

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Revision proposals published in *Pharmacopeial Forum* often elicit public comments that are forwarded to the appropriate Expert Committee for review and response. Some revision proposals can advance to official status with necessary modifications without requiring further public review. In such cases a summary of comments received and the Expert Committee's responses are published in the *Commentary* section of 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 Committee's responses will be included in the briefing that accompanies the publication.

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 for 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.

Where appropriate, the *Commentary* includes a separate discussion of proposals related to international harmonization of the USP, the *European Pharmacopoeia*, and the *Japanese Pharmacopoeia* in order to highlight such proposals.

The Commentary is presented in the following order: USP Monographs, Dietary Supplement Monographs, General Chapters, NF Monographs.

USP MONOGRAPHS

Monograph/Section: Allopurinol/Multiple sections

Expert Committee: MD-GRE

No. of Commenters: 2

Comment summary #1: Commenter suggested that a proposal for Related compounds, previously submitted by the commenter and published in *PF* 28(5), be reconsidered by the Committee.

Response: Comment not incorporated. The Committee decided that it is beneficial to have a single method for impurity analysis in the monograph, as compared to two separate methods proposed by the commenter.

Comment summary #2: Commenter requested the Related compounds proposal be deferred from becoming official until the required USP Reference Standards are available for sale, and the commenter can evaluate the proposed method.

Response: Comment not incorporated. The Committee recognized that the required USP Reference Standards will be available by the time the 1st Supplement to *USP 30* becomes official. Although the Committee is not delaying approval of the monograph for official status on this point, the Committee is willing to consider further changes to this monograph in the future if the commenter submits a Request for Revision.

Monograph/Section: Aluminum Sulfate and Calcium Acetate for Topical Solution/Title

Expert Committee: NOM

Expert Committee-initiated change for the title: The Committee reviewed the submitted title "Aluminum Sulfate and Calcium Acetate Powder for Topical Solution." The Committee noted that there are currently no USP monographs with titles like "[Drug][Powder] for Oral Solution" or "[Drug][Powder] for Topical Solution." Therefore, the title was changed from "Aluminum Sulfate and Calcium Acetate Powder for Topical

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Solution” to “Aluminum Sulfate and Calcium Acetate for Topical Solution” and corresponding changes were made in the monograph.

Monograph/Section: Amlodipine Besylate

Expert Committee: MD-CV

No. of Commenters: 2

Comment Summary: Two commenters stated that the proposed Related compounds test cannot detect all of the process impurities and the degradation products. One of the commenters is developing a new method that can detect all of the impurities.

Response: Comment not incorporated at this time because the comment was not supported by the required data. The Committee will consider publishing a revision in a future *PF* upon receipt of the new method and the associated validation data.

Monograph/Section: Bismuth Subsalicylate Oral Suspension

Expert Committee: MD-CCA

No. of Commenters: 1

Comment Summary: Commenter indicated that the proposed storage statement is overly restricted and does not reflect the current marketed product label storage conditions. The commenter suggested that storage conditions be modified from “Store between 15 and 30°” to read: “Protect from freezing. Avoid excessive heat (over 40°).”

Response: The Committee decided not to incorporate the comment at this time since the proposed change will appear in *PF* 33(1) and to temporarily remove the Packaging and Storage section from the monograph.

Monograph/Section: Bismuth Subsalicylate Tablets

Expert Committee: MD-CCA

No. of Commenters: 1

Comment Summary: Commenter indicated that the proposed storage statement is overly restricted and does not reflect the current marketed product label storage conditions. The commenter suggested that storage conditions be modified from “Store between 15 and 30°” to read: “Avoid excessive heat (over 40°).”

Response: Comment not incorporated at this time because the change proposed by the commenter appeared as an In-Process Revision in *PF* 32(5).

Expert Committee-initiated Change: Because the Packaging and Storage section of the monograph is the subject of an In-Process Revision published in *PF* 32(5), the Committee decided to move the monograph into official status without the Packaging and Storage, with that section to be made official at a later date.

Monograph/Section: Bisoctrizole

Expert Committee: MD-OOD

No. of Commenters: 1

Comment Summary #1: Commenter suggested that the broader requirements in General Chapter <467> Residual Solvents should be applied.

Response: Comment incorporated. The Committee decided to delete the Limit of residual solvents according to the USP’s policy on residual solvents. The control of the residual solvents is covered in the USP General Notices.

Comment Summary #2: Commenter suggested that a test for Residue on Ignition (ROI) be added.

Response: Comment not incorporated at this time because the Committee reviewed the *USP* 29 and found that most monographs for UV filters used in sunscreen products do not have a ROI test.

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Comment Summary #3: Commenter suggested that a test for Loss on Drying (LOD) be added.

Response: Comment not incorporated. The Committee determined that this test is unnecessary because the assay is calculated on the as-is basis.

Monograph/Section: Budesonide

Expert Committee: MD-PS

No. of Commenters: 4

Comment Summary #1: Commenter suggested the following changes:

- Change the test solution concentration in the Identification test B, Ultraviolet Absorption <197U> from 50 µg per mL to 25 µg per mL because the absorbance reading is too high at 50 µg per mL.
- Change the name of sodium dihydrogen phosphate, the reagent used to prepare the Buffer solution in the Assay, to monobasic sodium phosphate, the correct name provided in the Reagent section of USP.

Response: Comment incorporated.

Comment Summary #2: Commenter suggested the following changes:

- Change the limit of 21-acetate of budesonide from NMT 0.1% to NMT 0.10% in the test for Limit of 21-acetate of budesonide.
- Add the following missing information to the Procedure in the test for Limit of 11-ketobudesonide “Maintain the column at 50°.”
- Change the column particle size from 3.5 µm to 5 µm in the Chromatographic system section under the test for Related compounds.
- Specify the limits of the following impurities to two decimal places in the test for Related compounds: D-homobudesonide from NMT 0.1% to NMT 0.10%, 14,15-dehydrobudesonide from NMT 0.1% to NMT 0.10%, and “any other unknown impurity” from NMT 0.1% to NMT 0.10%.
- Add a relative retention time of 0.66 to the relative retention time of 0.61 provided for 21-dehydrobudesonide because the two epimers of this impurity are resolved in the Related compounds procedure.
- Add the following missing information to the procedure for preparing the Standard preparation “The proportion of acetonitrile in the Standard preparation does not exceed 30%.”
- Change the formula provided under Procedure in the Assay to calculate percentage of epimer A in Budesonide rather than the quantity of epimer A.

Response: Comment incorporated.

Comment Summary #3: Commenter suggested the following changes in the Limit of 21-acetate of budesonide, Limit of ketobudesonide, and Related compound procedures:

- Change the detector wavelengths in each procedure from 254 nm to 245nm.
- Develop a single procedure for determining both 21-acetate of budesonide and ketobudesonide.
- 11-ketobudesonide could potentially co-elute with budesonide in the Related compounds and the 21-acetate of budesonide procedures.

Response: Comment not incorporated due to the lack of supporting data. The Committee is willing to consider revising these procedures once USP receives the required supporting data.

Comment Summary #4: Commenter noted that 11-ketobudesonide could potentially co-elute with budesonide in the Related compounds and in the Assay procedures.

Response: Comment not incorporated since there is a separate test for limit of 11-ketobudesonide. Also see Response to Comment Summary #3.

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Expert Committee-initiated change: Included a chemical structure of Budesonide and designated epimer A and epimer B in the Definition.

Expert Committee-initiated change: Added the following note “Protect all solutions containing budesonide from light” at the beginning of the monograph and removed similar statements from different sections of the monograph.

Expert Committee-initiated change: Deleted the Limit of methanol test since this is manufacturer-specific test and the limit provided for this solvent is covered by the requirements of the Residual solvents <467> General Chapter, as stated in the General Notices.

Expert Committee-initiated change: Provided chemical names of all impurities listed in the Table under the test for Related compounds.

Monograph/Section: Cefepime Hydrochloride/Limit of N-methylpyrrolidine; Related compounds

Expert Committee: MD-ANT

No. of Commenters: 1

Comment Summary #1: Commenter suggested a new column rinse solution for the Limit of N-methylpyrrolidine test to more adequately clean the column and decrease analysis time.

Response: Comment incorporated.

Comment Summary #2: For the Related compounds test the commenter questioned the validity of adjusting the pH of the Mobile phase component solutions after the addition of organic.

