



## **Commentary**

### ***Interim Revision Announcements posted July 31, 2020***

#### **July 31, 2020**

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 re-publication in *PF*, a summary of comments received and the appropriate Expert Committee's responses are published in the Proposal Status/Commentary page of USP.NF.com 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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**Comments were received for the following when they were proposed in PF:**

**General Chapters**

<7> Labeling

**Monographs**

Temozolomide Capsules

**No comments were received for the following when they were proposed in PF:**

Temozolomide

Temozolomide for Injection

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**General Chapters**

**Chapter/Section:** <7> *Labeling*

**Expert Committee:** Nomenclature and Labeling

**General Comments**

**Commentary Summary #1:** The commenter stated that the 4-digit year format should be clarified and is necessary. Our preferred approach is YYYY-MMM-DD (i.e., 2019-MAY-30)

**Response:** The comment was incorporated.

**Commentary Summary #2:** Changing from 2-digit to 4-digit year will occupy more space. Recommended format change: DD/MM/YYYY.

**Response:** It is the recommendation of the Nomenclature and Labeling Expert Committee that the 4-digit year comes first. The format of 4-digit year, 2-digit month or 4-digit year, 3-letter month are acceptable options.

**Commentary Summary #3:** The commenter stated that replacing the dash separating the year, month, and date with either no space or with a space after the year, month, and date as proposed by Chapter <7> *Labeling*, will create difficulties with vision systems required by DSCSA. The systems have a difficult time “reading” any dashes as they have a lower number of pixels and invariably, there will be a printer port blocked in the character resulting in an increase rejection rate.

**Response:** Language has been clarified to replace dash with hyphen. Both hyphens and forward slashes are acceptable, which can be read by current industry standards vision systems. The NL EC has determined that the use of a "space" does not provide the optimal format. Allowing spaces may result in suboptimal formatting.

**Commentary Summary #4:** Commenter proposed that both MM/YYYY and YYYY/MM should be acceptable as was proposed by the USP in the past. The commenter noted that some vendors use a “space” or a “dot” to separate the month from the year, and that dashes or forward slashes would cause space constraints. The commenter further expressed that the “expiration date” has to be abbreviated on the drug packaging, causing space constraints on products where space permits only the expiry date itself to be printed.

**Response:** NL EC recommends that the year comes first. The three letters "EXP" have been removed from the examples in the chapter to reduce confusion regarding the required format.

**Commentary Summary #5:** Changing from a 2-digit year to a 4-digit year expiration date format can provide more clarity.

**Response:** Acknowledged.

**Commentary Summary #6:** Several commenters requested that more expiration date formats be allowed which are unambiguous and are presently accepted in the United States and other

countries. The commenters presented several additional format examples for consideration. All-numeric proposed formats: MM-YYYY, MM/YYYY, MM (space)YYYY. Alphanumeric proposed formats: MMM-YYYY, MMM/YYYY, MMM-DD-YYYY, MMM/DD/YYYY.

**Response:** NL EC recommends that the year comes first. The use of a "space" does not provide the optimal format. Allowing spaces may result in suboptimal formatting.

**Commentary Summary #7:** Commenter presented several additional format examples for consideration. All-numeric proposed formats: MMYYYY. Alphanumeric proposed formats: DDMMMYYYY & MMMYYYY.

**Response:** NL EC recommends that the 4-digit year comes first.

**Commentary Summary #8:** Commenter requested that, in certain instances, a 2-digit year be acceptable (for example: when space is extremely limited on the label and/or package).

**Response:** NL EC recommends that the year format shall always contain 4 digits.

**Commentary Summary #9:** Commenter noted the potential need to modify manufacturing line equipment, change and validate label artwork, revise internal system formats, and/or revise regulatory documentation are extremely expensive. The commenter requested the removal of the required expiration date formats and to include example formats only. The commenter further noted that there was not an apparent benefit to change the format from a 2-digit year to a 4-digit year from a product quality perspective.

