5.5. Impurities

This chapter provides guidance on the control of impurities in drug substances and formulated preparations described in IP monographs. It applies mainly to totally synthetic organic medicinal substances and those substances obtained by synthetic modification of a naturally produced precursor. It is not necessarily relevant to other organic substances e.g., herbal products and crude products of plant or animal origin, biological and biotechnology products, oligonucleotides, radiopharmaceuticals, fermentation products and semi-synthetic products derived there from; inorganic substances and pharmaceutical excipients. Although the thresholds stated in this general chapter do not apply, the general concepts of reporting, identification (wherever possible) and qualification of impurities are equally valid for these classes. It provides an approach to the setting of limits for impurities in articles for which the individual monographs do not provide either a test or specific limits.

Impurities are critical quality attributes of drug substances and drug products because they have the potential to affect the safety and efficacy of the product. The monographs of the Pharmacopoeia have been designed to ensure the minimum acceptable quality of drug substances and drug products for users. Tests for related substances have also been provided in many monographs to limit impurities and degradation products. Although one of the primary objectives of the Pharmacopoeia is to guarantee the identity, strength, purity and quality of official articles, it is not possible to include in each monograph a test for every impurity or contaminant or even an adulterant that might be present. The exclusion of a limit for impurities in a monograph does not absolve the manufacturer of providing assurance to the user on the safety of a drug. It is incumbent on the manufacturer to follow Good Manufacturing Practices (GMP) and to ensure the limitation of impurities based on knowledge of the properties of the chemical entity and the likelihood of related substances being associated with the end product during production and subsequent storage.

Impurity measurements for drug products using chromatographic methods could present a challenge to the Pharmacopoeial standards setting due to low concentrations of the impurity and complexity of matrix. As a consequence, some of the monographs for Pharmacopoeial preparations rely on chromatographic assays. Where more significant impurities are known, some monographs set forth specific tests for these impurities.

In general, the tests in a monograph are tests for purity that provide information on the extent of known potential or actual impurities rather than for guaranteeing freedom from all possible impurities. The tests are not necessarily designed to detect any foreign contaminants or adulteration. Material found to contain an impurity not detectable by the prescribed tests of a monograph may be deemed to be not of Pharmacopoeial quality particularly if the nature of the impurity (ies) found is not compatible with GMP.

Chemical tests that limiting the levels of particular impurities or classes of impurities are often augmented by physical tests such as specific optical rotation, absorbance, melting point, clarity and colour of solution and for liquids, refractive index, boiling point range and weight per ml etc. Besides, non-specific tests such as sulphated ash, loss on drying etc. contribute to the assurance of the general quality of the article and of the use of GMP in its production, the avoidance of contamination especially by inorganic substances and the removal of volatile solvents.

Notwithstanding this situation, there is a need to limit impurities that may arise from various sources in the course of manufacture.

Classification of Impurities

Impurities can be classified into the following categories:

Organic impurities
Inorganic impurities
Residual solvents

**Organic impurities** may be drug-related or process-related and consist of identified, specified impurities, unidentified, specified impurities or total unknown impurities and are subject to control for all drug substances and drug products. In designing the specifications for any drug substance a manufacturer should determine the actual and potential impurities most likely to arise during the synthesis, purification and storage, on the basis of scientific knowledge of the chemical reactions involved in the synthesis. Organic impurities can arise during the manufacturing process and or storage of the drug substance include starting materials, intermediates, by-products, degradation products, reagents and ligands.

**Inorganic impurities** usually result from the manufacturing processes and include catalysts, reagents, elemental impurities and other residual metals, inorganic salts and other materials e.g., filter aids, charcoal. Impurities associated with input raw materials and storage conditions can also contribute to the impurity profile of the drug substance. The detection and quantification of such impurities by classical physicochemical methods should not present any problems. Elemental impurities can 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 heavy metals or elemental impurities are known to be present, have been added, or have the potential for, can be controlled with appropriate limits as specified in chapter 2.3.13 Heavy Metals or 5.10 Elemental Impurities respectively.

**Residual solvents** are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions during the synthesis of a drug substance. Since these are generally of known toxicity, they can be controlled with appropriate limits as listed in chapter 5.4 (Residual solvents). In addition to a general limit on solvents remaining behind in the final drug substances, some drugs need specific limits for specific solvents, where variation in levels of known solvents requires control e.g. methanol in Gentamicin Sulphate.

