



Timothy R. Franson, M.D., F.A.C.P.

Vice President
Clinical Research and Regulatory Affairs, U.S.

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.
Phone 317 277 1324 Fax 317 276 9960

0471 '00 SEP 19 19:49

E-Mail franson_timothy_r@lilly.com

September 19, 2000

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

Re: [Docket No. 00D-1306] Draft Guidance for Industry: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (65 Federal Register 38563; June 21, 2000)

Dear Sir/Madam:

Eli Lilly and Company ("Lilly") is pleased to have the opportunity to offer comments on the draft Guidance for Industry: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics. We commend the FDA for producing a document that provides a rational approach to communicating important, clinically useful safety information to health care professionals. Lilly is dedicated to creating and delivering innovative pharmaceutical-based health care solutions in order to provide patients with optimal clinical outcomes. For that reason, we are keenly interested in improving the communication of risk information to the prescribers of our pharmaceutical products. Attached please find our comments on the draft guidance. We hope that these comments will result in revisions that further enhance the positive impact of this guidance.

The comments that we have prepared are divided into two major sections: General Comments and Specific Comments. The latter section follows the format of the draft guidance document. Comments in this section are grouped under the corresponding section headings from the draft guidance.

General Comments

1. In the SUPPLEMENTARY INFORMATION section of the Federal Register notice, FDA announced several labeling initiatives as part of a comprehensive effort to make prescription drugs safer to use. Among these were a proposed rule that will revise the overall format of labeling, another proposed rule that will revise the current requirements for the pregnancy subsection, and multiple guidance documents on various sections of labeling. Given the extensive nature of these changes, it would be appropriate for FDA to wait for all of these requirements to be implemented at one time and not implement them in a piecemeal fashion.

00D-1306

C6

Answers That Matte

When these requirements are implemented, there should be a generous implementation period to allow for exhaustion of supplies of existing packaged inventory and printed materials and time to develop label copy. FDA also needs to be able to review the labeling supplements submitted to comply with the new rules in a timely fashion so as to allow sponsors to plan for the transition to use of the new labeling. A coherent implementation plan should be outlined in the proposed rule for the overall labeling format revisions.

2. Changes in the requirements for prescription drug labeling should be outlined in proposed rulemaking before labeling modifications are described in guidance documents. For that reason, FDA should clearly state that sponsors are not required to implement changes described in this draft guidance until the regulations are modified and an implementation period has been identified.
3. Given the complex nature of many of the issues discussed in this guidance document, it would be helpful if FDA would include an example of the proposed new design of the ADVERSE REACTION section in the final guidance document and compare that proposal to the current format. FDA also should consider including such a model in the proposed rules and the other guidance documents to be released in the near future.
4. This guidance document represents a major change in emphasis for the ADVERSE REACTION section of prescription drug labeling. There is a shift from inclusion of adverse *event* data to adverse *reaction* data. The Introduction section of the guidance document states that “Long, exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy, and not plausibly related to drug therapy, should be avoided.” Lilly agrees that labeling should include information that is clinically useful to prescribers when they are making treatment decisions, but, unfortunately, prescription drug labeling is also the center of substantial litigation in this country. For that reason, FDA should consider the inclusion of a separate subsection that lists all other reported adverse *events*, even if considered at the time to be unrelated to drug therapy. Using this approach, prescribers will be made aware of those adverse events that are most likely related to drug therapy, but they also will be given *all* information available to sponsors so that they can make fully informed prescribing decisions.

Also, this shift in emphasis from *events* to *reactions* may confuse physicians and patients. Without a separate subsection for all other reported adverse *events*, some adverse events are likely to be removed from the current versions of labeling.

Finally, the addition of this subsection could also serve to limit the number of unnecessary expedited adverse event reports submitted to FDA because events listed in labeling are considered “expected” and, therefore, are only required to be reported in periodic adverse drug event reports.