**Commentary Summary #10:** The 4-digit year aligns with the ISO format. USP recognizes that equipment modifications may need to be made; there will be a 3-year implementation period.

**Commentary Summary #11:** Commenter requested that the date format of MM/YYYY be retained as an acceptable date format for the expiration date on a drug product label in USP <7>.

**Response:** NL EC recommends that the 4-digit year comes first.

**Commentary Summary #12:** Commenter stated that there will not be any confusion about the year, since different date formats have been used by different countries, companies, agencies, etc.

**Response:** The NL EC is standardizing the format for the United States to minimize confusion and has evaluated ISO standards in order to harmonize the expiration date format.

**Commentary Summary #13:** Commenter requested that recommend that USP also include MM-DD-YYYY, MM-YYYY, MM(space)YYYY, MMM-DD-YYYY, and MMM-YYYY formats, because all formats meet the USP desired outcome and are readily understandable.

Commenter also noted that these formats are accepted in the United States and are allowed in other countries.

**Response:** NL EC recommends that the 4-digit year comes first.

**Commentary Summary #14:** Commenter stated that the 4-digit year format may be easier for consumer to understand.

**Response:** Acknowledged.

**Commentary Summary #15:** Commenter requested the removal of "slashes" as part of the formatting of all-numeric dates. Commenter further recommended that General Chapter <7> include a statement allowing alternate formats, per established marketing authorizations.

**Response:** The NL EC will retain slashes in the format. The expiration date format changes apply to products sold in the US market.

**Commentary Summary #16:** Commenter proposed that the expiration date format be harmonized with "HDA Guidelines for Bar Coding in the Pharmaceutical Supply Chain" and guidelines recommended by GS1, minimally. The commenter also suggested the allowance of the "space" character to be used as a separator between year, month, and day (i.e. 2020 JAN or 2020 JAN 31) to avoid future inspection issues with automated inspection system due to the use of the backslash ("/").

**Response:** The NL EC has evaluated the space and it will not be part of the acceptable format. USP General Chapter <7> does not address bar coding text.

**Commentary Summary #17:** Commenter proposed the inclusion of shorter formats as options for all drugs, regardless of space limitations. The commenter also noted that they are supportive of more flexible formats, including (YYYY-MM or MM-YYYY).

**Response:** NL EC recommends that the 4-digit year comes first. The format of 4-digit year, 2-digit month is and 4-digit year, 3-letter month are acceptable options.

**Commentary Summary #18:** Several commenters referenced FDA guidances that addresses expiration date formats.

**Response:** USP develops standards for expiration date formatting and recommends contacting FDA for the most current version of draft guidances.

**Commentary Summary #19:** Commenter stated that the change from a 2-digit year to a 4-digit year expiration date format may cause a reduction in confusion and will prevent dosing and storage errors.

**Response:** Acknowledged.

**Commentary Summary #20:** Several commenters requested the retention of the existing MM/YYYY format.

**Response:** NL EC recommends that the year format shall always contain 4 digits.

**Commentary Summary #21:** Commenter proposed that two original formats remain as acceptable format.

**Response:** NL EC recommends that the year format shall always contain 4 digits.

**Commentary Summary #22:** Several commenters requested that an extended implementation date be provided for stakeholders. This implementation date window would provide time for stakeholders to budget, plan, purchase new equipment and validate systems for the new expiration date format.

**Response:** The NL EC has agreed upon a 3-year implementation to meet new requirements within the Expiration Date and Beyond-Use section of General Chapter <7> *Labeling*.

**Commentary Summary #23:** Several commenters proposed that USP review the global impact of the proposed change to industry stakeholders. Commenters noted that multiple expiration date formats for different countries may lead to manufacturing inefficiencies. Commenters further suggested that some formats be retained by USP to coordinate with other countries.

**Response:** USP provides standards for the United States and has evaluated ISO standards in order to harmonize the expiration date format

**Commentary Summary #24:** Several commenters stated that there was not an apparent benefit to change the expiration date format from a public health need or a patient safety perspective.

