Richard L. Wolgemuth, Ph.D.
Senior Vice President
Global Regulatory Sciences
Pharmaceutical Research Institute

P. O. Box 4000 Princeton, NJ 08543-4000
Tel 609-252-6503 Fax 609-252-7350
Richard.Wolgemuth@bms.com

2006 APR 21 P2:03

Bristol-Myers Squibb Company
April 19, 2006

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

Re: Docket No. 2005D-0011; Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products, Draft Guidance, *Labeling for Human Prescription Drug and Biological Products--Implementing the New Content and Format Requirements* *(January 24, 2006)*

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified global health care company, is pleased to have the opportunity to offer comments on the draft guidance: *Labeling for Human Prescription Drug and Biological Products - Implementing the New Content and Format Requirements.* Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are interested in commenting on this draft guidance. Our comments are set forth below.

Summary of BMS Comments:
We believe that the *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products* (the final rule) represents a significant improvement over the format currently in use and will enhance the practitioner's ability to locate and use prescribing data in a convenient and prompt manner. We have reviewed the draft Guidance for Industry: *Labeling for Human Drug and Biological Products - Implementing the New Content and Format Requirements* and have found this guidance to be a valuable resource for providing insight into the new regulations and for making the new requirements actionable within our company. BMS therefore commends the Agency for the provision of this guidance along with the four fictitious example documents.

BMS has identified several key areas of the guidance that, in our opinion, require further explanation or clarification. Additionally, as the primary focus of the Implementation guidance is to address issues regarding "developing Highlights and distributing information among sections that have been substantially affected by this rule," BMS has included several requests for general clarifications regarding the final rule and accompanying guidance documents. We propose that any clarifications in response to our comments be included in the final form of this guidance to assist the industry in a timely and expeditious implementation of this major public health initiative. BMS also would welcome the opportunity to work collaboratively with FDA and other interested parties to address these concerns.

2005D-0011 C4

General Comments:
General comments and requests for Agency clarification are listed below. Illustrations from the fictitious example documents are provided where relevant.

Considerations for Revising Labeling
Data Analyses:
Per the Implementation guidance (page 4), most content for the final rule is already included under different subheadings, and FDA expects that most content can be moved with little or no modification as described in *Appendix C.* The Implementation guidance also states that FDA expects limited rewriting or reanalyses of data. However, according to the new regulations, if the information or section in the old format is inadequate, it must be revised (§201.56(a)(2) "...the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading."). BMS' concern surrounds the potential need for reanalysis of the Adverse Reactions section. If an adverse event table in the current format is truthful and accurate, we would like to confirm that the sponsor would not be required to reanalyze the data and reformat into an adverse reaction table. In this case, it appears that the most frequently occurring adverse **events** would be reflected in Highlights. However, it is our understanding that if a product gains a new indication, the sponsor would be required to present this data in a separate adverse **reaction** table in the Full Prescribing Information (FPI) and as a separate listing in Highlights. We request that the Agency clarify whether presentation of separate information for both adverse events (which are not considered false or misleading) and adverse reactions can be included in the Highlights section, as well as the FPI.

Distributing Information Among Sections:
We have noted that the FDA fictitious example documents appear inconsistent in applying concepts derived from the various guidance documents. The example below requires clarification on how to best interpret the Agency's intentions with regard to cross-referencing/distributing information between sections.

1. It appears that the fictitious example documents include cautionary statements in their Drug Interactions section (e.g., Imdicon - Phenytoin, section 7.2 and Fantom - CYP450, section 7.2), yet this information is not also located in the Warnings and Precautions section. When converting a product to the new format, instead of just distributing information to the appropriate sections per Appendix C of the Implementation guidance, please provide clarification whether the sponsor should take the initiative to include into Warnings and Precautions such cautionary text as above.

