Commentary

Interim Revision Announcements proposed in:
***Pharmacopeial Forum* 41(3) [May.–Jun. 2015]**

September 25, 2015, updated November 20, 2015[1]

In accordance with USP's Rules and Procedures of the Council of Experts ("Rules") and except as provided in Section 7.02 Accelerated Revision Processes, USP publishes proposed revisions to the United States Pharmacopeia and the National Formulary (USP–NF) for public review and comment in the Pharmacopeial Forum (PF), USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be republished in PF for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without republication in PF, a summary of comments received and the appropriate Expert Committee's responses are published in the Revisions and Commentary section of the USP Web site at the time the official revision is published.

The Commentary is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference between the contents of the Commentary and the official text, the official text prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the Commentary, shall prevail.

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[1] *The commentary was updated on November 20, 2015 to include the commentary for the Omega-3-Acid Ethyl Esters and Omega-3-Acid Ethyl Esters Capsules, which were proposed in *Pharmacopeial Forum* 41(3), but did not post on the website until November 20, 2015 due to additional time needed by Expert Committee to address comments on the proposed revisions

Comments were received for the following IRAs, when they were proposed in *Pharmacopeial Forum:*

Monograph/Sections:	Digoxin/Multiple Sections
Expert Committee:	Monographs—Dietary Supplements and Herbal Medicines
No. of Commenters:	1

Definition

Expert Committee-initiated Change #1: The plant family name for *Digitalis lanata* was changed from Scrophulariaceae to Plantaginaceae.

Expert Committee-initiated Change #2: The authority for *Digitalis lanata* was changed from “Ehrhart” to “Ehrh.” to avoid confusion with other authorities with the same name.

Assay

Comment summary #1: The commenter indicated that in the proposed method the linearity velocity of the HPLC method has been modified in a manner that is not consistent with allowances per General Chapter <621>.

Response: Comment not incorporated. The changes in the Assay, chromatographic column length, and flow rate, were made to correct errors in the current monograph, not to modify the method.

Related Glycosides

Comment summary #2: The commenter recommended adding a Relative standard deviation (RSD) requirement (as required in Assay) to allow the user to determine the number of required replicate standard injections based on General Chapter <621>. In the proposed method the *System Suitability* section does not contain a RSD requirement for replicate standard injections which is required if this is to be considered a quantitative test.

Response: Comment incorporated. The specification of %RSD is set to NMT 2.0% based on the testing result (0.4) from the USP lab.

Comment summary #3: The commenter indicated that in the proposed test method, the standard concentration matches that of the sample (0.5 mg/mL), which is atypical at 200 times higher than lowest impurity specifications (0.5%).The standard solution used for quantitation of related substances is typically prepared at a concentration closer to the specification, i.e. 0.5% (Table 2).

Response: Comment incorporated. The concentration of standard solution was revised to be 100 times further diluted. The current Standard solution will be designated as Standard stock solution.

Expert Committee-initiated Change #3: The monograph was corrected to include USP Digitoxin RS in the Standard stock solution and *USP Reference Standards <11>* section.

Monograph/Sections: Omega-3-Acid Ethyl Esters/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: **2**

General

Comment summary #1: The commenter recommended establishing two separate monographs for two products because they differ substantially in composition and specifications.

Response: Comment not incorporated. This comment is essentially a repetition of the comment made at the time of first publication of the monograph revision. In response to that comment at the time, the 2010-2015 Dietary Supplements and Herbal Medicines Expert Committee recommended the flexible monograph approach be used in this case, because the composition, acceptance criteria, and the labeling of the two products can be clearly addressed through this approach without widening the specifications for the individual types of Omega-3-Acid Ethyl Esters. Definitions for the Omega-3-Acid Ethyl Esters and Omega-3-Acid Ethyl Esters Capsules monographs were revised, because different production processes lead to sufficiently similar products that could be covered by a single monograph. Because the major chemical constituents claimed in the labels of both products are the same as those included in the *United States Adopted Names* (USAN) definition for the name "Omega-3-Acid Ethyl Esters" and the monograph *Identification test*, they should be under a single monograph, with the same monograph title reflecting the USAN name. Accordingly, the Expert Committee determined that a more preferable solution is to establish single monographs for the two products.

Comment summary #2: The commenter indicated that the proposed Omega-3-Acid Ethyl Esters monograph allows for other purification processes than urea fractionation followed by molecular distillation. They recommended keeping the purification process requirement for the 90% Omega-3-Acid Ethyl Esters product to assure the specific fatty acid ethyl ester (FAEE) profile of the Reference Listed Drug (RLD) and/or include a chromatogram for assay to guide the user to the correct FAEE profile. They also recommended adding a purification process requirement for the 78% Omega-3-Acid Ethyl Esters product and/or a typical chromatogram for assay to assure the correct FAEE profile.

