Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment

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Comment Deadline: 12–Nov–2019

An update to this Notice was posted on November 7, 2019 and can be found here.

As part of our commitment to ongoing monograph modernization, USP is updating organic impurities testing for articles subject to *USP–NF* standards. Our approach applies the ICH Q3A/B-based limits for identification and reporting of organic impurities and degradation products in drug substances and drug products. Currently, USP drug substance and drug product monographs' impurities tests with specifications for total impurities or total degradation products will in many cases include a reporting threshold consistent with the ICH guidelines.

In addition to setting criteria for a peak to be included in the total impurities, the reporting threshold also aligns with the approach to verify the system sensitivity. Monographs with recently modernized or new impurity procedures are expected to contain a sensitivity solution at a concentration corresponding to the reporting threshold, and a signal-to-noise requirement as a part of system suitability requirements. This approach is used for both drug substance and drug product monographs.

Beginning in 2016, the U.S. Food and Drug Administration (FDA) provided comments requesting that reporting thresholds not be included in drug product monographs. Since compendial monographs are not intended to identify every impurity and degradation product, the FDA is concerned that the inclusion of reporting thresholds could result in very toxic impurities not being identified or reported. The FDA commented that reporting thresholds for drug products vary based on product-specific factors and should be addressed as an application assessment issue. FDA uses ICH reporting thresholds as guidelines and deviates from them as needed based on application specific considerations.

FDA has recently notified USP that the same public health and safety concerns regarding the inclusion of reporting thresholds would also be applicable to drug substance monographs. Since a drug substance may be used in different products with different maximum daily doses, ICH Q3A limits (including reporting threshold) will vary due to product specific factors and should also be addressed as an application assessment issue.

To address the FDA's recommendation, USP is proposing the following policy change pertaining to inclusion of reporting thresholds in drug substance and drug product monographs which is presented here for a 90-day public comment period.

1. For the impacted monograph proposals, the Expert Committees will have an option of deleting the proposed reporting threshold at the ballot, without republishing the proposal in *Pharmacopeial Forum* (*PF*).
2. If this policy is finalized, USP will no longer include reporting threshold in *PF* proposals for drug substance and drug product monographs.
3. USP will continue including a sensitivity solution and signal-to-noise requirement in monographs, to ensure that the sensitivity of the equipment is sufficient to reliably integrate any impurities that are included for calculating the total impurities result.
4. For monographs that are already official, USP will not solely revise these monographs to remove the reporting threshold as a result of this policy change. However, as these monographs are identified for revision as part of the ongoing revision process, USP will remove the reporting threshold at that time.

After the 90-day public comments period, USP will review the comments and post an updated Compendial Notice. Until the policy is finalized, USP will continue including reporting thresholds in the drug substance and drug product monograph proposals being submitted for publication in *PF*.

Stakeholders are encouraged to contact USP and provide their comments and recommendations. The lists of drug product and drug substance monograph proposals impacted by FDA comments is included at the end of this Notice.

Should you have any questions or comments, please contact Elena Gonikberg, Ph.D., Principal Scientific Liaison, at EG@usp.org.

List of impacted drug product monographs

PF 44(1) [Jan.–Feb.] 2018 to PF 45(3) [May–June] 2019

Monograph title	**PF issue**
Albuterol Inhalation Aerosol	PF 44(1)
Atomoxetine Capsules	PF 44(1)
Carbidopa and Levodopa Orally Disintegrating Tablets	PF 44(1)
Desvenlafaxine Extended-Release Tablets	PF 44(1)
Pramipexole Dihydrochloride Tablets	PF 44(1)
Primidone Tablets	PF 44(1)
Terbutaline Sulfate Injection	PF 44(1)
Sertraline hydrochloride Tablets	PF 44(1)