Highlights

Date of Initial US Approval:

The Implementation guidance clearly states that for products with multiple formulations approved in multiple years, the initial approval date of the new molecular entity should be listed. Clarification is requested with regard to date of initial U.S. approval for new formulations that do not share a package insert with the established active ingredient such as the following examples:

1. New extended-release formulation with same active ingredient as original product, for same indication.

2. New transdermal patch formulation of established oral product, now approved for different indication.

Recent Major Changes:

The following requests for clarification seek to address the subsequent statements: *"The Agency believes it is important to also identify the* ***specific text*** *that has been changed so that practitioners will be able to locate changes and access the complete text (pg 3959, preamble).* In addition, §201.57(d)(9) states: *Sections or subsections of labeling that are identified as containing recent major changes under paragraph (a)(5) of this section must be highlighted in the full prescribing information by the inclusion of a vertical line on the left edge of the* ***new or modified text****.*

1. It is noted that for the Imdicon fictitious example, the vertical line does not extend to all text in section 1.2, although it appears that this is a completely new indication. Clarification is requested regarding whether the entire section should be marked, or just the specific text that has been changed.

2. We request clarification regarding the use of a vertical line for a Recent Major Change that only extends for one or two lines in the FPI (e.g., addition of a single drug interaction in a listing; slight modification to text that extends less than one line). In these circumstances, the vertical line is barely noticeable in either trade or promotional labeling and does not appear to fulfill its purpose of visibly drawing attention to the new text. We ask for clarification of this issue.

In addition, we ask the Agency whether it would be acceptable to abbreviate the name of the month (e.g., Jan, Feb, etc) in Recent Major Changes if it would be necessary to minimize use of space in the Highlights section.

Contraindications:

According to the final rule, if contraindications do not exist, "none" must be listed in both the Highlights section and the FPI. By using the term "none," there is concern for the potential exclusion of contraindications that may occur in the future. Therefore, we recommend that the Agency give consideration to the use of "none known" in order to clarify that new contraindications may become known in the future.

Adverse Reactions:
§201.57(a)(11)(i) states that the adverse reaction statement in Highlights must include: *A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate). Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in Highlights if they are included elsewhere in Highlights (e.g., Warnings and Precautions, Contraindications).* It is noted that the examples given by the Agency (serious or leading to discontinuation or dosage adjustments) would be appropriate for classification as a Warning or Precaution according to the draft Warnings and Precautions, Contraindications and Boxed Warning guidance (page 2). Therefore, we are uncertain as to what would be included in Adverse Reactions in Highlights as "important for other reasons" (or "important for reasons other than frequency") that would not already have been included in Warnings and Precautions or Contraindications sections of Highlights. We believe that an example from the Agency illustrating the concept "*important for reasons other than frequency*" would be valuable to understanding this new regulation.

In addition, uncertainty remains as to the Agency's thinking regarding serious postmarketing Adverse Reactions and the circumstances under which it would be appropriate to list these in Warnings and Precautions or Contraindications in the Highlights & FPI, and as "important for reasons other than the frequency" in the Adverse Reactions section of Highlights. An illustrative example of this concept is located in the Imdicon fictitious example document. Imdicon lists "allergic reactions (including angioedema, allergic pneumonitis and anaphylaxis)" as a postmarketing adverse reaction (6.2). According to §201.57(c)(5), "known hazards" or expected adverse reactions distinguishable from "theoretical possibilities" should be listed as contraindications, yet Imdicon is not contraindicated in patients with allergic reactions/hypersensitivity to the product. Clarification is requested regarding appropriate sections of the labeling in which to list serious postmarketing adverse reactions such as allergic reactions which are undoubtedly "important for reasons other than the frequency" and a "known hazard" to use of the product, yet neither appear in Warnings and Precautions, Contraindications, nor are listed under Adverse Reactions in Highlights.

Reactions listed in the postmarketing section are often "serious or otherwise clinically significant" (e.g., rhabdomyolysis, liver failure, anaphylaxis, etc). Since the fictitious examples do not appear to capture these types of adverse reactions in Warnings and Precautions or the Adverse Reactions section in Highlights, we seek clarification under what circumstances these would be included in the Highlights section as adverse reactions which are "important for reasons other than the frequency."

