



Commentary – Second Supplement to the USP 33-NF 28 Reissue

Revision proposals published in *Pharmacopeial Forum* often elicit public comments that are forwarded to the appropriate Expert Committee for review and response. In accordance with the Rules and Procedures of the 2005-2010 Council of Experts, revision proposals can advance to official status with minor modifications, as needed, without requiring further public review. In such cases a summary of comments received and the appropriate Expert Committee's responses are published in the *Commentary* section of the USP website at the time the revision becomes official. For those proposals that require further revision and republication in *Pharmacopeial Forum*, a summary of the comments and the Expert Committee's responses will be included in the briefing that accompanies each article.

The *Commentary* section 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.

For further information, contact:
USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790

No comments received for the following proposals:

General Chapters

<92> Growth Factors and Cytokines Used in Cell Therapy Manufacturing
<331> Amphetamine Assay
<645> Water Conductivity
<741> Melting Range or Temperature
<1072> Disinfectants and Antiseptics
<1075> Good Compounding Practices (omission)
<1231> Water for Pharmaceutical Purposes
<2040> Disintegration and Dissolution of Dietary Supplements
<2750> Manufacturing Practices for Dietary Supplements

Monographs

Acitretin	Cefuroxime Axetil for Oral Suspension
Amylene Hydate	<i>Ciprofloxacin</i>
Bacitracin Methylenedisalicylate Soluble Powder	<i>Ciprofloxacin Hydrochloride</i>
Benzethonium Chloride	<i>Ciprofloxacin Injection</i>
Bicalutamide	Ciprofloxacin Ophthalmic Solution
Boswellia Serrata	Ciprofloxacin Tablets
Boswellia Serrata Extract	Citalopram tablets
Capecitabine	Clarithromycin Tablets
Capecitabine tablets	Clobetasol Propionate
Cefdinir Capsules	Conjugated Estrogens
Cefdinir for Oral Suspension	Diclofenac Sodium Delayed-Release Tablets
Cefotetan for Injection	

No comments received for the following proposals (continued):

Dinoprostone	Powdered Andrographis
Disulfiram	Powdered Andrographis Extract
Ensulizole	Pentobarbital
Estradiol and Norethindrone Acetate Tablets	Riluzole
Fosinopril Sodium	Riluzole Tablets
Galantamine Tablets	Soluble Bacitracin Methylenedisalicylate
Hydroxypropyl Cellulose Ocular System	Sterile Purified Water
Lactobionic Acid	Sterile Vancomycin Hydrochloride
Leflunomide Tablets	Sterile Water for Inhalation
Methylbenzethonium Chloride	Sterile Water for Injection
Methylpyrrolidone	Sterile Water for Irrigation
Nevirapine Oral Suspension	Tartaric Acid
Norepinephrine Bitartrate	Terazosin Capsules
Omega-3 Acids Ethyl Esters	Tioconazole
Oxazepam capsules	Ursodiol Tablets
	Valsartan and Hydrochlorothiazide
	Vinpocetine
	Zidovudine Oral Solution

General Chapters

General Chapter/Section(s): <228> Ethylene Oxide and Dioxane (Introduction)

Expert Committee(s): Excipient General Chapters

No. of Commenters: 0

Expert Committee-initiated Change: For clarification, the following sentence is added into the introduction section: "Unless otherwise directed in the individual monograph, use *Method I.*"

General Chapter/Section(s): <670> Auxiliary Packing
Components/Cotton/Pharmaceutical Coil Rayon
Pharmaceutical Coil/Polyester Pharmaceutical Coil

Expert Committee(s): General Chapters–Packaging and Storage

No. of Commenters: 1

Comment Summary #1: The commenter suggested that Identification B test be omitted because it offers little value since the test produces a violet color change for both cotton and rayon.

Response: Comment not incorporated. The Expert Committee believes the current test does have value and is willing to consider alternate identification tests upon receipt of the appropriate supporting data.

Comment Summary #2: The commenter suggested that Identification C test be omitted because it is not a specific identification test, it only differentiates between cotton and rayon.

Response: Comment not incorporated. The Expert Committee believes the current test does have value and is willing to consider alternate identification tests upon receipt of the appropriate supporting data.

Comment Summary #3: The commenter suggested that the sample quantity for Identification D test be revised from 5g to approximately 1-5g.

Response: Comment not incorporated. No supporting data or rationale was given for the proposed revision.

Comment Summary #4: The commenter suggested that the Fluorescence test section be removed due to the high subjectivity and potential for false negatives.

Response: Comment not incorporated. The Expert Committee believes the current test does have value and is willing to consider alternate identification tests upon receipt of the appropriate supporting data.

Comment Summary #5: The commenter suggested that the Residual Hydrogen Peroxide Concentration test limits be revised from NMT 50 ppm to NMT 100 ppm.

Response: Comment not incorporated. No supporting rationale was provided for loosening of the specification.

Comment Summary #6: The commenter suggested that the Residue on Ignition limits be revised to NMT 0.40% to be harmonized with the EP

Response: Comment not incorporated. The Expert Committee believes the current limit is appropriate.

Comment Summary #7: The commenter suggested that the Water Soluble Substances limits be revised to NMT 0.50% to be harmonized with the EP

Response: Comment not incorporated. The Expert Committee believes the current limit is appropriate.

Comment Summary #8: The commenter suggested that the Fatty Matter acceptance criteria for the weight of residue be increased from NMT 0.50% to NMT 0.70%.

Response: Comment incorporated, consistent with USP Cotton monograph

Comment Summary #9: The commenter suggested that the Dyes section include a comparison to reference solutions identical to the EP, which would make it easier to evaluate.

Response: Comment not incorporated. The Expert Committee believes the current test method is appropriate.

Comment Summary #10: The commenter suggested that the Identification A test be omitted because it offers little value.

Response: Comment not incorporated. The Expert Committee believes the current test does have value and is willing to consider alternate identification tests upon receipt of the appropriate supporting data.

Comment Summary #11: The commenter suggested that Identification B test be omitted because it is not a specific identification test.

