



Abbott

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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Re: Docket No. 05D-0011

Draft Guidances for Industry:

- (1) Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements**
- (2) Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format**

Abbott Laboratories (Abbott) offers the following comments on the two draft Guidances for Industry, referenced above, as published in the Federal Register on January 24, 2006.

Attachment 1 contains our comments on the draft Guidance, *Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements*, and Attachment 2 contains our comments on the draft Guidance, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Should you have any questions, please contact Ms. Lauren Hetrick, Senior Director, Regulatory Intelligence/FDA Liaison Office at (301) 255-0080.

Sincerely,

Douglas L. Sporn
Divisional Vice President

ATTACHMENT 1

Comments on the Draft Guidance, Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements

The implementation of the new Content and Format requirements in the physician labeling rule (PLR) (21 CFR 201.56 and 201.57) should be closely aligned with Structured Product Labeling (SPL), such that it is apparent how the PLR will be implemented in SPL (e.g. style sheets, tagging of sections in the full package insert in SPL for presentation in *Highlights*).

While we appreciate the Agency's efforts to address class labeling issues in this draft guidance, we are concerned that the approach fails to recognize the unique aspects of a particular product and does not offer practical advice for members of a class with regard to how class labeling supplements will be managed by the Agency. For example, Lines 394-396 state that, *If the drug is a member of an established pharmacologic class, the information under Indications and Usage must include the statement "(Drug) is a (name of class) indicated for indication(s)." This statement is misleading by implying that all members of the class share the same indications, which is not true. On a more practical note, Lines 667-669 state, Applicants should propose content and location of class labeling statements in the new format in the draft labeling submitted with their applications or supplements. Yet it does not address how FDA will treat the first member of a class converting to the new format and whether subsequent applications submitted by other members of the class will be required to use identical verbiage and placement. Furthermore, it does not address whether FDA will use the Content and Format submissions to revise class labeling that is not currently uniform or is in flux.*

In addition to the general comments above, we offer these specific comments to make it easier for sponsors to write labeling that complies with the final rule on the content and format of physician labeling. We organize the comments below based on the order of their appearance in the draft guidance as indicated by section number and page reference.

III. CONSIDERATIONS FOR REVISING LABELING

Line 120: For products that were approved many years ago, we foresee difficulty in constructing new sections of labeling based on information that was not collected originally. In some instances, sponsors will lack the information to regroup information and present it to the new standards. When this is the case and the information in the Adverse Reactions section is accurate and not misleading, is it acceptable to display the information in the old format and add new information complying with the PLR as postmarketing reports become available?

Line 138- 140: The submission of an efficacy supplement (e.g. for a new indication) triggers the requirement to revise the product's labeling to conform to the PLR. However, it is not clear how the update to incorporate new information that causes the labeling to be inaccurate impacts the review of labeling for the efficacy supplement. These appear to be separate issues; the review of the efficacy supplement and the revised labeling for other purposes would have to be closely tracked in order for the efficacy supplement to be approved with a unified label.

IV. HIGHLIGHTS

Lines 272-282: In this section, it would be helpful to clarify that new molecular entity equates to *active moiety*, such that the “Initial U.S. Approval” date is that upon which FDA initially approved the NME (e.g. **active moiety**), new biological product, or new combination *Active moiety* could also be added to the second paragraph.

Line 310: We note that the *Adverse Reactions* section is no longer included in Highlights under the heading of the *Recent Major Changes* section as it was in the proposed rule. Was this an oversight or does the FDA assume that important adverse reactions would qualify for inclusion in the *Warnings and Precautions* section, thereby making the *Adverse Reactions* section redundant?

Lines 364-371: It is not clear what should be listed in the Recent Major Changes heading. Is it any changes that were approved by FDA within one year of the date upon which the converted labeling is submitted to the Agency or is it defined differently (e.g. changes that were incorporated into the labels printed in the prior year)? Please clarify.

Lines 422-425: We suggest that when there no contraindicated situations have been identified, this section states, *None in accordance with the CONTRAINDICATIONS section in the full prescribing information*. The next sentence about *Relative Contraindications* is unnecessary because the relative contraindications would have been eliminated from the full prescribing information and not available to summarize in Highlights.

Lines 465-468: As currently stated, adverse events may be reported to the manufacturer via phone and website, and to the FDA MedWatch program. However, a preference is not assigned to any method. It would be helpful to direct physicians to which should be used preferentially.

Lines 484-485: The fictitious examples (Imdicon and Fantom) do not help us to understand the types of drug interactions that would merit inclusion in Highlights. Please clarify this by providing examples.

V. PROCEDURAL INFORMATION

Line 563: It would be helpful to expand upon the last bullet of this list (Footnote 9) by also listing the types of supplements meeting this definition, which are not included in the bullets above.

VI. FORMATTING

Line 704: We recommend that when subsections are used, they be identified with another decimal point (e.g. 8.6 Renal Impairment, 8.6.1 Severe Renal Impairment, 8.6.2 Mild to Moderate Renal Impairment) to help with tagging for SPL2b.

ATTACHMENT 2

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

Overall the guidance provides valuable information regarding the somewhat confusing and seemingly arbitrary categorization of adverse events that appear in the labeling sections currently titled, Warnings, Precautions, Contraindications, and Boxed Warnings. We offer the following comments to make it easier for sponsors to write labeling that complies with the final rule on the content and format of physician labeling (21 CFR 201.56 and 201.57). We organize the comments below based on the order of their appearance in the draft guidance as indicated by section number and page reference.

