Biotechnology Industry Organization

June 24, 2013

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

Re: Docket No. FDA–2013-D-0401: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors."

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO supports FDA's efforts to help prescription drug and biologic product manufacturers minimize medication errors associated with their products. We recognize the importance of minimizing the risks of medication errors associated with the design of a drug products labeling and packaging. In 2007, BIO endorsed the Prescription Drug User Fee Act IV reauthorization and expansion that was signed into law as part of the Food and Drug Administration Amendments Acts of 2007 (FDAAA) (Public Law 110-85), which committed FDA to certain performance goals, including measures to reduce medication errors related to trade names, labeling, and packaging design.

BIO agrees that product container labels and carton labeling should clearly and accurately communicate information that is critical to the safe use of a medication. Safe use includes the ability to accurately and completely identify the specific product received by a patient, as incorrect attribution of adverse events to a particular product in safety reporting is itself a critical medication error. BIO offers specific, detailed comments to the Guidance seeking clarification and better understanding of the recommendations in the spirit of promoting patient well-being and safety, ensuring the utility and integrity of pharmacovigilance practices, and efficient and effective implementation.

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200
202.488.6306
bio.org

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett,
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

1201 Maryland Avenue SW
Suite 900
Washington DC 20024

202.962.9200 P
202.488.6306 F
bio.org

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
III. GENERAL CONSIDERATIONS		
Lines: 78-81	"The format and content of prescription drug and biological product labels must comply with FDA regulations in 21 CFR part 201 for drugs and 21 CFR part 610 subpart G-labeling standards for biologics, and should conform with all labeling requirements by the United States Pharmacopeia (USP)."	Please clarify the Guidance's interaction with labeling requirements for devices and/or combination products.
B. RISK ASSESSMENT DURING THE DESIGN STAGE CAN REDUCE THE RISK OF MEDICATION ERRORS		
Lines: 122-130	"Sponsors should assess and minimize the risk of medication errors resulting from the design of product container labels and carton labeling before submitting proposed labels and labeling for FDA review and approval. FDA recommends applying the principles described in this guidance and testing the overall design using well-established risk assessment methods at the pre-IND stage or during the early stages of label, labeling, and packaging development, and when changes or additions to an already marketed drug product occur throughout the product's life cycle."	Please clarify the testing expected and appropriate for label, labeling and packaging development at pre-IND and early development.

SECTION	ISSUE	PROPOSED CHANGE
C. CRITICAL PRODUCT INFORMATION SHOULD APPEAR ON THE PRINICIPAL DISPLAY PANEL		
Lines: 141	"Established name or proper name"	For clarity, BIO suggests including *(nonproprietary)* at the end of the clause. The new phrase would read: "Established name or proper name (nonproprietary)".
Lines: 144	"Warnings (if any) or cautionary statements (if any)"	Please clarify and provide examples of which warnings would need to be included on the "Principal Display Panel". Please also clarify whether these would be the warnings in the highlights section or other general warnings and precautions.
D. LABELS SHOULD BE LEGIBLE, READABLE, AND EASY TO UNDERSTAND		
Lines: 155-158	"FDA recommends that the text on the container label and carton labeling should be (1) generally orientated in the same direction; (2) placed in the same field of vision (i.e., readable without having to turn or rotate the container); and (3) surrounded by adequate white space to improve readability and avoid crowding."	Please clarify "generally orientated", or consider striking the word "generally". Please clarify and provide examples of "adequate white space."
Lines: 170-177	"Ideally, manufacturers should explore approaches to create larger container labels or unique packaging to accommodate all critical information on the immediate product container label. FDA regulations provide an exemption from some drug labeling requirements when the container is too small or otherwise unable to accommodate a label with enough space to include all required	Please clarify that the section is directed toward label size, as container and drug product compatibility with biological products may be significantly impacted if larger containers were required to accommodate additional content on the label.

SECTION	ISSUE	PROPOSED CHANGE
	information, provided that all required information is present on the carton labeling or in the prescribing information (21 CFR 201.10(i)). In such cases, the container label must include at minimum the product's proprietary and established name (if any); product strength; lot number; and the name of the manufacturer, packer, or distributor."	
Lines: 177-179	"USP requires the label of an **official drug product** to bear an expiration date.[11] Therefore, we also strongly recommend including the product's expiration date."	Please clarify that the expiration date may be placed on either a side label or the principal display panel.
Lines: 179-184	"For biological products, at a minimum, the name of the product, lot number, manufacturer name, and the recommended individual dose for multiple dose containers must be included (21 CFR 610.60(c)). Such exemptions are not available, however, if the lack of space is caused by failure to use all available space on the container, or the use of label space is for non-required information or other design-related elements (see 21 CFR 201.15(a)(3) through (a)(5) and 201.15(b))."	Please further define "name of product." BIO suggests the following: "For biological products, at a minimum, the *proprietary (if existing) and established* names of the product…." Please also clarify the criterion for "failure to use all available space" while also considering the concept of having adequate white space to improve readability and avoid crowding (line 157-158).
Lines: 186	"Text Size and Style"	Please clarify whether the heading recommendation applies to carton or container labels or to both.

