BRIEFING

⟨1086⟩ Impurities in Drug Substances and Drug Products, *USP 40* page 1270; and *PF* 41(3) [May–June 2015]. This revision is proposed on the basis of public comments received on the previous publication in *PF*. As part of an ongoing monograph modernization initiative, USP is updating this general chapter and proposing a new chapter, *Control of Organic Impurities in Drug Substances and Drug Products* ⟨476⟩, which addresses organic impurities testing for articles with monographs in relevant USP compendia. This chapter has been updated to align it with current scientific and regulatory standards and to help ensure the appropriate control of organic impurities in drug substances and drug products. In addition to providing updated general guidelines, this chapter introduces definitions for terminology used in drug substances and drug product monographs, and a decision tree for addressing impurities associated with drug substances and drug products. USP recognizes that the use of ICH terminology as is in the *USP* is evolving, and therefore this proposal is a starting point. These new resources should assist the user who may have questions related to the implementation of ⟨476⟩. Definitions related to impurities in excipients (concomitant component, other component, added substance, excipient impurity) have not been included in this chapter because they will be addressed separately in an upcoming *Stimuli* article.

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

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⟨1086⟩ IMPURITIES IN DRUG SUBSTANCES AND DRUG PRODUCTS

Change to read:

INTRODUCTION

▲Impurities are critical quality attributes of drug substances and drug products because they have the potential to affect safety and efficacy of the product.▲*USP42*

This general information chapter ~~is intended to provide common terminology for~~

▲provides guidance on the control of impurities (process▲*USP42*

impurities and degradation products) ~~that may be present in compendial~~

▲in▲*USP42*

drug substances and drug products

▲(Definitions of key terms used in this chapter can be found in *Appendix 1: Glossary*).▲*USP42*

~~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.~~

▲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, and 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.▲*USP42*

~~Communications~~

▲The regulatory and compendial standards for the control of impurities continue to evolve due to advancements in analytical science, technology, and toxicology. Therefore, communications▲*USP42*

about impurities and degradation products in ~~compendial articles may~~

▲drug substances and drug products can▲*USP42*

be improved by including in this Pharmacopeia the definitions of terms and the contexts in which these terms are used (see

▲*Appendix 1:*▲*USP42*
Glossary.) 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 *General Notices, 5.60 Impurities and Foreign Substances* ~~as well as the general chapter *Ordinary Impurities* ⟨466⟩~~

▲for additional information about impurities.▲*USP42*

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 *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.~~

▲▲USP42

Resolution of the active ingredient(s) from the excipients necessary ~~to the preparation~~

▲for the formulation▲USP42

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.~~

▲tests for these impurities.▲USP42

In general, this Pharmacopeia does not repeat impurity tests in ~~subsequent preparations~~

▲the monographs of drug products▲USP42

where these

▲tests▲USP42

appear in the monographs of drug substances and where these impurities are not expected to increase;

▲however, their presence may be limited by the total impurities acceptance criteria.▲USP42

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~~

▲a drug product▲USP42

raises a question of the ~~official~~

▲quality▲USP42

attributes of any of the drug substances used, subsequent analysis of retention specimens is in order.

Change to read:

DRUG SUBSTANCE

Classification of Impurities

Impurities

▲in drug substances▲USP42

can be classified into the following categories:

1. Organic impurities ~~(process- and drug-related)~~
   ▲▲USP42
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~~
   ▲Elemental impurities▲USP42
3. Inorganic salts
4. Other materials (e.g., filter aids, charcoal)

▲Elemental impurities include catalysts and environmental contaminants that may be present in drug substances. These impurities may occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container–closure system). When elemental impurities are known to be present, have been added, or have the potential for introduction, control to the specified levels is required (see *Elemental Impurities—Limits* ⟨232⟩).▲USP42

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~~

▲▲USP42
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~~ ▲▲USP42 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~~ ▲▲USP42 is validated and suitable for the detection and ~~quantification~~ ▲quantitation▲USP42 of impurities ~~or degradation products~~ ▲▲USP42 should be established.

Change to read:

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 ▲(e.g., predictive toxicology programs),▲USP42 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 International Council on Harmonization (ICH) ▲guidelines▲USP42 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~~ ▲▲USP42 is validated and suitable for the detection and quantification of impurities ~~or degradation products~~ ▲▲USP42 should be established.

▲Chapter ⟨232⟩ specifies limits for the amounts of elemental impurities in drug products.▲USP42
Drug products should contain levels of residual solvents no higher than can be supported by safety data (see ⟨467⟩).

