Frequently Asked Questions
General Chapter <1> *Injections*, Section on Labeling on Ferrules and Cap Overseals
August 4, 2010

USP and its Standards

1. What is USP?

The United States Pharmacopeial Convention (USP) is a nonprofit scientific organization founded in Washington, D.C., in 1820 that develops and disseminates public standards for medicines and other articles (Bylaws, Article II). USP's mission is "to improve the health of people around the world through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods." Standards for an article recognized in a USP compendium are expressed in the article's monograph and applicable general chapters (such as General Chapter <1> *Injections*). USP monographs and general chapters typically include standards for the identity, as well as the strength, quality and purity of medicines, food ingredients, and dietary supplement products and ingredients. They also may include standards for packaging and labeling. USP's primary compendia of standards are the *United States Pharmacopeia* and the *National Formulary* (*USP-NF*).

2. What is the role of USP standards in federal law?

Congress has consistently provided a role for USP standards in the adulteration and misbranding provisions of successive federal food and drug legislation, beginning with the Pure Food and Drugs act of 1906. Since adoption of the modern Federal Food, Drug, and Cosmetic Act (FDCA) in 1938, both compendia prepared by USP (*USP* and *NF*) have been recognized as "official compendia" (FDCA 201(j)). Under Federal law, a drug with a name recognized in *USP-NF* must comply with compendial identity standards, or be deemed adulterated, misbranded, or both (FDCA 501(b) and 502(e)(3)(b); FDA regulations 21 CFR 299.5(a&b)). To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs (FDCA 501(b); 21 CFR 299.5(c)). In addition, of particular relevance to the ferrules and cap overseals labeling standard, to avoid being deemed misbranded, drugs recognized in *USP-NF* must also be packaged and labeled in compliance with compendial standards (FDCA 502(g)).

USP has no role in enforcement of its standards. Enforcement of USP standards is the responsibility of FDA and other government authorities in the U.S. and elsewhere.

3. What labeling requirements does USP establish?

Consistent with its mission and governing authority, USP establishes standards for articles recognized in *USP-NF*, which are expressed in an article's monograph, applicable general chapters, or the General Notices (see GN 3.10). Specifically regarding labeling, USP General Notices has a section devoted exclusively to the subject of labeling (see GN 10.40 Labeling; "Articles in these compendia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the compendial requirements set forth for the articles."). Like other compendial requirements, labeling requirements may be contained in individual monographs or, like these revisions to General Chapter <1> *Injections*, in general chapters that are applicable to multiple products.

The new ferrules and cap overseals labeling standard is consistent with prior standards established by USP, where for example particular monographs have long contained “Labeling” requirements, including requirements not unlike those involved here. See, for example, the monograph for Potassium Chloride for Injection Concentrate, which has a “Labeling” section that includes a requirement that “The cap of the container and the overseal of the cap must be black, and both bear the words: ‘Must Be Diluted’ in readily legible type, in a color that stands out from its background OR . . . .” While requirements such as this are specific to individual products, the new standard is intended to address safety issues more broadly among injectable products.

THE STANDARD

4. What are Ferrules and Cap Overseals?

Injectable product containers are designed to hold a drug product in a closed, sterile environment, and allow a needle entry through an elastomeric closure (or stopper) to remove the medication. The stopper is connected to the vial by a metal or plastic wrap, which is called the "ferrule." Over the ferrule and stopper, there is a disc, typically plastic, that protects the stopper; this is called the "cap overseal." In order to administer an injectable product, a practitioner must remove the cap overseal, wipe the stopper with an alcohol swab, and then insert a needle through the stopper, which sits inside the ring of the ferrule.

5. What USP Expert Committee is responsible for developing and approving this standard?

The voting Expert Committee for this standard was the Nomenclature Expert Committee comprising independent experts from a variety of backgrounds including healthcare practitioners (physicians, pharmacists, and nurses), safety experts, nomenclature experts, and the pharmaceutical industry. In addition, three additional USP Expert Committees in the 2005-2010 cycle (Packaging and Storage, Parenteral Products—Industrial, and Safe Medication Use) were involved with the development of the standard. FDA representatives serve as non-voting liaisons to these and other USP Expert Committees.

