

# PHARMACOPEIAL FORUM

**35**

**NUMBER 4**

**BIMONTHLY: July-August 2009**

## **Featured in This Issue**

USP has identified the following content areas in the July-August 2009 issue of *Pharmacopeial Forum* as noteworthy for the pharmaceutical industry worldwide.

Interim Revision Announcements Pertaining to *USP 32-NF 27*  
(Official August 1, 2009)

- Hawthorn Leaf with Flower
- Powdered Hawthorn Leaf with Flower

## **Stimuli Articles**

- Co-processed Excipients
- Liquid-filled Gelatin Capsules

A detailed listing of the Table of Contents of the July-August issues of *Pharmacopeial Forum* follows



U.S. PHARMACOPEIA  
The Standard of Quality<sup>SM</sup>

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**USP ANNOUNCES REVISION TO HAWTHORN MONOGRAPHS.** The Dietary Supplements—Information Expert Committee has approved the deletion of the cautionary statement in the *Hawthorn Leaf with Flower* and the *Powdered Hawthorn Leaf with Flower* monographs. These monographs were previously printed as proposed *Interim Revision Announcements* in *Pharmacopeial Forum*, PF 34(5) [Sept.–Oct. 2008.] The approved *Interim Revision Announcements*, which appear elsewhere in this issue of *PF* and will become official on August 1, 2009, will supersede the monographs as presented in *USP 32–NF 27* until the revised versions of the monographs are published in *USP 33–NF 28*, which will be released November 1, 2009 and will become official on May 1, 2010.

The revisions to cautionary statements in *Dietary Supplements* are further clarified in the Compendial Notices announcement “USP Revises Admission Criteria and Safety Classification for Dietary Supplements,” which is posted on USP’s website. The Compendial Notices announcement also describes the cautionary statement revisions that apply to the *Green Tea Extract* monograph.

For further information on the Hawthorn monographs, contact Dandapantula Sarma, Ph.D., at 301-816-8354 or [dns@usp.org](mailto:dns@usp.org).

**USP ISSUES CALL FOR CANDIDATES FOR 2010–2015 COUNCIL OF EXPERTS, ITS EXPERT COMMITTEES, AND ITS EXPERT PANELS.** In accordance with the Bylaws of the USP Convention, USP is issuing a Call for Candidates for the 2010–2015 Council of Experts (COE). The 2010–2015 COE includes Expert Committees in the areas of Nomenclature, Small Molecules, Biologics and Biotechnology, Excipients, General Chapters, Reference Standards, Compounding, Food Ingredients, and Dietary Supplements. In the 2010–2015 cycle, USP is expanding the number of Expert Panels that report to Expert Committees.

These Expert Committees and Panels align with the new USP Strategic Plan, which focuses on expanding and enhancing USP’s core compendial and standards-setting activities. The ability to add Expert Panels according to USP’s needs introduces flexibility and scalability into USP’s activities. USP plans to continue to attract a global base of experts and therefore encourages any qualified individual to apply. Importantly, this approach also en-

ables USP to closely align its documentary and reference standards activities for a more efficient standards-setting process.

Specific Expert Committees and Expert Panels for which USP is seeking candidates are listed at USP’s nominations Web site ([www.usp.org/goto/nominate](http://www.usp.org/goto/nominate)). The deadline for applications for the COE (Expert Committee Chairs) is **December 31, 2009**. The deadline for applications for Expert Committee members is **May 15, 2010**. Recruitment for Expert Panel members will begin in July 2010 and will be continuous.

For further information, please contact Nelufar Mohajeri, Director, Volunteer Affairs and Compendial Initiatives ([nym@usp.org](mailto:nym@usp.org) or [nominate@usp.org](mailto:nominate@usp.org)).

**USP POSTS COMMENTARY TO INTERIM REVISION ANNOUNCEMENTS ON THE USP WEB SITE.** In order to maintain transparency for revisions made to proposed *Interim Revision Announcements* that become official in the *Pharmacopeial Forum*, USP posts commentary for the proposed *Interim Revision Announcements* on the *Revisions and Commentary* web page on the date that the official standard is released in *Pharmacopeial Forum*. Note that commentary to *In-Process Revisions* is posted on the *Revisions and Commentary* web page under the final book or supplement where the official standard appears.