Add the following:

▲ORGANIC IMPURITIES IN DRUG SUBSTANCES AND DRUG PRODUCTS

All drug substances and drug products are subject to control of organic impurities. A threshold-based approach described in the ICH Q3A and Q3B guidelines may be used for the control of organic impurities in drug substances or drug products generated during the manufacturing process or storage (for additional information, see *Control of Organic Impurities in Drug Substances and Drug Products* ⟨476⟩).

The organic impurities to be controlled in drug substances are the process impurities and degradation products. The organic impurities to be controlled in the drug product are those resulting from the degradation of the drug substance or 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. However, in some cases drug substance process impurities may be included in the drug product specifications, if appropriate.

For marketed products, the manufacturers are responsible for controlling organic impurities in accordance with current regulatory standards. Manufacturers should consider the chemical characteristics and safety aspects of impurities when they identify and classify impurities in a drug substance or drug product. Analytical procedures for the detection and quantitation of impurities should be verified or validated. (For additional information, see ⟨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 to ensure patient safety.

This chapter covers drug substances and drug products described in the *USP* and marketed in the United States based on approval 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.

If a new impurity is detected above the appropriate qualification threshold or when the level of a specified related compound increases as compared to its characteristic impurity profile, the manufacturer is responsible for evaluating the impact on the safety of the drug substance or drug product. If an 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 establishing appropriate acceptance criterion. USP requests submission of the alternate/additional procedure to evaluate for potential inclusion in the appropriate monograph(s).

(Definitions of key terms used in this chapter can be found in *Appendix 1: Glossary*. Additional sources of guidance on impurities in drug substances and drug products may be found in *Appendix 2: Additional Sources of Information and Guidance*.)▲*USP42*

Add the following:

▲ORGANIC IMPURITIES DECISION TREE

The decision tree shown in *Figure 1* provides guidance for impurities in drug substances and drug products.

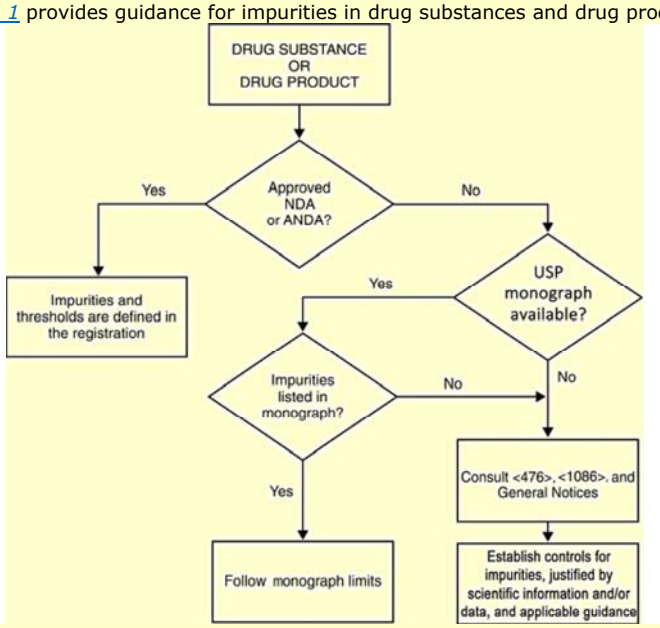

Figure 1. Decision tree for control of organic impurities in drug substances and drug products.

Note that all impurities specific to a given drug product formulation may or may not be included in the *USP* monograph. If the impurity is listed in the monograph, follow monograph limits. If the impurity is not listed, consult ⟨476⟩ and this chapter for guidance.▲*USP42*

Add the following:

▲TERMINOLOGY ASSOCIATED WITH ORGANIC IMPURITIES USED IN DRUG SUBSTANCE AND DRUG PRODUCT MONOGRAPHS

In general, if the structure of a specified impurity is known, its chemical name is provided. There are several scenarios for citing organic impurities in *USP–NF* monographs:

1. The name of the organic impurity is listed, its chemical structure is well known (characterized), and a reference material is available
2. The name of the organic impurity is listed, its chemical structure is well known (characterized), but a reference material is not available
3. The name of the organic impurity, its chemical structure is not known (non-characterized), and a reference material is not available

If an impurity is not listed, it is controlled as an individual unspecified impurity.

A *USP* monograph of a drug substance may contain acceptance criteria for:

1. Specified organic impurities
2. "Any unspecified impurity" or "Any other individual impurity"
3. Total impurities

In all cases, the terms "Any unspecified impurity" or "Any other individual impurity" corresponds to unspecified impurities.

Total impurities in drug substance monographs are the sum of all specified and unspecified impurities above the reporting threshold. Unless otherwise indicated, the same definition applies to total impurities in the 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.