Response: Comment not incorporated. The Expert Committee believes the current test does have value and is willing to consider alternate identification tests upon receipt of the appropriate supporting data.

Comment Summary #12: The commenter suggested that a definition for rayon be included

Response: Comment incorporated.

Comment Summary #13: The commenter suggested that the Fluorescence test section be removed due to its high subjectivity and potential for false negatives.

Response: Comment not incorporated. The Expert Committee believes the current test does have value and is willing to consider alternate identification tests upon receipt of the appropriate supporting data.

Comment Summary #14: The commenter suggested that the Fatty Matter sample size be reduced from 10g to 5g.

Response: Comment incorporated.

Comment Summary #15: The commenter suggested that the Fatty Matter acceptance criteria for the weight of residue be increased from NMT 0.50% to NMT 0.70%.

Response: Comment not incorporated. The Expert Committee believes the current limit is appropriate.

Comment Summary #16: The commenter suggested that Identification B test be omitted because it is not a specific identification test.

Response: Comment not incorporated. The Expert Committee believes the current test does have value and is willing to consider alternate identification tests upon receipt of the appropriate supporting data.

Comment Summary #17: The commenter suggested that a definition for polyester be included.

Response: Comment incorporated.

Comment Summary #18: The commenter suggested that for Identification A test, measurement down to 400 cm⁻¹ is imprecise for some equipment and is not necessary and recommend the range be 4000 to 650 cm⁻¹.

Response: Comment incorporated.

Comment Summary #19: The commenter suggested that Identification B test be omitted because it is not a specific identification test.

Response: Comment not incorporated. The Expert Committee believes the current test does have value and is willing to consider alternate identification tests upon receipt of the appropriate supporting data.

Comment Summary #20: The commenter suggested that the Other Foreign Matter section is not applicable for polyester and should be deleted.

Response: Comment incorporated.

No. of Commenters: 2

Comment Summary #21: The commenter suggested that the Loss on Drying acceptance criteria be increased from NMT 0.50% to NMT 1.0%.

Response: Comment incorporated. Historical data demonstrates that most certified rayon, used for pharmaceutical coil, has a maximum Loss on Drying of 1.0%.

General Chapter/Section(s): <1059> Excipient Performance

Expert Committee(s): Excipient General Chapters

No. of Commenters: 1

Comment Summary: The commenter suggested adding a graphical representation, such as a flow chart, to clarify how to use the general chapter.

Response: Comment not incorporated. The EGC Expert Committee reviewed the proposed suggestion and may add it in a future revision of the general chapter.

Expert Committee-initiated change #1: The Expert Committee made numerous textual changes based on alternative language to clarify the introduction.

Expert Committee-initiated change #2: The Expert Committee changed the term functionality to performance to clarify the intent of the general chapter.

General Chapter/Section(s): <1086> Impurities in Official Articles/Definitions

Expert Committee(s): General Chapters-General Chapters

No. of Commenters: 1

Comment Summary #1: The commenter suggested clarification to be more specific about the term “allowance” in the definition of Foreign Substances.

Response: Comment not incorporated because the sentence was not one of the recommended changes in this revision and the current text is aligned with the General Notices and Requirements, under 5.60. Impurities and Foreign Substances.

General Chapter/Section(s) <1211> Sterilization and Sterility Assurance of Compendial Articles/Introduction/ Methods of Sterilization/Sterilization by Ionizing Radiation

Expert Committee: Microbiology and Sterility Assurance

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the sentence “*In order to comply with ...such as temperature and time, humidity, and sterilizing gas concentration, or absorbed radiation...*” to make it generally applicable to both Moist Heat and Ethylene Oxide Sterilization, and include Pressure as an additional Critical Parameter.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended revising the sentence “*A typical validation program... but the principles are applicable to the other sterilization procedures discussed in this informational chapter,*” since, not all of the principles are applicable to other sterilization procedures.

Response: Comment incorporated.

Comment #3: The commenter recommended revising the sentence “*This determination requires the employment of ...or separate biological indicators (BIs) in operationally fully loaded autoclave configurations.*” to delete the recommendation of the use separate biological indicators not placed in the product, since this is not a common practice unless correlational studies have been done.

Response: Comment incorporated.

Comment Summary #4: The commenter recommended revising the sentence “*The effectiveness of heat delivery or penetration into the actual articles and the time of the exposure are the two main factors that determine the lethality of the sterilization process.*” to include moisture, since, it is equally important.

Response: Comment incorporated.

Comment Summary #5: The commenter recommended revising the statement “*It is generally accepted that terminally sterilized injectable articles or critical devices purporting to be sterile, when processed in the autoclave, attain a 10⁻⁶ microbial survivor probability, since the ability to attain a 10⁻⁶ microbial survivor probability is a function of all terminal sterilization processes, not just autoclave sterilization processes.*”

Response: Comment incorporated.

Comment Summary #6: The commenter recommended revising the statement “*It is generally accepted ...attain a 10–6 microbial survivor probability, i.e., assurance of less than 1 chance in 1 million that viable microorganisms are present in the sterilized article or dosage form*” to reflect the definition of SAL as assurance of less than or equal to 1 chance in 1 million

Response: Comment incorporated.

Comment Summary # 7: The commenter recommended revising the statement “*In this latter instance, the development of the sterilization cycle depends heavily on knowledge of the microbial burden of the product...*” and clarify that knowledge of population and resistance is required of any bioburden based approach.

Response: Comment incorporated.

Comment Summary #8: The commenter recommended generalizing the definition of D value to include other modes of sterilization.

Response: Comment incorporated.

Comment Summary #9: The commenter recommended providing additional details in the section on Steam Sterilization to include over pressure moist heat sterilization

Response: Comment not incorporated. Will be considered in a future revision.

Comment Summary #10: The commenter recommended revising the statement “*The sterilization process is generally carried out in a pressurized chamber...*” to reflect that the sterilization process is generally carried out in an evacuated chamber to prevent leak of EO.

Response: Comment incorporated.

Comment Summary # 11: The commenter recommended adding a new paragraph on Dose Mapping prior to dose setting in the section on Sterilization by Ionizing Radiation

Response: Comment not incorporated. Will be considered in a future revision.

