COMMENTARY—TO *USP31 - NF26*

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 modifications without further public review, unless the Expert Committee determines that additional review is needed due to the nature or significance of the comments received or the changes made. When no additional review is needed, 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.

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GENERAL CHAPTERS

Monograph/Section: <1005> Acoustic Emission
Expert Committee: GC
Number of Commenters: 1
Comment Summary #1: Commenter suggested the chapter could have better flow if the FACTORS AFFECTING MEASUREMENT section was placed before the Qualification and Verification of Acoustic Emission Instruments section.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested the FACTORS AFFECTING MEASUREMENT section could be made more clear by adding appropriate headings before each different factor, and by dividing #5 into three sections
Response: Comment incorporated.
Comment Summary #3: Commenter recommended the following statement be added to the INSTRUMENTATION section: "Piezoelectric transducers are constructed from piezoelectric crystalline solids connected to transducer control circuitry by electrical leads. They can be used to both detect and generate acoustic signals. When configured as a detector, an acoustic wave that impinges on the piezoelectric element is transformed into an electrical signal in the transducer control circuitry. When configured as an acoustic generator, an electrical signal applied to the piezoelectric element by the control circuitry creates an acoustic wave that can propagate into the medium to which the transducer is attached. Typically, acoustic emission detectors can also be operated as acoustic wave generators."
Response: Comment incorporated.
Comment Summary #4: Under Qualification and Verification of Acoustic Emission Instruments, the commenter suggested changing the sentence that read "This drift will underlay any trends plots ... but will not impact chemometric models based purely on endpoint determination" to: "Care should be taken to make sure that signal drift (due to normal variation in processing parameters) does not impact chemometric models used for endpoint determination." This clarifies that chemometric models are not affected by drift.

Response: Comment incorporated.
Comment Summary #5: The commenter suggested adding the word “acoustic” to the sentence that reads "All these tests require the use of a pulse generated electrically." in the last paragraph of Qualification and Verification of Acoustic Emission Instruments.
Response: Comment incorporated.
Comment Summary #6: Commenter recommended that the term "endpoint condition" which appeared in "Training/calibration" and “Modeling" be changed because it could be misinterpreted in meaning and in application under practical situations.
Response: Comment incorporated.

EXCIPIENTS

Monographs/Section: Polydextrose and Hydrogenated Polydextrose
Expert Committee: EM2
Number of commenters: 1
Comment Summary # 1: Commenter indicated that Polydextrose and Hydrogenated Polydextrose are different products only in the relative amount of reducing vs. non-reducing polymer chain end groups. Functionally they perform about the same, with the exception that Hydrogenated Polydextrose has a slight sweet taste and does not brown on heating. No nickel catalyst is used and no traces of nickel are present in Polydextrose. Hydrogenated Polydextrose is Polydextrose that has been catalytically hydrogenated with nickel catalyst. Only Hydrogenated Polydextrose contains trace amounts of nickel, but less than 2 ppm in any case.
Response: Comment incorporated. The Expert Committee deleted the other name “Modified Polydextrose” in the monograph and deleted the text “It may be partially reduced by transition metal catalytic hydrogenation in an aqueous solution.” from the *Definition*. *Limit of nickel* was removed from the monograph. A new monograph “Hydrogenated Polydextrose” will be generated.
Comment Summary #2: Commenter indicated that current the *PF* proposal includes Polydextrose K (Polydextrose Potassium) which should have a separate monograph as it presents different properties in pH and Residue on ignition.
Response: Comment incorporated. The Expert Committee deleted the text “It may be untreated, or neutralized with potassium hydroxide and decolorized and deionized for further purification” in the monograph *Definition* and changed the specifications in *pH* to “between 2.5 and 5.0, in a solution (1 in 10)” and *Residue on ignition* to “not more than 0.3%.”
Expert committee-initiated change: The Expert Committee changed the “randomly bonded polymer” in the monograph *Definition* to “randomly branched polymer”.
Expert committee-initiated change: The Expert Committee removed the statement “No storage requirements specified” in the *Packaging and storage* section and added "Store in a cool and dry place".
Expert committee-initiated change: The Expert Committee changed “Insoluble in alcohol” to “Soluble in alcohol” under the **Description and Solubility**.