Response: Comment not incorporated. The Committee believes that the current Mobile phase preparation is valid. The commenter did not supply data to support a revision.

Comment Summary #1: Commenter provided data to demonstrate that the *Test solution* is stable for up to 6 hours if maintained at 5°.

Response: Comment incorporated. A Note was added to the monograph to reflect this.

Monograph/Section: Chlorhexidine Gluconate Solution /Definition and Assay

Expert Committee: MD-AA

No. of Commenters: 1

Comment Summary: Commenter suggested changing the molecular weight of Chlorhexidine Gluconate from 897.77 to 897.76 to be consistent with that in the USP Dictionary.

Response: Comment incorporated.

Monograph/Section: Chlorhexidine Gluconate Oral Rinse/ Assay

Expert Committee: MD-AA

No. of Commenters: 1

Comment Summary: Commenter suggested changing the molecular weight of Chlorhexidine Gluconate from 897.77 to 897.76 to be consistent with that in the USP Dictionary.

Response: Comment incorporated.

Monograph/Section: Ciprofloxacin and Dexamethasone Otic Suspension/Multiple sections

Expert Committee: MD-AA

No. of Commenters: 1

Comment Summary #1: Commenter suggested that the formula for ciprofloxacin related compounds should include multiplication by (331.34/367.81) since the

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concentration of the Dilute standard preparation is in terms of USP Ciprofloxacin Hydrochloride RS but L is the label claim as ciprofloxacin free base.

Response: Comment incorporated.

Comment Summary #2: Commenter suggested the limit for the 21-dehydro-17-deoxy related compound in the test for Dexamethasone related compounds be changed from NMT 0.6% to 1.0% and the sum of all related compounds be changed from NMT 3.0% to 3.5% to be consistent with approved specification in NDA.

Response: Comment incorporated.

Expert Committee-initiated change: In the Limit of ciprofloxacin formamide, Test solution; Assay for ciprofloxacin, Assay preparation; and Assay for dexamethasone, Assay preparation sections, the wording was changed from “transfer an accurately weighted portion...” to “transfer an accurately measured volume ...” to be consistent with the term “volume” used in the corresponding formula in each section.

Monograph/Section: Desmopressin Acetate

Expert Committee: BB-PP

No. of Commenters: 4

Comment Summary #1: One commenter suggested replacing the UV ID test with HPLC retention time. Another commenter suggested replacing the UV ID test with an IR ID test.

Response: Comment partially incorporated. The UV ID test was removed from the monograph. An HPLC retention time is already included in the monograph. The Committee determined that an additional IR ID test is not necessary at this time.

Comment Summary #2: Commenter questioned the need for a Microbial limits test for material that may only be used in a solid oral dosage form.

Response: Comment not incorporated. The Committee decided microbial contamination should be limited in the material because of the potential effects of microbial contamination on the stability of the material.

Comment Summary #3: Commenter suggested raising the total aerobic microbial count to “does not exceed 1000 cfu per g.”

Response: Comment not incorporated. The Committee decided not to raise the aerobic microbial count limit to 1000 cfu per g due to concerns about the effect of microbial contamination on the stability of the peptide.

Comment Summary #4: Commenter suggested changing the Water test to method 1c to allow a smaller amount of sample to be used.

Response: Comment incorporated.

Comment Summary #5: Commenter suggested adding a lower limit of not more than 3% acetate.

Response: Comment incorporated.

Comment Summary #6: Commenter suggested that the Assay and Chromatographic purity methods are not entirely consistent with FDA approved methods, and that a validated method is needed.

Response: Comment not incorporated. Both the Assay and Chromatographic purity methods had validation packages submitted with the proposed monograph.

Comment Summary #7: Commenter suggested that a 1:100 dilution of the test solution be used in the Chromatographic purity test instead of a preparation using the reference standard. The commenter also indicated that the reference standard needs to be corrected for both water and acetic acid content.

Response: Comment not incorporated. The concerns raised by the commenter may be addressed by the format of the reference standard. The Committee may recommend

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that the reference standard be packaged in such a manner that the content of water and acetic acid do not need to be determined.

Comment Summary #8: Commenter suggested allowing an alternative method for Amino Acid Content test.

Response: Comment incorporated. The monograph was changed to allow for other methods of Amino Acid Analysis.

Comment Summary #9: Commenter suggested adding lower limit of not more than 3% for acetic acid in the Acetic Acid Content test.

Response: Comment incorporated.

Comment Summary #10: Commenter suggested adding a limit test for trifluoroacetic acid.

Response: Comment not incorporated because trifluoroacetic acid is considered a process impurity and may not be present if other methods of synthesis are used.

Comment Summary #11: Commenter suggested adding specifications for residual solvents.

Response: Comment not incorporated at this time.

Monograph/Section: Desmopressin Acetate Injection

Expert Committee: BB-PP

No. of Commenters: 1

Comment Summary: Commenter proposed the addition of a Chromatographic Purity test to the monograph.

Response: The Committee believes that a Chromatographic Purity test or a Related compounds is appropriate for this monograph and will add one as soon as one becomes available.

Monograph/Section: Desogestrel and Ethinyl Estradiol Tablets/Multiple Sections

Expert Committee: MD-PS

No. of Commenters: 5

Comment Summary #1: Two commenters suggested the Thin-layer chromatographic identification test use the same solvent (ether) to prepare both the test solution and standard solution

Response: Comment incorporated.

Comment Summary #2: Commenter suggested replacing “25 Tablets” with powdered tablets equivalent to 1.5 mg desogestrel and 0.3 mg ethinyl estradiol in the Thin-layer chromatographic identification test to ensure the concentrations of the drug substances in the test solution and standard solution are the same.

Response: Comment incorporated.

Comment Summary #3: Three commenters suggested revising the test for Related compounds. One commenter suggested the test be revised for the following reasons: the detection limits of some of the impurities are close to the specified limits; well known degradation products of the drugs are not specified but the procedure rather specifies process impurities; and there may be severe interference from an excipient. Another commenter suggested that the test be revised because the procedure is inadequate in specifying known impurities of desogestrel and ethinyl estradiol. A third commenter suggested revising the test for the following reasons: known degradation products of the drugs are not specified but the procedure rather specifies process impurities; excessive baseline noise; and the system suitability requirements could not be met.

Response: Comment incorporated; the Related compounds test is not being made official at this time because of this and several other reported deficiencies. The Committee is willing to consider a revised Related compounds test capable of determining the known impurities of these drugs.

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Comment Summary #4: Commenter suggested a correction to the formula in the Assay for calculating the content of desogestrel and ethinyl estradiol.

Response: Comment incorporated.

Comment Summary #5: Commenter suggested that the test for Water be deleted.

Response: Comment incorporated. See Expert Committee-initiated change below.

Expert Committee-initiated change:

- Added an identification test that compares the retention times of peaks obtained from standard and sample preparations in the Assay.
- Deleted the Loss on drying test and the test for Water because the total water content is dependent upon the identity of the excipients and it would be difficult to establish meaningful criteria that would apply to all formulations. The drug product manufacturer should establish the limits for their product based on scientific evaluation of their own formulation performance and stability data.

Monograph/Section: Didanosine/Related compounds and <11>

Expert Committee: MD-AA

Expert Committee-initiated change: Since all the related compound USP Reference Standards for this test were not expected to be available at the time of publication of the First Supplement, the Committee decided not to include the related compounds section in the monograph at this time. This section will be reviewed at a later time when all the related compounds Reference Standards become available. Therefore, the related compounds Reference Standards were deleted from <11> section of this monograph.

Monograph/Section: Diphenoxylate HCl and Atropine Sulfate Oral Solution and Tablets/Assay

Expert Committee: MD-GRE

No. of Commenters: 2

Comment summary: Two commenters reported a problem meeting a tailing requirement for diphenoxylate peak, and suggested that the tailing requirement be modified or removed from the monograph.

Response: Comment incorporated. The Committee agreed to remove the tailing requirement for the diphenoxylate peak from the monograph, and to add a Note suggesting that maintaining column temperature may be helpful if a significant tailing of diphenoxylate peak is observed. Because no comments were received regarding the tailing factor for the atropine peak, this requirement was retained. The Committee recognizes that despite the tailing problem for one of the components, it is beneficial to have a single Assay method for both components as proposed in these revisions.