Comment Summary # 12: The commenter recommended revising the following sentence “*Dose-setting and dose-substantiation procedures are used to validate the radiation dose*” to indicate more traditional methods are still appropriate and allowed.

Response: Comment incorporated.

Comment Summary #13: The commenter recommended deleting the following sentence “*However, the total temperature input during the passage of the product should be equivalent to that achieved during the chamber process.*” since the “equivalency” of the two processes is irrelevant as long as processes are validated to provide the required level of sterilization and/or depyrogenation assurance.

Response: Comment incorporated.

Comment Summary #14: The commenter recommended to clarify that in accordance with CFR211.72, use of Asbestos Filters is prohibited.

Response: Comment incorporated.

Comment Summary #15: The commenter recommended that the title of the section: “*Unidirectional Aseptic Processing*” should be left as “*Aseptic Processing*” since the general discussion on aseptic processing does not support the change in title.

Response: Comment not incorporated because there is discussion in the section on the importance of unidirectional airflow in critical areas of aseptic processing environments.

General Chapter/Section: <1117> *Microbiological Best Laboratory Practices*/ Multiple Sections

No. of Commenters: 1

Comment Summary #1: The commenter indicated that the sentence "*Water of lesser quality should not be used for microbiological media preparation*" is overly prescriptive and recommended its revision.

Response: Comment not incorporated. The previous sentence in the section notes exceptions to this and indicates use of other types of water, if appropriate.

Comment Summary #2: The commenter recommended that the sentence "*Be sure that the cleaning process removes debris and foreign matter, and that the detergent is thoroughly rinsed out with Purified Water*" be modified to allow the use of distilled water for this purpose.

Response: Comment not incorporated. An earlier sentence in the same section allows the use of distilled water, if appropriate.

Comment Summary #3: The commenter indicated that it should be clarified that it is not necessary to check the pH of purchased media since it is already tested for Growth Promotion.

Response: Comment incorporated.

No. of Commenters: 1

Comment Summary #4: The commenter suggested that the sentence "*The molten agar medium should be held in a monitored water bath at a temperature of 45 to 50 C for not more than 8 hours*" should be revised and should read "*.... at a temperature of not more than 45C....*"

Response: Comment not incorporated.

Comment Summary #5: The commenter recommended that the sentence "*The number of transfers of working control cultures should be tracked to prevent excessive subculturing that increases the risk of phenotypic alteration or mutation.*" should be clarified to include the allowed number of passages.

Response: Comment incorporated.

Comment Summary #6: The commenter recommended inclusion of checking and cleaning of seals.

Response: Comment incorporated.

Comment Summary #7: The commenter recommended revising the sentence "*For incubation times expressed in days, incubations started in the morning or afternoon should generally be concluded at that same time of day*" to indicate that this is a recommendation and not a requirement.

Response: Comment not incorporated. This is a general information chapter and the sentence already says "generally."

Comment Summary #8: The commenter recommended re-wording the paragraph "*Competency may be demonstrated ...understanding.*", and deleting the following sentences a) "*Further, it is expected that laboratory supervisors and managers have a demonstrated level of competence in microbiology at least as high as those they supervise*" since, according to the commenter, this notion is unrealistic and inconsistent with the principles of management, and, b) "*It should be noted that microbiology is a scientifically based discipline that deals with biological principles substantially different from those of analytical chemistry and engineering disciplines. Many times it is difficult for individuals without specific microbiological training to make the transition.*"

Response: Comment not incorporated because this is a best practice recommendation (title of the chapter indicates that) only and not a requirement.

Comment Summary #9: The commenter recommended inclusion of information on handling of charts or graphs in lab notebooks.

Response: Comment incorporated.

General Chapter/Section(s): <1235> Vaccines for Human Use- General Considerations

Expert Committee(s): Biologics and Biotechnology—Vaccines and Virology

No. of Commenters: 4

Comment Summary #1: Under *Media for Cell Culture for Viral Vaccines*, the chapter states that "If human albumin is used in a U.S.-licensed vaccine, it must be licensed by FDA." Commenter

suggested that the general chapter should be revised to indicate that human albumin used in a U.S.-licensed vaccine, should either be licensed by the FDA or derived from donors from whom appropriate screening and testing has been conducted.

Response: Comment not incorporated, because donor screening is not considered sufficient for albumin sourcing.

Comment Summary #2: Under the section on *Fermentation and Cell Culture Media*, commenter suggested adding a statement on avoiding media components known to cause allergic reactions.

Response: Comment incorporated. New statement reads "Culture media should be suitable for their intended purpose and should be free from adventitious agents. Moreover, medium components that are known to cause allergic reactions should be avoided"

Comment Summary #3:

Commenter asked for clarification on container and closure under *Analytical Measurements*.

Published statement read "Additionally, other common assays typically are performed as part of the stability study and may address physical or chemical changes in the product that may or may not affect its potency (e.g., general safety, degree of aggregation, pH, moisture, container, preservative, and enclosure)."

Response: Comment incorporated. Change to "Additionally, other common assays typically are performed as part of the stability study and may address physical or chemical changes in the product that may or may not affect its potency (e.g., general safety, degree of aggregation, pH, moisture, container closure integrity and preservative)."

Comment Summary #4: Under *Common Tests*, commenter suggested that "LAL should replace pyrogen (after validation)."

Response: Comment not incorporated because USP allows substitution and so does the CFR (LAL for bacterial endotoxins and rabbit pyrogen test for others).

Comment Summary #5: Commenter proposed that for some of the items (cell lines, spec ...) the definitions need to be aligned with WHO, EP, ICH.

Response: Not incorporated. As much as possible, USP tries to adhere to international harmonized text. In cases where US regulatory requirements are different from others, then USP will refer to CFR.

Comment Summary #6: The *Bacterial Endotoxins* section states that "Each lot of final containers of a vaccine intended for use by injection is tested for bacterial endotoxins, as indicated in *Bacterial Endotoxins Test <85>*". Comment says that Viral vaccines are not tested for LAL.