Monograph/Section: Superglycerinated Fully Hydrogenated Rapeseed Oil
Expert Committee: EM2
Expert committee-initiated change: Due to a concern about the starting material (glycerin), the Expert Committee added the following note under the monograph *Definition*. Add “NOTE: Use compendial grade of glycerin as a starting material.”

USP MONOGRAPHS

Monograph/Sections: Calcitriol/Multiple sections
Expert Committee: MD-GRE
No. of Commenters: 2
Comment Summary #1: Commenter requested that the molecular weight for the monohydrate form be added to the monograph.
Response: Comment incorporated.
Comment Summary #2: Commenter agreed that material should be stored as per approved labeling instructions and based upon stability data, and requested that the list of examples of the various storage conditions be omitted from the Packaging and Storage section.
Response: Comment incorporated.
Comment Summary #3: Commenter requested that the Standard and Assay preparations be clarified to address possible solubility issues.
Response: Comment incorporated.
Comment Summary #4: Commenter stated that the proposed change of the Definition from "solvent-free" to "as is" basis does not adequately convey the expectations to correct the assay value for residual solvents, and requested that the currently official "solvent-free basis" statement be left unchanged. Alternatively, the Commenter proposed to include a Loss on drying test using a thermogravimetric analysis techniques and to report the results on the dried basis.
Response: Comment incorporated. The Expert Committee agreed to leave the currently official "solvent-free basis" statement unchanged, and to cancel the proposal to specify the assay calculations on an "as-is basis".

Monograph/Section: Cladribine/Residual solvents
Expert Committee: MD-OOD
No. of Commenter: 1
Comment Summary: Commenter suggested deleting the residual solvent method since this is a manufacturer-specific test and the limits provided are covered by the requirements of General Chapter <467> Residual Solvents, as stated in the General Notices.
Response: Comment incorporated.

Monograph/Sections: Divalproex Sodium/Multiple sections
Expert Committee: MD-PP
No. of Commenters: 3
Comment Summary #1: Commenter suggested that the chemical structure above the double chevron needs to include the designation as oligomer, to reflect the entry in USAN.
Response: Comment incorporated
Comment Summary #2: Commenter requested the inclusion of a Melting range test.
Response: Committee decided not to incorporate this request because no data was submitted to support the request
Comment Summary #3: The commenter indicated that the proposal uses a related compound that is not a process impurity for system suitability. The commenter recommended that USP should use some other compound.
Response: Comment not incorporated because the suggestion is not practical.

Monograph/Section: Doxazosin Mesylate/Related compounds
Expert Committee: MD-GRE
No. of Commenters: 2
Comment Summary: The commenters asked whether Doxazosin Related Compounds G and H can be identified in the chromatograms if Doxazosin Related Compounds G and H reference standards are not used for the preparation of the standard solution and their relative retention times are not specified by the method.

Response: Comment incorporated by adding the following statement: "Note: These two related compounds are the mesylate salts and have the same retention time."

Monograph/Section: Estradiol Transdermal System/Multiple sections
Expert Committee: MD-PS
No. of Commenters: 2
Comment summary #1: Commenter requested that a labeling requirement regarding the total amount of estradiol in the transdermal system and the release rate be added to the monograph.
Response: Comment incorporated.
Comment Summary #2: Commenters suggested that the *Alcohol content* test be deleted as the test is not applicable to all available products.
Response: Comment not incorporated. However, the Expert Committee added the phrase "*if present*" to indicate the test is to be performed only on products that contain alcohol.
Comment Summary #3: Commenter requested that a Related compounds test be added to the monograph.
Response: Comment not incorporated. The Committee will consider the addition of a test for Related compounds once a submission with supporting data is received.

