BRIEFING

⟨476⟩ Organic Impurities in Drug Substances and Drug Products, *PF* 41 (3) [May–June 2015]. This revision is proposed on the basis of public comments received on its previous publication in *PF*. As part of an ongoing monograph modernization initiative, USP is updating *Impurities in Drug Substances and Drug Products* ⟨1086⟩ and proposing this new chapter that addresses organic impurities testing for articles with monographs in relevant USP compendia. This new chapter has been created to align with current scientific and regulatory approaches and to help ensure the appropriate control of organic impurities in drug substances and drug products. The goal is to provide a science-based approach for the control of impurities in relevant monographs, and thereby ensure the quality of the product as it relates to safety. A delayed implementation is being considered.

It is proposed that upcoming revisions to drug substance and drug product monographs will include a cross reference to this chapter in the organic impurities section, on a case-by-case basis, when appropriate.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

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Add the following:
Change to read:

▲⟨476⟩

▲CONTROL OF▲ *USP42*

ORGANIC IMPURITIES IN DRUG SUBSTANCES AND DRUG PRODUCTS

Change to read:

INTRODUCTION

This chapter covers

▲policies and▲ *USP42*

requirements for controlling

▲drug-related▲*USP42*
organic impurities in drug substances and drug products described in *USP* monographs. ~~All drug substances and drug products are subject to control of organic impurities.~~

▲▲*USP42*
A threshold-based approach described in the International Council for Harmonisation (ICH) Q3A and Q3B ~~guidances~~
▲guidelines▲*USP42*
may be used for the control of organic impurities
▲(process impurities and degradation products)▲*USP42*
in drug substances or drug products generated during the manufacturing process
▲and/▲*USP42*
or storage. ~~The organic impurities to be controlled in the drug substance are the process impurities and degradation products. The organic impurities to be controlled in the drug product are only the degradation products of the drug substance or those resulting from the interaction of the drug substance with excipients and/or the primary container closure. Drug substance process impurities need not be controlled in the drug product unless they are also degradation products.~~

▲(For additional guidance and definition of terms, see *Impurities in Drug Substances and Drug Products* ⟨1086⟩).▲*USP42*

This chapter covers drug substances and drug products ▲described in the *USP* and▲*USP42* marketed in the United States based on approval ▲of applications▲*USP42* by the FDA either via New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs) or through the FDA over-the-counter (OTC) monograph system.

This chapter does not cover veterinary products, biological/biotechnological products, peptides, oligonucleotides, fermentation products and semisynthetic products derived from them, polymorphic forms, radiopharmaceuticals, herbal products, or crude products of animal or plant origin. In addition, impurities present in the drug product originating from excipients or leached from the

container–closure system, inorganic/elemental impurities, and residual solvents are out of the scope of this chapter.

If a new impurity is ~~uncovered~~

▲detected above the appropriate qualification threshold▲*USP42*

or when the level of a ~~known impurity~~

▲specified related compound▲*USP42*

increases as compared to ~~an existing monograph~~

▲its characteristic impurity profile,▲*USP42*

the manufacturer is responsible for evaluating the impact on the safety ~~and~~

~~efficacy~~

▲▲*USP42*

of the drug

▲substance or drug product.▲*USP42*

If an individual monograph ~~is inadequate to control~~

▲does not include a procedure for quantifying▲*USP42*

an impurity

▲or acceptance criterion for an observed impurity,▲*USP42*

the manufacturer is responsible for developing and validating ~~appropriate~~

▲▲*USP42*

analytical procedures and establishing

▲appropriate▲*USP42*

acceptance criteria. ~~and communicating with USP.~~

▲USP requests submission of the alternate/additional procedure to evaluate for potential inclusion in the appropriate monograph(s).▲*USP42*

Change to read:

IDENTIFICATION OF IMPURITIES ~~AND DEGRADATION PRODUCTS~~

▲▲*USP42*

Impurities present ~~at or~~

▲▲*USP42*

above the identification threshold for drug substances and drug products at release and on storage shall be ~~identified~~ ▲investigated and all reasonable attempts shall be made to identify these impurities.▲*USP42*

The identification threshold can be established using current applicable regulatory guidances. ~~or other acceptable scientific means.~~

▲▲*USP42*

Lower thresholds may be required for impurities known or suspected to be ~~highly~~ ▲unusually▲*USP42* toxic (e.g., genotoxic) or ~~that~~ ▲to▲*USP42* produce undesired pharmacological effects.

▲Higher thresholds may be applied if scientifically justified.▲*USP42*

Change to read:

ANALYTICAL PROCEDURES FOR IMPURITIES ~~AND DEGRADATION PRODUCTS~~

▲▲*USP42*

Manufacturers shall validate ▲or verify, as appropriate,▲*USP42* analytical procedures and must demonstrate their suitability for the detection and quantitation of impurities in drug substances and drug products. Manufacturers shall develop acceptance criteria for impurities justified by appropriate safety considerations and consistent with current applicable regulatory guidances.