Response: Comment not incorporated. Both the products are approved to provide the determined amount of EPA and DHA ethyl esters for the same indications. FDA approval of the new product was based on 505(b) (2) process[2], which relies on information gathered on the reference product already in the market, indicating the similarity between the two products. *Table 1*, *Table 3*, the *Limit of Total Unidentified Fatty Acids Ethyl Esters* test, and the *Limit of Non-Omega-3-Acid Ethyl Esters* test are intended to address the differences in composition and purity profiles of the two products keeping the 90% requirement for the original product and the 78% for the newly introduced product. Information obtained from these tests is sufficient to guide the

[2]*Guidance for Industry Applications Covered by Section 505(b)(2)*
http://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf

user to the pertaining product profile; therefore, the inclusion of a chromatogram would be redundant and unnecessary.

Definition

Comment summary #3: The commenter recommended that the definition should specify the differences between the two active ingredients so that the user clearly understands that the monograph applies to two distinct APIs. The differentiation can be described in the form of a table.

Response: Comment not incorporated. The definition for a monograph expands on the meaning of the title name. Information to differentiate the product types are addressed in the *Identification* test, *Assay* table, and other tests within the monograph. Inclusion of the *Assay* table in the definition would be redundant and unnecessary.

Comment summary #4: The commenter recommended that the definition should also specify the source of the APIs.

Response: Comment not incorporated. USP has proposed to delete the information about article sources and purification processes in the monograph definition because this would create a lock out specification that discourage innovators from developing alternative processes for the same articles meeting the monograph quality requirements.

Identification B

Comment Summary #5: The commenter indicated that correlating an *Identification* requirement directly to an *Assay* limit is not something they have seen before in the *USP–NF*. They asked that USP to clarify if this approach has been taken for other monographs.

Response: Comment not incorporated. The commenter is correct in stating that this is the first time that USP links *Assay* acceptance criteria to an identification test. However, different acceptance criteria are allowed under flexible monograph approach and therefore, linking an *Identification* requirement to the *Assay* acceptance criteria is consistent with this approach.

Assay

Comment Summary #6: The commenter indicated that the information presented in *Table 1* of the *Assay* may cause unnecessary confusion as it is not completely apparent that the criteria apply to two distinct APIs. They recommended creating a separate monograph for the Omega-3-Acid Ethyl Esters type A drug substance or improve the text in the monograph to minimize confusion by the user.

Response: Comment not incorporated. USP does not believe that the information presented in *Table 1* may cause unnecessary confusion. The *Criteria I* and *Criteria II* are clearly stated in *Table 1* which differentiate which one is omega-3-acid ethyl esters and which one is omega-3-acid ethyl ester type A. The recommendation to create separate monographs was already addressed in response to the comments received during the first publication of the proposal for revision. Because both types of ingredients contain the same major components indicated under the USAN name “Omega-3-Acid Ethyl Esters” and in the monograph *Identification* test, and because both product types are approved to provide the same amount of EPA and DHA ethyl

esters (900 mg / dosage form) in the same ratio, the two types should be covered by a single monograph under the same title.

Cholesterol
Comment Summary #7: The commenter recommended replacing the current Cholesterol test procedure with the new, improved Cholesterol procedure published in *Pharmeuropa 26.4*.
Response: Comment not incorporated. The Expert Committee will consider the cholesterol method published in *Pharmeuropa 26.4* in future revisions to the monograph.

Limit of Dioxins, Furans, and Polychlorinated Biphenyls (PCBs)
Comment Summary #8: The commenter recommended revising the limit for the sum of PCBs from NMT 0.5 ppm to NMT 0.015 ppm to align with the current approved NDA limit.
Response: Comment not incorporated. The Expert Committee will consider future revision of the sum of PCBs' limit upon the receipt of necessary supporting data.

Comment summary #9: The commenter recommended a limit of 2 ng/g for the sum 7 PBDEs (congeners 28, 47, 49, 99, 100, 153 and 154) and a limit of 5 pg/g WHO-TEQ for the sum of PCDDs/PCDFs and di-PCBs to harmonize with the *European Pharmacopoeia* monograph.
Response: Comment not incorporated. The Expert Committee will consider the sponsor provided information pertaining to the current approved NDA limit in future revisions to the monograph

Limit of Non-Omega-3-Acid Ethyl Esters
Comment summary # 10: The commenter recommended adding the non-omega-3-acid ethyl ester, C18: 1 n-9, which is required in the *Limit of Non-Omega-3-Acid Ethyl Esters* test, to *Table 3* as an identified ethyl ester.
Response: Comment not incorporated. The Expert Committee will consider future revision to this monograph upon the receipt of necessary supporting data.