Some monographs may state "disregard any peak below a certain value" in chromatographic tests. In this context, the disregard limit is the decision criterion (the numerical value) for the user whether a peak response of an impurity is to be included or excluded in the total impurities.

Typically, the disregard limit for substances covered by a monograph is set in accordance with the reporting threshold given in ⟨476⟩. When a limit for the total of impurities is prescribed, a reporting threshold needs to be included in the test for related substances. This threshold helps to establish the minimum sensitivity need for the analytical system used. Peaks corresponding to the blank can also be disregarded, as well as other peaks that the monograph explicitly states are to be disregarded. In other words, if impurities (specified or unspecified) are above the disregard limit, they should be taken into account for the calculation of the total impurities.

In chromatographic tests, during quantitation, disregard peaks caused by solvents and reagents or arising from the mobile phase or the sample matrix. When the impurity test prescribes the total of impurities or there is a quantitative determination of an impurity, choice of an appropriate threshold setting and appropriate conditions for the integration of the peak areas is important. In such tests the limit at or below which a peak is disregarded is generally 0.05% but not higher than the reporting threshold. Thus, the threshold setting of the data collection system corresponds to at least half of this limit. Integrate the peak area of any impurity that is not completely separated from the principal peak, preferably by valley-to-valley extrapolation (see *Chromatography* ⟨621⟩).▲*USP42*

Change to read:

▲APPENDIX 1:▲*USP42*
GLOSSARY

~~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 immediate container–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 *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 known 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.~~

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

Disregard limit: See *Reporting threshold*. [NOTE—It may appear in a monograph as "Disregard any peak below [...]%."]

Drug substance process-related impurity: An impurity generated during drug substance manufacturing. Process-related impurities may include starting materials, byproducts, intermediates, reagents, ligands, and catalysts.

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

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

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: In chromatographic tests, it is the limit above which an impurity should be reported and should be taken into account for calculating total impurities. In pharmacopeial monographs, the disregard limit and the reporting threshold are considered synonyms, with "reporting threshold" being a preferred term. Synonyms also include "reporting level" and "reporting limit". [NOTE—Peak responses must be corrected by the relative response factor when the information is provided in the individual monograph.]

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

Total impurities: In a drug substance monograph, total impurities are the sum of all specified and unspecified impurities above the reporting threshold. Unless otherwise indicated, the same definition applies to total impurities in the 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/degradation products above the reporting threshold, with the exception of these designated process-related impurities. Unless otherwise stated in the drug product monograph, peak responses arising from excipients and excipient impurities or impurities that are leached from the container–closure system are not included in the total impurities. For drug product monographs, the term "total degradation products" is considered a synonym to "total impurities", with "total impurities" being a preferred term.

Unspecified impurity/degradation product: An impurity or degradation product that is not individually listed with its own specific acceptance criterion in the drug substance or drug product monograph. In pharmacopeial monographs, any impurity/degradation product that is not individually listed is considered "unspecified" and is limited by a general acceptance criterion. Unless otherwise stated in the drug product monograph, peak responses arising from excipients and excipient impurities or impurities that are leached from the container–closure system are not included. Synonyms include "other impurity/degradation product" or "other individual impurity/degradation product", with "unspecified impurity" being a preferred term.▲*USP42*

Add the following:

▲APPENDIX 2: ADDITIONAL SOURCES OF INFORMATION AND GUIDANCE

1. International Council for Harmonisation. Q3A(R2) Impurities in new drug substances. 2006. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2_Guideline.pdf. Accessed 6 September 2017.
2. International Council for Harmonisation. Q3B(R2) Impurities in new drug products. 2006. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2_Guideline.pdf. Accessed 6 September 2017.
3. International Council for Harmonisation. Q6A Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances. 1999. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf. Accessed 6 September 2017.
4. International Council for Harmonisation. M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. 2017. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_31Mar201 Accessed 6 September 2017.
5. U.S. Food and Drug Administration. Guidance for industry. NDAs: impurities in drug substances. 2000. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070577.pdf. Accessed 6 September 2017.

6. U.S. Food and Drug Administration. Guidance for industry. ANDAs: impurities in drug products. 2010. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf. Accessed 6 September 2017.
7. *Organic Impurities in Drug Substances and Drug Products ⟨476⟩.* USP. In: *Pharm Forum* 43(6) [Nov.–Dec. 2017]. Rockville (MD): United States Pharmacopeial Convention; 2017. http://www.usppf.com.
8. Consumer Healthcare Products Association. Your Health at Hand: Guide to OTC Active Ingredients in the United States. 2010. http://www.yourhealthathand.org/images/uploads/Your_Health_at_Hand_Book.pdf. Accessed 6 September 2017.