8505 '01 JUN 28 P1:05

May 2, 2001

Dockets management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

Dear sirs,

The following comments from the Department of Veterans Affairs (DVA) concern Food and Drug Administration proposal 21 CFR Part 201, Docket No. RIN 0910-AA94, "Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Labels."

We agree that drug labels have grown increasingly more complex over the years (page 8, line 11). Your agency has correctly noted that this increase in detail has paradoxically made it more difficult for clinicians and consumers to locate and use relevant information. We additionally note that the existing Label is inadequately standardized and lacks computable elements. Such standards and elements are increasingly needed for computerized information systems such as our VistA (Veterans Integrated Services and Technology Architecture) patient care system. For example, DVA expends considerable resources to create and maintain a VistA National Drug File. Data fields in the NDF would be more effectively populated and maintained by means of standardized, computable labeling standards promulgated in your labeling proposal and most particularly by the proposed Highlights. Linked to a medication reference terminology (mRT), the Highlights and the new Label would allow improvements to VistA NDF that would enhance the ability of DVA to share VistA patient medication and prescription data with other DVA partners such as the Department of Defense.

In particular, we have reviewed a draft of the proposed labeling changes for Capoten (captopril) as an example of the new rules and conclude that this format will greatly enhance the availability and utility of clinically relevant information. Aside from improvements in computability made possible by the new standard, the proposal simply provides a more readable, relevant, and accessible drug product information. The Highlights are particularly indispensable in order to deliver accurate, highly pertinent drug information to the Federal physicians, nurses, and other practitioners. Even disregarding the likely improvements in computerization that will flow from the new Label, DVA practitioners who simply read the Highlights section in particular and the new Label in general (especially the index) will find that it meets their information needs much better than the current Label.

The DPI survey done by FDA to examine labeling features, subsequent prototype Label models, and continued refinement of these models through physician focus group testing demonstrate to DVA that the FDA has taken a careful and scientifically valid approach to

determine practitioners' drug information needs. You have clearly targeted your labeling redesign to meet those needs, which are congruent with the needs we perceive for our clinicians, information systems developers, and administrative users. The DVA supports the use of such careful surveys to determine the best approach for labeling, as opposed to trying to merely guessing what physicians need, or letting commercial and marketing concerns drive drug labeling.

With regards to the new labeling, we believe the FDA should move expeditiously to require that all old drugs be moved to the new labeling requirements. DVA would support the alternative (quicker) implementation time-line proposed.

The DVA has the following comments upon the 15 enumerated issues in the NPRM upon which a response was specifically requested:

> (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;

DVA cannot see any circumstances under which it is inappropriate to adopt this highly desirable new labeling practice.

> (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 (1) titling this section "Highlights" rather than "summary," and (2) 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;

DVA believes that, to the contrary, the less useful format of the current Label may lead to inadequate patient care and increase the risk of subsequent legal action compared to the risks contingent upon the proposed new labeling. To be most useful, the Highlights section should be populated with adverse events and warnings that are created using a medication Reference Terminology (mRT). Each Highlight's summary list of warnings and adverse events can be substantially complete, and linked to complete detailed information in the remainder of the Label. In this case, the DVA (and other health care organizations) can better create their own clinical information systems that computerize and hyper-link these lists and their links. The Highlights approach allows the Label to be more accessible (as free text), better computerized as an indexed list that is amenable to order checking technologies, and more effectively linked to complete prescribing information by means of computerized information systems. In this way clinicians' experiences with labels would be enhanced, clinical safety would actually be improved,

and health care organizations can take charge of determining which warnings or adverse affects are the most salient for a particular patient or health care encounter. We would suggest that this approach would actually reduce the liability of pharmaceutical companies.

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

Boxed warnings should be summarized in a format consistent with the remainder of the "Highlights of Prescribing Information section", and indexed to the full warning in the comprehensive section of the Label as described above.

An additional reason that Boxed warnings should be uniquely denoted in the Highlights in a consistent format is so that computer information systems can separate them from "routine" warnings. For example, FDA proposes the use of a unique identifier ("!") to set off the Boxed warnings. These identifiers should be unique and amenable to parsing so that computer information systems can correctly identify Boxed or other critically important warnings.