Response: Comment incorporated by adding a sentence at the end of the paragraph to say "Live viral vaccines are excluded." Typically live virus vaccines are not tested for bacterial endotoxins or pyrogenic substances.

Comment Summary #7: In the introductory paragraph, under the *Intermediates* section, a commenter suggested expanding on how intermediates are included in a formal stability program.

Response: Comment incorporated by providing more details as follows: "These intermediates can be stored and their shelf-life or holding time should be defined with stability data, according to a formal stability program."

Comment Summary #8: Under the section Tests for Final Bulk, a comment suggested that (1) Adventitious agent testing are never performed on the final bulk product, they are performed on the crude harvest for live attenuated viral vaccines only.(2) Mycoplasma testing is never performed on the final bulk product but on the crude harvest of a viral vaccine.

Response: Comment incorporated by (1) deleting for the following sentence under Tests for Final Bulk: "The list includes, for example, tests for the absence of adventitious agents, mycoplasma, and other microorganisms." (2) Moving the sentence right after the first paragraph under *Propagation and Harvest*, to read as follow: "The final bulk may be the appropriate stage to test some quality attributes. The list includes, for example, tests for the absence of adventitious agents, mycoplasma, and other microorganisms."

Comment Summary #9: Under Formal Evaluation of Stability Data and Product Dating Period, *Stability Protocol* section, commenter suggested replacing "specifications" by "acceptance criteria" to be consistent with ICH Q6B terminology.

Response: Comment incorporated.

Comment Summary #10: Commenter suggested that before the section on intermediates, a section about Inactivation is expected (how to inactivate a vaccine and how to check the inactivation).

Response: Viral inactivation will be addressed in a USP general chapter under development.

Monographs

Monographs/Sections: Ashwagandha, Powdered Ashwagandha, and Powdered Ashwagandha Extract / Multiple sections

Expert Committee: Dietary Supplements—Botanicals

Number of Commenters: 2

Comment Summary #1: The commenters suggested that the name and definition of the Ashwagandha monograph should be changed to Ashwagandha Root. Since only the root is described in this monograph. The commenters made similar requests for the USP monographs for Powdered Ashwagandha and Powdered Ashwagandha Extract. The commenters indicated that extracts made from the leaves of *Withania somnifera* are also available in trade.

Response: The USP has developed the monograph under a memorandum of understanding with the Indian Pharmacopoeia (IP) and adopted the titles of the article from IP. However, according to the comment, extracts made from the leaves of *Withania somnifera* are also available in trade. Keeping this in mind, DSB EC will specify the plant part (Root) in the title of the monographs.

Comment Summary #2: The commenters objected to the proposed Ashwagandha definition as the “dried mature roots of *Withania somnifera*.” “Mature” roots should not be included as part of the definition, as this would support the use of old root stocks, resulting in an inferior product. Commercially available extracts of Ashwagandha derived from old roots are generally devoid of sitoindosides or contain only traces of sitoindosides. Moreover, if old (*i.e.*, “mature”) roots are used, the resultant ashwagandha product would contain high levels of undesirable polysaccharides that can adversely affect the bioavailability of beneficial components, as well as scopolamine-type alkaloids that can be harmful to human health.

Response: Comment not incorporated. The IP and the Ayurvedic Pharmacopoeia of India define Ashwagandha as “mature roots”. In India, the herbal industries / practitioners consider thin immature roots to be of superior quality compared to the thick mature roots. However, there appears to be no scientific comparison available to justify / support this belief. The DSB EC requested further information / research demonstrating the superiority of immature roots.

Comment Summary #3: The commenters objected to the acceptance criteria in the definition of Ashwagandha as:

“it contains NLT 0.3% of withanolides, calculated on the dried basis as the sum of withanolide aglycones, calculated as withanolide A, and withanolide glycosides, calculated as withanoside IV.”

The commenters’ preferred approach is to create minimum constituent levels for the withanolide glycosides and the withanolide aglycones, each as a distinct marker. The commenters’ rationale for this position is based on scientific data demonstrating that the withanolide glycosides predominate and are the desired constituents. The aglycones, however, are known to produce cytotoxic effects when present in significant quantities.

Response: Comment not incorporated. In the USP proposed monographs, both withanolide glycosides and aglycones are recommended only as analytical markers and not as the active principles. DSB EC’s position is that the compounds responsible for biological activities of *Withania somnifera* are not clearly established. In such a situation, it is probably pre-mature to label some constituents as desirable and others as undesirable. In fact, there is authoritative information and some publications which point to components other than withanolides as “bioactive” in ashwagandha (references provided to the commenters).

Comment Summary #4: The commenters’ view is that as part of the definition of Powdered Ashwagandha Extract, the content of withaferin A should be limited to NMT 2%. This is because withaferin A is known to produce cytotoxic and immune-suppressive effects when present in large

quantities.

Response: Comment not incorporated. The DSB EC requested information / research supporting the need to treat withaferin A as a negative marker.

Comment Summary #5: The commenters suggested that any specification for withanolide aglycones should be calculated as withaferin A instead of withanolide A, which is the standard currently used in the monographs. The commenters indicated that withaferin A is the most predominant form of the aglycones.

Response: The DSB EC did not incorporate the comment. Initially DSB EC had planned to use Withaferin A as the standard for the aglycones. However, because of the stability concerns of Withaferin A in solution, Withanolide A was used as the standard. The inclusion of relative response factors in the monographs allows calculating each substance as its own regardless of the reference standard used.

Comment Summary #6: The commenters suggested that the term withanolide A should be dropped because it is a misnomer.

Response: Comment not incorporated. To DSB EC understanding, withanolide A is not a misnomer. Various research articles mentioning the presence of withanolide A in *Withania somnifera* were provided to the commenters.

Comment Summary #7: In the USP Powdered Ashwagandha Extract monograph, the commenters requested that the percentage of withanolides should include only the total withanolide glycosides and should not include withanolide aglycones. The commenters' rationale is that it is well-established in the scientific literature that the withanolide glycosides are distinct from withanolide aglycones, with different chemical properties and bioactivity. The withanolide glycosides are the desired constituents, whereas the withanolide aglycones should be limited.

