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▲⟨476⟩ CONTROL OF ORGANIC IMPURITIES IN DRUG SUBSTANCES AND DRUG PRODUCTS

INTRODUCTION

This chapter covers requirements for controlling drug-related organic impurities in drug substances and drug products described in *USP* monographs. A threshold-based approach described in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3A(R2) *Impurities in New Drug Substances* and Q3B(R2) *Impurities in New Drug Products* guidelines may be used for the control of organic impurities in drug substances or drug products generated during the manufacturing process and/or storage. (For additional information and definition of terms, see *Impurities in Drug Substances and Drug Products* ⟨1086⟩.)

This chapter applies to drug substances and drug products described in the *USP* when referenced in the individual monograph. This chapter addresses organic impurities arising during the manufacturing process and/or storage of the drug substance. Also the chapter covers those impurities in drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container–closure system (collectively referred to as "degradation products").

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

This chapter does not cover mutagenic impurities as described in ICH Guideline M7(R1) *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*.

ANALYTICAL PROCEDURES FOR IMPURITIES

Manufacturers shall validate or verify, as appropriate, 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 that are justified by appropriate safety considerations and consistent with current applicable regulatory guidances.

For impurities known or suspected to be unusually toxic (e.g., mutagenic impurities) or to produce undesired pharmacological effects, the limit of detection and limit of quantitation of the analytical procedures shall be commensurate with the acceptance criteria and the current applicable regulatory guidances to ensure patient safety.

REPORTING IMPURITIES

The reporting threshold can be established using current applicable regulatory guidances or other acceptable scientific means. The preferred terms applicable to organic impurities procedures are "impurity" and "total impurities" in the drug substance monographs and "degradation product" and "total degradation products" in the drug product monographs. Impurities presenting above the reporting threshold shall be reported according to the relevant analytical procedure.

Impurity results shall be reported as numerical values and rounded according to conventional rules (see *General Notices, 7.20. Rounding Rules*). All impurities at a level greater than (>) the reporting threshold shall be summed and reported as a value for total impurities, unless otherwise indicated in the monograph.

IDENTIFICATION OF IMPURITIES

Impurities present above the identification threshold for drug substances and drug products at release and on storage shall be investigated and all reasonable attempts shall be made to identify these impurities. The identification threshold can be established using current applicable regulatory guidances or other acceptable scientific means. Lower thresholds may be required for impurities known or suspected to be unusually toxic (e.g., mutagenic impurities) or to produce undesired pharmacological effects. Higher thresholds may be applied if scientifically justified, according to ICH Q3A(R2) and ICH Q3B(R2).

QUALIFICATION OF IMPURITIES

Qualification is the process of establishing the biological safety of impurities at the specified level(s). Qualification of impurities shall be based on a combination of factors including safety, intended use, applicable guidances, and scientific rationale.

SETTING ACCEPTANCE CRITERIA FOR IMPURITIES

Acceptance criteria shall be set for all impurities present above the reporting thresholds for drug substances and drug products. Specified impurities/degradation products can be either identified or unidentified. Specified identified impurities/degradation products should be included along with specified unidentified impurities/degradation products estimated to be

present at a level greater than (>) the identification threshold. Unspecified impurities/degradation products are limited by a general acceptance criterion, which is NMT (≤) the identification threshold and NLT (>) the reporting threshold. A rationale for the inclusion or exclusion of impurities in the specification should be documented. 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.

A monograph for a drug substance shall include acceptance criteria for 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

Unless otherwise indicated, total impurities in the drug substance monographs are the sum of all specified (identified and unidentified) and unspecified impurities above the reporting threshold.

A monograph for a drug product shall include acceptance criteria for 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

Unless otherwise indicated, total degradation products in the drug product monographs are the sum of all specified and unspecified degradation products above the reporting threshold.

The preferred terminology applicable to organic impurities procedures is “impurity” and “total impurities” in the drug substance monographs, and “degradation product” and “total degradation products” in the drug product monographs, respectively. Drug substance process impurities need not be controlled in the drug product unless they are also degradation products. However, in some cases drug substance process-related impurities may be included in the drug product specifications, if appropriate, and limited by appropriate acceptance criteria. Drug substance process-related impurities also detected in the drug product and included in its specification may have a note that certain drug substance process-related impurities are listed only for information and should not be included in the total degradation products. When this note is included, the total degradation products should only include all specified and unspecified impurities/degradation products above the reporting threshold, with the exception of these designated process-related impurities.

Acceptance criteria for impurities (including unusually toxic, for example, mutagenic impurities) should be supported by appropriate toxicological evaluation, using current applicable guidances. Lower thresholds may be required for impurities known or suspected to be unusually toxic.

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-related impurities and degradation products. They can be identified or unidentified. Process-related impurities are generated during drug substance manufacturing, such as byproducts, residual starting materials, intermediates, reagents, and ligands. Impurities that increase over time on storage are considered degradation products.

When there are changes to the chemistry, manufacturing, and/or controls of the drug substance (e.g., a different manufacturer or manufacturing site, scale/equipment, starting materials, synthetic pathways, and/or purification steps) described in a monograph, they should be evaluated to determine if the differences affect the impurity profile listed in the existing monograph. If the individual monograph does not include a procedure for quantifying an impurity or acceptance criterion for an observed impurity, the manufacturer is responsible for developing and validating analytical procedures and then establishing appropriate acceptance criterion. USP requests submission of the alternative/new procedure to evaluate for potential inclusion in the appropriate monograph(s).

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*). 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

Maximum daily dose	≤2 g	>2 g
Reporting threshold	0.05%	0.03%
Identification threshold	0.10% (1.0 mg)[a]	0.05%
Qualification threshold	0.15% (1.0 mg)[a]	0.05%

[a] The total daily intake (TDI; in parentheses) applies if it is lower than the calculated value.

Principles for Setting Acceptance Criteria for Impurities in drug substances are discussed in this chapter and also in ICH guidelines and FDA guidances for New Drug Applications (NDAs) and Abbreviated New Drug Applications (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.

ORGANIC IMPURITIES IN DRUG PRODUCTS

Usually, the organic impurities to be controlled in the drug product are only the degradation products resulting from the degradation of the drug substance or 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. Drug substance process-related impurities need not be monitored or specified in drug products unless they are also degradation products.

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*). The amount of drug substance administered per day is based upon the manufacturer's maximum recommended labeled dosage per day. 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

Maximum daily dose	<1 mg	≥1 to <10 mg	10 mg	>10–100 mg	>100 mg–1 g	>1–2 g	>2 g
Reporting threshold	0.1%	0.1%	0.1%	0.1%	0.1%	0.05%	0.05%
Identification threshold	1.0% (5 µg)[a]	0.5% (20 µg)[a]	0.5% (20 µg) [a]	0.2% (2 mg)[a]	0.2% (2 mg)[a]	0.2% (2 mg)[a]	0.10%
Qualification threshold	1.0% (50 µg)[a]	1.0% (50 µg)[a]	0.5% (200 µg)[a]	0.5% (200 µg)[a]	0.2% (3 mg)[a]	0.2% (3 mg)[a]	0.15%

[a] Whichever is lower, calculated value or TDI (in parentheses).

Principles for Setting Acceptance Criteria for Impurities in drug products are discussed in this chapter and also 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 the grouping of impurities, if appropriate and scientifically justified [according to ICH Q3B(R2)].

For drug products that contain multiple drug substances, degradation products from each active ingredient should be controlled. Manufacturers should provide rationale and supporting data to justify the acceptance criteria for impurities associated with each drug substance, as applicable.▲ (USP 1-May-2021)