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

A graphic icon would help to demark a boxed warning inside of the Highlights section when the Label was printed. In addition to any graphic, developers and users of computerized information systems will require a unique alphanumeric character or character string Label, reserved from other uses.

More importantly, the FDA should support the development and use of a controlled medication Reference Terminology containing sufficient semantics to uniquely identify the various types of adverse actions that drugs may have, so that these can be computed. The current MEDRA system does not contain sufficient semantics to support this function adequately.

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

Research in diffusion of medical innovation (e..g, clinicians such as Lomas and cognitive psychologists such as Elstein) demonstrates that clinicians are slow to become aware of new innovations and adopt them in practice (e.g., use of angiotensin converting enzyme inhibitors to treat diabetic proteinuria). Recent labeling changes should probably remain active in print for at least two years, and possibly three or four, especially when well-supported scientific evidence indicates that the new Label information is of major importance to patient care. We propose that you consider flagging each part of the Label with a time-stamp so that computerized information systems can document when each part was added or updated. Then developers and users of clinical information systems

can determine for themselves what Label changes, and what time frame, are relevant to them. Again, this approach should actually reduce manufacturer liability by moving these decisions to drug product consumers.

(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;

These indications and uses should be summarized in a bulleted format in order to be maximally useful to clinicians. The bulleted items should be chosen from a controlled medication Reference Terminology in order that they can be adequately (unambiguously) computerized. Clinicians can always read the verbatim indications from the comprehensive section. In computer systems, the verbatim indications can be hyper-linked so that complete prescribing information is always available to clinicians whilst preserving the availability and utility of the Highlights format. FDA should support development of a controlled, maintainable, reference terminology with adequate semantics in order to regularize indications and make them amenable to computer processing.

(7) Whether it is necessary to include the proposed requirement for an index section given the proposed requirement for a Highlights section (i.e., do the additional purposes served by the index justify its inclusion?);

The index is a highly useful section because it allows the user to more quickly move from the Highlights to the appropriate detail in the comprehensive section. It will also support computerized indexing and hyper-linking of the Label. Furthermore, a user of a printed Label without benefit of an index must laboriously scan the full text of the comprehensive section. Such a scan, under the time pressure of clinical work, is likely to be cursory and error-prone, resulting in more medication errors, decreased patient safety, and increased cost of adverse events and outcomes. We support the re-ordering of the comprehensive information section to put the most frequently referenced and important sections in the beginning. The user surveys, focus groups, FDA's own experience, and the public comments of the information's consumers and users should guide the reorganization of the proposed labeling.

(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;

It is appropriate to begin to move towards a reference terminology and semantics for headings used in the warnings and precautions section. Appropriate experts from standards development organizations such as the HL7 Vocabulary special interest group and government agencies such as Department of Veterans Affairs, FDA, and National Library of Medicine should be involved in creating the medication Reference Terminology and its supported headings.

(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;

This is helpful and should be denoted with unique identifiers that can be parsed for inclusion in computer information systems such as the DVA National Drug File and other computer systems used by DVA. .

(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;

We believe the FDA has adequately addressed these issues. The interest in supporting consumer health and safety should be paramount.

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

Bolding appears to be adequate in a printed Label. All labels with graphic or text style emphasis should also receive unique alphanumeric labels that can be parsed by computerized information systems.

(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;

The Highlights should not be inordinately expanded substantially beyond that which is already proposed. Such an expansion would greatly reduce their usefulness. However, a substantially complete, bulleted list of Highlights information (e.g., warnings, on-Label indications), linked through the Index to full prescribing information, should be included.

(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;

A unique identifier of FDA's choosing that is reserved and amenable to computerized methods of parsing, as well as visually striking, should be adequate.

(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;

Elderly patients who may read labeling information and aging physicians will likely appreciate 10-point fonts. The key point is that a new Label containing a Highlights section based on a medication Reference Terminology can be parsed and displayed by computerized clinical information systems. These systems can be designed to display information in a format and style that meets users needs. For example, DVA hires a substantial number of visually disabled veterans and other disabled employees. These employees receive special assistance and computerized systems in order to do their work. Computerized labels made possible in VistA by means of the proposed rule would substantially enhance our ability to help our disabled veteran and other disabled employees.