Response: Please see responses for the comments 3 and 4 above.

Comment Summary #8: The commenters suggested that the HPLC methods proposed by USP are problematic insofar as the HPLC chromatogram signals obtained by following the USP methods do not properly resolve and differentiate the two classes of compounds, the withanolide glycosides and the withanolide aglycones."

Response: Comment not incorporated. The validated method contained in the monograph proposals has been tested in the USP laboratories and several other laboratories in India, USA and Australia. Results of testing proved that the method resolves the two classes of compounds present.

Comment Summary #9: The commenters requested that the USP acceptance criteria for ashwagandha extract should include that the extract be devoid of toxic tropane alkaloids (e.g. scopolamine and equivalents) due to their deleterious effect on memory and cognition which relates specifically to the safety of any ashwagandha preparation.

Response: Comment not incorporated. The DSB EC agrees that there are reports of the deleterious effects of tropane alkaloids on memory and cognition. At the same time, the DSB EC is unaware of the presence of tropane alkaloids (e.g. scopolamine and related alkaloids) in alcoholic and hydro alcoholic extracts of *Withania somnifera* roots. In this regard, the DSB EC requested that the commenters provide scientific data on:

- 1) Tropane alkaloids, which have been isolated and characterized from *Withania somnifera* roots
- 2) Content of tropane alkaloids in the roots of *Withania somnifera*
- 3) Deleterious effects of *Withania somnifera* roots tropane alkaloids reported till date

Monograph/Sections: Aztreonam/Multiple Sections

Expert Committee (s): Monograph Development—Antibiotics

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the acceptance criterion in the *Limit of Alcohol* test from 4% to 1.4%.

Response: Comment not incorporated. The acceptance criteria included in the monograph are consistent with the sponsor's FDA-approved regulatory filing.

Comment Summary #2: The commenter requested revising the acceptance criteria in the Assay from 92.0 – 105.0% to 95.0 – 102.0%.

Response: Comment not incorporated. The acceptance criteria included in the monograph are consistent with the sponsor's FDA-approved regulatory filing.

Comment Summary #3: The commenter requested revising the acceptance criteria for the specified impurities in the *Organic impurities* test to more stringent limits.

Response: Comment not incorporated. The acceptance criteria included in the monograph are consistent with the sponsor's FDA-approved regulatory filing.

Comment Summary #4: The commenter requested including an acceptance criterion for t-butyl aztreonam.

Response: Comment not incorporated because the commenter's product has not yet received full FDA approval. The Expert Committee will consider addressing this comment as part of the USP Pending Monographs initiative.

Expert Committee-initiated Change: The *System suitability* section in the Assay was revised to delete the column efficiency requirement. The remaining requirements are sufficient to ensure chromatographic suitability.

Monograph/Section(s): Balsalazide Disodium/Organic Impurities and Water

Expert Committee(s): Monograph Development—Gastrointestinal, Renal and Endocrine

No. of Commenters: 2

Comment Summary #1: The commenter indicated that balsalazide related compounds A and B are not completely soluble in the *Diluent* specified under *Organic impurities, Procedure 1*, and requested to add a *Note* under the *Standard solution* that a small amount of acetonitrile may be added to facilitate dissolution.

Response: Comment incorporated.

Comment Summary #2: The commenter indicated that the impurity profile of the drug substance manufactured by their company is different from the profile included in the *PF* proposal, and the procedure in *PF* cannot be used for the analysis due to co-elution of peaks. The commenter proposed adding *Procedure 2* for *Organic impurities* using a flexible monograph approach and submitted the necessary supporting information.

Response: Comment incorporated. *Procedure 2* for *Organic impurities*, which is based on an analytical procedure validated with the Waters Atlantis T3 brand of L1 column, is added to the monograph. The typical retention time for balsalazide peak is about 28 min.

Comment summary #3. The commenter requested widening the specification for *Water* from "7.8% - 8.8%" to "7.8% - 9.0%", to be consistent with the commenter's approved specification.

Response: Comment incorporated.

Monograph/Section(s): Clenbuterol Hydrochloride/Residue on Ignition

Expert Committee(s): Veterinary Drugs

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the amount of the sample from "1 g" to "1-2 g", to be consistent with the requirements in General Chapter <281> *Residue on Ignition*.

Response: Comment incorporated.

Monograph/Section: Cyclophosphamide/Organic Impurities

Expert Committee: Monograph Development—Ophthalmology, Oncology, and Dermatology

No. of Commenters: 2

Comment Summary #1: The commenter suggested addressing a safety concern by adding detailed instructions for the preparation of Reagent A in *Procedure 1*.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested indicating that the adsorbent used under *Procedure 2* contains a fluorescent indicator.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested including an option for spraying the TLC plate with Reagent B in *Procedure 2*, in addition to dipping.

Response: Comment incorporated.

Monograph/Section(s): Diclofenac Sodium Extended-Release Tablets/Identification

Expert Committee: Monograph Development—Cough, Cold and Analgesics

No. of Commenters: 1

Comment Summary #1: The commenter requested adding “Protect solution from light” under *Identification-B*.

Response: Comment incorporated.

Monograph/Section: Docetaxel/Multiple Sections

Expert Committee: Monograph Development—Ophthalmology, Oncology, and Dermatology

No. of Commenters: 3

Comment Summary #1: The commenter suggested changing the monograph title from Docetaxel to Docetaxel Trihydrate to be consistent with the title used in the *European Pharmacopoeia* and to differentiate between the trihydrate form and the anhydrous form.

Response: Comment not incorporated because the title “Docetaxel” has been approved by the Nomenclature Expert Committee based on the USAN name. It is a USP policy to consider hydrated forms and polymorphs within the same monograph, and not to define them in the title. The molecular weight of the anhydrous form is added in the monograph for information only.

Comment Summary #2: The commenter suggested including procedures <197K> and <197M> in the *Identification* section-A, in addition to <197S>.

