BRIEFING

⟨1086⟩ **Impurities in Drug Substances and Drug Products,** *USP 37* page 828. As part of an ongoing monograph modernization initiative, the United States Pharmacopeial Convention (USP) is updating this general chapter, ⟨1086⟩ *Impurities in Drug Substances and Drug Products*, and proposing a new chapter, ⟨476⟩ *Organic Impurities in Drug Substances and Drug Products*, which addresses organic impurities testing for articles with monographs in relevant USP compendia. ⟨1086⟩ has been updated to align it with current scientific and regulatory standards and to help ensure the appropriate control of organic impurities and degradation products in drug substances and drug products. In addition to providing updated general guidelines, ⟨1086⟩ introduces definitions and a decision tree for addressing impurities associated with drug substances and drug products. These new resources should assist the user who may have questions related to implementation of ⟨476⟩. Over time, ⟨466⟩ *Ordinary Impurities* may be used less frequently and may be withdrawn.

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

(GCPA: A. Hernandez-Cardoso.)
Correspondence Number—C133392

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⟨1086⟩ IMPURITIES IN DRUG SUBSTANCES AND DRUG PRODUCTS

Change to read:

INTRODUCTION

This general information chapter is intended to provide common terminology for impurities and degradation products that may be present in compendial drug substances and drug products. Impurities or degradation products in drug substances can arise during the manufacturing process or during storage of the drug substance. The degradation products in drug products can arise from drug substances or reaction products of the drug substance with the environment, with an excipient, or an immediate container–closure system. Biological and biotechnological products, fermentation products and semisynthetic products derived therefrom, and radiopharmaceutical products are not covered in this chapter.

Communications about impurities and degradation products in compendial articles may be improved by including in this Pharmacopeia the definitions of terms and the contexts in which these terms are used. (See *Definitions* below.) There has been much activity and discussion

in recent years about the definition of terms. Certain industry-wide concerns about terminology and context deserve widespread publication and ready retrievability and are included here. See section *5.60, Impurities and Foreign Substances* in section *5, Monograph Components* under *General Notices and Requirements,* as well as the general chapter *Ordinary Impurities* ⟨466⟩. Some other general chapters added over the years have also addressed topics of purity or impurity as these have come into focus or as analytical methodology has become available. Analytical aspects are enlarged upon in the chapter *Validation of Compendial Procedures* ⟨1225⟩.

Purity or impurity measurements for drug products present a challenge to Pharmacopeial standards-setting. Where degradation of a drug product over time is at issue, the same analytical methods that are stability-indicating are also purity-indicating. Resolution of the active ingredient(s) from the excipients necessary to the preparation presents the same qualitative problem. Thus, many monographs for Pharmacopeial preparations feature chromatographic assays. Where more significant impurities are known, some monographs set forth specific limit tests. In general, however, this Pharmacopeia does not repeat impurity tests in subsequent preparations where these appear in the monographs of drug substances and where these impurities are not expected to increase. It is presumed that adequate retention specimens are in storage for the exact batch of drug substances used in any specific lot of a drug product. Whenever analysis of an official article raises a question of the official attributes of any of the drug substances used, subsequent analysis of retention specimens is in order.

DRUG SUBSTANCE

Classification of Impurities—Impurities can be classified into the following categories:

1. Organic impurities (process- and drug-related)
2. Inorganic impurities
3. Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the drug substance. They can be identified or unidentified, volatile or nonvolatile, and include the following:

1. Starting materials
2. Byproducts
3. Intermediates
4. Degradation products

5. ~~Reagents, ligands, and catalysts~~
6. ~~Geometric and stereoisomers~~

~~Inorganic impurities can result from the manufacturing process. They are normally known and identified and include the following:~~

1. ~~Reagents, ligands, and catalysts~~
2. ~~Heavy metals or other residual metals~~
3. ~~Inorganic salts~~
4. ~~Other materials (e.g. filter aids, charcoal)~~

~~Residual solvents are organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a drug substance. Because these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see *Residual Solvents* ⟨467⟩).~~

~~Concepts for setting impurity or degradation product limits in drug substances are based on chemistry and safety concerns. As such, limits for organic and inorganic impurities and residual solvents should be established for drug substances. The basic tenet for setting limits is that levels of impurities or degradation products in a drug substance must be controlled throughout its development to ensure its safety and quality for use in a drug product.~~

~~Documented evidence that the analytical procedure used to evaluate impurities or degradation products is validated and suitable for the detection and quantification of impurities or degradation products should be established.~~