5. Where internationally agreed-upon definitions have already been established (e.g., CIOMS III definitions for frequency; ICH definitions of adverse event, adverse reaction, and serious; etc.), they should be utilized.
6. The term adverse *reactions* is used throughout this guidance document, as opposed to adverse *events*. The guidance seems to use the two terms interchangeably in several places. FDA should be cognizant of this issue and be sure to use the appropriate term in the correct context.
7. FDA should address how class labeling will be impacted by the proposals set forth in the guidance document.
8. To date, we at Lilly are not aware of any current or upcoming regulatory requirement for using a specified standard dictionary, such as MedDRA, to facilitate coding for pre-marketing case reports. We anticipate that it may be several years before such a requirement is enacted and/or the transition period required to move to a standard coding dictionary for pre-marketing case reports will occur. As such, since it is generally pre-marketing data that is used to develop labeling decisions we do not recommend that any one dictionary be required in the 'guidance document' at this time. In addition, regardless of which dictionary is being used, we recommend that the level of terminology used for labeling be at the preferred or class term level - or higher as appropriate. We discourage the use of terms at the lower or entry level that serve more to facilitate/link the coding from the 'verbatim' or 'as reported' term to a term that better represents a medical concept.

Specific Comments

II. ADVERSE REACTIONS SECTION-CONTENT AND FORMAT

A. OVERVIEW-CONTENT AND FORMAT

There are risks associated with the possibility that physicians will only read the Overview section and not the entire ADVERSE REACTIONS section of the label. The addition of a boiler plate statement that reminds the reader that it is necessary to read the entire package insert for full prescribing information may address this concern.

The Overview section should contain a brief statement regarding the data sources in addition to the full description of the data sources included in the Discussion section.

1. Serious and Important Adverse Reactions Described in Other Labeling Sections

The term "important" is not explicitly defined in the document. Without a definition, it is difficult to determine which adverse reactions to include in this section.

3. Adverse Reactions Most Commonly Resulting in Clinical Intervention

The information in the Overview section may be redundant with other parts of the ADVERSE REACTIONS section without adding value. For that reason, the interventions described in this section should only address those that are life-saving.

B. DISCUSSION OF ADVERSE REACTION INFORMATION-CONTENT AND FORMAT

1. STATEMENT CONCERNING THE SIGNIFICANCE OF ADVERSE REACTION DATA OBTAINED FROM CLINICAL TRIALS

Inclusion of this language in the labeling of every drug product, undermines its value to some extent. These issues should be addressed through physician education efforts, potentially in medical schools. If this section is included, we generally agree with the concepts but have the following suggestions for revision:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events *that may possibly be related to drug use* and *a basis for* approximating rates.

The above listed revisions are made based on the ICH definition for *adverse reactions*, which is highlighted in footnote 6 of the guidance document. The language proposed in the guidance document boiler plate language, that reads "...that appear to be related to drug use...", leads the reader to believe that there is a stronger causal relationship than actually may exist based on the ICH definition.

2. DESCRIPTION OF DATA SOURCES

Throughout the guidance document the use of adverse *reaction* information is promoted, but this section indicates that the description of the data sources should include a "rationale for not basing rates on all reported events." Please clarify this apparent contradiction. If all adverse *events* are to be included in the table, this should be noted in the description as well.

The clinical data sources are often described in detail in other sections of labeling such as the CLINICAL STUDIES section or the CLINICAL PHARMACOLOGY section. This information should not be duplicated.

3. TABULAR PRESENTATION OF ADVERSE REACTION DATA

The guidance document refers to active-controlled data as "less informative" and of "lower quality" than placebo-controlled data. Active-controlled trials performed under appropriately rigorous conditions provide valuable information and should be included in the package insert if the information proves informative. Including this data in tabular form may be the best format for disclosure and, therefore, its inclusion should not be deterred in the presence of placebo-controlled data.

4. WHEN ADDITIONAL TABLES MAY BE NEEDED

As opposed to emphasizing that “multiple tables should be avoided in most cases,” Lilly would propose alternate language to stress that “multiple tables may be included if each presents valuable information that is best conveyed in a tabular format.”

6. PRESENTATION OF LESS COMMON EVENTS

Lilly suggests the following revision to this sentence in the second paragraph:

In contrast, events that are serious but very unusual in the absence of drug therapy (e.g., liver failure, agranulocytosis, significant hemolytic anemia, thrombocytopenia, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception, acute renal failure) should be included, even if there are only one or two reports, *if after considering concurrent illnesses and concomitant medications, as well as the exposure rates and timing of the event, a causal relationship is still possible.*

In the third paragraph, the parenthetical statement “(usually not the case)” should be removed from the fourth sentence. This establishes unnecessary presumptions when determining if rates and/or numbers of less common events should be included.

III. ORGANIZING AND PRESENTING ADVERSE REACTION DATA IN A TABLE

◆ QUANTITATIVE DATA

In some cases, there may be a need to include mean change not just rates of the events above a certain level. This information is often useful to physicians to understand the magnitude of risk.

