July 31, 2020

Dr. Elena Gonikberg
Principal Scientific Liaison
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 07-20-021-N

Dear Dr. Gonikberg,

This is regarding USP's Compendial Notice: "Reporting Threshold in USP-NF Monographs: Proposed Policy Change" posted on August 13, 2019.

Since 2016, the agency has had multiple discussions with USP on the inclusion of "Disregard Limits/Reporting Thresholds" in drug substance and drug product monographs. We appreciate USP publishing the Compendial Notice to remove reporting thresholds and making the comments received publicly available. We have carefully reviewed all the comments shared and are writing this letter to clarify our rationale and the reasons for our recommendation to not include Reporting Thresholds or Disregard limits in individual USP monographs. FDA did not respond to the Compendial Notice because we believed it was a step in the right direction. We welcome scientific discussion on the issue and respectfully request that USP not reach any conclusion on the matter and/or proceed with any monograph revisions including Reporting Thresholds until our comments noted below are fully addressed.

General comments on the concept of Reporting Thresholds and its application by FDA, USP:

1. FDA is committed to international harmonization and has participated in ICH as a Founding Member since 1990. We implement all ICH Guidelines as FDA Guidance for Industry. Reliance on ICH guidelines are an important aspect of FDA application quality assessment. The ICH Q3A(R2) and Q3B(R2) guidelines (*Impurities in New Drug Substances* and *Impurities in New Drug Products*, respectively) provide information on impurity reporting thresholds based on Maximum Daily Dose (MDD). FDA relies on reporting thresholds as described in ICH guidelines, taking into account any clinical safety considerations related to the clinical use of the product. These thresholds are not solely based on the analytical procedure used to measure the impurities.

2. USP[1] has made significant efforts to replace outdated analytical procedures with current technology. However, many monographs continue to lack an adequate listing of impurity

[1] USP is a private non-governmental organization and its standards are recognized in the Food Drug and Cosmetic Act.

specifications. While FDA actively reviews and comments on the adequacy of monograph proposals published by USP, we are unable to provide direct input on specifications, including for impurities, because such information is generally considered confidential and trade secret.

Specific comments:

1. **Concepts and Terminology:** Reporting Threshold and Disregard Limits based on analytical Limit of Quantitation (LOQ) seem to be used synonymously in USP General Chapters and monographs. We recommend USP use the term "Reporting Threshold" in USP standards in a manner consistent with ICH terminology. FDA does not believe that the two terms are synonyms, as previously communicated to USP in meetings and written communications. Please see FDA comment letter on General Chapter proposal for *<1086> Impurities in Drug Substances and Drug Products* which was published in PF 45-1 (REF: 05-19-005-T).

2. **The complexity of establishing appropriate ICH reporting thresholds in individual monographs:** The setting of a reporting threshold as defined in ICH (ICH reporting threshold) in a monograph can be impacted by multiple product-specific factors including maximum daily dose (MDD), unusually toxic impurities, different types of formulations covered under a monograph, clinical use of the products, etc. The following points explain how USP reporting thresholds might deviate from ICH reporting thresholds.

    a. **MDD**: Calculation of MDD can be a complex process. We have provided to USP examples of incorrect MDD calculations leading to inaccurate reporting thresholds in USP monographs. Maximum daily dose determination for CDER products is often dependent on clinical knowledge of how a product will be used and determining MDD as part of the quality assessment for an application sometimes requires clinical input. Furthermore, the MDD for a product may change when a new indication is added or clinical use of a product changes, which could further complicate the setting of a reporting threshold in USP monographs.

    b. **A monograph covering multiple formulations**: ICH reporting thresholds in drug substance monographs and some drug product monographs may differ depending on the indication of the drug product in which the drug substance is used. When USP establishes a single reporting threshold in a monograph covering multiple formulations with different MDDs, it creates challenges for the various manufacturers of those formulations to follow that one reporting threshold. Flexibilities should be provided for reporting thresholds for different formulations when justified based on clinical considerations.