II. WARNINGS AND PRECAUTIONS (W&P)

As described, we anticipate this section will be much larger than the current sections as it will contain more adverse events in more detail. Due to the expansion of this section, each adverse event may be less noteworthy than in current labels, impairing the clinician's ability to quickly and conveniently identify major risks. Therefore, headers, subheaders, and cross referencing are critical.

Line 62: The description of *otherwise clinically significant* is broad. For example, a headache treated with an OTC pain reliever would qualify as a *clinically significant event* as currently defined because it would require the addition of another drug. A cough associated with the use of an ACE inhibitor that leads to a change in the prescription would also qualify via regimen adjustment. There is a good deal of subjectivity in deciding what non-serious adverse reactions warrant inclusion; this has the potential to result in differing opinions between sponsors and the Agency as well as differing opinions across reviewing divisions. We note that *otherwise clinically significant* is not listed in the Glossary; it would be helpful if it were listed to establish this new definition in regulatory terms. It is important to distinguish this definition from that of *serious adverse reaction* as they should not be used interchangeably in this draft guidance (as occurs at Line 327).

Line 68: *Adverse events that significantly affect patient compliance* is also broad. It would be helpful for to explain how this is determined. For instance, nausea, a relatively common adverse event might affect compliance with an oral medication, resulting in the inclusion of nausea in W&P section.

Line 71 (and Lines 92 and 193): The inclusion of *Expected Adverse Reactions* in the W&P section should be more limited. Listing them as currently described will undermine the distinction between the safety profiles of drugs because reactions "expected" with other drugs in class will be mixed with actual events that were observed with a drug. Each member of a class may not be associated with the exact same events or extent of events as other members of the class due to chemical differences. Minimally, Line 193 should be revised to permit sponsors to

subcategorize adverse reactions by separating reactions observed from those yet to be observed, but possibly expected.

Line 100: It is appropriate to consider the severity of the disease for which the drug is indicated when deciding whether to include an event in the W&P section. However, we note that the examples given (rhinitis, cosmetic conditions, transient insomnia, and cancer) may result in inconsistent W&P sections across products when nausea, pruritis, and alopecia are considered clinically significant for Product X for rhinitis, cosmetic conditions, and insomnia but not for Product Y for cancer. This may dilute the overall effectiveness of the W&P section across products.

Line 112: Please provide additional guidance on the use of incidence. Examples would be helpful to distinguish how to quantify the concern that merits inclusion.

Line 120: It is not clear how the ability to manage or prevent an adverse reaction plays into the decision to discuss an adverse reaction in the W&P section. Many serious adverse reactions can be managed; should they all be listed?

Lines 131-135: Sponsors should also be permitted to include a specific warning relating to an unapproved use as this takes advantage of a primary source of valuable information. It would be helpful to give examples of what would prompt inclusion of reactions linked primarily to an unapproved use. For example, is this information learned from clinical trials for new indications, from postmarketing reports, from medical publications, etc.?

Lines 142-144: We note that *clinically significant outcomes* is not defined here or listed in the Glossary; it would be helpful if it were listed to establish this new definition in regulatory terms.

Line 146: Item 6, *Monitoring*, strays into the practice of medicine, information that is not currently included in product labels. Laboratory tests helpful in monitoring response or adverse reactions must be individualized based on underlying disease, concomitant medications, and comorbid conditions. It is more appropriate to offer limited recommendations for more frequent monitoring for select adverse reactions when concomitant medications may increase the risk of the reactions. These recommendations may be derived from clinical trials to determine the value of lab testing and appropriate monitoring frequency; however, this is not feasible based on post-marketing reports.

Line 160 (Footnote 4): Please clarify how "early exposure" is defined? The rates for crude risk and risk adjusted for duration of exposure are applicable to data generated from clinical trials, but are most difficult to generate from post-marketing reports.

Lines 190-194: Please clarify the Agency's preference as to the subheaders used to group related events (e.g. by body system). This is not explicitly stated in the final rule or in the accompanying draft guidance.

III. CONTRAINDICATIONS

This section provides a welcome, detailed, and clear description of when to contraindicate a drug.

Lines 229-230: We suggest that it is preferable to state no known contraindications in a full sentence on Lines 229-230, such that it reads, *There are no known contraindications to the use of (drug name)*.

Line 299: We notice inconsistency. The examples provided by FDA (e.g. Imdicon) do not contain subheaders for each contraindication and suggest that subheaders are redundant if each contraindication is listed by bullet or separated with space.

IV. BOXED WARNING

It is critical that the significance of the boxed warnings not be diluted by too much detail or listing too many events. Therefore, we recommend that the criteria of including serious adverse reactions that can be prevented or reduced in frequency be removed. This group is overly broad, and includes serious drug-drug interaction-related events, as well as serious reactions related to use in patients with a specific co-morbid disease (e.g. renal insufficiency). It would be better to limit the criteria used for inclusion in the Boxed Warning. We suggest that the second bullet (at Line 327) be removed in its entirety.

Lines 336-337: The statement, *A boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber*, is vague and subjective. It offers no additional value beyond the examples covered in the bullets above it. Therefore, we suggest that this paragraph be deleted.

Lines 346-347: This paragraph should contain the same disclaimer as in Lines 92-99, *In these cases, the labeling should acknowledge that the adverse reaction has not been observed but may be expected to occur*.

Line 348: This information should only be included in the Boxed Warning section if the *Indications* section of the label limits the product to second-line use. The decision to use a drug as first- or second-line therapy is a medical practice decision, and is dependent on factors beyond adverse reactions.