

Overview of USP General Chapters <476> and <1086>

Prescription/Non-Prescription
Stakeholder Forum
October 19, 2017



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Introduction



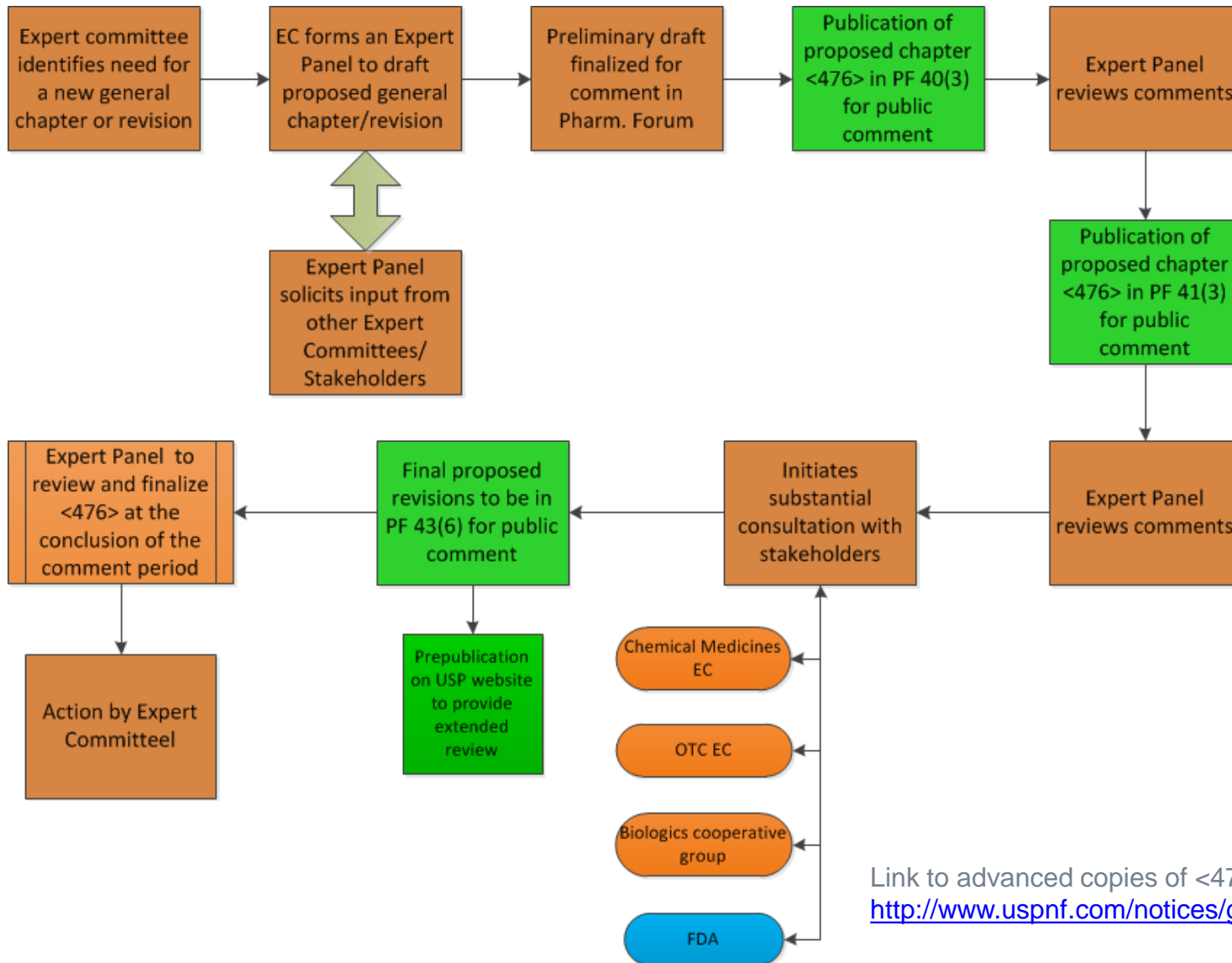
- ▶ Periodic review of existing general chapters
 - Typically an approximately 5 year cycle
 - Evaluate currency of information
 - Review changes in regulations or Health Authority expectations
 - Identify any potential gaps in standards