    c. **Impurity profile**: Setting an appropriate reporting threshold in individual monographs is challenging without knowledge of the complete impurity profiles of the substances or products covered by a monograph. ICH Q3A(R2) and Q3B(R2) specifically note that lower thresholds can be appropriate if the impurity is unusually

toxic. However, the impurity profiles in USP monographs may not include all impurities as they are usually based on a submission by a single or a small subset of FDA-approved manufacturers or testing by USP. Please see Example 2 in the Appendix, where the reporting threshold is set as the same as the acceptance criteria for a specified impurity and unspecified impurities. Please also see Example 4 where the disregard limit is set at higher than the acceptance criterion for a specified impurity.

d. **Special routes of administration**: Some formulations used for special routes of administration including nasal sprays and ophthalmic products may require tighter limits for unspecified impurities than ICH identification thresholds, due to high sensitivity of these organs. For example, as described in the FDA guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation*, all related impurities appearing at levels of 0.1 percent or greater should be specified. For these formulations, reporting thresholds lower than ICH Q3B(R2) or 0.1% may be necessary as reporting thresholds should not be identical to the unspecified impurity limit required by FDA. Please see Example 7 where the acceptance criterion for "any unspecified impurity" is not aligned with current FDA expectations outlined in the above-mentioned guidance, and the addition of reporting threshold at 0.1% would be identical to the FDA recommended limit at which all impurities should be specified.

e. **Reporting threshold based on LOQ**: USP's Reporting Thresholds/Disregard Limits are often based on the analytical procedures adopted from sponsors or developed by USP labs or other sources. USP's Reporting Thresholds and Disregard Limits serve as an approach to verify sensitivity and performance of the chromatographic system. While it is critical to ensure sensitivity/performance of the chromatographic system for impurity testing, the values of such Reporting Thresholds are pertinent only to the analytical procedures in the monographs. Alternate methods are frequently used by applicants in FDA-approved submissions and are mentioned in USP General Notices; USP's method-specific "Reporting Thresholds" are likely to create confusion for users of the monograph, especially when they deviate from ICH. Please see Example 3 in the Appendix, where two different reporting thresholds are listed in the monograph for the Impurity test. Example 1 in the Appendix illustrates the situation where the reporting threshold is based on LOQ which is higher than ICH reporting threshold. Examples 6 and 8 illustrate that the Reporting Thresholds and Disregard Limits are significantly lower than ICH reporting thresholds, which can impose unnecessary burden on the manufacturers. Example 3 illustrates a situation in which a flexible approach for organic impurities was adopted in the monograph; however, the reporting threshold varies based on the analytical procedure.

f. **Compendial standards development involves multiple sources of information:** It is important to note that the current process for establishing impurity standards in USP monographs combines information from multiple sources on reporting thresholds, specified/unspecified impurity limits and total impurity limits. This issue complicates the process of setting appropriate compendial standards when a reporting threshold is adopted from one sponsor and the total impurity limit is adopted from

another sponsor which may not have the same reporting threshold. It is therefore challenging for FDA and industry stakeholders to assess compendial compliance of the approved products during the Pharmacopeial Forum commenting period. As reporting thresholds were not part of the regulatory specifications in the past, it is unclear whether USP is able to consistently adopt ICH reporting thresholds in the monographs when there is a discrepancy between the LOQ and ICH reporting threshold.

3. **Administrative burden:** In cases where a monograph "Reporting Thresholds" are not aligned with ICH reporting thresholds and with previous FDA approved products, a pending monograph process may need to be initiated; however, such cases may not qualify for an accelerated revision due to the nature of the change involved. This could potentially delay FDA approvals for products under review and add to the agency's and applicants' administrative burden. Furthermore, it is highly challenging for the agency and other stakeholders to determine during the Pharmacopeial Forum commenting process whether a USP Reporting Threshold is consistent with the corresponding ICH reporting threshold while also ensuring that it does not cause compliance issues. Examples are noted in the Appendix where there are discrepancies between USP "Reporting Thresholds/Disregard Limits" in monographs and ICH reporting thresholds.

