Organic Impurities in Drug Substances and Drug Products

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Potential sources of drug impurities during development

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Initiative to revise chapter <1086> Impurities in Drug Substances and Drug Products

Chapter <1086> refers to
- <466> Ordinary Impurities
- General Notices (GN) 5.60. Impurities and Foreign Substances

Challenges
- Outdated procedure
- Lack of clarity

Basis for revisions:
- ICH Q3A (R2) – Impurities in New Drug Substances
- ICH Q3B (R2) – Impurities in New Drug Products
- Guidance For Industry: ANDAs – Impurities in Drug Products
USP Expert Panel:

Modernization of Organic Impurities Testing in Drug Substances and Drug Products
(Previously “Modernization of Impurities in Drug Products”)

- To revise the USP General Chapter <1086> to be in line with current regulatory thinking on OTC and generic products regarding organic impurities testing.

- To evaluate the advantages and disadvantages of moving relevant text to a new general chapter below 1000.

Challenge: How to Handle Complex and Legacy Products
Survey to Stakeholders

Percent Very Supportive Of Modernizing *USP-NF* Written Standards On Organic Impurities In Selected Ways (Top Areas For Modernization, Aided)

- Revising monographs that include outdated tests: 74%
- Achieving harmonization between *USP-NF* General Chapter<466> and General Notices 5.60 with the International Conference on Harmonization (ICH): 74%
- Offering alternative testing options when a general standard cannot be used for a particular material: 71%
- Streamlining the development of missing monographs on impurities: 65%
- Replacing thin layer chromatography (TLC) testing with another instrumental method: 65%
Impurities in Drug Substances and Drug Products

<476> Organic Impurities in Drug Substances and Drug Products
- New general chapter
- First published in *PF 40*(3) [May-June 2014; comments due July 31, 2014]
- Republished to address comments in *PF 41*(3) [May-June 2015; comments due July 31, 2015]

<1086> Impurities in Drug Substances and Drug Products
- Extensive revisions proposed to existing general chapter
- First published in *PF 40*(3) [May-June 2014; comments due July 31, 2014]
- Republished to address comments in *PF 41*(3) [May-June 2015; comments due July 31, 2015]

Modernization of Organic Impurities Testing in USP Drug Substance and Drug Product Monographs
- *Stimuli Article published in* *PF 40*(3) [May-June 2014]
- Acknowledged industry Survey (2013) Results
- Recommend Updates to General Notices 5.60 *Impurities and Foreign Substances* after the final text for both chapters is developed
- Provide an Implementation Strategy
Revised <1086> and New <476>

Promotes a Science based approach

- Current regulatory guidance documents
- Sound scientific principles to control the level of impurities
- A threshold-based approach

Covers Highly Toxic Impurities (e.g. Genotoxic)

- For impurities known or suspected to be highly toxic (e.g., genotoxic).
- 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 guidances
Outline

- Introduction
- Drug Substance
- Drug Product
- Decision Tree
- Glossary
- Additional sources of information
Scope

- This general information chapter provides guidance on the control of impurities in drug substances and drug 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, 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.
Decision tree for control of organic impurities in drug substances and drug products
Glossary

- **Degradation Product**: An impurity resulting from a chemical change in the drug substance brought about during manufacturing 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.

- **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 as stated in the specific monograph. Process-related impurities may include starting materials, byproducts, intermediates, reagents, ligands, and catalysts.

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

- **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.]
Glossary

- **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.

- **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 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.

- **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.
Outline

- Introduction
- Identification of Impurities in DS and DP
- Analytical Procedures
- Reporting Impurities in DS and DP
- Impurities in DS and DP in Specifications
- Qualification of Impurities in DS and DP
Scope

- This chapter covers USP drug substances and USP drug products marketed in the United States based on approval of applications by the Food and Drug Administration (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, 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.
Table 1. Drug Substance Impurity Threshold

