U.S. Pharmacopeia
The Standard of Quality℠

General Chapter <1> *Injections – Labeling on Ferrules and Overseals*
Webcast
Friday, June 27, 2008
9:00 a.m. to 11:00 a.m., EDT

Notes

Attendees—see last page

1. Welcome and Introductions
Angela Long welcomed attendees from both industry and the FDA to the web meeting on General Chapter <1> *Injections*—Labeling on Ferrules and Overseals. She indicated that this was a special topic meeting of the Prescription/Nonprescription Stakeholder Forum (PNP SF), and that attendees at this meeting are serving as representatives of one of 12 trade organizations that have membership in the PNP SF. At this meeting, there were nearly 50 attendees representing six PNP SF groups, the FDA, an invited manufacturer (West Pharmaceuticals), an Expert Committee member (Scott Messner) and USP staff. Ms. Long indicated that three Expert Committees are involved in this topic, Parenteral Products—Industrial, Nomenclature, and Safe Medication Use. She noted that Expert Committee members are not participating in this call, but the liaisons for each of those Expert Committees are participating.

Gina Trimble added that this topic was originally targeted to be on the agenda for the May 2008 PNP SF, but that an already full agenda and a desire to experiment with a topic-specific web meeting led to this approach for the meeting.

2. USP Activities Related to Chapter <1> Labeling and Packaging Sections
Dr. Darrell Abernethy, USP's Chief Science Officer, presented USP's activities related to General Chapter <1> Labeling and Packaging sections. He indicated that USP began activities in this area in 1991 with a joint FDA-USP Advisory Panel on Simplification and Improvement of Injection Labeling. These activities led to a report and *Stimuli* article**.** Historical Data (1997) suggested major concern with need for visibility of warnings on caps was based on overcrowding of injectable labels. At about the same time, deaths involving the misadministration of Potassium Chloride Injection prompted USP to revise the monograph labeling to require a black cap and overseal with a cautionary statement ("Must Be Diluted"). The new standard also included a new name (Potassium Chloride for Injection Concentrate) and a boxed label warning. In 2003, USP added these packaging requirements to General Chapter <1>. In 2004 USP added packaging requirements including cautionary statement for Neuromuscular Blocking Agents. And in 2006, USP added the requirement for "only" cautionary statements to appear on the caps and overseals of injectable products, with a delayed official date of February 2009.

Dr. Abernethy indicated that recent activity included a proposal in *Pharmacopeial Forum* (*PF*) 33(3) that was later canceled because references to anti-counterfeiting features are premature until the committees have a better understanding of the various anti-counterfeiting options. He emphasized that all three Expert Committees with an interest in this standard voted to keep the wording of the chapter as currently published in *USP 31-NF 26*.

He also announced that the Parenteral Products—Industrial Expert Committee has voted to postpone the official date of the Labeling section's official date in the General Chapter by one year to allow industry more time to implement the standard, and that the final approval must be granted by the Chair of the Council of Experts.

He concluded by indicating that the USP Executive Committee recently has adopted an Anticounterfeiting Statement that indicates that all requests for incorporation of anti-counterfeiting measures in USP's standards-setting activities should be referred to the Council of Experts Executive Committee for discussion and, as appropriate, action. This statement is posted on the USP website in the "USP-NF Notices" area.

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Dr. Abernethy asked the FDA to provide comments and Mr. Larry Ouderkirk indicated the following:

- There are many FDA participants on the call, showing the significance of the topic to FDA.
- FDA has deliberated internally on the topic and is in support of the restriction to cautionary statements only on the top of injection caps and overseals. Logos are not appropriate on the tops of such vials. The reason is patient safety.
- While FDA is in support of anti-counterfeiting measure in general, these measures should be placed in other areas than on the vial top unless invisible to the unaided eye.
- He again emphasized that FDA is in support of the language as currently written in General Chapter <1> in *USP 31-NF 26.*
- He further indicated that FDA has no comment on the timing of making the standard official.

