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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. 2005D-0011 – Draft Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Availability.

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and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, Draft Guidance

Merck & Co., Inc. is a leading worldwide human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck drug product candidates through developmental testing, clinical trials and licensure, Merck scientists address issues affected by this proposed Guidance on labeling. We have extensive experience in the development and licensure of drug and biological candidates and concomitant development of appropriate labeling; we have utilized those experiences to author the comments below.

General Comments

We commend the Food and Drug Administration (the Agency or FDA) for their commitment to providing guidance to industry concerning implementation of the recently issued final rule amending the requirements for the content and format of labeling for

human prescription drug and biological products[1]. We have identified significant comments on the draft guidance outlining the content and format of warnings and precautions, contraindications and boxed warning sections of labeling. Our major comment concerns the proposed linkage between the clinical significance of an adverse reaction and the relative seriousness of the disease or condition for which the drug is indicated (see lines 100 – 110). This approach will cause an inconsistency in the way similar adverse reactions are communicated across labeling for various products. We do not believe that the placement of the adverse reaction (in the Warnings and Precautions Section) should be driven by the indications for the product but should be driven by the characteristics of the adverse reaction.

Specific Comments

We have tabulated our specific comments as follows: identification of the line in the draft guidance (in *italics*) followed by suggested edits (underlined) and our rationale supportive of the proposed changes. Our specific comments may be found in Attachment 1.

We appreciate the opportunity to share our comments with respect to the FDA Draft Guidance for Industry on Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format. Please do not hesitate to contact me, should you have any questions.

Sincerely,

Taryn Rogalski-Salter, PhD
Director
US Regulatory Policy

Attachment enclosed

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[1] 21CFR Parts 201, 314, and 601. Docket Number 2000N-1269. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products. Final Rule

Attachment 1

Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale
II A	Lines 69-70	Consider clarifying the statement: "*The product interferes with a laboratory test*" by adding the text: "<u>The product interferes to a clinically significant degree with a laboratory test essential to the correct diagnosis or monitoring of one of more of the approved indications, or the management of a serious or life-threatening condition</u>."	As currently written, the bullet "*OR The product interferes with a laboratory test*" contains no mention of criteria by which interference with a laboratory test may be judged to rise to the level of a Warning or Precaution. While in rare cases, interference with a lab test crucial to the diagnosis or management of one or more of the indications may fit in this category, in many cases the interference may be minor and/or of minimal clinical significance. In such cases, the interaction might better be placed in the CLINICAL PHARMACOLOGY, DRUG INTERACTIONS, CLINICAL STUDIES, PATIENT COUNSELING, or DOSAGE AND ADMINISTRATION sections.
II A	Lines 100-110	*"The relative seriousness of the disease or condition for which a drug is indicated will influence whether an adverse reaction would be considered clinically significant and thus appropriate for inclusion in the WARNINGS AND PRECAUTIONS section. For example, for a drug intended to treat a minor, self-limiting condition (e.g. allergic rhinitis, cosmetic conditions, transient insomnia), a nonserious adverse reactions (e.g. nausea, pruritis, alopecia) may be considered clinically significant and, therefore, appropriate for inclusion in the section. For a drug intended to treat a serious or life-threatening condition (e.g., cancer), the same adverse reaction may be considered much less clinically significant and not appropriate for inclusion in the section."* Consider omitting this text from this section of the Guidance (*II. WARNINGS and PRECAUTIONS SECTION*) and relocating a variation of the language (omitting reference to *WARNINGS and PRECAUTIONS*) to another section such as Patient Counseling Information and Adverse Reactions.) For example, you may consider relocating the text: "*The relative seriousness of the disease or condition for which a drug is indicated will influence whether an adverse reaction would be considered clinically significant".* .	The clinician should be advised primarily of truly serious adverse reactions in the WARNINGS AND PRECAUTIONS SECTION of the label, and the standard should be constant across drug products. As written, this section will drive inconsistencies across labels and run afoul of the intent of the rule to standardize information and facilitate physician's prescribing. Elevating less serious events to WARNINGS AND PRECAUTIONS just because the targeted indications may be minor, self-limited conditions artificially raises the importance of such events and dilutes the implied gravity of WARNINGS AND PRECAUTIONS sections across different drug products. The inclusion of a complete adverse event profile in the ADVERSE REACTIONS and other sections (e.g. Patient Counseling, Use in Specific Populations) should enable the clinician to make an appropriate risk/benefit determination, without implying that non-serious events are more serious than they actually are. Benefit/risk information may be communicated in locations in the label which permit a more balanced discussion by indication and which do not suggest artificial degrees of seriousness for non-serious events such as Patient Counseling, Use in Specific Populations, and Adverse Reactions.

Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale
II A	Lines 112-118	Consider adding underlined text: *Typically, the* serious *nature of an adverse reaction* ~~*and a drug's indication*~~ and its causal *association are the most influential factors in determining whether an adverse reaction should be included in the WARNINGS AND PRECAUTIONS section. In some cases, however, the absolute* or relative *risk or rate of* a serious *adverse reaction can be an important factor when deciding whether to include the reaction in this section (e.g., when the risk or rate is high).*	While it is true that the incidence of an adverse reaction is an important parameter, it is important to emphasize that incidence alone should not drive inclusion in WARNINGS AND PRECAUTIONS; because many non-serious events may be relatively high incidence yet should not rise to the level of WARNINGS AND PRECAUTIONS. Suggest omitting "*indication*" as noted, and adding "serious" and "causal association". Relative risk may at times be important, even if absolute risk is small, if the adverse event is serious. In addition, another reason to add adverse reactions to the WARNINGS AND PRECAUTIONS section is if the reaction may result in a hazard to the patient and the patient is required to take certain actions [precautions] e.g. monitoring serum potassium in patients on potassium sparing diuretics. This point is not reflected in this section of the draft guidance.
II A	Lines 127-137	*4. Adverse Reactions Associated with Unapproved Uses. FDA may require a specific warning relating to an unapproved use if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard (§ 201.57(c)(6)(i)). Clinically significant adverse reactions that appear to be linked primarily to an unapproved use of a drug (e.g., use for a disease, condition, or population not included in the INDICATIONS AND USE section, use of an unapproved dose or regimen) should be identified and discussed in the WARNINGS AND PRECAUTIONS section. The discussion should include a statement indicating that safety and effectiveness have not been established in that setting and that the use is not approved by FDA.*	This section does not provide sufficient information to guide the sponsor on when to include information on unapproved uses. We suggest the Agency provide greater guidance in order for the sponsor to better understand what would trigger the inclusion of information in this section.

Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale
II A	Lines 146-151	*"6. Monitoring* *The WARNINGS AND PRECAUTIONS section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions (§ 201.57(c)(6)(iii)), and, if appropriate, information about the frequency of testing and expected ranges of normal and abnormal values."* Consider clarifying the section above to indicate that directions for monitoring of less serious adverse reactions do not belong in the WARNINGS AND PRECAUTIONS section by adding the following text: <u>The monitoring section of WARNINGS and PRECAUTIONS should focus primarily on the identification of possible serious adverse reactions or the monitoring of the patient's response to treatment for a serious and life-threatening condition.</u> <u>Monitoring of efficacy for less serious adverse reactions would best be addressed in alternative locations (e.g. Clinical Pharmacology, Indications and Usage, Use in Specific Populations, Clinical Studies, or Patient Counseling Information).</u>	While it is reasonable that monitoring for adverse reactions belongs in WARNINGS and PRECAUTIONS, it is less clear that suggestions for monitoring efficacy (*patient's response*) belongs in this section, unless lack of efficacy is itself a serious safety concern (as in cancer chemotherapy or immunomodulators to prevent transplant rejection). Clinicians will look to WARNINGS and PRECAUTIONS primarily for safety rather than efficacy issues. We suggest addressing efficacy monitoring in sections such as Clinical Pharmacology, Indications and Usage, Use in Specific populations, Clinical Studies, Patient Counseling Information

Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale
II B	Line 160 and Footnote 4	*"[4] When the risk for an adverse reaction is highest during early exposure, crude risk (# of adverse reactions / # patients exposed) may be the best estimate. For adverse reactions that occur after prolonged exposure, there should be an adjustment for duration of exposure by use of either overall exposed person time if the risk is constant over time, or by calculation of cumulate incidence for a specified exposure time in a survival analysis."* We suggest deleting footnote 4, or editing the text to suggest the approach is one option, rather than a mandate. *"[4] When the risk for an adverse reaction is highest during early exposure, crude risk (# of adverse reactions / # patients exposed) may be the best estimate.* <u>Consider expressing the estimate of risk or adverse reaction rate in CIOMS terms: Common" (greater than 1/100, less than 1/10), "Uncommon" (greater than 1/1000, less than 1/100), "Rare" (greater than 1/10,000, less than 1/1000)).</u> *For adverse reactions that occur after prolonged exposure*, <u>consider using</u> *an adjustment for duration of exposure by use of either overall exposed person time if the risk is constant over time, or by calculation of cumulative incidence for a specified exposure time in a survival analysis.*	We suggest including language to reflect the sponsor has the option to use CIOMS definitions; which are widely accepted, useful to and understandable by clinicians, yet general enough to have a reasonable labeling longevity. (e.g. "Common" (greater than 1/100, less than 1/10), "Uncommon" (greater than 1/1000, less than 1/100), "Rare" (greater than 1/10,000, less than 1/1000)). The suggestions in footnote 4, while excellent for publication, will be less meaningful for clinicians and less readily compared among drug products, and across geographic regions.

Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale
III A	Lines 225-230	*"A. When to Contraindicate* *A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, must be listed. If there are no known contraindications for a drug, this section must state "None." "* Consider the addition of the following clarification: <u>Contraindication against hypersensitivity to any of the components in the drug product should be regarded as a known hazard and labeled as such even before actual reports of such occurrences arise.</u>	For a number of products, it is inevitable that hypersensitivity reactions to one or more of the components will develop in some patients during the life of a medication. A reminder to the physician of hypersensitivity reactions can be an important preventive public health measure and should not be delayed until events occur.
III A 3	Footnote 8 at line 279	*" [8]There should be consistency across labeling for contraindicated products (i.e., if use of drug A with drug B is contraindicated in the labeling for drug A, the use of drug B with drug A should be contraindicated in the labeling for drug B). For drugs that are regulated in different reviewing divisions, there should be cross-divisional coordination and agreement on contraindicated coadministration of drugs".*	We are requesting that the Agency provide details concerning the regulation of labeling and review management for contraindicated products. For instance, how will a sponsor be notified about the need for such labeling? Will there be a mechanism for interaction between the two sponsors and the Agency?

Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale
III C	295-299	*C. Format* *1. Subheadings* *FDA recommends that each contraindication be identified by its own subheading.* We request the following text be added to this section: *FDA recommends that each contraindication be identified by its own subheading* <u>or contained in a bulleted list.</u>	We are requesting more flexibility in formatting the subheadings of the Contraindications section to allow the use of a bulleted or numbered list.