Monograph/Section: Doxepin Hydrochloride/Related compounds

Expert Committee: MD-PP

No. of Commenters: 3

Comment Summary #1: Two commenters requested that a Note be added to the Related compounds test indicating the need to include both E and Z isomers responses of doxepin in the calculation of unspecified impurity.

Response: Comment incorporated.

Comment Summary #2: Commenter indicated that there may be selectivity change depending on the type of column and therefore provision must be made to ensure the proper identification of Related compounds B and C.

Response: Comment incorporated. The concentration of Related compound C has been increased by a factor of two to enable easy identification.

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Monograph/Section: Dronabinol/Related compounds

Expert Committee: MD-GRE

No. of Commenters: 1

Comment summary: Commenter requested the proposal to be deferred from becoming official until the required USP Reference Standards are available for sale, and the Commenter can evaluate the proposed method.

Response: Comment not incorporated because the required USP Reference Standards will be available by the time the 1st Supplement to *USP 30* becomes official. Although the Committee is not delaying approval of the monograph for official status, the Committee is willing to consider further changes to this monograph in the future if the commenter submits a Request for Revision.

Monograph/Section: Drospirenone

Expert Committee: MD-PS

No. of Commenters: 1

Comment Summary: Commenter suggested that known impurities should be identified and relative response factors provided for calculating the limits in the Chromatographic purity section.

Response: Comment not incorporated. The sponsor indicated that relative response factors were not used when the limits were established. The Committee is willing to consider a revised Chromatographic purity test that uses the relative response factors to calculate the impurity limits with corresponding revised impurity limits.

Expert Committee-initiated change: Changed the title of the residual solvent test to "Limit of 1,2-dimethoxyethane and diisopropyl ether, if present." The residual solvent test is manufacturer-specific, but the limits provided for the test are not covered by the requirements of General Chapter <467> Residual Solvents.

Monograph/Section: Estradiol and Norethindrone Acetate Tablets

Expert Committee: MD-PS

No. of Commenters: 2

Comment Summary #1: Commenter suggested the following changes:

- Reinstate the limit of NMT 0.5% for any individual unknown impurity in the Chromatographic purity test as published in the original proposal; and clarify that the total limit for the combined estradiol and norethindrone acetate impurities is NMT 1.0%.
- Delete limits erroneously included for estradiol and norethindrone acetate in the impurity tables in the Chromatographic purity test.
- Correct all concentrations provided as μL per mL to μg per mL in the Assay.

Response: Comments incorporated.

Comment Summary #2: Commenter suggested replacing the Thin-Layer Chromatographic Identification test with an identification test that compares the retention times of peaks obtained from standard and sample preparations in the Assay.

Response: Comment partially incorporated. The Committee has added a second identification test based on the retention times of the drug substances in the Assay.

Comment Summary #3: Commenter suggested replacing the test for Loss on drying with a test for Water.

Response: Comment partially incorporated. The Committee deleted the test for Loss on drying but concluded that the water content is dependent upon the identity of the excipients and it thus would be difficult to establish meaningful criteria that would apply to all formulations.

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Comment Summary #4: Commenter suggested deleting all process related impurities that are monitored in the Chromatographic purity test.

Response: Comment not incorporated. The Committee is retaining the process related impurities in the Chromatographic purity procedure but is willing to consider deleting these impurities from the test in the future if related compound tests that monitor these impurities are included in the official monographs for the two drug substances.

Expert Committee-initiated change: The Microbial limits section was deferred from becoming official because the proposed test contains tests for the absence of Salmonella, which is not recommended for tablets.

Monograph/Section: Famotidine Injection

Expert Committee: MD-GRE

No. of Commenters: 1

Comment summary #1: Commenter reported a significant tailing when the proposed method for Related compounds and Assay was used. No alternative procedure was submitted with the comment.

Response: Comment not incorporated. Although the Committee is not delaying approval of the monograph for official status, the Committee is willing to consider further changes to this monograph in the future if a Request for Revision is submitted.

Comment Summary #2: Commenter suggested that the proposed requirements for the Content of Benzyl alcohol be revised to include a reference to General Chapter <1> Injections. General Chapter <1> Injections allows a wider range of benzyl alcohol content than the currently proposed range of 90.0-110.0% of the labeled amount.

Response: Comment incorporated.

Monograph/Section: Fexofenadine Hydrochloride Tablets

Expert Committee: MD-PS

No. of Commenters: 2

Comment Summary #1: Commenter suggested the following changes in the limits of impurities in the Related compounds test:

- Increase the limit of fexofenadine related compound A from NMT 0.35% to NMT 0.4%.
- Increase the limit of any individual other impurity from 0.1% to 0.2%.
- Delete the requirement of NMT 0.15% for total other impurities.

Response: Comment incorporated to accommodate multiple manufacturers.

Comment Summary #2: One commenter suggested that a process impurity, fexofenadine related compound B, could potentially co-elute with fexofenadine in the Related compounds test and also in the Assay.

Response: Comment not incorporated since some manufacturing processes do not produce this impurity. Although the Committee is not delaying approval of the monograph for official status, the Committee is willing to consider further revisions to the monograph to accommodate products that have this impurity if a Request for Revision is submitted.

Expert Committee-initiated change: Deleted the test for Water because the total water content is dependent upon the identity of the excipients and it would be difficult to establish meaningful criteria that would apply to all formulations. The drug product manufacturer should establish the limits for their product based on scientific evaluation of their own formulation performance and stability data.

Expert Committee-initiated change: Increased the relative standard deviation requirement for replicate injections of the Standard solution in the Related compounds procedure from NMT 1.4% to NMT 2.0% for fexofenadine and from NMT 2.8% to NMT

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3.0% for fexofenadine related compound A to make the requirements less restrictive. The Committee similarly increased the relative standard deviation requirement for replicate injections of the Standard preparation in the Assay procedure from NMT 1.4% to NMT 2.0% for fexofenadine.

Monograph/Section: Fluorometholone Acetate

Expert Committee: MD-PS

No. of Commenters: 2

Comment Summary: Commenters suggested the following changes which are based on updated data and information:

- Change Assay limits from 98.0 – 102.0% to 98.0 – 101.0%
- Delete the absorptivity calculation requirement included in the identification test B.
- Delete the third identification test included in the monograph -- thin-layer identification test.
- Change the Chromatographic purity test to the improved Related compounds test that lists in a tabular form, the related compounds of fluorometholone acetate and provide relative response factors for the calculation of the limits of these impurities.
- Two commenters suggested changing the Mobile phase composition from water and acetonitrile (50:50, v/v) to water and acetonitrile (60:40, v/v), in the Related compounds test and the Assay.
- Rename the Resolution solution in the Assay and Related compounds test, System suitability solution and change the concentration of fluorometholone acetate and fluorometholone from 0.5 mg per mL each to 0.03 mg per mL each.
- Under Chromatographic system in the Assay, two commenters suggested changing the flow rate from 1.0 mL per minute to 1.5 mL per minute. One commenter also suggested changing the resolution requirement of 4.0 between fluorometholone and fluorometholone acetate to 10, and add column efficiency requirement of 10,000 plates.
- Change the injection volume from 20 µL to 10 µL under Procedure in the Assay.

Response: Comment incorporated. The Committee determined after review of available data that the changes in the chromatographic system are necessary for the separation and quantitation of fluorometholone acetate and related compounds.

Expert Committee-initiated change: Inserted fluorometholone acetate chemical structure and the chemical name in the monograph

Expert Committee-initiated change: Specified the use of peak height in the calculation of levels of fluorometholone and fluorometholone diacetate as used for these two impurities in the validation of the Related compounds test.

Monograph/Section: Fluvoxamine Maleate Tablets/Related compounds

Expert Committee: MD-PP

No. of Commenters: 1

Comment summary: Proposed related compounds test will not allow a specified impurity to be quantified due to co-elution.

Response: Comment incorporated. The Committee has adopted a flexible monograph approach by adding a second test.

Monograph/Section: Fosinopril Sodium

Expert Committee: MD-CV

No. of Commenters: 4

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Comment Summary #1: Commenter suggested a revision of the chemical names of fosinopril related compound B and fosinopril related compound F in the footnotes under Table 1.

Response: Comment incorporated.

Comment Summary #2: Commenter requested a revision to the Related compound test method as the peak for impurity A is very broad and is difficult to quantitate and because the LOD is same as the limits specified for impurity A. The commenter also stated that the method is non specific with respect to the impurity F and impurity D.