When converting to the new format, we understand that if the sponsor believes that the Adverse Event section is not false and misleading, then the section in the FPI of the new format can maintain the current Adverse Event list/table without reanalysis. However, the correct terminology to use in such a case is not clear (i.e., can the sponsor maintain the term "Adverse Events" or is the sponsor required to use the term "Adverse Reactions" for the same data?). Additionally, an example would be valuable presenting the appearance of a Highlights and an FPI Adverse Reaction section for a drug converted to the new format with original Adverse

Event data, but that later adds new Adverse Reactions data (e.g., Adverse Events for older data, along with a second listing for Adverse Reactions for newer data).

Drug Interactions:
According to the Implementation guidance (page 13), drugs with a large number of clinically significant interactions for which it would not be possible to summarize all critical information in Highlights could include a statement to alert the prescriber to the presence and significance of the information in the FPI. We request confirmation that this is not an option for other sections (i.e., Warnings and Precautions) where further important information may not be presented in Highlights due to size constraints.

FDA recommends a tabular format in Highlights for a drug with numerous clinically significant interactions (page 13, Implementation guidance). However, none of the FDA fictitious examples are provided with a table of drug interactions. An example of this format is requested.

Use in Specific Populations:
We have noted that when there is a warning regarding a specific population in the FPI, this information has often been captured in the Use in Specific Populations section of Highlights. We have provided the following illustrative examples, and request clarification if all risk information, including warnings, pertinent to a specific population added to Highlights should be located in the Use in Specific Populations section.

1. Regarding the Fantom fictitious example (classified as Pregnancy category D), the pregnancy warning is located in Use in Specific Populations section of Highlights although information regarding the warning is located in both the Use in Specific Populations and the Warnings and Precautions section of the FPI. Please provide clarification as to why the statement is not located in the Warnings and Precautions section of Highlights. Similarly, for a Pregnancy category X product, please clarify how the information would best be distributed between Use in Specific Populations and Contraindications in Highlights to minimize redundancy.

2. If one had a statement in the Warnings and Precautions section of the FPI specific to a certain population that merited inclusion in Highlights (e.g., warning regarding CVA risk specific to geriatric patients), clarification is requested as to where this statement would most appropriately be located in the Highlights section. If placed in Warnings and Precautions, please clarify if it would also be mentioned in Use in Specific Populations.

Procedural Information

Clarifications regarding CBE and Prior Approval:
BMS is committed to providing safety information to health care providers and patients in an expeditious manner. As a prior approval is now required by regulation for any change (including safety) to the Highlights section, we note concern for the potential extension of the review time for safety submissions that would previously have been submitted as a CBE and implemented. In the preamble to the final rule (pg 3934), the Agency states that "*...manufacturers typically consult with FDA prior to adding risk information to labeling.*" However, we are not aware that

this is generally the case and do not believe that this should be assumed. We therefore request clarification from the Agency regarding the role that a CBE will assume in this new environment, specifically with regard to the comments and clarifications set forth below:

1. We request clarification regarding the turnaround time for Agency review of safety information, previously submitted as a CBE but now to be submitted as a prior approval due to inclusion of information in Highlights.

2. The preamble to the final rule states that a "...sponsor may not use a CBE to make **most** changes to Highlights" (page 3934). This statement lends itself to the assumption that there is a possibility of a change to Highlights with a CBE; however, this change is not apparent in the final rule or guidance documents. Based on the Implementation guidance, all changes to Highlights require prior approval (except for those identified under §314.70 and §601.12, e.g., change to revision date, removal of recent major changes, other revisions to be described in an annual report). However, if there is a change to the Warnings and Precautions section of the FPI that would not be reflected in Highlights under the Warnings and Precautions section (e.g., not considered per the Implementation guidance to be one of the "most clinically significant safety concerns"), please clarify if this still requires prior approval or if this would this be an example of a change that could be made as a CBE, and only captured in the Recent Major Changes section of Highlights. We also request guidance regarding under what circumstances industry can submit a change to the Adverse Reaction section of the FPI with a CBE as there may be potential that the adverse reaction would be considered a Warning or Precaution by FDA, which could then be elevated to Highlights.