~~Analytical procedures for FDA OTC monograph drug products may require a case-by-case approach, depending on the complexity of dosage forms. These procedures shall be verified or validated to be suitable for their intended purpose.~~

▲▲*USP42*

A lower limit of detection and limit of quantitation may be required for impurities known or suspected to be ~~highly~~ ▲unusually▲ *USP42* toxic (e.g., genotoxic) or to produce undesired pharmacological effects.

▲In cases of complex impurity profiles, it may not be feasible to resolve each impurity individually or detect them and quantify them using a single analytical procedure. In such cases, manufacturers should consider the use of multiple analytical procedures to test for impurities.▲ *USP42*

Change to read:

REPORTING IMPURITIES ~~AND DEGRADATION PRODUCTS~~

▲▲ *USP42*

Impurities present ~~at or~~ ▲▲ *USP42* above the reporting threshold shall be reported according to the relevant analytical procedure. The reporting threshold can be established using current applicable regulatory guidances or other acceptable scientific means.

Impurity results shall be reported as numerical values and rounded according to conventional rules (see *General Notices and Requirements, 7.20 Rounding Rules*). ~~Individual impurity values~~ ▲All impurities at a level greater than (>) the reporting threshold▲ *USP42* shall be summed and reported as ▲a value for▲ *USP42* total impurities.

Change to read:

SETTING ACCEPTANCE CRITERIA FOR IMPURITIES ~~AND DEGRADATION PRODUCTS~~

▲▲ *USP42*

Acceptance criteria shall be set for all impurities present ~~at or~~ ▲▲ *USP42*

above the ~~qualification~~

▲identification▲*USP42*

thresholds for drug substances and drug products. ~~at release and through the shelf life.~~

▲A rationale for the inclusion or exclusion of impurities in the specification should be documented.▲*USP42*

The acceptance criteria shall be based on applicable guidances or other acceptable scientific means, with safety as the primary consideration and not solely based on process capability. ~~Drug substance process impurities need not be monitored or specified in drug products unless they are also degradation products.~~

▲▲*USP42*

The acceptance criteria for drug substances

▲and drug products▲*USP42*

shall include the following, where applicable:

- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity with an acceptance criterion of NMT the identification threshold
- Total impurities

~~The acceptance criteria for drug products shall include the following, where applicable:~~

- ~~Each specified identified degradation product~~
- ~~Each specified unidentified degradation product~~
- ~~Any unspecified degradation product with an acceptance criterion of NMT the identification threshold~~
- ~~Total degradation products~~

~~For FDA OTC monograph products, manufacturers may need to determine acceptance criteria on a case-by-case basis. Factors such as quantitative structure-activity relationship (QSAR) of the drug substance, route of administration, the likely consumption patterns such as duration of treatment and the patient population, and historical safety of the drug may be considered in justifying the acceptance criteria.~~

▲Total impurities in the drug substance monograph are the sum of all specified and unspecified impurities above the reporting threshold. Unless otherwise indicated, the same definition applies to total impurities in drug product monographs. Drug product monographs may include a note that certain drug substance process-related impurities identified by relative retention times should not be included in the total impurities. When this note is included, the total impurities should include all specified and unspecified impurities above the reporting threshold, with the exception of these designated process-related impurities.

Drug substance process-related impurities are typically controlled in drug substances and not to be monitored or specified in the drug products unless they are expected to increase over time as degradation products.▲*USP42*

Acceptance criteria for ~~highly toxic (e.g., genotoxic) impurities or degradation products shall be addressed~~

▲impurities (including unusually toxic, for example, mutagenic impurities) should be supported by appropriate toxicological evaluation,▲*USP42*

using current applicable guidances.

Change to read:

QUALIFICATION OF IMPURITIES ~~AND DEGRADATION PRODUCTS~~

▲▲*USP42*

▲Qualification is the process of establishing the biological safety of impurities at the specified level(s).▲*USP42*

Qualification of impurities shall be based on ~~safety, applicable guidances, scientific rationale, or history of product use. Higher or lower qualification thresholds may be appropriate for some impurities based on scientific rationale. The level of any impurity or degradation product present in a drug substance or drug product that has been adequately tested in safety and/or clinical studies would be considered qualified. Impurities or degradation products that are also significant metabolites present in animal and/or human studies are also generally considered qualified. For additional guidance and definition of terms, (see *Impurities in Drug Substances and Drug Products* ⟨1086⟩.)~~

▲a combination of factors including safety, intended use, applicable guidances, and scientific rationale.▲*USP42*

Add the following:

▲ORGANIC IMPURITIES IN DRUG SUBSTANCES

Organic impurities in drug substances arising from the manufacturing process and/or storage should be controlled. A rationale for the inclusion or exclusion of impurities in the specification should be documented. The organic impurities to be controlled in the drug substance are the process impurities (starting materials, byproducts, intermediates, reagents, ligands, and catalysts) and degradation products. They can be identified or unidentified. Impurities that increase over time on storage are considered degradation products and should be monitored.