(15) Whether application of the revised format and content requirements 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 five years prior to the effective date of the final rule is appropriate, or whether alternative criteria should be used.

In summary, DVA believes that the proposed labeling revision is absolutely necessary for the proper performance of the FDA's functions and to enhance patient care within DVA. The quality, utility, and clarity of the information, particularly in the Highlights section, would be enhanced by FDA support for and requirements for use of a medication Reference Terminology for key elements such as dose form, drug classes, molecular structure, and eventually for clinical indications and adverse reactions. The use of such a reference terminology would also have the happy side effect of easing the burden of data collection upon the industries affected. Currently, the lengthy and undifferentiated nature of the drug Label makes it much less useful to us in our computer information systems and for patient care. DVA strongly supports the proposed rule making and urges it's speedy adoption and publication in the Federal Register without further substantial revision.

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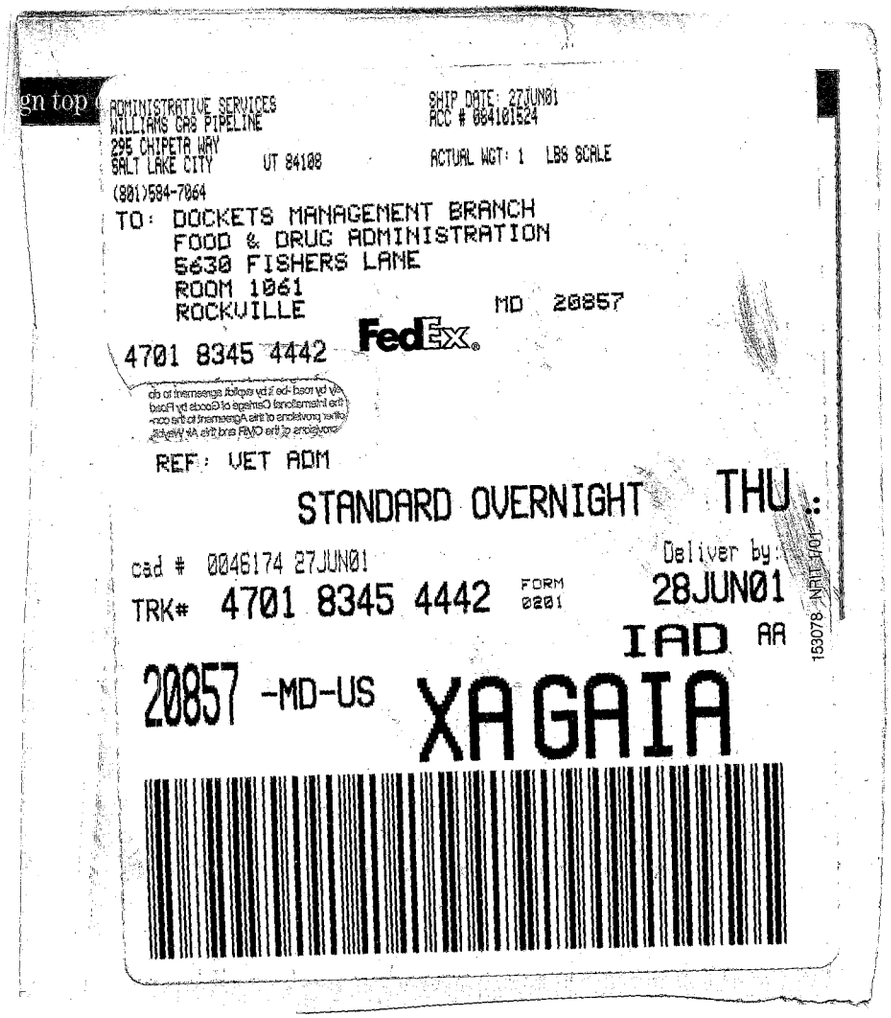

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