Response: Comment not incorporated at this time. The commenter's suggested method is not completely validated for all the related compounds. The Committee will consider publishing a revision to this monograph in a future *PF* upon receipt of a Request for Revision.

Comment Summary #3: Commenter is not able to meet the resolution requirement in Test 3 for fosinopril related compound E and fosinopril related compound F. Other commenters stated that there is no issue with this test.

Response: No change made to Test 3 at this time. However, the Committee is willing to consider future revision and requested additional information.

Comment Summary #4: Commenter suggested revising the relative retention time (RRT) for impurity 1 (0.12 in *PF* to 0.58) and impurity 2 (0.24 in *PF* to 0.71).

Response: Comment incorporated after confirming the RRT of these two impurities (0.53 and 0.67). The RRT information is provided in the monograph for information purposes only and is not a compendial requirement.

Monograph/Section: Fosinopril Sodium and Hydrochlorothiazide Tablets

Expert Committee: MD-CV

No. of Commenters: 1

Comment Summary: Commenter questioned whether the final dilution in preparing the resolution solution for the Dissolution test is to be done using water or methanol.

Response: Comment incorporated. The language was revised to indicate that water was used to dilute the resolution solution.

Monograph/Section: Gonadorelin Acetate/Multiple Sections

Expert Committee: BB-PP

No. of Commenters: 2

Comment Summary #1: Commenter suggested the following changes:

- In Limit of acetic acid and trifluoroacetic acid test, change the limit of acetic acid from “between 8% and 12.5%” to “between 4.0% to 7.5%.”
- In Related compounds test, change the limit of any individual impurity from “not more than 1%” to “not more than 0.5%.”

Response: Comment not incorporated. The Committee understood that both comments related to the drug substance as it is approved for manufacture into human drug products. According to information later received by the Committee, all human products in the United States have been discontinued. The only FDA-approved gonadorelin acetate products currently marketed in the United States are for veterinary use; the proposed monograph was developed according to the tests and specifications of a FDA-approved veterinary article. Thus, the Committee has declined to change the limits for acetic acid and for individual impurities.

Comment Summary #2: In the Packaging and storage section, Commenter suggested changing the storage temperature conditions from “between –25° and –10°” to “not more than 8°; the latter temperature is similar to that stated for this article in the *European Pharmacopoeia* and the commenter provided supporting stability data.

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Response: Comment partially incorporated. The Committee reviewed the submitted data and changed the storage temperature to “not more than 8°.”

Comment Summary #3: In Identification A, Commenter suggested replacing the mass spectrometric test with a TLC test.

Response: Comment not incorporated. The Committee declined to replace the mass spectrometric test with a TLC test at this time, being of the opinion that a TLC test is not sufficiently specific to identify a small peptide.

Comment Summary #4: In Water test, Commenter suggested changing the limit of water content from “not more than 7.0%” to “not more than 7.0% for the monoacetate form and from 4.0% to 7.0% for the diacetate form.”

Response: Comment not incorporated. This comment related to articles intended for manufacture of human dosage forms and the human drug products have been discontinued in the United States. As indicated below, the Committee decided to add a Labeling statement indicating that the article be labeled for “veterinary use only.”

Comment Summary #5: In Related compounds test, Commenter suggested replacing the proposed methods with an alternative.

Response: Comment not incorporated, as the commenter did not provide a rationale for this replacement.

Expert Committee-initiated Change: To reflect the current regulatory status of gonadorelin acetate in the United States, the following Labeling statement has been added to the monograph: “Label it to indicate it is for veterinary use only.”

Monograph/Section: Human Insulin Isophane Suspension and Human Insulin Injection

Expert Committee: NOM

No. of Commenters: 1

Comment Summary: Commenter objected to the term Biphasic Isophane Insulin Human Suspension in that this product is a combination product and this nomenclature is not consistent with the current label.

Response: Comment incorporated. The Committee approved the name Human Insulin Isophane Suspension and Human Insulin Injection.

Monograph/Section: Hydrocodone Bitartrate/ Related compounds test

Expert Committee: MD-CCA

No. of Commenters: 1

Comment Summary: Commenter indicated that they encountered co-elution and resolution problems with the proposed Related compounds test proposed in *PF* 30(5).

Response: The Committee decided not to make the Related compounds test section official at this time. The Committee will work to develop a more satisfactory method for future adoption.

Monograph/Section: Hydrocodone Bitartrate and Homatropine Methylbromide Tablets

Expert Committee: MD-CCA

No. of Commenters: 0

Expert Committee-initiated change: The Committee decided to approve the monograph as official with the exception of the dissolution section, which has not yet been approved by the Biopharmaceutics Committee.

Monograph/Sections: Ibuprofen/ USP Reference standards; Limit of; Assay.

Expert Committee: MD-CCA

No. of Commenters: 1

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Comment Summary #1: Commenter claimed that the title “impurity C”, a specified impurity, is already assigned to an amide in Ph. Eur. while the 4-isobutylacetophenone (IBAP) (referred to as impurity C in the USP) is already assigned as impurity E in the former publication. Commenter suggests harmonization with existing Ph. Eur. monograph and name IBAP as “Related Compound E” to prevent confusion within the industry.

Response: Comment not incorporated because it is against USP's policy to approve a name change to a reference standard which has already appeared in the Reference Standard Catalog.

Comment Summary #2: Commenter suggested USP harmonize with Ph. Eur. and adopt a gradient HPLC method (in lieu of the current isocratic LC method) that would detect potential impurities present in Ibuprofen to safeguard public safety.

Response: Comment not incorporated. The Committee suggests putting the entire gradient HPLC method in future *PF* for public comments. The Committee requests that the commenter provide chromatograms that indicate that the current USP method is incapable of detecting these impurities.

Monograph/Sections: Ibuprofen Oral Suspension/ USP Reference standards; Limit of; Assay

Expert Committee: MD-CCA

No. of Commenters: 1

Comment Summary #1: Commenter claimed that “impurity C”, a specified impurity, is already assigned to an amide in Ph. Eur. while the 4-isobutylacetophenone (IBAP) (referred to as impurity C in the USP) is already assigned as impurity E in the former publication. Commenter suggests harmonization with existing Ph. Eur. monograph and name IBAP as “Related Compound E” to prevent confusion within the industry.

Response: Comment not incorporated because it is against USP's policy to approve a name change to a reference standard which has already appeared in the Reference Standard Catalog.

Monograph/Sections: Ibuprofen Tablets/ USP Reference standards; Limit of; Assay.

Expert Committee: MD-CCA

No. of Commenters: 2

Comment Summary #1: Commenter claimed that “impurity C,” a specified impurity, is already assigned to an amide in Ph. Eur. while the 4-isobutylacetophenone (IBAP) (referred to as impurity C in the USP) is already assigned as impurity E in the former publication. Commenter suggests harmonization with existing Ph. Eur. monograph and name IBAP as “Related Compound E” to prevent confusion within the industry.

Response: Comment not incorporated because it is against USP's policy to approve a name change to a reference standard which has already appeared in the Reference Standard Catalog.

Summary Comment #2: Commenter objected to the revision to the preparation of the (4-IBAP) standard solution and recommended deleting the current concentration “of about 0.12 mg per mL” as it is an approximation and could be misleading.

Response: Comment incorporated.

Monograph/Section: Irbesartan/Multiple sections

Expert Committee: MD-CV

No. of Commenters: 4

Comment Summary #1: The commenter suggested the following Assay limit of 98%-102% be revised to 97%-102.5%.

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Response: Comment not incorporated. The Committee will consider further revisions to the monograph as suggested if the commenter is able to provide validation for the suggested limits.

Comment Summary #2: Commenter suggested revising the concentration of the test solution from 0.5 mg/ml to 1 mg/ml.

Response: Comment incorporated.

Comment Summary #3: Commenter suggested revising the calculations for the other impurities.

Response: Comment incorporated.

Comment Summary #4: Commenter suggested deleting the preparation of the Diluted standard solution.

Response: Comment incorporated.

Monograph/Section: Irbesartan Tablets

Expert Committee: MD-CV

No. of Commenters: 1

Comment Summary #1: Commenter suggested using tablets for preparing the sample solution in the Assay instead of powdered tablets,

Response: Comment not incorporated. The Committee believes that grinding tablets prior to extraction allows for a more robust procedure and the analyst should be able to handle the extra precautions necessary.