3. General Chapter <1> *Injections – Labeling on Ferrules and Overseals Industry Perspectives*

Mr. Sam Azer presented the PhRMA perspective on the topic. He indicated that PhRMA companies are concerned about patient safety but are uncertain that the current approach is best given other patient safety concerns that are unaddressed and impeded by the current focus (including anti-counterfeiting efforts by industry to assure that practitioner have better assurances of the legitimate origin of products being administered). The overarching desire of PhRMA groups is to have less restrictive language in the General Chapter. He indicated other issues include:

- Implementation timing
- The number and type of cautionary statements allowed and/or required is not clearly defined.
- The term "labeling" and its appropriateness for these packaging standards (labeling has specific expectations by the FDA while "information" does not)
- A suggestion for USP to host a meeting of practitioners to determine how they rely on cap notices.
- A suggestion that USP consider less restrictive language than currently defined to allow manufacturers (working with regulatory authorities) the ability to respond to specific identified patient safety concerns in an appropriate and timely manner.
- A suggestion that USP apply the cautionary language to only specific monographs, not globally to all products through a General Chapter.
- Impact on both domestic and global registrations be given greater consideration

Ms. Debbie Thomas of West Pharmaceuticals presented a packaging manufacturer's perspective on the topic, in which she too calls for less restrictive language in the General Chapter. West's concerns include the following:

- There is ambiguity in the language regarding cautionary statements and clarification is necessary
- Many current caps and overseals include dosing information or product handling information. West indicated that this is a "second layer of protection" after the drug label, which must be read by practitioners.
- The authentication of products also is important in cap technology, and RFID often is included in the caps, although there is no current infrastructure for RFID to be used globally.
- A universal cautionary cap design could include an exclamation point in a triangle printed on a yellow cap.
- An extended implementation timing is key as It can take 26 weeks to retool cap processes for one product.

Ed Smith of the Packaging Science Interest group of PDA also presented slides on the topic, which echoed concerns already provided by previous speakers.

4. Discussion

Discussion of the following topics continued after the presentations were given.

- Timing: implementation
    - A round table poll of participants indicated that most industry groups were in support of the extension of the official date by 12 months to 2010.
        - GPhA is in support of the delay.
        - NJPQCA indicated that regulatory approvals for Prior Approval Supplements can take six months and therefore the revision should be postponed. They also encouraged USP to reconsider the cautionary language to set a clear standard.
        - Midwest cannot comment but will take it back to the group.

- PDA supports the delay but prefers that a change in the language be considered and that USP take into consideration filings around the world.
- PhRMA indicated that a delay is appropriate and also pointed out that products in development at the Pre-NDA stage also will be affected. Exact timeline needed for implementation is not certain (minimum of 12 month delay is needed. PhRMA representatives requested additional dialogue prior to defining the length of the postponement.
- West indicated that because the retooling can take up to 26 weeks that 12 months is not enough time, and that they cannot talk about implementation until there is clarity of what they are implementing.
- FDA indicated that the definition of a cautionary statement is a statement that is "intended to prevent imminent and life threatening situations."
- FDA clarified the definition of "labeling," indicating that the FDCA [Sec. 201(m)] defines it as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." The FDCA [Sec. 201(k)] defines "label" as a "display of written, printed, or graphic matter upon the immediate container of any article…."
- USP indicated that it is working on defining the cautionary statements and that industry participation is welcome in this activity.
- E-pedigree requirements of California as well as the Kennedy and Dingell legislation were brought up as additional discussions on-going and space limitations for inclusion of all pertinent information on injectable products.
- A PhRMA representative indicated that industry often ships product unlabeled to other countries and the inability to print additional information on the overseal and/or ferrule (such as the product's Trade name, dose information, etc) adds complexity to managing inventory.
- FDA clarified that the cautionary statements are not limited to only the ones listed as examples in the chapter, but there may be others as decided on a "case-by-case" basis.
- Industry would like greater clarity on cautionary statement use and has concerns with the individual approvals by the FDA being determined on a case-by-case basis.
- FDA asked for industry to supply data that informs the agency of the products and the specific cap and overseal labeling.
- The word "only" is limiting.
- FDA indicated that the purpose of the standard is to restrict use of cap printing to only cautionary statements so that the health care practitioner is more likely to read the cautionary statement.
- FDA indicated that filing of most changes **involving deletion** of information to cap labeling to comply with the revised General Chapter <1> can likely be made by Annual Report.
- Industry expressed concern about the filing expectations and determination of cautionary statements needed on products that currently do not have them on the ferrules and overseals.
- Industry voiced concerns on interpretation of the caps and overseals as "labeling" and requested further guidance on topics such as labeling inspection and reconciliation expectations.
- The agency revisited the concerns raised by industry and examples of current overseal uses prior to the conclusion of the meeting and expressed a need to have further dialogue with both industry and USP on the cautionary statements.