SECTION	ISSUE	PROPOSED CHANGE
Lines: 188-191	"Sponsors should choose a font that is easy to read, not lightweight or condensed. A number of published references recommend a larger font size such as 12-point sans serif (e.g., Arial) to improve readability.[12,13] FDA recommends the use of at least a 12-point font whenever label size permits."	Please clarify whether the recommendation applies to carton or container labels or to both. BIO also recommends striking the phrase "not lightweight or condensed", due to its subjective nature. Moreover, it is not always practical to use 12-point san serif font due to packaging or container size. BIO recommends the Guidance reference the use of established reference standards (i.e. ANSI/AAMI HE-75) that provide Sponsors with a guide for font, size and style and allow for use of a smaller font size in certain circumstances. Please also clarify whether using 'bold' or 'italics' is an acceptable means of adding prominence.
Lines: 192	"Contrast of Text and Background Color"	Please clarify whether the heading recommendation applies to carton or container labels or to both.
Lines: 198-201	"Text that is raised or recessed (i.e., embossed or debossed) on clear, transparent, or translucent containers (e.g., LDPE vials) is generally illegible. For these types if container labels, we recommend individually overwrapping the product so that a legible label is applied to the overwrap, and the product should be retained in the overwrap until it is administered."	Please clarify whether embossed or debossed text can be in color that contrasts with the background. Please clarify what labeling information should be included in the overwrap; is it the same information as the Guidance recommends for the principal display panel (PDP). Please also consider overwrap recommendations in relationship to "green" packaging.
Lines: 203	"Information Crowding and Visual Clutter"	Please clarify whether the heading recommendation applies to carton or container labels or to both.

SECTION	ISSUE	PROPOSED CHANGE
Lines: 207-209	"Lines or blocks of text should be separated by sufficient white space to avoid crowding or clutter. We recommend placing less important information on a side or back panel of the container label and carton labeling, rather than on the PDP, or placing it, as appropriate, in the prescribing information."	Please clarify and provide examples of "sufficient white space", and "less important information."
Lines: 211-212	"Apart from required information about a product's manufacturer, distributor or packer (see § 201.1), information about business partnerships should not appear on the label or labeling."	Please clarify and provide examples of types of business partnership information which would not be acceptable.
Lines: 214-217	"The use of logos, bars, stripes, watermark graphics, lines, and symbols is discouraged on container labels and/or carton labeling because they can distract the reader from important information and add to label clutter. When such items are included, the graphic design should not compete with, interrupt, or distort important information."	BIO suggests that Guidance recognizes that the inclusion of such visual cues should be acceptable in situations where these cues can assist in highlighting important information. For example, for products with multiple strengths, it could be beneficial for a user to distinguish between dosage forms and strengths by use of color, graphics, and other visuals. Please clarify that the recommendation excludes labeling information included as part of anti-counterfeiting measures. Please revise the Guidance to recognize that there are required symbols, such as those relating to controlled substances.

SECTION	ISSUE	PROPOSED CHANGE
Line 228	"**nonproprietary**"	The term nonproprietary is bolded but not captured in the Glossary. Please either provide a definition or unbold.
Lines: 229-230	"Images should represent the actual tablet or capsule and reflect the true, size, color, and imprint. Schematic or computer-generated images should not be used."	Providing an image, whether computer-generated or an actual image of the drug product, provides clarity to users that they have the correct product and may help prevent medication errors. Actual size and image may not be feasible in all circumstances. Please clarify whether an image should not be used on a container label unless the image is an actual image and actual size.
Lines: 233-236	"Dangerous Abbreviations, Acronyms, and Symbols" "Certain abbreviations, acronyms, and symbols are dangerous and should not be used because they are frequently misinterpreted and can lead to mistakes that result in patient harm."	Please clarify whether the section applies to carton or container labels or to both. BIO also recommends striking the word "dangerous" in both the heading and the text, as abbreviations, acronyms, and symbols are not inherently dangerous; it is their misinterpretation that may be dangerous.
Lines: 242-247	"For these reasons, sponsors should avoid using error-prone abbreviations or symbols for product names, doses, and strength designations on container labels and carton labeling. We refer you to The Joint Commission's "Do Not Use" list, as well as the Institute for Safe Medication Practices (ISMP) List of Error Prone Abbreviations, Symbols, and Dose Designations for a list of commonly	Please clarify whether it is permissible to use abbreviations not otherwise recommended due to size constraints of a label, for example, a small container label with limited space. Please clarify whether it is acceptable if the small container label use abbreviations; whereas the carton and prescribing information spells out the term. Please clarify the scope in this section. Does it apply to all