Comment Summary #2: Commenter suggested revising the limits for the irbesartan related compound A, and the total impurities from 0.3% and 0.6% to 0.2% and 0.5%.

Response: Comment incorporated.

Comment Summary #3: Commenter suggested revising the verbiage used in the description of the procedure to prepare the test solution.

Response: Comment not incorporated. The Committee believes that the current USP text conveys the intended message without any confusion to the user.

Monograph/Section: Isosorbide Mononitrate Tablets

Expert Committee: MD-CV

No. of Commenters: 1

Comment Summary: Commenter suggested revising the Isosorbide mononitrate RS and the Isosorbide related compound A RS to Diluted Isosorbide mononitrate RS and Diluted Isosorbide mononitrate related compound A RS.

Response: Comment incorporated.

Monograph/Section: Lidocaine and Prilocaine Cream

Expert Committee: MD-PS

No. of Commenters: 1

Comment Summary #1: Commenter suggested the following changes based on their approved product:

- Change Assay limits from 95.0 – 105.0% to 90.0 – 110.0%.
- Change the storage requirements from "store at controlled room temperature" to "do not store above 30° and do not freeze."
- Consider using prilocaine free base as the USP reference standard rather than prilocaine hydrochloride.
- Revise the test of pH to include determinations on undiluted Cream.

Response: Comment incorporated.

Comment Summary #2: Commenter suggested making the following changes in the test for Related compounds:

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

- Delete all process related impurities that are monitored in the test.
- Clarify the definitions of the following terms used in the formula for calculating impurities: r_u , r_s , and L .
- Change the limit of o-toluidine from NMT 0.1% to NMT 2.0% and change the limit of 2,6-dimethylaniline from NMT 0.1% to NMT 0.04%.
- Simplify the sample preparation procedure.
- Delete requirement to keep solutions at 10° during injection as the samples are stable at room temperature.
- Improve the procedure to resolve prilocaine and related compound B as these are not baseline resolved.

Response: After reviewing available data, the Committee concluded that issues related to the impurity limits and other aspects of the Related compounds test need to be resolved before the test is made official. Therefore, the Committee approved the monograph as official without the Related compounds test. The limit for total impurities in the Related compounds test is NMT 1.0.

Expert Committee-initiated change: Made editorial changes in the Identification test to indicate that the retention times of both lidocaine and prilocaine from injections of Standard preparation and Assay preparation are compared.

Monograph/Section: Meloxicam

Expert Committee: MD-CCA

No. of Commenters: 1

Comment Summary: Commenter pointed out that the method proposed in *PF* used an Intersil ODS-2 column and a mobile phase pH buffer of 9.1, and that the manufacturer's recommended pH range for the column is 2-8.

Response: Comment not incorporated at this time. The Committee feels that the sponsor of the monograph had demonstrated adequately that the high pH did not affect the stability of the column. The Committee will consider a flexible monograph approach because the commenter has provided a fully validated proposal.

Expert Committee-initiated change: The Committee decided to approve the monograph as official without the dissolution section which has not yet been approved by the Biopharmaceutics Expert Committee.

Monograph/Section: Mupirocin Calcium

Expert Committee: MD-ANT

No. of Commenters: 2

Comment Summary #1: Commenter recommended that the Crystallinity test be removed as it would exclude other forms of Mupirocin.

Response: Comment incorporated.

Comment Summary #2: A commenter requested that an X-ray diffraction test be added.

Responses: Comment not incorporated. The Committee did not incorporate the X-ray diffraction test as it could exclude other forms of Mupirocin.

Monograph/Section: Mupirocin Cream

Expert Committee: MD-ANT

No. of Commenters: 1

Comment Summary: Commenter requested that the pH range be widened.

Response: Comment not incorporated. The Committee did not find the supporting documentation adequate to support the change.

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Monograph/Section: Norgestimate and Ethinyl Estradiol Tablets

Expert Committee: MD-PS

No. of Commenters: 3

Comment Summary #1: Commenter suggested that the Assay limits be changed from 90.0 – 110.0% to 88.0 – 112.0%

Response: Comment not incorporated, following the Committee's review of the available data and comments.

Comment Summary #2: Commenter suggested the following changes to the Assay:

- Change the pore size of the filter used to filter Standard preparation and Assay preparation in the Assay from 0.2 µm to 0.45 µm.
- Change the relative standard deviation requirement for replicate injections of (Z)-norgestimate, (E)-norgestimate, and ethinyl estradiol from 3.0% to 2.0% in the Chromatographic system section of the Assay.

Response: Comment incorporated.

Comment Summary #3: Commenter suggested the following changes to the Assay:

- Change the detection wavelength from 230 nm to 225 nm.
- Change flow rate from 2.1 mL per minute to 1.2 mL per minute.
- Change injection volume from 25 µL to 50 µL.

Response: Comments not incorporated, following the Committee's review of the available data and comments.

Comment Summary #4: Two commenters suggested changing the relative standard deviation requirement for replicate injections of norgestimate and ethinyl estradiol from 3.0% to 2.0% in the Chromatographic system section of the Chromatographic purity test.

Response: Comments incorporated

Monograph/Section: Prednicarbate Cream

Expert Committee: MD-PS

No. of Commenters: 1

Comment Summary: Commenter suggested that the limit of individual unspecified impurity in the Related compounds test for the Cream be changed from 0.1% to 0.5% per ICH guidance (Q3B(R)). The commenter also suggested clarifying that the specification for both prednicarbate related compound B and prednicarbate related compound C is NMT 2.0%.

Response: Comment incorporated.

Monograph/Section: Prednicarbate Ointment

Expert Committee: MD-PS

No. of Commenters: 1

Comment Summary #1: Commenter suggested that the limit of individual unspecified impurity in the Related compounds test for the Ointment be changed from 0.1% to 0.5% per ICH guidance (Q3B(R)). The commenter also suggested clarifying that the specification for both prednicarbate related compound B and prednicarbate related compound C is NMT 2.0%.

Response: Comment incorporated.

Monograph/Section: Ondansetron/Packaging and Storage

Expert Committee: MD-PP

No. of Commenters: 0

Expert Committee-initiated change: Packaging and storage statement added.

Monograph/Section: Quinapril Tablets/Packaging and storage

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Expert Committee: MD-CV

No. of Commenters: 0

Expert Committee-initiated change: The Committee approved the monograph as published in *PF* 29(4) with the addition of a storage statement.

Monograph/Section: Ropivacaine Hydrochloride Injection

Expert Committee: MD-PS

No. of Commenters: 1

Comment Summary #1: Commenter suggested deleting references to small volume injections in the test for Particulate matter since there are both small and large volume presentations of the Injection.

Response: Comment incorporated.

Comment Summary #2: Commenter suggested deleting the formula for calculating the limit of related compound A in the Limit of 2,6-dimethylaniline (ropivacaine related compound A, base) test and instead comparing the peak response of related compound A obtained from the Test solution with the corresponding peak in the Standard solution.

Response: Comment incorporated.

Comment Summary #3: Commenter suggested correcting the formula provided in the Assay for calculating the concentration of ropivacaine hydrochloride in the Injection.

Response: Comment incorporated.

Monograph/Section: Topiramate

Expert Committee: MD-PP

No. of Commenters: 2

Comment Summary: The commenters suggested that the proposed related compounds test is not adequate to reflect the products on the US market.

Response: The Committee decided to approve the monograph as official without the Related compounds test. The Committee will revise the Related compounds test as needed via additional In-Process Revisions.

Expert Committee-initiated Change: Because all the solvents listed are at or below <467> limits, and the General Notices specifically refer to Residual solvents, this requirement has been removed from the monograph.

Monograph/Section: Vasopressin/Identification-B

Expert Committee: BB-PP

No. of Commenters: 1

Comment Summary: Commenter suggested that the monograph should allow for either an animal bioassay or the mass spectrometry (MS) test identification test B in the monograph.

Response: Comment not incorporated. The Committee decided that the animal assay should be removed from the monograph as part of the USP effort to reduce animal testing. The Committee decided that the MS test along with other tests in the monograph is sufficient to ensure the identity and bioactivity of the molecule. The Committee also reached consensus that MS has developed sufficiently to become a routine release test for peptide drugs.