Cefepime for Injection	PF 44(2)
Clindamycin Hydrochloride Capsules	PF 44(2)
Clindamycin Injection	PF 44(2)
Clindamycin Phosphate Topical Solution	PF 44(2)
Clobetasol Propionate Ointment	PF 44(2)
Dacarbazine for Injection	PF 44(2)
Escitalopram Oral Solution	PF 44(2)
Minoxidil Tablets	PF 44(2)
Pyridostigmine Bromide Extended-Release Tablets	PF 44(2)
Sodium Phenylbutyrate Oral Powder	PF 44(2)
Sodium Phenylbutyrate Tablets	PF 44(2)
Testosterone Cypionate Injection	PF 44(2)
Benztropine Mesylate Injection	PF 44(3)
Benztropine Mesylate Tablets	PF 44(3)
Clonazepam Tablets	PF 44(3)
Cromolyn Sodium Oral Solution	PF 44(3)
Norethindrone Acetate and Ethinyl Estradiol Tablets	PF 44(3)
Fluconazole Tablets	PF 44(3)
Galantamine Extended-Release Capsules	PF 44(3)
Galantamine Oral Solution	PF 44(3)
Galantamine Tablets	PF 44(3)
Hydrocortisone Acetate Cream	PF 44(3)
Hydroxychloroquine Sulfate Tablets	PF 44(3)
Nitroglycerin Injection	PF 44(3)
Sitagliptin and Metformin Hydrochloride Tablets	PF 44(3)
Sitagliptin and Metformin Hydrochloride Extended-Release Tablets	PF 44(3)
Triamcinolone Acetonide Injectable Suspension	PF 44(3)
Triamcinolone Acetonide Lotion	PF 44(3)
Bimatoprost Ophthalmic Solution	PF 44(4)
Brimonidine Tartrate Ophthalmic Solution	PF 44(4)
Bupropion Hydrochloride Extended-Release Tablets	PF 44(4)
Bupropion Hydrochloride Tablets	PF 44(4)
Clarithromycin Extended-Release Tablets	PF 44(4)

Clindamycin Phosphate Gel	PF 44(4)
Clindamycin Phosphate Vaginal Cream	PF 44(4)
Quinapril Tablets	PF 44(4)
Tizanidine Capsules	PF 44(4)
Methylprednisolone Sodium Succinate for Injection	PF 44(4)
Atovaquone and Proguanil Hydrochloride Tablets	PF 44(5)
Baclofen Injection	PF 44(5)
Clozapine Tablets	PF 44(5)
Quinine Sulfate Capsules	PF 44(5)
Repaglinide and Metformin Hydrochloride Tablets	PF 44(5)
Triamcinolone Acetonide Cream	PF 44(5)
Triamcinolone Acetonide Dental Paste	PF 44(5)
Hydrocortisone Cream	PF 44(6)
Hydrocortisone Ointment	PF 44(6)
Hydrocortisone Tablets	PF 44(6)
Norgestimate and Ethinyl Estradiol Tablets	PF 44(6)
Prednisolone Acetate Ophthalmic Suspension	PF 44(6)
Venlafaxine Extended-Release Tablets	PF 44(6)
Diazepam Injection	PF 45(2)
Diazepam Tablets	PF 45(2)
Granisetron Hydrochloride Injection	PF 45(2)
Granisetron Hydrochloride Tablets	PF 45(2)
Selegiline Hydrochloride Capsules	PF 45(2)
Lacosamide Injection	PF 45(3)
Lacosamide Oral Solution	PF 45(3)
Lacosamide Tablets	PF 45(3)
Nadolol Tablets	PF 45(3)
Prednisone Tablets	PF 45(3)
Sorafenib Tablets	PF 45(3)
Sulfasalazine Delayed-Release Tablets	PF 45(3)
Sulfasalazine Tablets	PF 45(3)
Trihexyphenidyl Hydrochloride Oral Solution	PF 45(3)

List of impacted drug substance monographs

Monograph title	PF issue
Ceftazidime	PF 45(3)
Formoterol Fumarate	PF 45(3)
Guanfacine Hydrochloride	PF 45(3)
Labetalol Hydrochloride	PF 45(3)
Lacosamide	PF 45(3)
Mupirocin Calcium	PF 45(3)
Nadolol	PF 45(3)
Phenobarbital Sodium	PF 45(3)
Phentermine Hydrochloride	PF 45(3)
Pindolol	PF 45(3)
Rabeprazole Sodium	PF 45(3)
Tetrahydrozoline Hydrochloride	PF 45(3)
Tranexamic Acid	PF 45(3)