6. How did USP develop this standard?

USP Expert Committees and staff have been engaged in evaluating the evolving scientific literature, reviewing U.S. medication error reporting databases (MEDMARX and the USP-ISMP Medication Error Reporting Program), facilitating U.S. stakeholder meetings, and routinely consulting with the Food and Drug Administration (FDA) regarding this issue. USP standards are in a process of continuous review and revision based upon new evidence, emerging public health concerns, and public requests for revision. The ongoing role of USP Expert Committees is to evaluate new data and to shape standards based upon the available evidence, public input and the Expert Committee’s expertise.

7. Has FDA been involved in setting this standard?

FDA has been consistently involved in developing and reviewing this standard beginning in 1991 with the USP-FDA Joint Advisory Panel on Simplification and Improvement of Injection Labeling. Several agency representatives serve as FDA Liaisons to the Nomenclature Expert Committee and have participated in the discussions and dialog on the matter. FDA representatives, however, do not vote as members of USP Expert Committees.

8. Is USP trying to limit patient safety information?

No. The USP standard is designed to help ensure the visibility of the most critical safety messages (those intended to prevent imminent life-threatening situations) by reducing

nonessential text. Thus, products that do not require such messages should be free of information so that those containing such messages are immediately apparent. In addition, the standard applies only to ferrules and cap overseals, and permits other types of safety information to appear elsewhere.

9. How are anticounterfeiting mechanisms impacted by this standard?

The USP Nomenclature Expert Committee considers anticounterfeiting issues important to overall patient safety, and recognizes there are many mechanisms for ensuring product accountability, which involve technologies and approaches other than labeling ferrules and cap overseals.

STANDARDS-SETTING AND EXPERT COMMITTEE PROCESS

10. How does a USP standard become official?

The USP standards-setting process enables anyone to bring a standards-setting issue to the attention of USP. Once a standard is developed, it is proposed for 90-day public review and comment period in the *Pharmacopeial Forum* (*PF*). After the public review and comment period, the Expert Committee considers the comments received and determines whether further changes to the standard should be made. A proposal published in *PF* for comment is generally not reprinted in *PF* for additional comment prior to publication in the *USP* or the *NF* unless the Expert Committee or the Council of Experts Chairperson determines that reprinting is necessary due to the nature or significance of the comments received or changes made to the proposal.

To finalize the standard, the Expert Committee members vote on the proposal through an electronic balloting system where they vote independently. A quorum of members (at least 51%) is required, and a majority of yes votes (51% of those voting) is required for a standard to be adopted. Expert Committee members are held to strict conflict of interest provisions, and must abstain from voting if they have a real or perceived conflict of interest as defined in USP's governing documents.

IMPLEMENTATION OF THE STANDARD

11. When will this standard become official?

The standard will become official on December 1, 2013. Normally, new standards become official (requiring compliance) six months after publication of final approved text. In this case, however, the Expert Committee has established a delayed official date, which is in keeping with General Chapter <1121> *Nomenclature* for title and labeling changes for products that involve multiple companies.

12. How should manufacturers work with the FDA to implement the standard?

Manufacturers have until 2013 to comply with the standard. According to the FDA, if manufacturers believe they need to include a cautionary statement about an imminent life threatening situation on the ferrule or cap overseal of their product, manufacturers will need to provide a rationale to FDA for why the situation addressed in the statement is considered to be life threatening. In addition, FDA will expect manufacturers to provide data to support that the statement is safe, unambiguous, and provides the best message to minimize the life threatening situation.

13. What current statements on ferrules and cap overseals will be prohibited by implementation of the standard?

The following are examples of statements or information that will be prohibited on ferrules and cap overseals (note: any of these items may still be able to appear on the label or the side of the ferrule):

- "Flip Off"
- Trade name of product
- Company logo
- Company name

14. Could the dosage strength of a specific medication be printed on the ferrule or cap overseals? A statement reflecting potency (dose) may be included on the ferrule or cap overseal if it meets the requirements of the standard.

15. Are there processes for appealing or delaying this standard?

There are two mechanisms provided in the Rules and Procedures of the Council of Experts, postponement and appeals.

Postponement: Anyone may file a postponement request, with a statement of grounds. The Expert Committee that adopted the standard has authority to postpone the official date subject to review and approval by the Chairperson of the Council of Experts (and referral to the USP Executive Committee). A request for postponement received within 30 days of the official date may be refused as untimely (in which case it would be considered a Request for Revision).

Appeal: There is provision for the Executive Committee of the Council of Experts to receive and rule upon all appeals for reconsideration, revision, or abrogation of standards adopted by an Expert Committee (Bylaws Article VII, Section 6). A standard may be appealed only up to 30 days prior to its official date.