Irrespective of the nature of these impurities or degradation products, limits and acceptance criteria in drug substances are based on chemistry and safety concerns and have to be worked out on the basis of factors such as toxicity, process capability, manufacturing practices and so on. Elemental impurity limits for a drug substance may be required depending on the outcome of the risk assessment for the finish product. The basic principle for setting limits is that levels of impurities 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 is validated and suitability for the detection and quantitation of impurities should be established.

**Organic Impurities**

**Test methods**

It is usual to include a test for related substances in a monograph for a medicinal substance or product. These may be manufacturing impurities (intermediates or by-products) or degradation products or both. When preparation of a monograph is initiated the manufacturer is asked to provide information concerning the nature of such impurities, the reason for their presence, the amounts that may be encountered in material prepared under conditions of Good Manufacturing Practice (GMP) and the manner in which proportions may vary on storage, together with an indication of the toxicity of any impurities in relation to that of the substance itself. Where there is only one manufacturer of a substance, Pharmacopoeial limits are set in the knowledge that the level of impurities in production batches of the substance will have been accepted by the registration authority after a full consideration of the toxicity studies and clinical trials carried out before the granting of a license. Such studies and trials will have been carried out on material with an impurity profile that is qualitatively and quantitatively similar to that of subsequent production batches. Any subsequent changes to the manufacturing process by the original manufacturer or the introduction of material from another manufacturer utilizing a different route of synthesis will be subject to the need to demonstrate essential similarity or to provide equivalent data to the regulatory authority. In some cases a change in production or source may give rise to impurities that are not adequately controlled by the Pharmacopoeial monograph. Appropriate revisions of the monograph will be carried out provided that the Pharmacopoeial authority is notified of the need and that it is supplied with the relevant information.

The most widely used methodology is chromatography which is the basis of the test for related substances. The test may be specific or general. Specific tests may be supplemented by a more general test controlling other impurities. A specific test is one where a particular impurity arising from the manufacturing process or from degradation needs to be limited on grounds of toxicity or any other special reason. Where the impurity is known to be particularly toxic, this should be taken into account. Such specific tests include a chromatographic or colorimetric comparison with a sample of the named substance e.g. salicylic acid in aspirin. Both types of tests require the use of Reference substances. In chromatographic determinations, in the absence of a reference substance it is usual practice to limit the level of impurities by the simple test of comparison of the unknown spot or peak with a spot or peak obtained with a dilute solution of the substance under examination.

Meaningful limitation of impurities is possible only with validated analytical methods that can help in determining the limits of detection and quantitation. With drug products the methods should be validated to demonstrate that the drug product components and impurities unique to the drug substance and excipients do not interfere with or are separated from specified and unspecified degradation products in the final product.

Thin-layer chromatography (TLC) is quick and is particularly useful in process monitoring and in detecting impurities during the course of manufacture. However, it has its limitations in fixing limits for specific impurities in the final product although for long it was the most widely used for this purpose.
Total impurities can be determined by gas chromatographic and liquid chromatographic tests, where the total impurity levels can be obtained by summation of the peak areas due to related substances (usually in the range 1 to 2 per cent) are applicable till the end of the shelf-life. Here again, this procedure is rarely adopted in TLC tests because of the semi-quantitative nature of estimating individual spots and the imprecise nature of expressing results for the total impurities. This drawback can be overcome to an extent by the use of two- and three-level tests. In the former, in addition to a nominal concentration of the reference solution, another at a lower concentration is used for spotting the plate; in the latter, two more solutions at different lower concentrations are used.

In liquid chromatographic tests the relative detector correction factor that expresses the sensitivity of a detector relative to a standard substance is an important factor to be considered. As a general thumb rule, if the correction factor of an impurity is between 0.8 and 1.2, it may be considered the impurity has a similar response to that of the drug substance. Also, correction factors less than 0.2 or more than 5 are not recommended. In such cases, the method needs to be amended to bring the correction factor within the acceptable range by either choosing a different wavelength of measurement or a different method of visualisation.

Unknown impurities may be limited by reference to a dilution of the substance under examination used as a reference solution.

Manufacturers shall develop acceptance criteria for impurities that are justified by appropriate safety considerations and consistent with current applicable regulatory guidances. Impurities known or suspected to be unusually toxic (e.g., mutagenic impurities) or to produce undesired pharmacological effects in drug substances and drug products require more stringent control compared to non-mutagenic impurities and therefore, in such cases, the limit of detection and limit of quantitation of the analytical procedures shall be commensurate with the current applicable regulatory guidances and the acceptance criteria to ensure patient safety.