5. Next Steps

- Industry to submit data on existing cap statements to USP and the FDA.
- USP and FDA to review data submitted to try to come up with a general list of cautionary statements applicable to the caps and overseals, if feasible. USP also to work with industry and West on these statements.
- USP to inform industry about the timing of the postponement.

Ms. Trimble thanked USP, FDA and the Stakeholders for participation in the meeting and expressed industry's desire to remain engaged with on-going discussions and action items related to this topic. Dr. Abernethy thanked participants for their very helpful comments. He emphasized that members of industry should not contact Expert Committee members on this topic (or any topics) but should continue to work through staff. In this case, Ms. Long is the point of contact since it has elevated to an industry-wide topic. Ms. Long indicated that USP would be in touch with Larry Ouderkirk of FDA and Gina Trimble of PhRMA to execute the action Items.

Attendees

GPhA

1. Laurel Benyo, Ben Venue Labs
2. Elizabeth Gasparac, Hospira
3. Gordon Johnston, GPhA
4. Cathleen Richesson, Ben Venue Labs
5. Richard Stec, Hospira

Midwest Compendial Discussion Group

6. Bruce Hastings, GSK
7. Phil Travis, Pfizer

NJPQCA

8. Joe Albanese, Centecor
9. Barbara Ferguson, Schering Plough
10. Tony Robertson, Packaging Science and Device Technology
11. Larry Starke, Organon USA, Inc.

PDA

12. Janeen Skutnik, Pfizer
13. Chris Smalley, Wyeth
14. Ed Smith, Pharmaceutical Packaging Consulting and Training

PhRMA

15. Sameh Azer, J&J
16. Jill Arent, Wyeth
17. Heather Crandall, Wyeth
18. Edward Dzwill, J&J
19. Joe Garber, AstraZeneca
20. Ron Guido, J&J
21. James Murphy, Wyeth
22. Jim Pierantozzi, Wyeth
23. Eli Lilly representatives
24. Jonathan Smollen, Wyeth
25. Gina Trimble, Wyeth
26. Luciano Virgili, BMS
27. Mark Wiggins, Merck

Invited Industry Participants

28. Carol Mooney, West Pharmaceuticals
29. Debbie Thomas, West Pharmaceuticals

FDA

30. Ilisa Bernstein (OPPL)
31. Janice Brown (ONDQA)
32. Jennifer Devine (OC)
33. Carol Holquist, OSE
34. Kay Kim, CDER/FDA
35. Steve Langille, OPS
36. Yana Mille, CDER
37. Larry Ouderkirk, CDER

USP Expert Committee Members

38. Scott C. Messner, Monograph Development: Antivirals and Antimicrobials

USP STAFF

39. Darrell Abernethy, M.D., Ph.D., Chief Science Officer
40. Colleen Brennan, Manager, Safe Medication Use Expert Committee
41. Todd Cecil, Ph.D., Vice President, Compendial Sciences
42. Anthony DeStefano, Ph.D., Vice President, General Chapters
43. Desmond G. Hunt, Ph.D., Scientist
44. Helen Kharab, Project Manager, Volunteer and Organizational Affairs
45. Angela G. Long, Vice President, Volunteer and Organizational Affairs
46. Andrzei Wilk, Ph.D., Senior Scientist