- ▶ Chapters already present in USP providing guidance for impurities
 - <197> Spectrophotometric Identification Tests
 - <231> Heavy Metals
 - <232> Elemental Impurities-Limits
 - <233> Elemental Impurities-Procedures
 - <466> Ordinary Impurities
 - <1086> Impurities in Drug Substances and Drug Products

- ▶ Gap identified in standard: Potential new chapter <476> Control of Organic Impurities in Drug Substances and Drug Products (developed and concepts introduced in PF)

- ▶ Periodic review of <1086> as well as questions received post-publication suggested a need for revision. A focused survey to stakeholders confirmed the support to harmonized the impurities policy with ICH Q3A/B

Chapters development: <476> and <1086>



Link to advanced copies of <476> and <1086> :
<http://www.uspnf.com/notices/gc-476-1086>

Revised <476> and New <1086>



□ Promotes a Science based approach

- Current regulatory guidance documents and sound scientific principles may be used to control the level of impurities.
- A threshold-based approach described in ICH Q3A/B is used for the reporting/identification/qualification of impurities.
 - Higher thresholds may be applied if scientifically justified.
 - Lower thresholds may be appropriate for highly toxic impurity.

□ Considerations for Highly Toxic Impurities (e.g. Genotoxic) included

- For impurities known or suspected to be highly toxic (e.g., genotoxic), the quantitation/detection limit of the analytical procedures should be commensurate with the acceptance criteria.
- Highly toxic (e.g., genotoxic) impurities or degradation products shall be addressed using applicable guidelines (e.g. ICH M7)



New General Chapter
“<476> *Control of Organic Impurities in Drug
Substances and Drug Products*”
- Update

Objectives <476> and <1086> to be published in PF 43(6)



- ▶ Address public comments received from previous publication in *PF*. As part of a permanent ongoing process.
- ▶ Aligned requirements in <476> with proposed revisions to <1086> *Impurities in Drug Substances and Drug Products* that were proposed as part of the monograph modernization initiative.
- ▶ Aligned the proposed USP standard with current scientific and regulatory best practices and expectations for the appropriate control of organic impurities in drug substances and drug products.
- ▶ Intended to provide a science-based approach for the control of impurities in relevant monographs to ensure product quality and safety
- ▶ Intent is to have drug substance and drug product include a cross reference to this chapter in the organic impurities section, where appropriate on a case-by-case basis, during the monograph modernization initiative.

Strategic changes/concepts included in <476>



- ▶ Significant revisions were included based on extensive review with internal and external groups and prior public comments from PF 41(3)
 - Included internal USP alignment with Chemical Medicines EC, OTC EC, USP lab staff and Biologics Collaborative Group
 - Input from Stakeholders groups and FDA have been incorporated
- ▶ Discussion of specific limits moved from <1086> to <476>
 - Recommended limits aligned with ICH Q3A & B have been included in <476>
- ▶ References to specific handling of potential genotoxic impurities are included in <476>
 - Justification of levels aligned with ICH M7



Revisions of General Chapter
“<1086> *Impurities in Drug Substances and
Drug Products*”
and final proposed General Chapter
“<476> *Control of Organic Impurities in Drug
Substances and Drug Products*”

<476> Scope



- ❑ This chapter covers drug substances and drug products marketed in United States based on approval by the FDA either via NDA, ANDA or OTC
- ❑ Does not cover – veterinary, peptides, biological or biotechnological, oligonucleotides, fermentation products or semisynthetic, polymorphic forms, radiopharmaceuticals, herbal and crude products of animal or plant origin
- ❑ Introduces the following limits:
 - **Reporting Threshold** – Disregard Limit (some monographs have this designated with the phrase do not report for levels below this limit)
 - **Identification Threshold** – Any Unspecified Impurity or Unspecified Degradation Product
 - **Qualification Threshold** – Specified Impurity or Specified Degradation Product

<476> Thresholds for Drug Substances



Table 1. ICH Recommended Thresholds for Impurities in Drug Substances

	Impurity Thresholds	
Maximum daily dose	$\leq 2 \text{ g}$	$\geq 2 \text{ g}$
Reporting	0.05%	0,03%
Identification	0.10% (1.0mg) ^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

- Organic impurities in drug substances arising from the manufacturing process and or storage should be controlled (from process impurities)
- A rationale for the inclusion or exclusion of impurities in the specification (at release and through shelf life) should be presented
- Higher threshold may be applied if scientifically justified
- Lower threshold may be applied if the impurity is unusually toxic
- For OTC drug products, total daily intake is based upon the manufacturer's recommended labeled dosage per day.