~~DRUG PRODUCT~~

~~The specification for a drug product should include a list of degradation products expected to occur during manufacture of the commercial product and under recommended storage conditions. Stability studies, knowledge of degradation pathways, product development studies, and laboratory studies should be used to characterize the degradation profile. The selection of degradation products in the drug product specification should be based on the degradation products found in batches manufactured by the proposed commercial process.~~

~~This rationale should include a discussion of the degradation profiles observed in the safety and clinical development batches and in stability studies, together with a consideration of the degradation profile of batches manufactured by the proposed commercial process. For degradation products known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should~~

be commensurate with the level at which the degradation products should be controlled.

For drug products the concept for setting degradation product limits is based on sound scientific judgment as applied to available data on the safety and stability of the drug product, data that may include the degradation pathways of the drug substance, the manufacturing process, known excipient interactions, any safety assessment studies, stability studies conducted under the recommended storage conditions, and ancillary studies that may provide additional information on the stability profile of the drug product. Impurities that are not degradation products (e.g., process impurities from the drug substance) are often not controlled in the drug product, as they are typically controlled in the drug substance and these impurities are not expected to increase over time. Additional guidance for setting limits can be found in various ICH and FDA guidance documents, as well as in the USP monograph submission guidelines.

Documented evidence that the analytical procedure used to evaluate impurities or degradation products is validated and suitable for the detection and quantification of impurities or degradation products should be established.

Drug products should contain levels of residual solvents no higher than can be supported by safety data (see *Residual Solvents* ⟨467⟩).

DEFINITIONS

Concomitant Components—Concomitant components are characteristic of many drug substances and are not considered to be impurities in the Pharmacopeial sense. Limits on contents, or specified ranges, or defined mixtures are set forth for concomitant components in this Pharmacopeia. Examples of concomitant components are geometric and optical isomers (or racemates) and antibiotics that are mixtures. Any component that can be considered a toxic impurity because of significant undesirable biological effect is not considered to be a concomitant component.

Degradation Product—An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediatecontainer–closure system.

Foreign Substances (Extraneous Contaminants)—An impurity that arises from any source extraneous to the manufacturing process and that is introduced by contamination or adulteration. These impurities cannot be anticipated when monograph tests and assays are selected. The presence of objectionable foreign substances not revealed by monograph tests

and assays constitutes a variance from the official standard. Examples of foreign substances include ephedrine in Ipecac or a pesticide in an oral liquid analgesic. Allowance is made in this Pharmacopeia for the detection of foreign substances by unofficial methods. (See section *5.60, Impurities and Foreign Substances* in section *5, Monograph Components* under *General Notices and Requirements.*)

Identified Impurities and Identified Degradation Products—Impurities or degradation products for which structural characterizations have been achieved.

Impurity—Any component of a drug substance that is not the chemical entity defined as the drug substance and in addition, for a drug product, any component that is not a formulation ingredient.

Inorganic Impurities—Inorganic impurities can result from the manufacturing process (e.g., residual metals, inorganic salts, filter aids, etc.). Inorganic impurities are typically controlled by tests such as *Heavy Metals* ⟨231⟩ and *Residue on Ignition* ⟨281⟩. Information found in *Plasma Spectrochemistry* ⟨730⟩ and *Ion Chromatography* ⟨1065⟩ may also be of value.

Intermediate—A material that is produced during steps of the synthesis of a drug substance and that undergoes further chemical transformation before it becomes a drug substance. The intermediate is often isolated during the process.

Ordinary Impurities—Some monographs make reference to ordinary impurities. For more details see *Ordinary Impurities* ⟨466⟩.

Other impurities—See section *5. Monograph Components* under *General Notices and Requirements.*

Polymorphs—Different crystalline forms of the same drug substance. These can include solvation or hydration products (also knows as pseudopolymorphs) and amorphous forms. Although polymorphs are not impurities by definition, an understanding of the crystalline forms, hydration or solvation states, or amorphous nature is critical to the overall characterization of the drug substance.

Process Contaminants—Process contaminants are identified or unidentified substances (excluding related substances and water), including reagents, catalysts, other inorganic impurities (e.g., heavy metals, chloride, or sulfate); and may also include foreign substances (extraneous contaminants). These contaminants may be introduced during manufacturing or handling procedures.

Reagent—A substance other than a starting material, intermediate, or solvent that is used in the manufacture of a drug substance.

