is unnecessary in the labeling. If this is retained in the final rule, it clearly should not appear in 2 locations. Furthermore, neither of the proposed locations is logical. If a contact reporting statement is to appear in the labeling, it should be located at the end of the text in close proximity to the manufacturers name and address.
(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.	Not Applicable for Pharmacia, a large pharmaceutical company.
(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.	Refer to Section III, part B,4 – Format, Graphic Elements Bolding, consistent with current practices, is appropriate for labeling.
(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.	Refer to Section III, part B,1 – "Highlights" Section Pharmacia strongly disagrees with the concept of a "Highlights" section because we believe that adequate information cannot be presented. Alternatives that would result in selecting or abbreviating the labeling are also not acceptable.
(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.	Refer to Section III, part B,4 – Format- Graphic Elements Vertical lines simply would not work as proposed because of the multi-column format of labeling. The only reasonable means of citing sections that have changed since last revision would be to list the changed section in a portion of the labeling dedicated to this purpose (e.g., "Labeling Changes" section).
(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.	Refer to Section III, part B,4 – Format – "Size" Font size should not be specified because of the tremendous impact this change would have on the required labeling that accompanies the product, i.e., "package insert" on "outsert".

FDA Specific Issues	Pharmacia Response
(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.	Refer to Section IV, part A Alternative criteria should be applied. Pharmacia supports implementation of any new format and content requirements only for new products as of the effective date of the final rule. A new product would be a product containing a new chemical entity (NCE) within a new drug class or a novel compound within an existing class. NCEs within an existing, well-established class (e.g., triptans, antidepressants) should be exempt from the new format and be modeled after previously approved products within the same class.

FROM

16284108

PHARMACIA CORPORATION
BLDG 298
7000 PORTAGE RD

KALAMAZOO MI 49001

Kathy Day (616) 833-8301

TO

Food and Drug Administration
Dockets Management Branch, HFA-305
Room 1061
5630 Fishers Lane
Rockville MD 20852
(301) 827-6860

Payment

Bill to:
Receiver ☐ 3rd Party ☐
Paid in Advance ☐

Origin

BTL 5018073620

AIRBORNE EXPRESS

EXP (Letter - 150 lbs)

NAS (Letter - 5 lbs)

SDS (Letter - 150 lbs)

Billing Reference will appear on invoice

MS 140 0632-0423

# of Pkgs	Weight (LBS)	Packaging: Letter Express	One box must be checked: Express Pack	Other Packaging
1	1	☑	☐	☐

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501 807 3620

MLDAHX

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