Identification of peaks is generally not based on absolute retention times since these may be too ‘system dependent’; however, advice such as ‘the principal peak has a retention time of about ‘x’ minutes may be given. Although in some cases, where a simple chromatogram is expected to show a limited number of impurities, an expected relative retention time may be given to designate impurities.

**Reporting of Impurities**

The reporting threshold can be established using current applicable regulatory guidance’s or other acceptable scientific means. 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, Rounding Rules). All impurities at a level more 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 Table 1 and 2. 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 and ICH Q3B.

**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.

**Acceptance criteria for Impurities**

Acceptance criteria shall be set for all impurities present above the reporting thresholds for drug substances and drug products and taking into account the qualification (the acquisition and evaluation of data establishing the safety of an impurity) of the degradation products, accelerated and long-term stability data, the expected expiry period and the recommended storage conditions for the drug product. Allowance should be made for the normal variations in manufacturing, analysis and the stability profile.
Specified impurities/degradation products can be either identified or unidentified. Specified identified impurities/degradation products should be included along with specified unidentified /degradation products estimated to be present at a level more than (>) the identification threshold. Unspecified impurities/degradation products are limited by a general acceptance criterion, which is Not More Than (≤) the identification threshold and Not Less Than (>) 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. 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. In the case of a complex impurity profile, it may not be feasible to resolve each of the impurities individually or to detect them and quantify them using a single analytical procedure. In such cases manufacturers should consider alternate approaches such as the use of multiple analytical procedures to test for impurities or acceptance limits may be established based on grouping of impurities, as appropriate. Similar principles may be applied to set thresholds and acceptance criteria for degradation products in over-the-counter (OTC) monograph drug products and should be reported, identified and/or qualified. Measurement of degradation products can be challenging for products containing multiple drug substances and complex formulations. The use of placebo as controls may aid in the deconvolution of chemical changes in stability studies that could be related to excipients rather than the drug substance.

It is recommended that the specifications for a drug substance should include the acceptance criteria for the following, where applicable,

- each specified identified impurity,
- each specified unidentified impurity,
- any unspecified impurity with acceptance criteria of Not More Than the identification threshold,
- total impurities
  - inorganic impurities (Controlled as per 2.3.13. Heavy metals or 5.10 Elemental impurities)
  - residual solvents (Controlled as per 5.4. Residual solvents)

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.

The specifications for a drug product should 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 Not More Than 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.

In Indian Pharmacopoeia, the preferred terminology applicable for organic impurities(specified and unspecified impurities/ Degradation Products) is “any secondary peak”, any other secondary peak and “sum of all the secondary peaks” in the drug substance and drug product monographs. There are several scenarios for citing specified organic impurities in an IP monograph. For identified impurities/degradation products, the chemical name is provided. Unidentified impurities /degradation products are named with a general designation along with the product name e.g., Impurity A, Impurity B. Specified impurities/ degradation products can be either identified or unidentified. They are listed and limited with a specific acceptance criterion in a monograph. In all the cases “Any secondary peak” and “Any other secondary peak” correspond to unspecified impurities. Total impurities in the drug substance/ drug product monograph are the sum of all specified and any other secondary peak above the reporting threshold i.e., ignore any peak less than (certain value or disregard limit). Typically, disregard limit covered by a monograph is set in accordance with the reporting threshold as mentioned above under Organic impurities.

In some cases, drug substance process-related impurities are also detected in the drug product, if appropriate, and limited by appropriate acceptance criteria. Drug substance process-related impurities detected in the drug product and included in its specification may include 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
impurities/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.

In chromatographic tests, during quantitation, peaks caused by solvents and reagents or arising from the mobile phase or sample matrix shall be disregarded, as well as other peaks that the monograph explicitly states are to be disregarded. During quantitative determination of an impurity in liquid and gas chromatographic tests, choice of an appropriate threshold setting and appropriate conditions for the integration of the peak areas is important. Principles from 2.4.14, 2.4.13 and 2.5.10 such as signal-to-noise ratio, quantification limits, and quantitation methods, peak separation between impurities and the substances under examination should be observed to confirm that performance of the system is satisfactory. The quantitation limit for the analytical procedure should not be more than the reporting threshold.