4. **Miscellaneous comments:**

    a. **Response to comments received by USP:** Harmonization with EP: We note that majority of the drug substance monographs have not been harmonized with the European Pharmacopeia through the Pharmacopeial Discussion Group (PDG) process. Additionally, the European Pharmacopeia does not have monographs for drug products.

    b. **Other considerations**: We are aware that for products not within scope of the relevant ICH guidances such as fermentation antibiotics, or atypical APIs, special accommodation for reporting thresholds may be necessary. These issues need further discussion between FDA, USP, and industry stakeholders. Please see Examples 6 and 9, where the rationale for setting the Reporting Thresholds is unclear, and the proposed values may not be acceptable.

5. **Path forward:** We recommend that the concept of reporting threshold should be described in a general chapter (e.g., proposed USP General Chapter <476>) instead of being established case-by case based on the adopted analytical procedure in each individual monograph. If needed, the monograph can provide a reference to the general chapter so that the monograph users can use the general chapter as a guideline to calculate appropriate reporting thresholds.

    We support USP's proposal of adding sensitivity solutions in the system suitability tests in monographs without adding reporting thresholds. We believe that the use of a sensitivity solution in the system suitability test would fulfill the need for checking sensitivity of the chromatographic systems for a specific compendial test for the purpose

of demonstration of compendial compliance. We request that the concentration of sensitivity solution be set no higher than the ICH reporting threshold, especially for products covered within the scope of the ICH guidances. This approach can ensure the sensitivity of the chromatographic system for analyzing regular compendial impurities, while also enhancing flexibility to use lower reporting thresholds for analyzing non-compendial impurities using techniques with higher sensitivity.

Below are a few points that should be considered for inclusion in a General Chapter (e.g., GC <476>):

1. Explain the difference between Reporting Thresholds and LOQs as they are not the same. LOQs should be below the reporting thresholds and fit for purpose.
2. Reporting thresholds are for informational purposes and not requirements. The reporting thresholds should generally follow ICH Q3A(R2) and Q3B(R2); however, flexibility should be allowed based on clinical considerations related to use of the product.
3. Reporting thresholds do not apply to unusually toxic impurities or mutagenic impurities. ICH M7(R1) *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* should be considered when setting thresholds for potential mutagenic impurities.

In the interim, we request that USP not introduce new reporting thresholds into monograph proposals during the Pharmacopeial Forum process until these issues have been fully addressed. We also request that USP not make monograph proposals official with newly added reporting thresholds, because it will be challenging to fix any errors in the monographs once they become official.

We hope these comments will be helpful to USP. Please feel free to contact me at pallavi.nithyanandan@fda.hhs.gov if there are any questions. Please use the reference number provided above on any ensuing correspondence.

Sincerely yours,

Pallavi Nithyanandan -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000443938, cn=Pallavi Nithyanandan -S
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Appendix: Examples of Reporting Thresholds in USP monographs.

Example 1: Altretamine (Proposed in PF 43(6))

Acceptance criteria: The reporting threshold is NMT 0.06%.

Name	Relative Retention Time	Relative Response Factor	Detector (nm)	Acceptance Criteria, NMT (%)
Altretamine diketo analog	0.21	0.44	242	0.1
Altretamine chloro keto analog	0.35	0.60	215	0.1
Altretamine keto analog	0.56	1.3	242	0.1
Altretamine dichloro analog	0.87	0.87	242	0.1
Altretamine monochloro analog	0.96	1.3	242	0.1
Altretamine	1.00	1.0	215, 242	—
Any other individual impurities	—	—	242	0.1
Total impurities	—	—	—	0.3

Example 2: Ethosuximide (Proposed in PF 44(1))

Acceptance criteria: The reporting threshold for impurities is 0.1%.