**Response:** The NL EC determined that an update to the expiration date format was needed after review of medication errors that were related to inconsistent expiration date formats.

**Commentary Summary #25:** Commenter stated that a manufacturing date should also be present on the label.

**Response:** The presence of a manufacturing date is not a requirement for drug products.

**Commentary Summary #26:** Several commenters recommended additional formats for space constraints that contain two-digit year formats, including MM-YY (e.g., 06-20) and MM/YY (e.g., 06/20). The commenters also noted that a 2-digit year would not be ambiguous for consumers.

**Response:** NL EC recommends that the 4-digit year comes first. The formats that are proposed by the NL EC are unambiguous.

**Commentary Summary #27:** Commenter recommended adding the provision to eliminate dashes or forward slashes when space is limited.

**Response:** The proposed format only allows the elimination of hyphens or forward slashes (alphanumeric only) for small containers YYYYMMM. The NL EC recommends that the 4-digit year come first.

**Commentary Summary #28:** Commenter noted that YYYYMMM will most likely appear too small to find on the container.

**Response:** The NL EC has created provisions to address small containers.

**Commentary Summary #29:** Commenter suggested the allowance of the “space” character to be used as a separator between year, month, and day (i.e., 2020 JAN or 2020 JAN 31) to avoid future issues anticipated with ink transfer during printing.

**Response:** The NL EC finds that the inclusion of a hyphen or forward slash improves readability.

**Commentary Summary #30:** Commenter recommended that an allowance should be made (due to space constraints), for the wording relating to expiration date not to be included.

**Response:** The proposed text included the following statement: "If there is a lack of space in close proximity to the expiration date, the term designated to represent “expiration date” (e.g., EXP) may be omitted if the specific alphanumeric format, YYYYMMM, is used. "

**Commentary Summary #31:** Commenters noted that additional clarification should be included as part of the general chapter as to the applicability to levels of packaging

**Response:** The NL EC is addressing container labels in General Chapter <7> unless stated differently.

**Commentary Summary #32:** Commenter recommend using the word “shall” in the following sentence: "When all-numeric dates are used, they shall ~~must~~ be formatted using the year, the month, and if applicable, the day ... "

**Response:** Comment not incorporated. The NL EC will use the word "must".

**Commentary Summary #33:** Commenter suggested adding the word “drug” in front of “products” in this sentence: “The monographs for some drug products state how the....”

**Response:** The comment was incorporated, as the context of the sentence has changed in this revision.

**Commentary Summary #34:** Commenter suggested additional revision to the dietary supplement sentences regarding expiration dates.

**Response:** The sentence has been further revised for clarity.

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## **Monographs**

**Monograph/Section:** Temozolomide Capsules/Dissolution

**Expert Committee:** Chemical Medicines Monographs 3

**Comment Summary #1:** The commenter indicated that Methanol used for Solution A and Diluent should be replaced with Water in Dissolution test.

**Response:** Comment incorporated. The solvent used for Solution A and Diluent changed from Methanol to Water.

**Monograph/Section:** Travoprost Ophthalmic Solution

**Expert Committee:** Chemical Medicines Monographs 3

**Comment Summary #1:** The commenter indicated that the chemical names in Table 1 were not consistent with the current IUPAC style.

**EC Response:** Comment incorporated. The Impurities’ chemical names in Table 1 will be updated as follows.

	Name	Chem Name
Current	5,6-trans Isomer	(5E,13E)-(9S,11R,15R)-9,11,15-Trihydroxy-16-(m-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid,  isopropyl ester.
Proposed update	5,6-trans Travoprost	Isopropyl (E)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(R,E)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]but-1-enyl]cyclopentyl]hept-5-enoate
Current	15-keto derivative	(5Z,13E)-(9S,11R)-9,11-Dihydroxy-15-oxo-16-(m-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid,  isopropyl ester.
Proposed update	15-Keto-Travoprost	Isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E)-3-oxo-4-[3-(trifluoromethyl)phenoxy]but-1-enyl]cyclopentyl]hept-5-enoate