SECTION	ISSUE	PROPOSED CHANGE
	confused abbreviations, symbols, and dose designations."	abbreviations listed in the ISMP or only the ones specified in the Guidance (e.g., mcg versus µg)? There are some abbreviations such as a slash symbol "/" versus the word "per" that is specified in the ISMP list; however, the product strength section of the Guidance provides examples that indicate this is acceptable (line 405, and 415).
E. AVOID LOOK-ALIKE CONTAINER LABELS AND CARTON LABELING		
Lines: Section E	Section III. E when read in its entirety and in conjunction with section III.A seems to imply that a Sponsor should not have a standard template design for its labels and that every label should be unique not only within a single Sponsor's product line, but also with other Sponsor's products.	Please clarify the Agency's position on labeling consistency. Consistency is helpful to find critical information without sacrificing the ability to discriminate error prone information such as dosage strength. Unique drug labels for every drug with the same dosage strength, established name, dosage form, expiration date, lot number, etc., may not serve the goal of medication error prevention.
Lines: 253-256	"Sponsors should create a container label and carton labeling design that is sufficiently distinct from that of their other products and the products of other manufacturers so that the end user is able to correctly identify, select, dispense, and administer the appropriate medication, strength, and dose."	Please also clarify the scope of "products of other manufacturers." Please provide guidance on how Sponsors can ensure that their carton/container labeling design is sufficiently distinct from products marketed by other Sponsors; is there a searchable database?
IV. SPECIAL CONSIDERATIONS AND RECOMMENDATIONS		
A. PROPRIETARY, ESTABLISHED, AND PROPER NAMES		
Lines: 328-334	"Sponsors should maximize the readability of proprietary, established, and proper names on the container label and carton	Please clarify that the use of upper case letters is not required on cartons or containers, but would be acceptable in the prescribing information. Per the *Guidance for*

SECTION	ISSUE	PROPOSED CHANGE
	labeling. We recommend capitalizing only the first letter in the proprietary name because words written in all-capital letters are less legible than words written in mixed case letters. Moreover, the established or proper name and proprietary name should be displayed in a manner consistent with the FDA regulations, taking into account all pertinent factors, including typography, layout, contrast, and other printing features (for drugs see 21 CFR 201.10(g)(2)); for biologic products see 21 CFR 610.62)."	*Industry, Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements*, the *Highlights Title and Limitation Statement* suggests the following: "We [FDA] recommend that the name of the drug product be presented in upper case letters to improve its prominence." To ensure consistency, BIO recommends that the trade/proprietary name be formatted the same in all labels/labeling.
Lines: 336-338	"The established name for drug products should include the finished dosage form. If space does not permit the finished dosage form to appear on the same line as the active ingredient, we recommend placing the finished dosage form on the next line below the active ingredient."	Please clarify the meaning of "finished dosage form" in the Guidance. Is it the form that needs to be available for administration or as it is present in the packaging (e.g., lyophilized powder requiring reconstitution)?
B. PRODUCT STRENGTH		
Lines: 401-406	"To avoid such confusion, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per milliliter enclosed by parenthesis. For example:	The example shown to represent the strength per total volume is: 500 mg/10mL (50 mg/mL). Please clarify whether the following presentation is also permissible: 50 mg/mL in 10 mL vial.

SECTION	ISSUE	PROPOSED CHANGE
	500mg/10mL (50 mg/mL)"	
Lines: 421-422	"Dry powder products should express the strength in terms of the total amount of drug per vial as follows: XX mg/vial or XX mg per vial"	Please clarify expression of strength when the total amount per vial is different than the total amount to be administered.
Lines: 426-430	"Instructions for reconstituting the product and the resultant concentration should be included on the vial, if space permits. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted. If space permits, information on the expiration date and post-reconstitution storage should also be included."	Please clarify that this section does not apply to products with weight-based dosing, as such dosing varies among patients and applying the section to such products may not be consistent with instructions for use.
Lines: 461-463	"The net quantity statement should appear on the PDP but should be separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)."	As there are cases, especially with injectable drug products, where the net quantity is an important factor in distinguishing between product configurations, please clarify that if the net quantity is a main distinguishing factor, it should be prominently displayed along with the strength.