*Commentary* is not part of the official text of the monograph and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of the Expert Committee’s response to public comments. If there is a difference between the contents of the *Commentary* section and the official monograph, the text of the official monograph prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the *Commentary* section, shall prevail.

**PHARMACOPEIAL FORUM PUBLIC REVIEW AND COMMENT PERIOD DEADLINES.** The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. In accordance with the Rules and Procedures of the 2005–2010 Council of Experts, USP has implemented a 90-day comment period by providing a deadline for each issue of *PF* unless otherwise stated in the individual briefing. The listing of comment period deadlines and the targeted official publications appears below.

Pharmacopeial Forum	Comment Deadline	Targeted Official Publication	Release Date	Official Date
PF 35(2)	June 15, 2009	USP 33–NF 28 1st Supplement	February 2010	August 1, 2010
PF 35(3)	August 15, 2009			
PF 35(4)	October 15, 2009	USP 33–NF 28 2nd Supplement	June 2010	December 1, 2010
PF 35(5)	December 15, 2009			
PF 35(6)	February 15, 2010	USP 34–NF 29	November 2010	May 1, 2011
PF 36(1)	March 31, 2010			

All official revisions are published in the annual edition or *Supplements* to USP–NF (twice yearly). Between these publications, official revisions are published in PF in the *Interim Revision Announcement* section and incorporated in the upcoming USP–NF or *Supplement*. They may also be published as *Revision Bulletins* on www.usp.org in the “New Official Text” section. The official publication in which an *Interim Revision Announcement* (IRA) is incor-

porated will depend upon publication deadlines. See the table below. The electronic version of USP–NF is updated as each *Supplement* becomes available and, therefore, contains all official text up to and including the contents of the latest *Supplement*. The table below outlines the publications and their release and official dates, and the USP–NF or *Supplement* that supersedes them.

### Publication Schedules

Publication	Release Date	Official Date	Superseded by
USP 32–NF 27	November 1, 2008	May 1, 2009	1st Supplement to USP 32–NF 27
IRA [PF 35(1)]	January 1, 2009	February 1, 2009	2nd Supplement to USP 32–NF 27
1st Supplement to USP 32–NF 27	February 1, 2009	August 1, 2009	2nd Supplement to USP 32–NF 27
IRA [PF 35(2)]	March 1, 2009	April 1, 2009	2nd Supplement to USP 32–NF 27
IRA [PF 35(3)]	May 1, 2009	June 1, 2009	USP 33–NF 28
2nd Supplement to USP 32–NF 27	June 1, 2009	December 1, 2009	USP 33–NF 28
IRA [PF 35(4)]	July 1, 2009	August 1, 2009	1st Supplement to USP 33–NF 28
IRA [PF 35(5)]	September 1, 2009	October 1, 2009	1st Supplement to USP 33–NF 28
IRA [PF 35(6)]	November 1, 2009	December 1, 2009	2nd Supplement to USP 33–NF 28
USP 33–NF 28	November 1, 2009	May 1, 2010	1st Supplement to USP 33–NF 28

**PRIORITY NEW MONOGRAPH ITEMS.** USP is seeking monographs for the following drug substances and drug products that are, or soon will be, off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monographs are marked “Received” upon receipt of a monograph proposal. Received monographs are removed from this list upon publication in *Pharmacopeial Forum* or when posted in the *USP Pending Monographs* section of the USP website

(<http://www.usp.org/standards/pending/>). This list has been updated as of April 15, 2009; monographs received since the last update to the list are noted in bold.

Monograph sponsors should consult USP’s Guideline for Submitting Requests for Revision to the USP–NF at <http://www.usp.org/USPNF/submitMonograph/subGuide.html>.

For additional information, contact Karen A. Russo, Ph.D., [kar@usp.org](mailto:kar@usp.org).

### Small Molecules (Drug Substances)—As of April 15, 2009

1. Allopurinol Sodium	2. Aminopropazine Fumarate	3. Aminopterin Sodium
4. Anagrelide Hydrochloride <b>(Received)</b>	5. Arsenic Trioxide	6. Auranofin
7. Azelaic Acid <b>(Received)</b>	8. Bentoquatam	9. Benzphetamine Hydrochloride
10. Bivalirudin <b>(Received)</b>	11. Calcipotriene	12. Calcium Trisodium Pentetate
13. Calfactant	14. Candesartan Cilexetil <b>(Received)</b>	15. Ceftibuten
16. Cetorelix	17. Cevimeline Hydrochloride <b>(Received)</b>	18. Chloroxine
19. Choline Salicylate	20. Cysteamine Bitartrate	21. Dalfopristin

## INSTRUCTIONS TO AUTHORS

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously in any language or medium and that they are not simultaneously under consideration by any other publication.