Related Substances—Related substances are structurally related to a drug substance. These substances may be (a) identified or unidentified impurities arising from the synthesis manufacturing process, such as starting materials, intermediates, or by-products, and do not increase on storage, or (b) identified or unidentified degradation products that result from drug substance or drug product manufacturing processes or arise during storage of a material.

Residual Solvents—An organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a drug substance (see *Residual Solvents* 〈467〉).

Specified Impurities and Specified Degradation Products—Previously referred to as Signal Impurities, specified impurities or specified degradation products are impurities or degradation products that are individually listed and limited with specific acceptance criteria in individual monographs as applicable. Specified impurities or specified degradation products can be identified or unidentified.

Starting Material—A material that is used in the synthesis of a drug substance and is incorporated as an element into the structure of an intermediate and/or of the drug substance. Starting materials are often commercially available and have well-defined chemical and physical properties and structure.

Stereomeric Impurity—A compound with the same 2-dimensional chemical structure as the drug substance but differs in the 3-dimensional orientation of substituents at chiral centers within that structure. In those cases where all chiral centers are in the opposite orientation, the impurity is an enantiomer (enantiomeric impurity). Determinations of impurities in this category often require special chiral chromatographic approaches. Diastereomeric or epimeric impurities occur when only some of the chiral centers are present in the opposite orientation.

Toxic Impurities—Toxic impurities have significant undesirable biological activity, even as minor components, and require individual identification and quantification by specific tests. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles. Based on validation data, individualized tests and specifications are selected. These feature comparison to a Reference Standard of the impurity, if available. It is incumbent on the manufacturer to provide data that would support the classification of such impurities as toxic impurities.

Unidentified Impurities and Unidentified Degradation Products—Impurities or degradation products for which structural characterizations have not been achieved and that are identified solely by qualitative analytical properties (e.g., chromatographic retention times).

~~**Unspecified Impurities and Unspecified Degradation Products—**Impurities or degradation products that are limited by general acceptance criteria but not individually listed with their own specific acceptance criteria in individual monographs.~~

■INTRODUCTION

This general information chapter provides guidance regarding impurities that may be present in drug substances and drug products (see *Appendix 1: Definitions* and *Appendix 2: Additional Sources of Information and Guidance* for further information).

Because of scientific and technological advancements, impurity measurements and control strategies continue to evolve. These changes, in combination with advancements in the field of toxicology, have contributed to the evolution of regulatory and compendial standards for the control of impurities in drug substances and drug products.

Manufacturers should consider the chemical characteristics and safety aspects of impurities when they identify and classify impurities in a drug substance or drug product. They should list impurities in specifications for the drug substance and drug product, and should describe the analytical procedures used to identify and quantify these impurities. Analytical procedures should be validated and demonstrated to be suitable for the detection and quantitation of impurities (for additional information, see *Validation of Compendial Procedures* 〈1225〉).

For impurities that are known or suspected to be highly toxic (e.g., genotoxic) or that produce undesired pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the acceptance criteria. However, analytical procedures should be developed for those impurities at levels NMT the identification threshold.

DRUG SUBSTANCE

Acceptance criteria for impurities in drug substances should be based on chemical characteristics and safety considerations. As such, acceptance criteria for organic and inorganic impurities and residual solvents should be established for drug substances.

Impurities in drug substances are classified into the following three categories: 1) organic impurities (process- and drug-related), 2) inorganic impurities, and 3) residual solvents.

Organic impurities can arise during the manufacturing process and/or storage of the drug substance. They can be identified or unidentified, volatile or nonvolatile, and may include the following:

1. Starting materials
2. Byproducts
3. Intermediates
4. Degradation products
5. Reagents, ligands, and catalysts
6. Residual solvents

Inorganic impurities can result from the manufacturing process. They are usually known and identified, and may include the following:

1. Reagents, ligands, and catalysts
2. Heavy metals or other residual metals
3. Inorganic salts
4. Other materials (e.g., filter aids, charcoal)

The control of inorganic impurities is defined in chapters *Elemental Impurities—Limits* 〈232 〉, *Elemental Impurities—Procedures* 〈233〉, and *Residue on Ignition* 〈281〉. Additional information in *Plasma Spectrochemistry* 〈730〉 and *Ion Chromatography* 〈1065〉 may also be of value. The control of residual solvents is described in *Residual Solvents* 〈467〉.