Expediting FDA review for Prior Approvals:
It was noted during the March 21 FDA/DIA Webinar, that to best expedite the review of a document converted from the old to the new format, a cover letter detailing the conversion should be included. BMS is committed to working with the Agency to submit documents which will best help the Agency expedite reviews of converted documents. We request clarification on what to include in this cover letter.

In addition, please clarify if it would assist reviewers if the sponsor submitted an 8 1/2 x 11 page (i.e., a Word document) demonstrating that the Highlights length and formatting regulations have been met.

Voluntarily Converted Products:
The Implementation guidance states that FDA encourages applicants to voluntarily revise products to which the final rule does not apply (page 14). To maximize use of Agency and industry resources, we request comment regarding the order by which the Agency will review conversions accelerated from the original submission schedule and conversion of older products not affected by the final rule. Please clarify if the Agency will first review the products required to be converted according to the implementation schedule, or will they review applications in the order of submission (i.e., if an older drug is converted before a drug required to convert, will priority be given to the drug that falls within the implementation schedule or the first product to be submitted?).

New NDAs, BLAs and Efficacy Supplements:
According to the Implementation guidance, a change to the size of a population (broadening or narrowing) would trigger a revision to new format (page 14).

1. Clarification is requested as to whether conversion to the new format would be required for products with an expanded population without a change to the indication, but information was added to the package insert.

2. Please clarify if pediatric data under FDAMA (e.g., not indication seeking, but information is added to Use in Specific Populations, or other sections) would trigger a conversion.

3. Clarification is requested if the addition or removal of a contraindication from labeling would trigger conversion to the new format (e.g., significantly decreases or increases the size of the population).

4. If there is a product line extension which may potentially change the size of the population (e.g., from tablet to oral solution) and only bioequivalence data is required (no additional clinical efficacy information; dose remains the same), please clarify if will FDA require conversion to the new format at that time.

Class Labeling:
As noted in the Implementation guidance, "Applicants should propose content and location of class labeling statements in the new format in the draft labeling submitted with their applications or supplements" (page 17). It is noted that this may potentially lead to inconsistency between drugs in same class and/or duplicate efforts after the Agency has approved placement and wording for the first class member sharing the statement. Please clarify if FDA will proactively provide class labeling information to industry once the first product with a class statement has gained approval, or if industry should continue to submit and negotiate text.

Formatting
Subheadings:
According to the Warnings and Precautions, Contraindications, and Boxed Warning guidance (page 8), FDA recommends that each contraindication be identified by its own subheading (subheadings are defined per regulations §§201.57(c) and 201.56(d)(2)). However, BMS is unable to locate an example where contraindications have been listed under subheadings, and the Imdicon example uses bulleting in lieu of subheadings. We request that FDA provide clarification as to which approach is supported by the Agency.

The draft Warnings and Precautions, Contraindications, and Boxed Warning guidance states that each adverse reaction or constellation of reactions should have its own subheading, but there would ordinarily be no reason to further subcategorize (pg 5-6). We request clarification regarding under what circumstances or sections (if any) are further subcategorizations appropriate, as we have noticed that the Imdicon Clinical Studies section lists studies under the headings of 1 and 2 rather than only using italics.

Omission of sections or subsections:
We agree with the Agency that any required section, subsection, or specific information that is clearly inapplicable to the drug should be omitted. However, the Agency prescribes that if sections or subsections are omitted from the FPI, the following statement must appear at the end of the Contents section: **Sections or subsections omitted from the Full Prescribing Information are not listed.*" We believe that including this statement in the labeling without listing the specific omitted sections may have a result contrary to the Agency' s intention. The majority of health care professionals will not intuitively discern which sections are missing and may continue to search for a section that has been omitted. Therefore we recommend that the Agency permit sponsors to modify the omission statement to list the sections or subsections that are not included.

Cross-Referencing:
The Implementation guidance states that the use of italics to achieve emphasis for cross-references is encouraged (page 19). Many companies currently use bolded text to emphasize cross-references, and clarification is requested as to whether this is still an acceptable practice under the new regulations, as none of the fictitious examples display bolded cross-references.