Monograph/Section: Fosinopril Sodium/Related compounds
Expert Committee: MD-GRE
No. of Commenters: 1
Comment Summary #1: Commenter pointed out that the Assay *System suitability solution* currently requires the use of the USP Fosinopril Related Compound A RS, but there is no specification for it under the Chromatographic system. Commenter suggested that it should be removed from the System suitability solution.
Response: Comment incorporated.
Comment Summary #2: Commenter pointed out that Related compounds Test 1 refers to the Assay System suitability solution. Commenter suggested that instead, Related compounds Test 1 could be written into the current System suitability solution of the Assay (with the USP Related Compound A RS included), because the relative retention times given in Table 1 are useful.
Response: Comment incorporated.

Monograph/Section: Fosinopril Sodium and Hydrochlorothiazide Tablets**/**Related compounds
Expert Committee: MD-GRE
No. of Commenters: 1
Comment Summary #1: Commenter suggested that the word "hydroxy" be removed from the name of the Related compound A.
Response: Comment incorporated.

Monograph/Section: Gabapentin/Assay
Expert Committee: MD-PP
No. of Commenters: 2
Comment Summary #1: Commenter requested the addition of another system suitability criterion in Assay.
Response: Comment incorporated. The Expert Committee added an additional system suitability criterion.
Comment Summary #2: Commenter requested the lowering of the limit of any unspecified impurity to 0.05% to be consistent with ICH guidelines.
Response: Comment not incorporated. The Expert Committee did not lower the limit of unspecified impurity because it will not reflect approved products on the market.
Comment Summary #3: Commenter indicated that the Impurities solution section should not contain Gabapentin RS.
Response: Comment incorporated.

Monograph/Section: Gabapentin Capsules/Related compounds
Expert Committee: MD-PP
No. of Commenters: 1
Comment Summary #1: Commenter requested the addition of another Related compounds test or revision of the *PF* proposal as the related compounds method does not work for commenter's approved product.
Response: The Expert Committee did not incorporate any changes to the Related compounds method because the commenter has not clearly demonstrated the need to monitor in the dosage form certain impurities that are process impurities in drug substance manufacturing process.
Comment Summary #2: Commenter requested clarification of the terms in the calculation.
Response: Comment incorporated. The Expert Committee has revised the calculation to add clarity to the definition of terms.

Monograph/Section: Gabapentin Tablets/Related compounds
Expert Committee: MD-PP
No. of Commenters: 1
Comment Summary #1: Commenter requested the addition of another Related compounds test or revision of the *PF* proposal as the related compounds method does not work for their approved product.
Response: The Expert Committee did not incorporate any changes to the Related compounds method because the commenter has not clearly demonstrated the need to monitor in the dosage form certain impurities which are process impurities in drug substance manufacturing process.
Comment Summary #2: Commenter requested clarification of the terms in the calculation.
Response: Comment incorporated. The Expert Committee has revised the calculation to add clarity to the definition of terms.

Monograph/Section: Metformin Hydrochloride Extended Release Tablets/Assay
Expert Committee: MD-GRE
No. of Commenters: 1
Comment summary: Commenter requested that USP provide more details regarding the Assay preparation which requires the use of a homogenizer.
Response: Comment incorporated. A Note with a suggested homogenization sequence is added to the Assay preparation. The committee is also willing to consider further changes to this monograph in the future and encourages manufacturers of this dosage form to submit alternative sample preparation techniques that do not require a homogenizer.