Response: Comment incorporated. A *Note* is added that procedures <197K> and <197M> can also be used.

Comment Summary #3: The commenter suggested changing the relative standard deviation of the system suitability requirement in the *Assay* from NMT 1.0% to NMT 2.0%.

Response: Comment not incorporated because the system suitability requirement in the monograph is consistent with the sponsor’s validation data.

Comment Summary #4: The commenter suggested changing the resolution of the system suitability requirement in the *Organic impurities* from NLT 4 to NLT 2.

Response: Comment not incorporated because the system suitability requirement in the monograph is consistent with the sponsor’s validation data.

Comment Summary #5: The commenter suggested deleting the relative standard deviation requirement in the *Organic impurities* because the impurities are calculated by area normalization.

Response: Comment incorporated.

Monograph/Section(s): Dofetilide/Organic Impurities

Expert Committee(s): Monograph Development—Cardiovascular

No. of Commenters: 2

Comment Summary #1: The commenters suggested correcting the solvent ratios in the *Diluent* from “Acetonitrile and Buffer (22:3)” to “Acetonitrile and Buffer (3:22)”.

Response: Comment incorporated.

Monograph/Section(s): Fentanyl/Multiple Sections

Expert Committee: Monograph Development—Cough, Cold and Analgesics

No. of Commenters: 1

Comment Summary #1: The commenter suggested that the flexible monograph approach be considered to account for the impurities observed in their impurity profile.

Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Comment Summary #2: The commenter suggested that their Assay procedure be added as an option in the monograph.

Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Monograph/Section(s): Hydrogenated Polydextrose/Multiple Sections

Expert Committee(s): Excipient Monographs 2

No. of Commenters: 1

Comment Summary #1: In the *Water Determination, Method I <921>*, the lab data indicated that hydrogenated polydextrose didn't completely dissolve in anhydrous pyridine and recommended using a mixture of Hydranal solvent and Hydranal formamide dry (2:1) as a solvent and performing the titration at 50° in a jacketed beaker.

Response: Comment incorporated based on data from three collaborative labs.

Expert Committee-initiated Change: In the *Limit of Lead*, replace "Injection Size: see *Samples* under *Analysis* below" with "Autosampler, Sample volume: 10 µL; Alternative volume: 10 µL of *Matrix modifier solution*". Under the *Analysis, Samples*, replace "10-µL aliquots of the five *Standard solutions*" with "10 µL of the *Matrix modifier solution* was added into each 10-µL aliquots of the five S.

Monograph/Section(s): Leflunomide/Assay

Expert Committee: Monograph Development–Cough, Cold and Analgesics

No. of Commenters: 1

Comment Summary #1: The commenter suggested rewriting the *Standard solution* to maintain consistency with the *Sample solution*.

Response: Comment incorporated.

Monograph/Section(s): Methacrylic Acid Copolymer/Organic Impurities, Procedure: Limit of Monomers

Expert Committee(s): Excipient Monographs 2

No. of Commenters: 2

Comment Summary #1: In the *Organic Impurities, Procedure: Limit of Monomers*, the commenter indicated that "for Type C" was missing in defining r_s and should be included.

Response: Comment incorporated.

Comment Summary #2: In the *Organic Impurities, Procedure: Limit of Monomers*, the commenter recommended changing RSD from 2.0% to 5.0%.

Response: Comment incorporated.

Monograph/Section(s): Methacrylic Acid and Ethyl Acrylate Copolymer/Organic Impurities, Procedure: Limit of Methacrylic Acid and Ethyl Acrylate

Expert Committee(s): Excipient Monographs 2

No. of Commenters: 1

Comment Summary #1: In the *Organic Impurities, Procedure: Limit of Methacrylic Acid and Ethyl Acrylate*, the commenter recommended changing RSD from 2.0% to 5.0%.

Response: Comment incorporated.

Monograph/Section(s): Methacrylic Acid and Methyl Methacrylate Copolymer/ Organic Impurities, Procedure: Limit of Methacrylic Acid and Methyl Methacrylate

Expert Committee(s): Excipient Monographs 2

No. of Commenters: 2

Comment Summary #1: In the *Organic Impurities, Limit of Methacrylic Acid and Methyl Methacrylate*, the commenter indicated that "Procedure" was missing before the "Limit of Methacrylic Acid and Methyl Methacrylate" and should be included.

Response: Comment incorporated.

Comment Summary #2: In the *Organic Impurities, Procedure: Methacrylic Acid and Methyl Methacrylate*, the commenter recommended changing RSD from 2.0% to 5.0%.

Response: Comment incorporated.

Monograph/Section(s): Polydextrose/Multiple Sections

Expert Committee(s): Excipient Monographs 2

No. of Commenters: 1

Comment Summary #1: In the *Water Determination, Method I <921>*, the commenter suggested lab data indicated that polydextrose didn't completely dissolve in anhydrous pyridine and recommended using a mixture of Hydranal solvent and Hydranal formamide dry (2:1) as a solvent and performing the titration at 50° in a jacketed beaker.

Response: Comment incorporated based on data from three collaborative labs.

Expert Committee-initiated Change: In the *Limit of Lead*, replace "Injection Size: see *Samples* under *Analysis* below" with "Autosampler, Sample volume: 10 µL; Alternative volume: 10 µL of *Matrix modifier solution*". Under the *Analysis, Samples*, replace "10-µL aliquots of the five *Standard solutions*" with "10 µL of the *Matrix modifier solution* was added into each 10-µL aliquots of the five *Standard solutions*."

Monograph/ Section(s): Mefloquine Hydrochloride/Assay

Expert Committee (s): Monograph Development—Antivirals and Antimicrobials

No. of Commenters: 1

Comment Summary #1: The commenter proposed broadening the acceptance criteria from 99.0-101.0% to 98.0-102.0% for the Assay to be consistent with the relative standard deviation (RSD) requirement of NMT 2.0%.

Response: Comment not incorporated because the acceptance criteria for the Assay reflect the FDA approved specifications. However, the Expert Committee approved the deletion of the RSD requirement as an interim solution, and will consider a future revision to tighten this requirement through the regular revision process via publication in a future *Pharmacopeial Forum*.