Limit of Total Unidentified Fatty Acids Ethyl Esters- Table 3
Comment summary #11: The commenter recommended that five fatty acid ethyl esters (C14:0, C18:0, C18:1 n-9, C18:2 n-6 and C24:6) proposed for Omega-3-acid ethyl esters 90 monograph in *Pharmeuropa 27.3* be added to *Table 3* of the monograph to harmonize with the *Pharmeuropa 27.3* proposal.
Response: Comment not incorporated. The Expert Committee will consider the *Pharmeuropa 27.3* proposal in future revisions to the monograph.

Labeling
Comment summary #12: The commenter suggested that the two APIs be labeled as Omega-3-Acid Ethyl Esters 90 (ref. subject title for DMFs 23369 and 28045) and Omega-3-Acid Ethyl Esters 78 (ref. subject title for DMF 2351 0). This would give the user direct information as to the minimum omega-3-acid ethyl ester content of the APIs.

Response: Comment not incorporated. The name of the product should not be used instead of the full specifications given in the monograph to determine the content. Because the dosage forms prepared with both type of ingredients provide the same amount of EPA and DHA ethyl esters, physicians and consumers could be confused from not knowing the significance of the numbers 90 and 78 in the ingredient names. The *Labeling* section in the USP proposed flexible monograph, which links to the *Assay* acceptance criteria in *Table 1* addresses the concern about potential mistakes indicated by the commenter.

Monograph/Sections:	Omega-3-Acid Ethyl Esters Capsules/ Multiple Sections
Expert Committee:	Non-Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 2

Identification B

Comment Summary #1: The commenter indicated that correlating an *Identification* requirement directly to a *Concentration* limit is not something they have seen before in the USP. They asked that USP to clarify if this approach has been taken for other monographs.

Response: Comment not incorporated. The commenter is correct in stating that this is the first time that USP links *Concentration* acceptance criteria in an identification test. However, different acceptance criteria are allowed under flexible monograph approach and therefore, linking an *Identification* requirement to the assay acceptance criteria is consistent with this approach.

Labeling

Comment Summary #2: The commenter recommended revising the current labeling statement *"Capsules intended to meet Acceptance criteria II of the test for Concentration of Omega-3-Acid Ethyl Esters are labeled as containing Omega-3-Acid Ethyl Esters type A."* to *"Capsules intended to meet Acceptance criteria II of the test for Concentration of Omega-3-Acid Ethyl Esters* ***shall be*** *labeled as Omega-3-Acid Ethyl Esters type A* ***Capsules****."* They stated that this approach was similar to that taken in the Miconazole Nitrate Cream monograph.

Response: Comment not incorporated. The Expert Committee considered that the proposed approach of labeling would result in the creation of a new name for the article, which was not the intention of the Expert Committee. The Expert Committee determined that the name of article should be consistent with the monograph title. The approach taken in the USP Miconazole Nitrate Cream monograph is an exception and should not be extended to this particular case. The EC recognizes that there may be other exceptions in the book, and recommended careful evaluation of the labeling requirements on a case-by-case basis.

Monograph/Sections:	Oxycodone Hydrochloride/Organic impurities
Expert Committee:	Monographs—Chemical Medicines 2
No. of Commenters:	5

Comment Summary #1: The commenter indicated that the chemical name of 8β-Hydroxyoxycodone (7,8-dihydro-8β-14-dihydroxycodeinone) under the footnote d in Table 1 needed to be corrected.
Response: Comment incorporated
Comment Summary #2: The commenter suggested clarifying why some impurities have the same limits and some do not between *Procedure 1* and *Procedure 3* and indicated that the specifications between different procedures should be harmonized.
Response: Comment not incorporated. The specifications for *Procedure 1* and *Procedure 3* are both approved by the FDA.
Comment Summary #3: The commenter indicated that adding an additional identification test to the two existing tests added little benefit.
Response: Comment not incorporated. One of the existing identification tests is the melting range measurement, which is not specific to the chemical identity. Adding *Identification* test *C* based on the retention time agreement using the existing *Assay* procedure will strengthen the identification tests.
Comment Summary #4: The commenter requested that each of the proposed names be accompanied in the monograph by a depiction of the chemical structure, if the intent is to replace the existing names.
Response: Comment not incorporated. Both the existing names and the proposed new names coexist in the monograph.
Comment Summary #5: The commenter requested permanent removal of *Procedure 2* from the monograph as it is postponed indefinitely in the current monograph.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph to remove *Procedure 2* upon receipt of additional supporting information.
Comment Summary #6: The commenter indicated that noroxymorphone and noroxycodone can be both derived from the same chemical pathway and requested that the potential impurity 8β-hydroxyoxycodone (7,8-dihydro-8B-14-dihydroxycodeinone) be utilized as the deciding factor for which organic procedure to use.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested providing additional information on which organic impurity procedure to use, if the potential impurities are not included in the monograph.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of additional supporting information.

No Comments were received for the following IRA, when it was proposed in *Pharmacopeial Forum*:

<87> Biological Reactivity Tests, in Vitro