<table>
<thead>
<tr>
<th>Maximum daily dose</th>
<th>Impurity Thresholds</th>
<th>Impurity Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting</td>
<td>≤2 g</td>
<td>&gt;2 g</td>
</tr>
<tr>
<td>Identification</td>
<td>0.05%</td>
<td>0.03%</td>
</tr>
<tr>
<td>Qualification</td>
<td>0.10% (1.0 mg)</td>
<td>0.05%</td>
</tr>
<tr>
<td>Qualification</td>
<td>0.15% (1.0 mg)</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

a The total daily intake in parentheses applies if it is lower than the calculated value.
<table>
<thead>
<tr>
<th>Maximum daily dose</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mg</td>
<td>0.1%</td>
</tr>
<tr>
<td>1–10 mg</td>
<td>0.1%</td>
</tr>
<tr>
<td>&gt;10–100 mg</td>
<td>0.1%</td>
</tr>
<tr>
<td>&gt;100 mg–1 g</td>
<td>0.1%</td>
</tr>
<tr>
<td>&gt;1–2 g</td>
<td>0.05%</td>
</tr>
<tr>
<td>&gt;2 g</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identification</th>
<th>Degradation Product Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0% or 20 µg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.5% or 2 mg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.2% or 2 mg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.2% or 2 mg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.2% or 2 mg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Qualification</th>
<th>Degradation Product Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0% or 50 µg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.0% or 50 µg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.5% or 200 µg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.2% or 3 mg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>0.2% or 3 mg TDI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.15%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Whichever is lower, calculated value or Total Daily Intake (TDI)
Ongoing Efforts

- Pursue inclusion of specific organic tests rather than referencing <466> Ordinary Impurities

- Use the OTC Initiative to address many challenges

- 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
SILDENAFIL CITRATE

Impurity E. Thin-layer chromatography (2.2.27).
...
Limit:
– impurity E: any zone due to impurity E is not more intense than the principal zone in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances. Liquid chromatography (2.2.29).
...
Limits:
– impurity A: maximum 0.3 per cent;
– unspecified impurities: for each impurity, maximum 0.10 per cent;
– sum of unspecified impurities: maximum 0.3 per cent;
– total: maximum 0.5 per cent;
– reporting threshold: 0.05 per cent.

IMPURITIES
Specified impurities: A, E.
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use): B, C, D.
SILDENAFIL CITRATE

IMPURITIES

- ORGANIC IMPURITIES

Add the following:

▲Other organic impurities (process impurities and degradation products), if present at a sufficient level, are limited by the general acceptance criteria for any individual impurity (unspecified impurity) or by the general chapter Control of Organic Impurities in Drug Substances and Drug Products <476>, whichever is lower. For more information, see the general chapter Organic Impurities in Drug Substances and Drug Products <1086>▲

Identification solution: 7.5 μg/mL of USP Sildenafil Related Compound A RS in Mobile phase

System suitability solution: Dissolve 70 mg of Sildenafil Citrate in 1 mL of a solution of hydrogen peroxide and anhydrous formic acid (2:1). Allow to stand for at least 10 min to generate sildenafil N-oxide, and then dilute with Mobile phase to 250 mL.

Acceptance criteria:

Sildenafil related compound A: NMT 0.3%
Any other unspecified individual impurity: NMT 0.10%
Total unspecified impurities: NMT 0.3%
Total impurities: NMT 0.5%. Disregard any peak less than 0.05%.
APREPIANT

IMPURITIES

• ORGANIC IMPURITIES

Add the following:

▲ Other organic impurities (process impurities and degradation products), if present at a sufficient level, are limited by the general acceptance criteria for any individual impurity (unspecified impurity) or by the general chapter Control of Organic Impurities in Drug Substances and Drug Products <476>, whichever is lower. For more information, see the general chapter Organic Impurities in Drug Substances and Drug Products <1086>▲

System suitability solution: 2.0 mg/mL of USP Aprepitant RS and 0.003 mg/mL of USP Desfluoro Aprepitant RS in Diluent, using sonication as necessary to dissolve

Sensitivity solution: 0.001 mg/mL of USP Aprepitant RS in Diluent

Acceptance criteria: See Table 2. Disregard any peak below 0.05%.

Table 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desfluoro aprepitant</td>
<td>0.85</td>
<td>0.15</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>0.10</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Next Steps

- Comments received on the *PF 41*(3) proposals addressed

- Publish updated versions of *<476>* and *<1086>* in *PF 43*(6):
  - Propose the inclusion of cross references in monographs
  - Include an implementation plan for the cross references in the Briefing
  - Coordinate with OTC, EXC, and BIO on how to synchronize approaches
  - Propose reintroduction of some terms and USP policies on impurities in official articles
  - Incorporate the decision made with FDA on “Disregard Limits” vs “Reporting Thresholds”
  - Discuss the possibility of delayed implementation

- Once the chapters are finalized, provide recommendations to revise to the USP *General Notices 5.60 and 5.60.10*
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.
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*. 
Thank You

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