<476> Thresholds for Drug Products



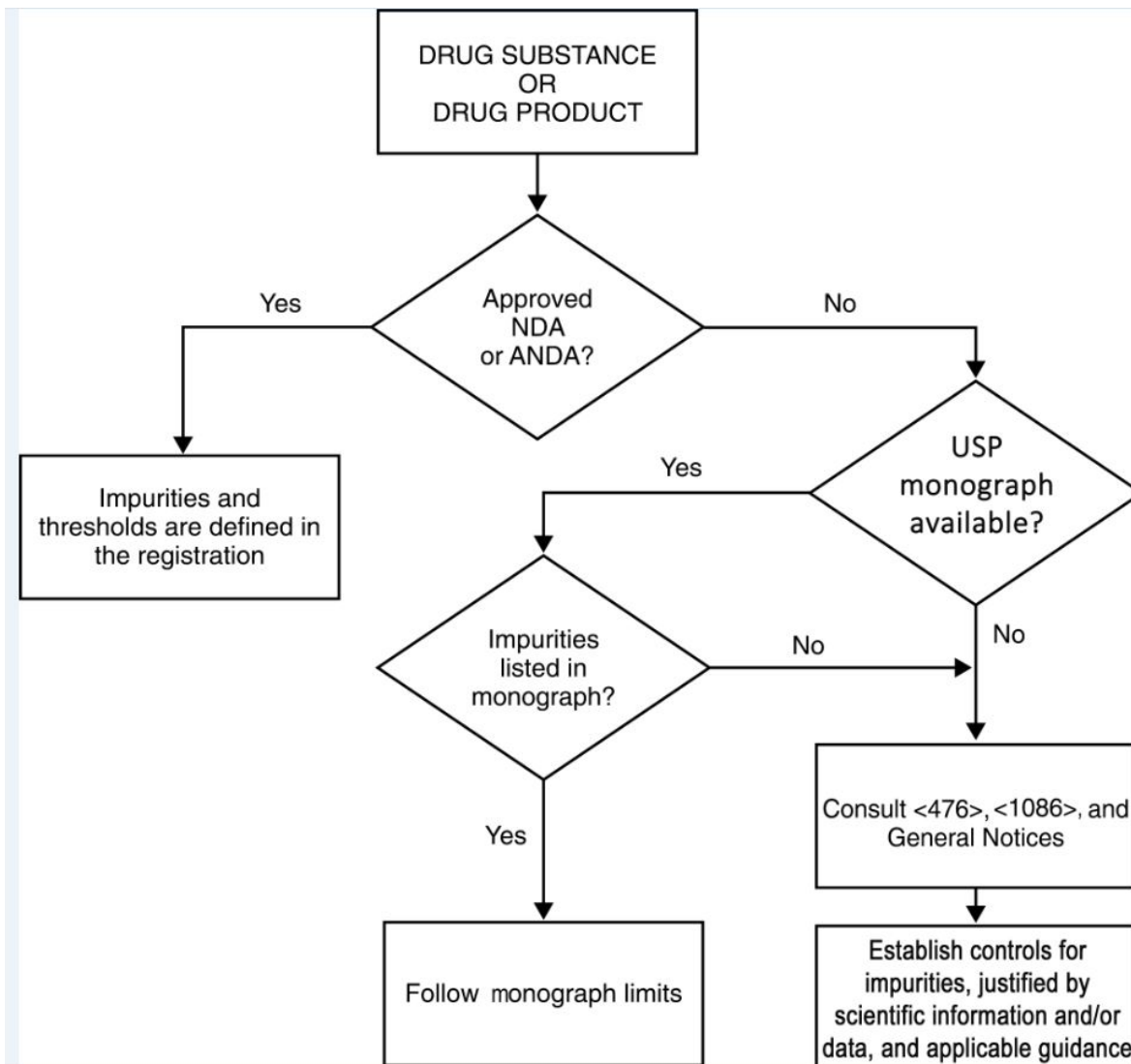
Table 2. ICH Recommended Thresholds for Impurities in Drug Products