Frequently Asked Questions
Proprietary and Established Names:
Question 4 of the Implementation guidance (page 21) states that "The proprietary and established names can be repeated at beginning of FPI or beginning of each page of the FPI (e.g., as a header) if this enhances product identification on subsequent pages of labeling." We understand this to be standard practice as current regulation §201.10(g)(1) states that every column must include the generic name at least once affiliated with trade name. Please clarify if listing the proprietary and established name at the beginning of each page or column of the FPI would act to fulfill this regulation.

Miscellaneous Comments
Revision Date:
During the question and answer session of the FDA/DIA Webinar on the final rule (March 21, 2006), it was stated that the revision date was based on new product and supplement approvals. Please note that this is not the way that we currently handle a change to the revision date. At present, any change in text (CBEs, minor editorial changes, annual report changes, etc.) will trigger a change to the revision date. Further clarifications regarding triggers for changes to the revision date are requested.

Route of Administration:
§201.57(a)(2) states that both the *dosage form* and *route of administration* should be listed in Highlights; however, fictitious examples do not always follow this regulation (e.g., Fantom and Imdicon). Injections can be administered by various routes (e.g., subcutaneous, intravenous, etc) as can capsules (e.g., oral, for use with inhalation devices, etc). We request clarification of when it is necessary to list the route or multiple routes of administration for a product.

Use of Nonspecific Terms:
The Adverse Reactions guidance (page 9) cautions against the use of nonspecific terms (e.g., rare, frequent, infrequent), although these types of terms are used throughout the fictitious example documents. Further clarification is requested as to use of these terms.

Pregnancy Category D:
§201.57(c)(9)(i)(A)(4) states: *Pregnancy category D. If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling must state: ''Pregnancy Category D. See 'Warnings and Precautions' section.'' Under the ''Warnings and Precautions'' section, the labeling must state: ''(Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.''*

1. According to §201.57(c)(9) (i)(A)(4), the human data and any pertinent animal data should be described in the Warnings and Precautions section. Contrary to the regulation, the Fantom example describes the data in the Use in Specific Population section, 8.1 Pregnancy. Clarification is requested as to appropriate placement of data supporting pregnancy categories.

Company Logo and Print Codes:
Neither the regulations nor the Implementation guidance provide instruction as to location or sizing for the company logo or print codes. We request further clarification regarding where to locate company logo and print codes:

1. Please clarify if the logo can be included at the beginning of Highlights, as is currently included at the beginning of the insert, realizing that the logo would be larger than type size of the Highlights section.

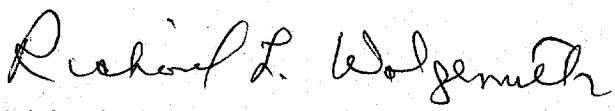
2. We request clarification as to placement of the logo and print code in the following situations: 1) the patient information is contiguous with the labeling (e.g., logo would follow physician and patient labeling) or 2) the patient information accompanies the labeling (e.g., perforated; logo would be placed at end of physician labeling as well as patient labeling).

Visibility of Product Name:
BMS believes that a readily visible product name is vital to enhancing the safe and effective use of prescription drug products and reducing medical errors. We are therefore concerned that the product name loses visibility when printed in the same font size as the rest of the labeling, as depicted in all four fictitious example documents. Page 3958 of the preamble states that "...this final rule establishes minimum type sizes, but does not prevent manufacturers from printing labeling in larger type sizes." Therefore, we request clarification if FDA permits the established

and proprietary name to be printed in a larger font than the remainder of the labeling for both trade and promotional labeling (e.g., 8 or 10 point font vs. 6 point font for rest of labeling for trade labeling).

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our request for clarifications and recommendations. We believe that any further clarifications from the Agency which can be reflected in this finalized guidance document will enable a streamlined and expeditious implementation of the final rule, and we would be pleased to provide additional pertinent information as may be requested.

Sincerely,



Richard L. Wolgemuth, Ph.D.
Senior Vice President
Global Regulatory Sciences