Comment Summary #2: The commenter indicated that the guard columns used for both the Assay and *Organic impurities* tests have the same packing material but slightly different dimensions. The commenter suggested using guard columns with the same dimensions to provide flexibility to conduct both tests using the same guard column.

Response: Comment not incorporated because the Assay was validated using a guard column with slightly different dimensions. However, the Expert Committee agreed that the guard column dimensions were not critical in this case and therefore approved to add the word "recommended" to guard column dimensions.

Monograph/Sections: Methylphenidate Hydrochloride Extended Release
Tablets/Organic Impurities

Expert Committee(s): Monograph Development—Psychiatrics and Psychoactives

Number of Commenters: 2

Comment Summary #1: The commenter indicated that the procedure in PF is different from the FDA-approved procedure.

Response: Comment not incorporated because all important parameters of the HPLC procedure, including mobile phase, column dimensions, monitoring wavelength and concentrations, are consistent with the sponsor's approved procedure.

Comment summary #2: The commenter requested the inclusion of an alternative sample preparation technique to allow for the differences in the formulation components.

Response: Comment incorporated.

Monograph/Section: Mycophenolate Mofetil Tablets/Multiple Sections
Expert Committee: Monograph Development—Ophthalmology, Oncology, and Dermatology

No. of Commenters: 1

Comment Summary #1: The commenter requested changing the *Identification* procedure from UV to IR.

Response: Comment not incorporated because the UV spectrum of the analyte is distinctive and is suitable for identifying the active ingredient in this drug product.

Comment Summary #2: The commenter indicated that the *Assay* procedure is not consistent with their approved procedure. No revision to the procedure was requested.

Response: Comment not incorporated because the *Assay* procedure in the monograph is based on the sponsor's FDA-approved regulatory filing.

Comment Summary #3: The commenter indicated that Z-mycophenolate mofetil is not a degradation product, and requested deleting the test for the *Limit of Z-Mycophenolate Mofetil* in the *Organic impurities*.

Response: Comment not incorporated because the Expert Committee has confirmed that Z-mycophenolate mofetil is considered to be a degradation product.

Monograph/Section: Mycophenolate Mofetil Capsules/Multiple Sections
Expert Committee: Monograph Development—Ophthalmology, Oncology, and Dermatology

No. of Commenters: 1

Comment Summary #1: The commenter requested changing the UV identification to IR identification.

Response: Comment not incorporated because the UV spectrum of the analyte is distinctive and is suitable for identifying the active ingredient in this drug product.

Comment Summary #2: The commenter indicated that the *Assay* procedure is not consistent with their approved procedure. No revision to the procedure was requested.

Response: Comment not incorporated because the *Assay* procedure in the monograph is based on the on the sponsor's FDA-approved regulatory filing.

Comment Summary #3: The commenter indicated that Z-mycophenolate mofetil is not a degradation product, and requested deleting the test for the *Limit of Z- Mycophenolate Mofetil* in the *Organic impurities*.

Response: Comment not incorporated because the Expert Committee has confirmed that Z-mycophenolate mofetil is considered to be a degradation product.

Monograph/Sections: Oxazepam Capsules/Identification
Expert Committee(s): Monograph Development—Psychiatrics and Psychoactives
Number of Commenters: 0

Expert Committee-initiated Change: The Expert Committee has revised the *Identification* procedure to be consistent with the revised *Assay* procedure.

Monograph/Section(s): Pantoprazole Oral Suspension
Expert Committee(s): Compounding Pharmacy
No. of Commenters: 2

Comment Summary #1: The commenter indicated that the Pantoprazole Oral Suspension monograph presents information contrary to the approved USP monograph for Pantoprazole Delayed Release Tablets. The monograph for the tablets clearly states that the tablets “must not be split, chewed or crushed before administration.”

Response: Comment not incorporated. The USP Compounding Pharmacy Expert Committee has developed a compounded preparation monograph for an oral liquid dosage form that utilizes the crushed tablets with the addition of an alkaline ingredient with sufficient acid-neutralizing capacity to facilitate the drug's safe passage through the stomach.

Comment Summary #2: The commenter indicated that pantoprazole is acid labile, therefore the tablets are enteric coated. Disruption of the enteric coating is not recommended.

Response: Comment not incorporated. An oral liquid dosage form requires the addition of an alkaline ingredient with sufficient acid-neutralizing capacity to facilitate the drug's safe passage through the stomach.

Comment Summary #3: The commenter indicated that a clinical study was published in the *American Journal of Health-System Pharmacy* (Vol 60, Jul 1, 2003) that showed that the suspension of the active ingredient in a sodium bicarbonate solution as contemplated in the draft monograph does not provide for a bioequivalent dose of pantoprazole. The data showed that the pantoprazole in a sodium bicarbonate solution is approximately 25% less bioavailability than the tablet formulation. Additionally, the bioavailability of this compounded formulation may be affected by variability in the amount of sodium bicarbonate used and the amount and type of flush solution used.

Response: Comment not incorporated. The Pantoprazole Oral Suspension monograph was based on the following article: *Stability of pantoprazole in an extemporaneously compounded oral liquid*, *Am J Health-Syst Pharm*-Vol 59, May 15, 2002. The compounded preparation monograph is for a liquid suspension for oral administration, not for nasogastric (NG) tube administration.

Comment Summary #4: The commenter indicated that the formulation, as described in the article published in the *American Journal of Health-System Pharmacy* (Vol 60, Jul 1, 2003), has only been studied in and is only intended for, patients with a nasogastric (NG) tube, and that it should not be an option for patients without a nasogastric tube who are unable to swallow tablets.

Response: Comment not incorporated. The Pantoprazole Oral Suspension monograph was based on the following article: *Stability of pantoprazole in an extemporaneously compounded oral liquid* *Am J Health-Syst Pharm*-Vol 59, May 15, 2002, which was an option for patients without a nasogastric tube.

Comment Summary #5: The commenter indicated that multiple source formulations may contain different excipients that could further affect the bioavailability of the drug substance in compounded preparations, which is not addressed in the proposed compounding monograph.