	Degradation Product Thresholds						
Maximum daily dose	<1 mg	≥1 to ≤ 10 mg	10 mg	>10 to 100 mg	>100 mg to 1 g	>1 to 2 g	>2 g
Reporting	0.1%	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	0.5% 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	0.5% 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)

- Organic impurities in drug products arising from the manufacturing process and/or storage of the drug product should be controlled.
- Manufacturers should provide rationale and supporting data to justify the acceptance criteria

<1086> Decision Tree



Decision tree provides guidance for impurities in drug substances and drug products 12

Manufacturers responsibilities in <1086> and <476>



Manufacturer's Responsibilities in General Chapter <1086>:

- If a new impurity is detected above the appropriate identification 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 and efficacy of the drug substance or drug product.
- For marketed products, the manufacturers are responsible for controlling organic impurities in accordance with current regulatory standards.

Manufacturer's Responsibilities in General Chapter <476>:

- If an individual monograph is inadequate to control does not include a procedure for quantifying an impurity or acceptance criterion for an observed impurity, the manufacturer is responsible for developing and validating appropriate analytical procedures and establishing appropriate acceptance criteria.
- Manufacturers shall validate or verify, as appropriate analytical procedures must demonstrate their suitability for the detection and quantitation of impurities in the drug substances and drug products
- Manufacturers shall develop acceptance criteria for impurities justified by appropriate safety considerations and consistent with current applicable regulatory guidances.

<476> Acceptance Criteria



The acceptance criteria for drug substances and drug products 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

Next steps



- ▶ Pursue inclusion of specific organic tests rather than referencing <466> Ordinary Impurities
- ▶ Use the OTC Initiative to address many challenges
 - Examples: proposed <321> *Drug Product Assay Tests-Organic Chemical Medicines* and <327> *Drug Product Impurities Tests* to establish procedures for known impurities by categories/families of OTC products published in *PF 41(1)*
- ▶ Evaluating a new proposal to introduce cross references to <476> in monographs, on a case by case basis, as appropriate
 - Possible tool to control “any individual unspecified impurity”
 - Approach would be similar to the European Pharmacopeia
- ▶ Review and consolidate public comments from publication in 43(6)
- ▶ Expert Committee to prepare recommendations for revisions to the General Notices for consideration by the Expert Council
 - 5.60. Impurities and Foreign Substances
 - 5.60.10. Other Impurities in *USP* and *NF* Articles

Thank You



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Questions



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Backup information



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5.60. Impurities and Foreign Substances

Tests for the presence of impurities and foreign substances are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also [*Impurities in Drug Substances and Drug Products \(1086\)*](#)).

Nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the tests provided in the individual monograph, where the presence of the impurity is inconsistent with applicable good manufacturing practices or good pharmaceutical practices.

Related General Notices - to be revised



5.60.10. Other Impurities in *USP* and *NF* Articles

If a *USP* or *NF* monograph includes an assay or organic impurity test based on chromatography, other than a test for residual solvents, and that monograph procedure does not detect an impurity present in the substance, the amount and identity of the impurity, where both are known, shall be stated in the labeling (certificate of analysis) of the official substance, under the heading *Other Impurity(ies)*.

The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater. The sum of all *Other Impurities* combined with the monograph-detected impurities may not exceed 2.0% (see [Ordinary Impurities \(466\)](#)), unless otherwise stated in the monograph.

The following categories of drug substances are excluded from *Other Impurities* requirements:

- ▶ Fermentation products and semi-synthetics derived therefrom,
- ▶ Radiopharmaceuticals,
- ▶ Biologics,
- ▶ Biotechnology-derived products,
- ▶ Peptides,
- ▶ Herbals, and
- ▶ Crude products of animal or plant origin.

Any substance known to be toxic shall not be listed under *Other Impurities*.