◆ ADVERSE REACTION RATES \leq TO PLACEBO RATES

In general, it is acceptable to exclude events that occur at rates lower than placebo, but there are situations where this information is valuable. For example, how do you report changes in event rates for events that are associated with the disease (e.g., a drug to treat migraine headaches may actually lower the incidence of vomiting)?

◆ SIGNIFICANCE TESTING

Suggested revisions to language:

Results of significance testing should be omitted unless they provide (delete the word “critically”) useful information or (change “and” to “or”) are based on a prespecified hypothesis in a study adequately powered to test that hypothesis.

IV. PRESENTING DATA IN THE ADVERSE REACTIONS SECTION OF LABELING

◆ RARE, SERIOUS EVENTS

Lilly suggests adding to the end of the first sentence: “

Serious adverse events that are unusual in the absence of drug therapy (e.g., liver failure, agranulocytosis, significant hemolytic anemia, thrombocytopenia, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception, acute renal failure) should be included in labeling even if there are only one or two reported events, ***if after considering concurrent illnesses and concomitant medications, as well as the exposure rates and timing of the event, a causal relationship is still possible.***

◆ **DETERMINING ADVERSE REACTION RATES**

This section seems to contradict the rest of the document in that it emphasizes that rates should be calculated based on “all adverse events reported in the database...” FDA should clarify whether adverse *reactions* or adverse *events* should be used to calculate rates.

◆ **CHARACTERIZING ADVERSE REACTIONS**

Characterizing adverse reactions with terms with accepted regulatory definitions should be allowed. There is a problem with the fact that these terms mean different things to different people, but this should be addressed with physician education. One suggestion would be to allow the inclusion of the definition of the terms in parentheses following their use [e.g., rarely (one in 1,000)]. FDA should consider use of the terms identified and defined in CIOMS III. Discontinuation data also may help characterize adverse reaction data (e.g., nausea occurred in X% of patients taking Drug Y, but only Z% patients treated with the drug discontinued therapy.)

V. UPDATING THE ADVERSE REACTIONS SECTION OF LABELING

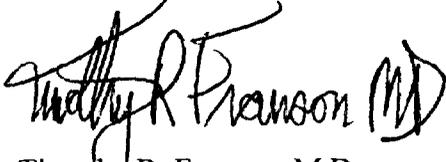
◆ **INCONSISTENT OR OUTDATED INFORMATION**

Page 9 footnote should be #5, not #7.

Lilly appreciates the opportunity to comment on this important *draft* guidance document.

Sincerely,

ELI LILLY AND COMPANY



Timothy R. Franson, M.D.
Vice President
Clinical Research and
Regulatory Affairs - U.S.

LTR 1 OF 1

JOE HOLLINS
(317) 276-3429
ELI LILLY & COMPANY
639 SOUTH DELAWARE STREET
INDIANAPOLIS IN 46285

SHIP TO:

SEE ATTACHED
SEPT 18, 2000
ADDRESS LABEL
ROCKVILLE MD 20852

Rockville, MD 20852

5630 Fishers Lane, Room 1061

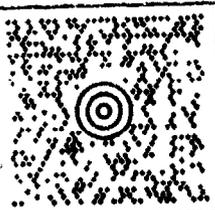
Food and Drug Administration

Dockets Management Branch (HFA-305)

SHIP TO:

ELI LILLY & COMPANY, LILLY CORPORATE CENTER, INDIANAPOLIS, IN 46285

Must be a unique number: 5630

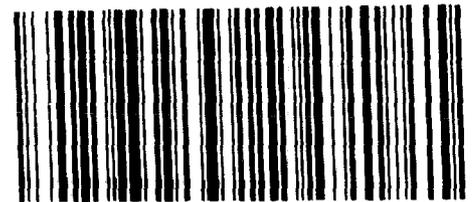
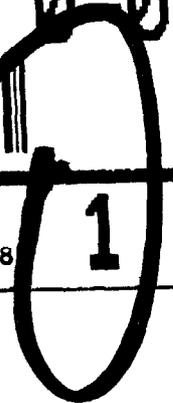


MD 207 0 04



UPS NEXT DAY AIR

TRACKING #: 1Z 447 298 01 5842 3428



See above the address label.

BILLING: PREPAID

REF 1: 370675