Organic impurities in drug substances are often specific to the manufacturing process and starting materials. Drug substances manufactured by alternative processes should be evaluated to ensure that a different synthetic route does not introduce any new impurities that are not described in the monograph. When new impurities are identified, the manufacturer should inform USP and provide additional tests and acceptance criteria to be applied to the applicable monograph.

Impurities in drug substances may need to be reported, identified, and/or qualified. A threshold-based approach as described in ICH Q3A, shown below in *Table 1*, is used for the reporting, identification, and/or qualification of impurities. Thresholds are based on the amount of drug substance administered per day. Higher thresholds may be applied if scientifically justified. Lower thresholds may be appropriate if the impurity is unusually toxic.

Table 1. Drug Substance Impurity Thresholds

	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.

DRUG PRODUCT

Potential sources of organic impurities in drug products include the following:

- ¿ Residual impurities from the drug substance
- ¿ Degradation products
- ¿ Extractables and leachables
- ¿ Impurities present in, or derived from, excipients

Organic impurities in drug products should be controlled. This chapter addresses only those impurities in drug products that are classified as degradation products of the drug substance or reaction products of the drug substance with excipients and/or the primary container closure—collectively referred to as "degradation products" in this chapter.

In addition to degradation products, elemental impurities (see ⟨232⟩) and residual solvents (see ⟨467⟩) are also to be controlled in drug products.

Generally, drug substance-related process impurities present in the drug product need not be monitored or specified in the drug product unless they are also degradation products. Principles of setting acceptance criteria for degradation products in drug products are discussed in ICH and Food and Drug Administration (FDA) guidances for new drug application (NDA) and abbreviated new drug application (ANDA) products.

A threshold-based approach as described in ICH Q3B (R2 or current version), shown below in *Table 2*, is used for the reporting, identification, and/or qualification of impurities. Thresholds are based on the amount of drug substance administered per day. Higher thresholds may be applied if scientifically justified. Lower thresholds may be appropriate if the degradation product is unusually toxic.

Table 2. Drug Product (NDA & ANDA) Degradation Product Thresholds

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

a Lower threshold may be appropriate for toxic impurities.

b Whichever is lower, calculated value or Total Daily Intake (TDI).

Similar principles may be applied to set thresholds and acceptance criteria for degradation products in drug products not discussed in ICH or FDA guidances [e.g., those for over-the-counter (OTC) drug products]. Degradation products in these drugs may also need to be reported, identified, and/or qualified. Thresholds should be justified based on historical information such as drug product stability and safety data, as well as the amount of drug substance administered per day. Higher thresholds may be applied if scientifically justified. Lower thresholds may be appropriate if the degradation product is unusually toxic.

Measurement of drug product impurities can be a challenging aspect of pharmacopeial standards-setting for products containing multiple drug substances and complex excipients (e.g., OTC products). The use of placebo products as controls in stability studies may aid in the deconvolution of chemical changes that could be related to flavors and dyes rather than the drug substance. For drug products that contain multiple drug substances, it is appropriate to quantify unidentified degradation products based on the drug substance present in the highest dose (i.e., to obtain the lowest threshold value).

The decision tree for impurities in drug substances and drug products (*Figure 1*) provides guidance regarding control of impurities, including organic impurities that may be present in drug substances and drug products.

Technical factors (e.g., the manufacturing process, a low drug substance-to-excipients ratio, or the use of excipients of animal or plant origin) may also be considered as part of the justification for selection of alternative thresholds based on manufacturing experience with the commercial process. However, acceptance criteria should not be based solely on process capability.