Monograph/Section: Phenoxybenzamine Hydrochloride/Multiple sections
Expert Committee: MD-GRE
No. of Commenters: 1
Comment Summary #1: Commenter suggested that the test solution preparation for Content uniformity be made to cover any label claim of phenoxybenzamine HCl by writing as follows: Carefully open 10 capsules (Stage 1) and transfer each immediately into separate volumetric flasks of a suitable volume to achieve a concentration of 0.2 mg/mL of phenoxybenzamine hydrochloride. Add acetonitrile to approximately 60% of the flask volume and sonicate for 15 minutes with occasional stirring (NOTE -- The capsule shell does not dissolve). Cool, dilute with acetonitrile to volume, mix, and pass through a 0.45 micron Nylon membrane filter, discarding the first few mL of filtrate. Use the subsequent filtrate as the Test solution.
Response: Comment incorporated.
Comment Summary #2: Commenter indicated that the calculation of mg/capsule for the Content uniformity test does not provide a result in milligrams as currently written. The T term for label claim should be removed, and the D term should be defined only as the dilution of the Test solution.
Response: Comment not incorporated. An explanation of the revised equation is available.

Comment Summary #3: Commenter suggested that the System suitability solution be mentioned under the Related compounds test because the System suitability solution provides a retention time marker for the tertiary amine degradant.
Response: Comment incorporated.
Comment Summary #4: Commenter suggested that the concentration terms be removed, and the Rs term be replaced with a total peak area term under the calculation formula for the percentage of each impurity.
Response: Comment incorporated
Comment Summary #5: Commenter suggested that the tertiary amine be identified as having a retention time of 0.31 relative to phenoxybenzamine hydrochloride.
Response: Comment incorporated.
Comment Summary #6: Commenter noted that under the section Assay, the mobile phase should be 45:55 Buffer solution and acetonitrile.
Response: Comment incorporated.
Comment Summary #7: Commenter suggested that the Standard preparation be 0.2 mg/mL. The last sentence of the Standard preparation should read: "Sonicate for 5 minutes to dissolve, then dilute to volume and mix well."
Response: Comment incorporated
Comment Summary #8: Commenter indicated that the Assay preparation should be rewritten to indicate the determination and use of average capsule fill weight, in order to correct for the actual weight of capsule powder taken for analysis. The calculation should be for "the quantity, in mg, of phenoxybenzamine hydrochloride per capsule." The current formula should be multiplied by the ratio of average fill weight to sample weight.
Response: Comment not incorporated. The USP calculations are similar to the recommendation.
Comment Summary #9: Commenter indicated that the resolution requirement for the phenoxybenzamine hydrochloride peak and the nearest peak should be not less than 2.
Response: Comment not incorporated as the data provided does not support the requested change. The Expert Committee decided to leave the resolution as 4 as in *PF*.

Monograph/Section: Risperidone Tablets/Related compounds
Expert Committee: MD-PP
Number of commenters: 2
Comment summary #1: Commenter requested the limit for unidentified impurities be lowered to 0.2%.
Response: Comment incorporated. The Expert Committee agreed to lower the unidentified impurity limit.
Comment summary #2: Commenter requested the addition of 9-hydroxyrisperidone and appropriate limits to the Related compounds test.
Response: Comment not incorporated. The Expert Committee did not incorporate the request to add 9-hydroxyrisperidone because the validation data suggested that it can be quantified as unspecified impurity.
Comment summary #3: Commenter requested the removal of bicyclorisperidone from the list of impurities as it can be formed only under extreme conditions.
Response: Comment not incorporated because such removal will not reflect the currently marketed product.

Monograph/Section: Salicylic Acid/Identification
Expert Committee: MD-OOD
No. of Commenters: 1
Comment Summary: Commenter indicated that the test of melting range in the Identification is redundant since the monograph already requires a separate melting range test, and suggested deleting it.
Response: Comment incorporated.

Monograph/Section: Tizanidine Hydrochloride/Assay
Expert Committee: MD-PP
Expert committee-initiated change: The Expert Committee lowered the resolution requirement in the Assay after collaborative testing demonstrated that the requirement, as proposed, was inappropriate.

Monograph/Section: Trimipramine Maleate/Related compounds
Expert Committee: MD-PP
Number of Commenters: 2
Comment Summary: Both commenters indicated that the Related compounds test does not adequately reflect the approved products on the market.
Response: Comment incorporated by including additional specified impurities to the impurity table in the proposal.