Monograph/Section: Verapamil Hydrochloride Injection/Multiple sections

Expert Committee: MD-CV

No. of Commenters: 1

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Comment Summary: Commenter suggested removing the cross references to the drug substance monograph and instead adding the tests for related compounds and Assay to this monograph.

Response: Comment incorporated.

Monograph/Section: Verapamil Hydrochloride Tablets/ Multiple sections

Expert Committee: MD-CV

No. of Commenters: 1

Comment Summary: Commenter suggested removing the cross references to the drug substance monograph and instead adding the tests for related compounds and Assay to this monograph.

Response: Comment incorporated.

Monograph Name/Section: Sterile Water for Inhalation

Expert Committee: PW

No. of Commenters: 0

Expert Committee-initiated Changes: The Committee clarified the requirements relating to Water Conductivity, to be sure that users complete only Step 4 of Stage 2 of Water Conductivity <645>, and do not proceed to Step 5. The Committee also implemented changes to improve clarity or definition, eliminate errors or redundancies, promote consistency with other portions of the USP-NF, or otherwise resolve textual problems.

Monograph Name/Section: Sterile Water for Irrigation

Expert Committee: PW

No. of Commenters: 0

Expert Committee-initiated Changes: The Committee clarified the requirements relating to Water Conductivity, to be sure that users complete only Step 4 of Stage 2 of Water Conductivity <645>, and do not proceed to Step 5. The Committee also implemented changes to improve clarity or definition, eliminate errors or redundancies, promote consistency with other portions of the USP-NF, or otherwise resolve textual problems.

Monograph Name/Section: Sterile Purified Water

Expert Committee: PW

No. of Commenters: 0

Expert Committee-initiated Changes: The Committee clarified the requirements relating to Water Conductivity, to be sure that users complete only Step 4 of Stage 2 of Water Conductivity <645>, and do not proceed to Step 5. The Committee also implemented changes to improve clarity or definition, eliminate errors or redundancies, promote consistency with other portions of the USP-NF, or otherwise resolve textual problems.

REVISED MONOGRAPH TITLES: Alumina, Magnesia, and Calcium Carbonate Tablets, Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets, Alumina, Magnesia, and Simethicone Tablets, Calcium Carbonate, Magnesia, and Simethicone Tablets, Dihydroxyaluminum Sodium Carbonate Tablets, Magaldrate and Simethicone Tablets, Phenytoin Tablets, and Thiabendazole Tablets.

Expert Committee: NOM

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

During its May 23-24, 2006 meeting, the Committee adopted the following policy for nomenclature and labeling of chewable tablets:

- (1) The format "[DRUG] Tablets" will be used for tablets that are swallowed whole or that MAY be chewed AND for which there is no intended alternative method of administration. When appropriate, there will also be a labeling statement indicating that the tablets MAY be chewed.
- (2) The format "[DRUG] Chewable Tablets" will be used for tablets that MUST be chewed AND for which there is no other alternative route of administration. There will also be a labeling statement indicating that the tablets MUST be chewed.

In the discussion of this topic, it was noted that the main issue is when should a product characteristic appear in the title and when should it appear in a labeling statement. The Committee agreed that ensuring the product is dispensed and used properly is the key consideration. One nomenclature option considered was that the word "chewable" should be part of the labeling statement but not part of the title. Another option was to use different nomenclature for a product that MAY be chewed vs. a product that MUST be chewed. As shown in policy points (1) and (2) above, the Committee agreed that the preferred nomenclature approach is to label a product that MAY be chewed as "Tablets" with a labeling statement indicating that the tablets MAY be chewed, while a product that MUST be chewed would be labeled "Chewable Tablets" with a labeling statement indicating that the tablets MUST be chewed.

Therefore, based on the above chewable tablets nomenclature policy, the titles for the monographs listed under "Revised Monograph Titles" above have been revised from the general form [DRUG(S)] Tablets to the general form [DRUG(S)] Chewable Tablets, with a delayed implementation date for the new titles. These monographs cover tablets that must be chewed before being swallowed, and the Committee felt that the addition of the term "Chewable" in these monograph titles represented a significant improvement in that the consumer will now be provided with added information, along with the labeling statement directing that "tablets are to be chewed before being swallowed," to hopefully assure that the product will be used properly to achieve the benefit of the medication.

The revised titles for the existing monographs will become official on February 1, 2010. Use of these titles would be permitted as of the August 1, 2007 official date of the First Supplement to *USP 30- NF 25*, but use of these titles would not become mandatory until February 1, 2010. The 30-months delayed implementation is intended to allow time for product label changes to be made and for health practitioners and consumers to become familiar with the revised terminology.

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

DIETARY SUPPLEMENTS

Monograph/Section: Asian Ginseng Capsules

Expert Committee: DSB

No. of Commenters: 1

Comment Summary: Commenter, the sponsor of Method 1 for the test Content of ginsenosides, observed problems of recovery in some of its soft gelatin capsule formulations and therefore requested the deletion of Method 1 from the monograph.

Response: Comment incorporated.

Monograph/Section: Methylsulfonylmethane

Expert Committee: DSN

No. of Commenters: 1

Comment Summary #1: Commenter suggested that a flow rate of 30 mL per minute, an error in the *PF* draft, and a split ratio of 20:1 be changed to a split ratio of 2:1 and a flow rate of 5 mL per minute in the Assay.

Response: Comment incorporated

Comment Summary #2: Commenter suggested that the Water test indicate that a larger sample size of 500 mg may be used.

Response: Comment incorporated

Comment Summary #3: Commenter suggested that a flow rate of 30 mL per minute, an error in the *PF* draft, and a split ratio of 20:1 be changed to a split ratio of 2:1 and a flow rate of 5 mL per minute. In addition, the commenter suggested that the final concentration of the Sensitivity check solution should be 2.0 micrograms per mL

Response: Comment incorporated.

Monograph/Section: Methylsulfonylmethane Tablets

Expert Committee: DSN

No. of Commenters: 1

Comment Summary: Commenter suggested that a flow rate of 30 mL per minute, an error in the *PF* draft, and a split ratio of 20:1 be changed to a split ratio of 2:1 and a flow rate of 5 mL per minute in the Assay

Response: Comment incorporated.

Monograph/Section: Tomato Extract Containing Lycopene

Expert Committee: DSB

No. of Commenters: 1

Comment Summary: Commenter suggested that in the Limits of aflatoxins test, language be added stating: “Except to spot 20 μ L of either Test solution 1 or Test solution 2.” This recommendation was intended to make the presumed amount in the test solution fall within the range specified by the standard solutions.

Response: Comment incorporated.

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

GENERAL CHAPTERS

Chapter Name: <11> USP Reference Standards

Expert Committee: RS

No. of Commenters: 2

Comment Summary #1: Commenter suggested changing the phrase “Suitability for use in nonofficial application(s) should be validated by the purchaser” to “Suitability for use in other application(s) rests with the purchaser.”

Response(s): Comment incorporated, with additional change as follows: “Assessment of the suitability for use in other application(s) rests with the purchaser.”

Comment Summary #2: Commenter suggested that under PROPER USE, allowance for small sample sizes to measure loss on drying for USP reference standards should be made. There has long been such a statement in the chapter for titrimetric water determinations.

Response: Comment incorporated.

Expert Committee-initiated change: The scope of USP reference standard categories was broadened to include those that may be developed to support monographs that are developed by USP, but not published in USP-NF.

Expert Committee-initiated change: The text: “USP does not provide Certificates of Analysis...” was changed to “USP generally does not provide Certificates of Analysis...”, since there are a few standards currently official which require that USP provide them.

General Chapter/Section: <730> Plasma Spectrochemistry

Expert Committee: GC

No. of Commenters: 0

Expert Committee-initiated change: A few editorial changes are made to clarify the text. These changes include 1) spelling correction in the Fourth paragraph under "Sample Preparation" and 2) removal of a redundant sentence in the fourth paragraph under "Sample Introduction."

General Chapter/Section: <1065> Ion Chromatography/Apparatus

Expert Committee: GC

No. of Commenters: 1

Comment Summary: Commenter suggested that in addition to specifying that a metal-free tubing system should be used for trace metal analysis, the column and guard column should also be metal-free.

Response: Comment incorporated. The Committee deleted the word tubing to indicate that a metal-free system should be used for trace metal analysis.