Response: Comment not incorporated. The Pantoprazole Oral Suspension monograph was based on the following article: *Stability of pantoprazole in an extemporaneously compounded oral liquid* *Am J Health-Syst Pharm*-Vol 59, May 15, 2002, which indicated that an oral suspension of pantoprazole using 40 mg delayed-release enteric-coated tablets was stable for 62 days at 2-8°C. The buffering capacity of the preparation did not decrease with storage time.

Comment Summary #6: With respect to the chromatographic system, the commenter suggested that retention times for known impurities be identified. They also recommended that the system suitability criteria be based on resolution between pantoprazole and known impurities, not just the pantoprazole retention time.

Response: Comment not incorporated. USP compounded preparation monographs consist of Assays only, not chromatographic purity or related compound testing. The USP Reference Standard only contains pantoprazole sodium. Therefore, only the peak for pantoprazole can be used to determine system suitability.

Monograph/Section(s): Propoxyphene Hydrochloride/Multiple Sections

Expert Committee: Monograph Development—Cough, Cold and Analgesics

No. of Commenters: 2

Comment Summary #1: The commenter suggested revising the *Mobile phase* in the *Assay* and the *Sample solution* of the *Organic impurities* test to remove the number of days after which the solution should be discarded.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested removing the relative response factor from the equation used to calculate the percentage of any other specified or unspecified impurity.

Response: Comment not incorporated because the values for the relative response factors listed in the monograph are consistent with the sponsor's validation data.

Monograph/Section(s): Ractopamine Hydrochloride Suspension/Diastereomer Ratio
Expert Committee(s): Veterinary Drugs
No. of Commenters: 1

Comment Summary #1: The commenter requested correcting the instructions for the preparation of the *Solution B*, to specify that it should be diluted with *Solution A* to 1000 mL before adjusting the pH.

Response: Comment incorporated.

Monograph/ Section(s): Ramipril Capsules/Organic Impurities
Expert Committee (s): Monograph Development—Cardiovascular
No. of Commenters: 3

Comment Summary #1: The commenters suggested correcting the chemical name for ramipril related compound D in the footnote of Table 3, from “6,7,8-trichloro-3,5-dihydroimidazol[2,1-b]quinazolin-2(1H)-one (ramipril Diketopiperazine)” to “ethyl (2S)-2-[(3S,5aS,8aS,9aS)-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate (ramipril diketopiperazine)”.

Response: Comment incorporated.

Comment Summary #2: The commenters suggested revising the acceptance criteria for *Organic Impurities* in accordance with their FDA approved product as follows:

- Increase the limit for ramipril diacid from “NMT 0.2%” to “NMT 1.0%” for 1.25 mg, 2.5 mg, 5 mg and 10 mg capsule strengths.
- Increase the limit of ramipril related compound D from “NMT 5.5%” to “NMT 8.0%” for 1.25 mg Capsule strength and from “NMT 2.5%” to “NMT 5.0%” for 5 mg and 10 mg Capsule strengths.
- Increase the total impurities limit from “NMT 6.0% for Capsule strengths 1.25 mg and 2.5 mg” to “NMT 8.0% for Capsule strength 1.25 mg” and “NMT 7.0% for Capsule strength 2.5 mg”, and from “ NMT 3.0%” to “NMT 6.0%” for Capsule strengths 5 mg and 10 mg increase “disregard limit” of 0.05% to 0.1%

Response: Comment incorporated.

Monograph/Sections: Risperidone Oral Solution/General
Expert Committee(s): Monograph Development—Psychiatrics and Psychoactives
Number of Commenters: 1

Comment Summary #1: The commenter requested the addition of a test to monitor limits of specified microorganisms.

Response: Comment not incorporated because this is a major revision and is not processed through the commentary process. The Expert Committee will consider this request through the regular revision process with via publication in a future *Pharmacopeial Forum*.

Monograph/Sections: Sumatriptan Tablets/Organic Impurities, Packaging and Storage
Expert Committee(s): Monograph Development—Psychiatrics and Psychoactives
Number of Commenters: 1

Comment Summary #1: The commenter requested modification of the storage temperature to reflect storage conditions approved by the FDA.

Response: Comment incorporated.

Comment Summary #2: The commenter indicated that the *Organic impurities* procedure is not sufficiently selective and requested replacing the procedure in PF with another approved procedure.

Response: Comment not incorporated because this is a major revision and is not processed through the commentary process. The Expert Committee will consider this request through the regular revision process with via publication in a future *Pharmacopeial Forum*.

Monograph/Section(s): Terazosin Tablets/Assay
Expert Committee(s): Monograph Development—Cardiovascular
No. of Commenters: 1

Comment Summary #1: The commenter suggested revising the preparation of the *Mobile phase* from “Acetonitrile:Water (7:3). Add 10.00 mL/L of glacial acetic acid, and degas “ to” Mix 700 mL of Acetonitrile with 300 mL of water. Add 10.00 mL of glacial acetic acid, and degas.”

Response: Comment not incorporated because the current text as stated is correct and is consistent with the new monograph format.

Monograph/Sections: Vancomycin Hydrochloride/Multiple Sections
Expert Committee (s): Monograph Development—Antibiotics
No. of Commenters: 2

Comment Summary #1: The commenters suggested the addition a list of known impurities in the under the *Composition of Vancomycin*.

Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Comment Summary #2: The commenter agreed with the proposed changes.

Response: No action required.

Monograph/Sections: Vancomycin Hydrochloride for Injection/Multiple Sections
Expert Committee (s): Monograph Development—Antibiotics
No. of Commenters: 1

Comment Summary #1: The commenter agreed with the proposed changes.

Response: No action required.

Monograph/Sections: Zolpidem Tartrate Tablets/Organic Impurities
Expert Committee(s): Monograph Development—Psychiatrics and Psychoactives
Number of Commenters: 1

Comment Summary: The commenter requested lowering the limit for any unspecified degradation product from 0.3% to 0.2% to be consistent with ICH guidelines.

Response: Comment incorporated.