All manuscripts are subject to review by USP headquarters staff, Committee members, or qualified outside referees, and if accepted for publication they will be subject to editing by USP staff. Accepted manuscripts become the property of the USP Convention (USPC) and may not be subsequently published elsewhere without written permission from the USPC. Authors are also responsible for obtaining permission for reprinting any illustrations that have been published elsewhere.

**Abstract**—Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.

**Style and Usage**—*Stimuli* articles generally follow the current *Chicago Manual of Style* except in scientific usage (numbers, abbreviations, etc.). For the latter, authors should use the current *AMA Manual of Style* or the current *ACS Style Guide*. Authors may usefully consult a current copy of *Pharmacopeial Forum*.

**References**—Consult the current *AMA Manual of Style*, which is generally consistent with the National Library of Medicine's *Recommended Formats for Bibliographic Citation*. A current copy of *Pharmacopeial Forum* will offer examples of reference formats.

**Copyright**—Copyright transfer documents will be sent to authors after manuscripts have been accepted for publication.

**Contact Person**—USP will designate a Scientific Liaison in the Documentary Standards Division as the corresponding author. This ensures that USP receives all comments generated by the *Stimuli* article. Authors should contact the Scientific Liaison if they would like to receive copies of comments generated by their *Stimuli* articles.

**Submission Instructions**—Manuscripts must be submitted both as an electronic file and as a printed copy of the electronic file. Submit the text in Microsoft® Word or another current word-processing application. The preferred format for graphics submitted electronically is tagged image file format (TIFF). Photocopies are not acceptable. Manuscripts submitted for publication should be addressed to:

*Pharmacopeial Forum*  
Executive Secretariat, USP  
12601 Twinbrook Pkwy.  
Rockville, MD 20852

## Co-processed Excipients

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**ABSTRACT** This *Stimuli* article summarizes the thinking of the USP Excipient Monographs 2 Expert Committee and USP staff regarding a class of excipients—collectively labeled *co-processed excipients*—that have been and continue to be introduced into the *National Formulary (NF)*. This article presents some suggested criteria for acceptance of such monograph proposals into *NF* and solicits public input.

### INTRODUCTION

In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. In response to these deficiencies, drug formulation scientists have relied on increasing numbers of combination excipients introduced by excipient manufacturers into the commercial market. Combination excipients fall into two broad categories: physical mixtures and co-processed excipients.

Physical mixtures, as the name suggests, are simple admixtures of two or more excipients typically produced by short duration low-shear processing. They may be either liquids or solids and are generally used for convenience rather than for facilitating the manufacturing process or improving the resultant pharmaceutical product. Examples of such physical mixtures include immediate-release film coating powders for dispersion that reduce the time required to prepare film coating suspensions and to minimize color variation of the final product. Such physical mixtures are not appropriate for consideration for *National Formulary (NF)* monographs because the individual components are isolated (distinct and intact) before mixing; i.e., the manufacturing process of each of the individual components has been taken to completion, and consequently these components can be adequately controlled before mixing.

Co-processed excipients are combinations of two or more excipients that possess performance advantages that cannot be achieved using a physical admixture of the same combination of excipients. Typically they are produced using some form of specialized manufacturing process. The performance benefits relate to the manufacture or performance of the finished pharmaceutical product. This improvement in performance has been a primary driver for the introduction of co-processed excipients into the marketplace. Co-processed excipients

are appropriate for consideration as new monographs because one or more of the components may be formed in situ, or the component may not be isolated prior to co-processing. That is, the manufacturing process for one component may not have been taken to completion before the addition of the other components, and/or the co-processed excipient combination cannot be adequately controlled using the monograph tests for the individual component excipients.