In cases of complex impurity profiles, it may not be feasible to resolve each impurity individually. Limits on combinations of impurities may be established, as appropriate. Manufacturers also can consider the use of multiple analytical procedures.
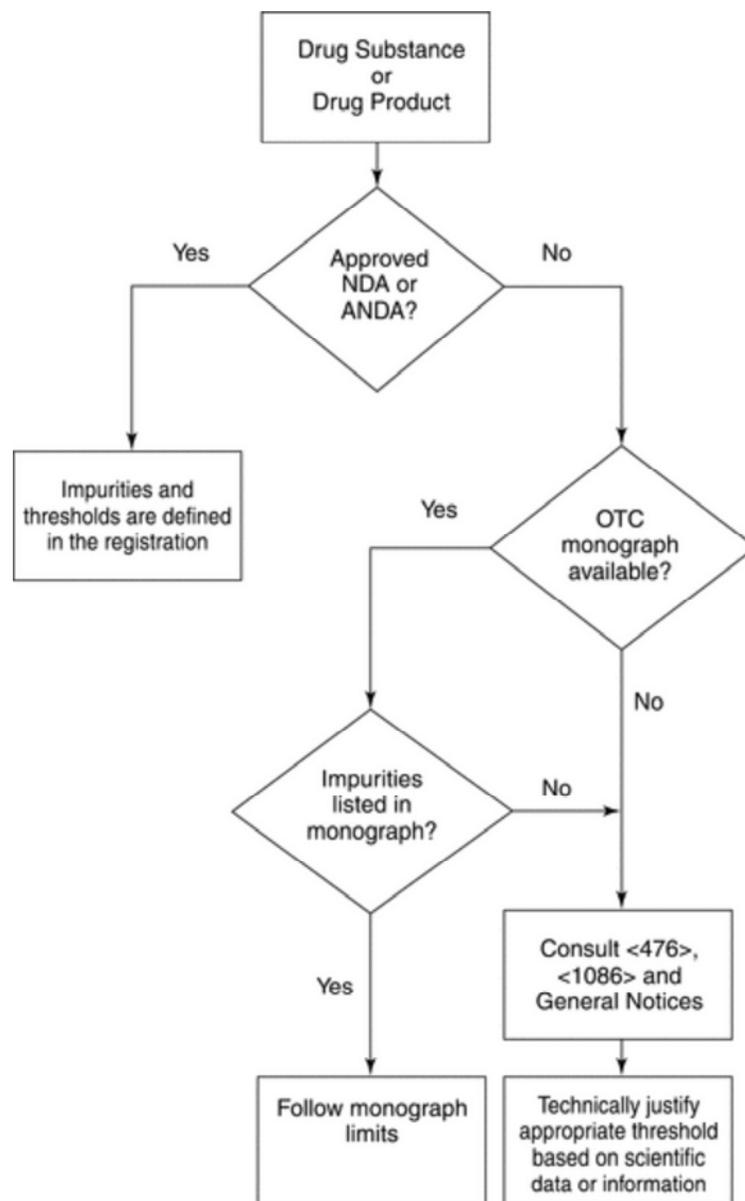
Figure 1. Decision tree for control of organic impurities in drug substances and drug products.

APPENDIX 1: DEFINITIONS

Degradation product: An impurity resulting from a chemical change in the drug substance brought about during manufacture or storage of the drug product by the effect of, for example, light, temperature, pH, or water, or by reaction with an excipient or the primary container–closure system.

Extraneous contaminants (foreign substances): An impurity that arises from any source extraneous to the established manufacturing process and that is introduced by contamination or adulteration.

Identified impurity/degradation product: An impurity or degradation product for which structural characterization has been established.

Identification threshold: A limit above which an impurity should be identified.

Impurity: For a drug substance, any component of the drug substance that is not the chemical entity that is defined as the drug substance; for a drug product, any component of a drug product that is not the drug substance or an excipient in the drug product.

Qualification: The process of acquiring and evaluating data that establish the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Qualification threshold: A limit above which an impurity should be qualified.

Reporting threshold: A limit above which an impurity should be reported.

Specified impurity/degradation product: An impurity or degradation product that is individually listed and limited with a specific acceptance criterion in the drug substance or drug product specification. A specified impurity or specified degradation product can be either identified or unidentified.

Unidentified impurity/degradation product: An impurity or degradation product for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified impurity/degradation product: An impurity or degradation product that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the drug substance or drug product specification.

APPENDIX 2: ADDITIONAL SOURCES OF INFORMATION AND GUIDANCE

- ¿ ICH. Q3A(R2) Impurities in new drug substances. 2006. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_F Accessed 24 January 2014.
- ¿ ICH. Q3B(R2) Impurities in new drug substances. 2006. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guid Accessed 24 January 2014.
- ¿ FDA. Guidance for industry. NDAs: impurities in drug substances. 2000. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guid Accessed 24 January 2014.
- ¿ FDA. Guidance for industry. ANDAs: impurities in drug products. 2010. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guid

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¿ *Impurities in Drug Substances and Drug Products* 〈 1086 〉. USP. In: *USP37–NF32*. Rockville (MD): United States Pharmacopeial Convention; 2014. pp. 828–831.

¿ Consumer Healthcare Products Association. Your health at hand book: guide to OTC active ingredients in the United States. 2010. http://www.yourhealthathand.org/images/uploads/Your_Health_at_Hand_Book.pdf. Accessed 24 January 2014.

■1S (*USP38*)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

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