General Chapter/Section: <1080> Bulk Pharmaceutical Excipients—Certificate of analysis

Expert Committee: EGC

No. of Commenters: 2

Comment Summary #1: Commenter suggested the following changes:

- 1) Under COMPENDIAL DESIGNATION, it is stated: "...the article, when stored correctly, will comply...". Commenter recommended this be changed to "...the article, when stored according to recommended conditions, will comply..."
- 2) Since this is a general information chapter, the commenter suggested the remaining use of the term "must" throughout the chapter be changed to "should".

Response: Comment incorporated.

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Comment Summary #2: In Expiration Date and Recommended Re-Evaluation Date, the last paragraph refers to "long term stability data." One commenter suggested further defining or clarifying "long term." Another commenter suggested that this section provide further clarification by replacing the phrase "If long term stability data are not available..." with "If data is not available from formalized stability studies...." That commenter suggested that the purpose of the sentence is to indicate that even where formalized stability studies have not been performed, the excipient manufacturer should at least provide some type of statement on the Certificate of Analysis related to the stability of the material so the user understands whether the material presents any stability concerns.

Response: Comment incorporated.

General Chapter/Section: <1118> Monitoring Devices-Time, Temperature, and Humidity/Data Loggers

Expert Committee: PS

No. of Commenters: 1

Comment Summary: The commenter felt that the revision as written suggests that radio frequency identification technology is capable of remotely monitoring temperature and humidity of a package while in transit. The current technology only allows for the storage of temperature and humidity data during transit, which can be downloaded to a database once the product reaches its destination.

Response: Comment incorporated. After reviewing the comments and text in question, the Committee agreed that the paragraph as written could be misleading about the capabilities of radio frequency identification technology. The paragraph has been rewritten to clarify the committee's original intent.

General Chapter/Section: <1184> Sensitization Testing

Expert Committee: GTMDB

Number of Commenters: 2

Comment Summary #1: Several commenters suggested non-substantive, editorial changes.

Response: Comment partially incorporated. The Committee reviewed each of these suggestions to determine whether it offered an improvement in clarity or, eliminated an obvious error or redundancy, or otherwise identified textual problems that were not previously noted by USP. Where the proposed alternative language or other changes suggested were superior to the proposal, they were adopted in substance or verbatim. Where the suggestions did not offer any improvement, the Committee declined to accept them. In finalizing these comments/ revisions, the Committee has taken into consideration that this is a general information chapter.

Comment Summary #2: Commenter suggested that this chapter is beyond the scope of the USP and does not include methods employed by a particular company and therefore should not be included in the *USP-NF*.

Response: Comment not incorporated. The purpose of this chapter is clearly informational and not prescriptive. The chapter provides a general overview of existing methods. The comment was not supported by specifics and therefore not accepted.

Comment Summary #3: Commenter proposed that the chapter be harmonized with the ISO standard 10993-10: Biological Evaluation of Medical Devices: Tests for Irritation and delayed-type hypersensitivity.

Response: Comment not incorporated. The Committee determined that this harmonization should not delay approval of the chapter as official, and instead could be considered in a future revision.

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

General Chapter/Section: <1208> Sterility Testing-Validation Of Isolator Systems/Multiple Sections

Expert Committee: MSA

Number of Commenters:

Comment Summary #1: Several commenters were favorable but suggested the need for minor changes to improve or clarify the revision proposal to the General Information Chapter.

Response: Comment partially incorporated. The Committee reviewed each of these suggestions to determine whether it offered an improvement in clarity or, eliminated an obvious error or redundancy, or otherwise identified textual problems that were not previously noted by USP. Where the proposed alternative language or other changes suggested were superior to the proposal, they were adopted in substance or verbatim. Where the suggestions did not offer any improvement, the Committee declined to accept them. In finalizing these comments/ revisions, the Committee has taken into consideration that this is a general information chapter.

Comment Summary #2: Commenter objected to language in the Introductory section on Isolators which states, "Although a pair of sterile gloves is frequently worn under the isolator gloves . . ." as the wearing of a second pair of non-sterile gloves should be an option.

Response: Comment not incorporated. The text as stated is merely an observation and does not mean that the wearing of gloves is a recommended practice.

Comment Summary #2: Commenter suggested that additional language be added to the section on Isolator Design and Construction which states "In general, both open and closed isolators are maintained at positive pressure relative to the surrounding environment and overpressures of 20 to 40 Pa are typical." Commenter suggested that this section include the statement: "The appropriate minimum pressure differential established by a user will depend upon the isolator design."

Response: Comment partially incorporated. The Committee recognized that there are isolators that operate typically at a higher pressure differential, and thus has changed the statement to read "...overpressures of 20 Pa or more are typical."

Comment Summary #3: Commenter objected to the following statement in the section on Isolator Design and Construction / Transfer Ports and Doors: "The exposed gasket should be treated with a sporicidal agent immediately after the connection is made." The commenter claimed that this created a requirement of having liquid sporicidal agents within your testing isolator and exposing that environment to sporicidal agents during testing. The commenter suggested that it would be more prudent to apply a sporicidal agent to the gasket of each RTP connection just prior to docking.

Response: Comment incorporated. The statement was changed to read "routinely disinfected immediately after the connection is made, and before materials are transferred through the RTP."

Comment Summary #4: Commenter suggested that additional language be added to the section on Validation of the Isolator System/ Operational Qualification / Isolator Integrity Check which states: "To safeguard against adventitious contamination, isolators are operated at a positive pressure differential of about 20-40 Pa during normal operation." Commenter suggested that the section include the statement: "The appropriate minimum pressure differential established by a user will depend upon the isolator design."

Response: Comment partially incorporated. Original statement changed to "To safeguard against adventitious contamination, isolators are operated at a suitable positive pressure differential during normal operation."

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Comment Summary #5: Commenter objected to the following statement in the section on Maintenance of Asepsis within the Isolator Environment: "Continuous nonviable particulate monitoring within the isolator's enclosure is ideal..." Commenter noted that a previous statement within the In-process Revision stated "isolator need not meet Class 5 conditions during operation." Commenter claimed that imposition of performing non-viable monitoring for sterility testing was unnecessary, provided little data, and imposed additional equipment, decontamination validation of the sensor, and cost to the user. According to the commenter, filters that are used in these isolators are extremely robust with a long history of integrity. With the type of activity associated with testing, particles are being generated continuously, and particle testing should be performed "at rest" and associated with OQ validation.

Response: Comment not incorporated. The statement as it appears is only suggestive of "ideal" scenario, and not prescriptive.

Comment Summary #6: Commenter objected to the following statement in the section on Operational Qualification (OQ): "Gas and vapor decontamination methods require fans in the isolator to distribute...." Commenter suggested that to meet current practices, the sentence should indicate that fans may be required, as follows: "Gas and vapor decontamination methods may require fans in the isolator to distribute..."

Response: Comment incorporated.

General Chapter/Section: <1217> Tablet Breaking Force

Expert Committee: PDF

No of Commenters: 2

Comment Summary #1: The third paragraph of the Introduction states that loading occurs across the tablet diameter and fracture occurs in that plane. The commenter suggested that clarifying language be included to better define the plane that is referenced.

Response: Comment not incorporated. The Committee determined that the content of the paragraph is not misleading. While any number of planes could contain the diameter across which the loading occurs, further clarification of a particular plane is not essential to the value of the Chapter.

Comment Summary #2: Two commenters voiced concern that the upper limits for platen speed of 3.0 mm per second are an unnecessary restriction on available instrumentation. One commenter described a tester that had produced data that was "reproducible and adequate for our purposes" and operated at 3.3 mm per second.

Response: Comments incorporated. The Committee changed the text to include a constant speed of 3.5 mm per second but only as a descriptive comment on currently available equipment. The wording was altered to eliminate the appearance of a specification.

Expert Committee-initiated Change: The third paragraph of the Rate and Uniformity of Loading section was altered from the *PF* proposal to emphasize the need to conduct the testing under consistent conditions if comparison of product quality is of interest. The comparability of data from different equipment using different designs should not be assumed.

Expert Committee-initiated Change: The Dependence of Breaking Force on Tablet Geometry and Mass section was modified from the *PF* proposed text to reinforce the notion that testing results will be meaningful only if the testing is performed in a consistent manner, and that testing will provide the greatest benefit as a manufacturing control if the procedure and the tablet failure can be related to the information on tablet breaking that was part of the product development.