Because many co-processed excipients contain a macromolecular excipient as one of the constituents, responsibility for reviewing these monographs and recommending them for inclusion in *NF* falls within the purview of the EM2 Expert Committee, one of three Expert Committees that set excipient standards for *NF* in USP's Council of Experts.<sup>d</sup> Recently there has been increased interest in *NF* monographs for co-processed excipients. The Expert Committee is therefore addressing the more general question of compendial acceptance of these types of excipients. To this end the EM2 Expert Committee believes that guidelines for the acceptance of monograph proposals for co-processed excipients would be useful.

### CURRENT STATUS OF CO-PROCESSED EXCIPIENT MONOGRAPHS IN *NF*

During the past 20 years, several monographs, each of which presents a co-processed combination of existing excipients, have appeared in *NF*. These excipients may be either liquids or solids. *Table 1* lists several examples of co-processed excipient combinations included in *NF 27 (2009)*. The co-processed excipient monographs listed in *Table 1* meet current *NF* submission requirements as defined by the following: Each of them is either included in an approved drug application (in the FDA inactive ingredient database) or has a Generally Recognized as Safe (GRAS) designation.

<sup>a</sup> Excipient Monographs 2 Expert Committee. Lawrence H. Block is the chair, and Richard C. Moreton is the vice chair.

<sup>b</sup> Director, Excipients, USP.

<sup>c</sup> Correspondence should be addressed to: Hong Wang, PhD, Scientific Liaison to Excipient Monographs 2 Expert Committee, Documentary Standards Division, US Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel. 301.816.8351; hw@usp.org.

<sup>d</sup> The other two Expert Committees that set excipient standards for *NF* are: Excipient Monographs 1 Expert Committee, which works with small-molecule excipients, and Excipient General Chapter Expert Committee, which prepares General Chapters for excipients.

## Liquid-filled Gelatin Capsules

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**ABSTRACT** This *Stimuli* article provides an overview of the manufacturing, characteristics, and in vitro performance evaluation of liquid-filled gelatin capsules. The intent of the article is to initiate discussion, to solicit public comments, and to invite participation of interested parties in the efforts of the USP Biopharmaceutics Expert Committee in either updating USP General Chapter *Dissolution* (711) or creating a new General Chapter that will address the particularities and special approaches required to develop and carry out in vitro performance evaluations of liquid-filled gelatin capsules.

### HISTORY OF LIQUID-FILLED GELATIN CAPSULES

Initially capsules were used because it was simple to formulate them as unit dosage forms for drugs in powdered or granular form and because they provided an easy-to-swallow container that effectively masked the bitter taste of drugs. With the advent of pellet technology that enabled modified drug release, capsules provided a useful vehicle into which multiparticulates could be filled without risk of modifying the release characteristics associated with other processing methods such as compression of multiparticulates into tablets (1). Since the early 1980s technology has been available to permit accurate dosing and sealing of liquids into hard gelatin capsules (2–4).

Advantages of liquid- and semisolid-filled hard gelatin capsules include:

- Improved bioavailability

- Improved content uniformity of low-dose active substances
- Reduced dust for handling potent compounds
- Process simplification for low-melting-point active substances
- Enhanced stability
- Sustained release.

Unlike soft gelatin capsules, in which the fill and the shell are manufactured in one operation, hard capsules are manufactured and supplied to the pharmaceutical manufacturer empty. The capsule first needs to be filled and then sealed. Most modern capsule-filling machines can be modified to allow hard gelatin capsules to be filled with hot or cold liquids. Equipment requirements that allow industrial manufacture of liquid-filled capsules are reported by Cole (5), and examples of some available models are given in *Table 1*.

**Table 1. Capsule-filling Machines for Liquid Filling of Hard Gelatin Capsules up to Production Scale**

Machine Type	Filling Action	Approximate Filling Rate (Capsules/h)
<b>Robert Bosch GmbH</b> <b>GKF 1400 L</b> <b>GKF 701 L</b>	Intermittent motion	60,000 36,000
<b>Harro Hoefliger GmbH</b> <b>KFM III-C</b>	Intermittent motion	25,000
<b>IMA Zanasi Division</b> <b>Zanasi 6/12</b> <b>Zanasi 25/40</b> <b>Zanasi Lab 8/16</b> <b>Zanasi Plus</b> <b>2E/48E/70E/85E</b>	All intermittent motion	6,000–12,000 25,000–40,000 8,000–16,000 32,000–85,000

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