SECTION	ISSUE	PROPOSED CHANGE
C. ROUTES OF ADMINISTRATION		
Lines: 479	"The route of administration should be described without abbreviation."	Please clarify whether the route of administration should be omitted or abbreviated if the full route of administration cannot be included on the container label, due to size restrictions or other complications.
D. WARNINGS FOR CRITICAL INFORMATION		
Lines: 488-489	"When warning statements are added to the container label or carton labeling, they should be written affirmatively."	BIO agrees with the Guidance's position on affirmative warning statements. We ask the Agency for clarification and provide specific examples of when negative statements are acceptable, such as in Lines 668 (information recommended for large volume parenterals) and 772 (child resistant information).
E. EXPIRATION DATES		
Lines: 495-507	"Accordingly, FDA recommends the expiration date be expressed in a standard format, using three-letter text for the month, two-digit numerals for the day (if included), and four-digit numeral for the year, as shown below: MMMYYYY (e.g., JAN2013) or MMMDDYYYY (e.g., JAN012013)"	The use of a standard date format ensures dates are unambiguous and clearly understood. However, the proposed format of Month, Day, Year (e.g., JAN 15, 2012) is divergent from the internationally recognized standard, ISO 8601, which established a common format for Year-Month-Day (e.g., 2012-01-15) or YEAR-MONTH (e.g., 2012-01) and the internationally recognized standard for in vitro diagnostic medical device labeling, ISO 18113-2, which apples ISO 8601. We recommend that the rule be amended to conform to the international ISO standard for date format.

SECTION	ISSUE	PROPOSED CHANGE
V. OTHER SPECIAL CONTAINER LABEL AND CARTON LABELING CONSIDERATIONS		
E. TRANSFERRABLE OR PEEL-OFF LABELS FOR INJECTABLE MEDICATIONS		
Lines: 709-720	"Currently, once an injectable medication is withdrawn from the commercial container closure (e.g., vial or ampule) into a syringe for administration, the syringe no longer provides information needed by the end user to verify the drug name and strength prior to administration. Such unlabeled medication has led to administration of the wrong drug and wrong strength. FDA recommends that sponsors develop, when possible, a transferable or peel-off label for the commercial container of injectable products. This type of label can help to minimize the use of unlabeled syringes because the label would be attached to the commercial container closure, present at the point of product preparation, and not be discarded as in the case with other auxiliary labels often provided with the carton."	Please clarify that the use of a peel-off label is voluntary as there is no guarantee the use of a peel-off label will prevent any medication errors. The use of a peel-off label may actually make the product more difficult to administer because the peel-off label may obscure the actual fill line for fill volume, potentially leading to medication errors. Please also clarify whether a similar peel-off transferable label should be used (voluntarily) for infusion products diluted in saline solution infusion bags. Please clarify whether the section applies to self-administered drug products as well as healthcare provider administered drug products.
H. COMMUNICATION OF IMPORTANT PRODUCT CHANGES		
LINES: 738-742	"Changes to marketed products such as new strengths or concentrations, or changes in formulation, or changes in certain inactive ingredients should be	Given the lead times needed for the development of packaging (carton labels, container labels and artwork) and implementation of updated versions of the prescribing information, this recommendation will prove extremely

SECTION	ISSUE	PROPOSED CHANGE
	communicated to health practitioners on the container label, if space permits, and on the carton labeling. For example, a change in product strength should be communicated as 'New Strength' or 'Note New Strength'. This statement should appear on the principal display panel for a period of 6 months."	challenging for Sponsors, straining production time and resources. We request that it be reconsidered.
K. PACKAGE TYPE		
LINES: 771-773	"In addition, when the product appears to be in a child-resistant container (e.g., unit-dose blister) but the container is NOT in fact child-resistant, it is important to include a statement on the label indicting the package is not child-resistant."	Please clarify that this information is not required for products solely administered by healthcare providers. Please clarify if such information, when required, is to be on the carton labeling.
GLOSSARY		
Lines: 863-864	"Tall Man Lettering: Tall man lettering involves highlighting the dissimilar letters in two names to aid in distinguishing between the two.[35]"	Please revise the definition to clarify that tall man lettering highlights dissimilar letters by using mixed case lettering.