COMMENTARY—1ST SUPPLEMENT TO USP30 - NF25

Expert Committee-initiated Change: The Committee added a statement in the Units, Resolution, and Calibration section giving preference to the use of standard (SI) units of force for the test results. This statement was meant to add emphasis to the caution regarding conversion between Strong Cobb units and Newtons or kiloponds.

General Chapter: <1222> Terminally Sterilized Pharmaceutical Products-Parametric Release

Expert Committee: MSA

Number of Commenters: 2

Comment Summary #1: Commenters suggested the need for minor changes to improve or clarify the revision proposal to <1222>.

Response Summary: Comment partially incorporated. The Committee reviewed each of these comments to determine whether it offered an improvement in clarity or, eliminated an obvious error or redundancy, or otherwise identified textual problems that were not previously noted by USP. Where the proposed alternative language or other changes suggested were superior to the proposal, they were adopted in substance or verbatim. Where the suggestions did not offer any improvement, the Expert Committee declined to accept them. In finalizing these comments/ revisions, the Expert Committee has taken into consideration that this is a general information chapter.

Comment Summary #2: Commenter suggested that the sentence in the Introduction section that reads “The agencies would need assurance that any marketed sample of product will be sterile and would pass the requirements for sterility as found in the general chapter Sterility Tests { 71 }” be re-written, as it could be interpreted that Sterility Tests should still be performed for products released under Parametric Release

Response: Comment incorporated.

Comment Summary #3: Commenter suggested a change to the following sentence in the Introduction section: “Therefore, once a sterilization process is fully validated and operates consistently, a combination of physical sterilization data such as accumulated lethality or dosimetry in combination with other methods, such as biological indicators or physicochemical integrators, ...” Commenter suggested that the term “biological indicators or physicochemical integrators” be replaced with the term “load monitors”, to better reflect the current definitions of indicators and integrators.

Response: Comment incorporated.

Comment Summary #4: Commenter noted that while the Introduction indicated that “[t]here are four modes of sterilization that theoretically and practically could qualify for parametric release, moist heat, dry heat, ethylene oxide, and ionizing radiation sterilization,” only three modes of sterilization are discussed. Commenter noted that it was unclear as to why dry heat sterilization is not discussed.

Response: Comment not incorporated. The chapter clearly indicates that it will only discuss “some specific modes of sterilization”

Comment Summary #5: Commenter suggested that the following sentence in the Introduction section was misleading and should be deleted: “SAL is often used to describe the process capability of aseptic processes...”.

Response: Comment incorporated.

Comment Summary #6: Commenter suggested that the following sentence in the Introduction section be deleted: “Certain bioburden processes may include products that may be inherently antimicrobial or that can withstand more lethal sterilization processes. Products in this category will require correspondingly less rigorous control of the manufacturing process and less restrictive in-process control points.” Commenter

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claimed it was inappropriate to associate product characteristics with the degree of process control.

Response: Comment incorporated.

Comment Summary #7: Commenter requested that the following statement in the Introduction section be revised or clarified: “Generally, process resistant biological indicators containing approximately 10^6 spores are used to establish the endpoint of the sterilization process “. Commenter noted that the endpoint of the sterilization process is not based on the BI challenge.

Response: Comment incorporated and sentence clarified

Comment Summary #8: Commenter requested that the following text in the Introduction section be clarified: “However, a spore population of N_0 can be chosen to provide an appropriate challenge to evaluate the process. Overkill is generally defined as a process that would produce a minimum of F_0 of 12 minutes (see Critical Operating Parameters below) and is demonstrated biologically based upon the spore log reduction of calibrated biological indicators.”

Response: Comment incorporated and text clarified

Comment Summary #9: Commenter suggested that the phrase “relative to the inactivation of bioburden” be removed from the General Review, Validation of Sterilization Process section.

Response: Comment incorporated.

Comment Summary #10: Commenter objected to the sentence in the General Review, Validation of Sterilization Process that reads: “The use of biological indicators for establishing or periodically validating gamma radiation sterilization processes is not required.” Commenter claimed that this statement was too restrictive and not necessarily true, and should not be included in a general information chapter.

Response: Comment incorporated and sentence revised accordingly.

Comment Summary #11: Commenter suggested that the phrase “when using a biological indicator microorganism with a D value of 1.0 minute” be deleted from the footnote in the Validation of Sterilization Process section, since the D value of the BI is not relevant to the definition of F_0 .

Response: Comment incorporated and text revised accordingly.

Comment Summary #12: Commenter suggested clarification of the following sentence in the General Review, Sterilization Microbiology Control Program section: “Monitoring of overkill processes for bioburden is generally required only in cases where the product is supportive of microbial growth, and, therefore, biological amplification of any bioburden is likely.”

Response: Comment incorporated and sentence revised accordingly.

Comment Summary #13: Commenter objected to the term “‘go-no go’ hurdles” in the General Review, Change Control System section as unclear.

Response: Comment accepted and sentence revised accordingly. The term “‘go-no go’ hurdles” has been deleted

Comment Summary #14: Commenter objected to the use of the term “may” in the sentence in the General Review, Release Procedures section that reads: “...results of indicators that may have been used to demonstrate process control.” Commenter noted that the word “may” was inappropriate since load monitors are required by current GMP policy.

Response: Comment incorporated and sentence revised accordingly.

Comment Summary #15: Commenter noted that in the Modes of Sterilization, Moist Heat Sterilization section there was no mention of dwell time as a critical parameter, and suggested that this be added.

Response: Comment incorporated.

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Comment Summary #16: Commenter objected to the statement in the Modes of Sterilization, Moist Heat Sterilization section that read: “F₀ is not listed as a critical parameter.....” Commenter claimed this language was confusing and not supported in this paragraph.

Response: Comment incorporated and text modified accordingly

Comment Summary #17: Commenter suggested with regard to the Modes of Sterilization, Moist Heat Sterilization section generally that it is inappropriate for USP to decide what is critical and what is secondary in this information chapter.

Response: Comment incorporated. The text has been suitably modified and is not prescriptive.

Comment Summary #18: Commenter objected to language in the Modes of Sterilization, Ethylene Oxide Sterilization section which suggested that the use of load monitors is optional.

Response: Comment incorporated and text modified accordingly

Comment Summary #19: Commenter suggested that in the Modes of Sterilization, Radiation Sterilization section, SAL be changed to PNS.

Response: Comment incorporated.

Comment Summary #20: Commenter suggested that the following text be deleted from the Modes of Sterilization, Radiation Sterilization section: "...because the radiation cycle is calculated on the basis of the bioburden, dosimetric release should include a batch evaluation of the bioburden number and of its radiation resistance." Commenter noted that the radiation dose is calculated on the basis of the bioburden, not the cycle.

Response: Comment incorporated.

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NF MONOGRAPHS

Monograph/Section: Calcium Silicate/Multiple Sections

Expert Committee: EM1

No. of Commenters: 2

Comment Summary: Commenter suggested that we retain the official temperature of 1300° in the Assay.

Response: Comment not incorporated. The Committee decided that the proposed change would require additional supporting data.

Comment Summary: Commenter suggested that the specification limit be changed from 10 µg to 50 µg in the Limit of fluoride.

Response: Comment not incorporated. The Committee decided that the proposed change would require additional supporting data, as the commenter's data is not sufficient to make an adequate determination.

Monograph/Section: Coconut Oil

Expert Committee: EM2

No. of Commenters: 0

Expert Committee-initiated change: Add a clarification in Alkaline impurities: Change the sentence from "Neutralize the solution if necessary with 0.01 N hydrochloric acid or 0.01 N sodium hydroxide" to "Neutralize the solution to green color if necessary with 0.01 N hydrochloric acid or 0.01 N sodium hydroxide".

Monograph: Erythritol

Expert Committee: EM1

No. of Commenters: 1

Comment Summary: Commenter suggested that the test for Water be changed to Water, Method I <921>: not more than 0.5%.

Response: Comment incorporated.

Monograph/Section: Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion

Expert Committee: EM2

No. of Commenters: 0

Expert Committee-initiated change: Change the sentence from "Identification, Infrared Absorption <197K>" to "Identification, Infrared Absorption <197K>—the test specimen dried as specified in the Loss on drying test."

Monograph/Section: Polyethylene Oxide/Multiple Sections

Expert Committee: EM2

No. of Commenters: 0

Expert Committee-initiated change: Heavy metal test by ICP proposal is canceled. Approved the other revisions as official without additional changes.