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VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

PhRMA

June 30, 2008

Rogers L. Williams, MD
Executive Vice President – Chief Executive Officer
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852

RE: USP General Chapter <1> - Labeling on Ferrules and Cap Overseals

Dear Dr. Williams:

In accordance with the Rules and Procedures of the 2005-2010 Council of Experts, section 9.10, "Appeals", the Pharmaceutical Research and Manufacturers of America (PhRMA), requests an appeal to indefinitely postpone the newly added section "Labeling on Ferrules and Cap Overseals" in USP General Chapter <1> until a resolution can be reached among USP, the relevant Expert Committees, PhRMA, FDA, and other stakeholders, to achieve a mutually acceptable labeling strategy and timeline.

PhRMA is a voluntary, nonprofit association that represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. Member companies are leading the way in the search for new cures. In the past decade alone, PhRMA members invested approximately $300 billion to develop new medicines.

PhRMA objects to the following text in the labeling section of Chapter <1>: "...only cautionary statements are to appear on the top (circle) surface of the ferrule or cap overseal" and "Under no circumstances would advertising such as company names, logos, or product names be permitted to appear on the top (circle) surface of any ferrule or cap overseal..." Our four major areas of concerns with the aforementioned text of Chapter <1> are (1) the current implementation timeline, (2) lack of clarity on requirements for cautionary statements, (3) potential consequences to anti-counterfeiting strategies, and (4) regulatory impact. The historical and sustained commitment of PhRMA members to the patients and healthcare practitioners to provide safe and effective medicines of the highest quality possible, necessitates this appeal to the current text in Chapter <1>, which contrary to its intent, may in fact adversely affect patient safety.

I. Regulatory Timeline

The current implementation timeline is now unfeasible. The text of interest as currently published in USP 31 has an effective date of February 1, 2009. We understand that the labeling language in this chapter was first introduced in 2005 (USP 30, supplement 1) and hence has been in review for several years. However, since the first publication of this new information, there have been numerous additions, deletions, revisions, and supersedes to the text. There have also been discrepancies between the hardcopy version(s) and the website. The frequent changes have made the expectations and requirements difficult to interpret and planning for implementation an unrealistic goal. Implementing this type of change is a significant endeavor requiring global change controls and coordination of technical, manufacturing and regulatory resources. Without a clear and settled set of expectations and requirements, it would have been a futile effort to initiate an implementation plan. Accordingly, the implementation timeline is now unrealistic.

There are also other packaging requirements that will need to be considered when developing a plan to implement the proposed changes in Chapter <1>. For example, the proposed USP requirements will impact our ability to comply with California's first in nation electronic pedigree legislation, which requires the individual serialization of each drug product container, including injectable products. Many pharmaceutical companies have diligently planned for the implementation of this program. Additionally, the International Diabetes Federation (IDF) is working with manufacturers of insulin products to implement a universal color code for product packaging. This initiative is already underway and hence adds a considerable level of complexity for additional packaging changes. Repeated changes to product packaging lines could lead to confusion with patients and practitioners. This is counterproductive to the goal of reducing medication errors.

II. Lack of Clarity About Cautionary Statements

Secondly, there is a lack of clarity on expectations, use and standards for warnings and cautionary statements referred to in the aforementioned text of Chapter <1>. The current requirements are too vague and insufficiently defined for a public standard. Prioritization information is not available for injectable products that may meet multiple warning requirements (e.g. Warning, Dilute Before Using, Paralyzing Agent, I.M Use Only, etc.). For example, it is unclear which warning should take precedence when a compound is a neuromuscular blocking agent AND the monograph requires that "Dilute before Use" is displayed on the cap, as in the case of Potassium Chloride, for example. Additionally, for some products, it is very important to be able to clearly and easily differentiate between doses to prevent dosing mistakes, or to describe the proper storage conditions, which can impact stability. Displaying this information on the top of the ferrules is important as this may be all that is visible to the hospital pharmacist who is managing a tray of products. However, as per the new requirements, strength and storage conditions would not be allowed. The lack of a comprehensive, mandatory reference could lead to inconsistencies

in labeling between products and create confusion when warnings appear for some products and not for others, leading to potential medication errors.

III. Potential Consequences to Anti-Counterfeiting Strategies

Thirdly, the new labeling requirements may weaken industry's anti-counterfeiting strategies. The US based Centre for Medicines in the Public Interest predicts that counterfeit drug sales will reach US$ 75 billion globally in 2010, an increase of more than 90% from 2005. The consequences to public health and safety are enormous, ranging from therapeutic failure, to allergic reactions, and even death. The current language in Chapter <1> allows only cautionary statements to appear on the top of the ferrule or cap overseals, meaning that any company names or logos would have to be removed. Manufacturers are using a multi faceted approach to deter counterfeiting tactics, and one successful method has been to develop a unique or complex packaging design as this feature aids in the confirmation of legitimate drug supply and can increase the packaging cost burden to counterfeiters. Logos and/or company names on the ferrules or cap overseals are examples of a unique packaging design and can be successful against a popular counterfeiting technique involving re-using discarded vials to fill with counterfeit product. It is cheap and easy to obtain ferrules and cap overseals, however, it is more difficult to produce a cap with a specific logo. We believe that disallowing the option to design drug product packaging with distinctive features on the ferrules or caps is not in the best interest of public health in the long run as it would decrease our ability to raise visibility of potential counterfeits products and limit our ability to combat the counterfeiters. Additionally, logos and or company names appearing in the same color as the cap would not interfere with the cautionary statements as Chapter <1> requires cautionary information to be in "contrasting color and conspicuous under ordinary conditions of use."

IV Regulatory Impact

Lastly, the regulatory impact of classifying these warnings as labeling must be considered. A technical and regulatory assessment is needed that includes any conflict or overlap with current FDA labeling requirements, evaluation of technical capabilities (font sizes and what is legible on different size caps), any language considerations (for example, Puerto Rico requires Spanish and English for labeling, but will this also be required for the cautionary statements?), and what injectable products are in scope or out of scope.

We believe that USP is committed to ensuring that the patient receives the highest quality medicines. In an effort to support this goal, PhRMA looks forward to USP's response to this appeal and USP's engagement in dialogue with the relevant stakeholders to achieve a resolution to the issues put forth regarding the labeling text in Chapter <1> and the implementation timeline.

Please contact me by e-mail at atill@phrma.org or by phone at (202)835-3564 for questions or to set up an appropriate meeting time for further discussion.

Sincerely yours,

Alice E. Till

Alice E. Till, Ph.D.