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ethosuximide	1.0	—
2-Ethyl-2-methylsuccinic acid	1.5	0.1
Any individual unspecified impurity	—	0.1
Total impurities	—	0.5

Example 3: Cefotaxime Sodium (Proposed in PF 40(1))
Organic Impurities, Procedure 1:

Acceptance criteria: The reporting threshold is 0.1%.

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Deacetylcefotaxime	0.26	1.0
Cefetamet	0.52	1.0
Cefotaxime related compound E	0.62	1.0
Cefotaxime	1.0	—
N-Formyl cefotaxime	1.8	1.0
E-Cefotaxime	2.2	1.0
Cefotaxime dimer	2.3	1.0
Cefotaxime dioxime	3.0	0.2
Any individual unspecified impurity	—	0.2
Total impurities	—	3.0

Organic Impurities, Procedure 2:

Acceptance criteria: The reporting threshold is 0.05%.

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Thiazolylglyoxalic methyloxime	0.13	0.15
7-Aminocephalosporanic acid	0.41	0.15

Deacetylcefotaxime	0.57	1.0
Cefotaxime open ring lactone	0.60	0.15
	0.71	0.15
Cefetamet	0.74	1.0
Cefotaxime	1.0	—
Cefotaxime related compound E	1.08	1.0
Cefotaxime dimer	1.26	1.0
E-Cefotaxime	1.34	1.0
Bromoacetyl analog	1.48	0.15
Any individual unspecified impurity	—	0.2
Total impurities	—	3.0

Example 4: Sodium Phenylbutyrate (Proposed in PF 39(4))

Acceptance criteria: Disregard any peak below 0.03%.

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Phenylbutyrate related compound A	0.3	0.1
Phenylbutyrate related compound B	0.7	0.01
Sodium phenylbutyrate	1.0	—
Any individual unspecified Impurity	—	0.05
Total impurities	—	0.1

Example 5: Naproxen Sodium Tablets (Proposed in PF 42(4))

Acceptance criteria: Disregard any peaks below LOQ (0.004% for naproxen methyl ester and any individual unspecified degradation product, 0.002% for naproxen related compound A, and 0.006% for naproxen related compound L).

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Naproxen related compound A	0.63	0.2
Naproxen	1.00	—
Naproxen related compound L	2.32	0.2
Naproxen methyl ester	3.19	0.2
Any other individual impurity	—	0.2
Total impurities	—	1.5

Example 6: Doxycycline Hyclate Tablets (Proposed in PF 43 (2))

Acceptance criteria: Disregard any impurity peaks less than 0.2%.

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Methacycline	0.64	—
4-Epidoxycycline	0.79	0.5
Doxycycline related compound A (6-epidoxycycline)	0.88	—
Doxycycline	1.0	—

Any individual unspecified impurity	—	0.5
Total impurities	—	2.0

Example 7: Butorphanol Tartrate Nasal Spray (Proposed in PF 46(2))

Acceptance criteria: The reporting threshold is 0.1%.

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
3,14-Dihydroxymorphinan	0.3	0.3
Δ6-Butorphanol	0.7	0.5
Butorphanol tartrate	1.0	—
Any unspecified impurity	—	0.3
Total impurities	—	1.0

Example 8: Linezolid Tablets (Proposed in PF 46(3))

Acceptance criteria: The reporting threshold is 0.005%.

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Linezolid related compound C	0.40	0.20
Linezolid	1.0	—
Linezolid related compound B	1.70	—
Linezolid related compound A	1.80	—
Any individual unspecified impurity	—	0.15
Total impurities	—	1.00

Example 9: Rifampin (Proposed in PF 46(4))

Acceptance criteria: The reporting threshold is 0.5%.

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
25-Desacetylrifampin	0.51	0.15
Rifampinquinone	0.62	1.5
Rifampin	1.0	—
Rifampin-*N*-oxide	1.1	1.0
3-Formyl rifampin	1.7	1.0
Any individual unspecified impurity	—	1.0
Total impurities (excluding rifampin quinone)	—	3.5