Drug substances manufactured by alternative processes (e.g., different starting materials, synthetic pathways, and/or purification steps) should be evaluated to determine if the differences affect the impurity profile listed in the existing monograph.

A threshold-based approach as described in ICH Q3A (R2) may be used for the reporting, identification, and/or qualification of impurities in drug substances. Because toxicity is a dose-related phenomenon, the thresholds are set based on the amount of drug substance administered per day (see *Table 1*). For OTC monograph drug products, total daily intake is based upon the manufacturer's recommended labeled dosage per day. Lower thresholds can be appropriate if the impurity is unusually toxic or produces undesirable pharmacological effects.

Table 1. ICH Recommended Thresholds for Impurities in Drug Substances

Impurity Thresholds		
Maximum daily dose	≤2 g	≥2 g
Reporting	0.05%	0.03%
Identification	0.10% (1.0 mg)[a]	0.05%
Qualification	0.15% (1.0 mg)[a]	0.05%
[a] The total daily intake in parentheses applies if it is lower than the calculated value.		

Acceptance criteria shall be set for all impurities present above the identification threshold. Principles of setting acceptance criteria for impurities in drug substances are discussed in ICH guidelines and FDA guidances for NDAs and ANDAs. The acceptance criteria shall be based on applicable guidances or other acceptable scientific means, with safety as the primary consideration and not solely based on process capability.▲*USP42*

Add the following:

▲ORGANIC IMPURITIES IN DRUG PRODUCTS

Organic impurities in drug products arising from the manufacturing process and/or storage of the drug product should be controlled. The organic impurities to be controlled in the drug product include degradation products resulting from

the degradation of the drug substance or from the interaction of the drug substance with excipients and/or the primary packaging configuration. They can be identified or unidentified. A rationale for the inclusion or exclusion of impurities in the specification should be documented. In some cases drug substance process-related impurities may be included in the drug product specifications, if appropriate. Principles of setting acceptance criteria for degradation products in drug products are discussed in ICH guidelines and FDA guidances for NDAs and ANDAs.

A threshold-based approach as described in ICH Q3B (R2) may be used for the reporting, identification, and/or qualification of impurities in drug products. Because the toxicity is dose-related, the thresholds are based on the amount of drug substance administered per day (see *Table 2*). Lower thresholds can be appropriate if the degradation product is unusually toxic or produces undesirable pharmacological effects.

Table 2. ICH Recommended Thresholds for Degradation Products in Drug Products

Degradation Product Thresholds						
Maximum daily dose	<1 mg	1–10 mg	>10 –100 mg	>100 mg–1 g	>1–2 g	>2 g
Reporting	0.1%	0.1%	0.1%	0.1%	0.05%	0.05%
Identification	1.0% or 5 µg TDI[a]	0.5% or 20 µg TDI[a]	0.2% or 2 mg TDI[a]	0.2% or 2 mg TDI[a]	0.2% or 2 mg TDI[a]	0.10%
Qualification	1.0% or 50 µg TDI[a]	1.0% or 50 µg TDI[a]	0.5% or 200 µg TDI[a]	0.2% or 3 mg TDI[a]	0.2% or 3 mg TDI[a]	0.15%

[a] Whichever is lower, calculated value or total daily intake (TDI).

Acceptance criteria shall be set for all degradation products present above the identification thresholds. Principles of setting acceptance criteria for impurities in drug products are discussed in ICH guidelines and FDA guidances for NDAs and ANDAs. The acceptance criteria shall be based on applicable guidances or other acceptable scientific means, with safety as the primary consideration and not solely based on process capability. In cases of complex impurity profiles, limits may be established based on grouping of impurities, as appropriate.

Similar principles may be applied to set thresholds and acceptance criteria for degradation products in FDA OTC monograph drug products, which are not discussed in ICH guidelines or FDA guidances. Degradation products in these drugs should be reported, identified, and/or qualified.

Measurement of degradation products can be challenging for products containing multiple drug substances and complex formulations. The use of placebo products as controls in stability studies may aid in the deconvolution of

chemical changes that could be related to excipients rather than the drug substance. For drug products that contain multiple drug substances, degradation products from each active ingredient should be controlled separately. Manufacturers should provide rationale and supporting data to justify the acceptance criteria for impurities associated with each drug substance.▲*USP42*

▲*USP42*