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

The entire procedure for decision on Organic Impurities is shown in Fig. 5.5-1

![Diagram](image)

**Fig. 5.5-1: Procedure for decision on organic impurities**

*Note: All impurities specific to a given drug product formulation may or may not be included in the IP. If the impurity is listed in the monograph, follow monograph limits. If the impurity is not listed, consult General chapters <5.5>, <5.10>, <5.4> and General Notices for guidance. Non-monograph 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.*
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.

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 by-products, 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.

Unless otherwise prescribed or justified and authorised organic impurities in a drug substance intended for human and
veterinary use, are to be reported, identified where possible, and qualified as indicated in Table 1. Because toxicity is a
dose-related phenomenon, the thresholds are set based on the amount of drug substance administered per day. Lower
thresholds can be appropriate if the impurity is unusually toxic or produces undesirable pharmacological effects.

Table 1. Reporting, identification and qualification of organic impurities in Drug substances

<table>
<thead>
<tr>
<th>Use</th>
<th>Maximum daily dose</th>
<th>Reporting threshold</th>
<th>Identification threshold</th>
<th>Qualification threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human or human and veterinary use</td>
<td>≤2 g</td>
<td>0.05 per cent</td>
<td>0.10 per cent (1.0 mg)</td>
<td>0.15 per cent (1.0 mg)</td>
</tr>
<tr>
<td>Human or human and veterinary use</td>
<td>&gt;2 g</td>
<td>0.03 per cent</td>
<td>0.05 per cent</td>
<td>0.05 per cent</td>
</tr>
<tr>
<td>veterinary use only</td>
<td>Not Applicable</td>
<td>0.1 per cent</td>
<td>0.2 per cent</td>
<td>0.5 per cent</td>
</tr>
</tbody>
</table>

- Total daily intake (TDI; in parentheses) applies if it is lower than the calculated value
- Higher reporting thresholds should be scientifically justified
- Lower thresholds can be appropriate if the impurity is unusually toxic

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.

Unless otherwise prescribed or justified and authorised organic impurities in a drug products intended for human and
veterinary use, are to be reported, identified where possible, and qualified as indicated in Table 2. Because the toxicity is
dose-related, the thresholds are based on the amount of drug substance administered per day. The amount of drug
substance administered per day is based upon the manufacturer's maximum recommended labelled dosage per day. Lower
thresholds can be appropriate if the degradation product is unusually toxic or produces undesirable pharmacological effects.

Table 2. Reporting, identification and qualification of organic impurities or degradation products in Drug products

<table>
<thead>
<tr>
<th>Use</th>
<th>Maximum daily dose</th>
<th>Reporting threshold</th>
<th>Identification threshold</th>
<th>Qualification threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human use</td>
<td>≤1 mg</td>
<td>0.1 per cent</td>
<td>1.0 per cent (5 µg)</td>
<td>1.0 per cent (50 µg)</td>
</tr>
<tr>
<td></td>
<td>≥1 mg to &lt;10 mg</td>
<td>0.1 per cent</td>
<td>0.5 per cent (20 µg)</td>
<td>1.0 per cent (50 µg)</td>
</tr>
<tr>
<td></td>
<td>≥10 mg</td>
<td>0.1 per cent</td>
<td>0.5 per cent (20 µg)</td>
<td>0.5 per cent (200 µg)</td>
</tr>
<tr>
<td>Range</td>
<td>0.1 per cent</td>
<td>0.2 per cent (2 mg)(^a)</td>
<td>0.5 per cent (200 µg)(^a)</td>
<td></td>
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<td>-------------</td>
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<td></td>
</tr>
<tr>
<td>&gt;10–100 mg</td>
<td>0.1 per cent</td>
<td>0.2 per cent (2 mg)(^a)</td>
<td>0.5 per cent (200 µg)(^a)</td>
<td></td>
</tr>
<tr>
<td>&gt;100 mg–1 g</td>
<td>0.1 per cent</td>
<td>0.2 per cent (2 mg)(^a)</td>
<td>0.2 per cent (3 mg)(^a)</td>
<td></td>
</tr>
<tr>
<td>&gt;1–2 g</td>
<td>0.05 per cent</td>
<td>0.2 per cent (2 mg)(^a)</td>
<td>0.2 per cent (3 mg)(^a)</td>
<td></td>
</tr>
<tr>
<td>&gt;2 g</td>
<td>0.05 per cent</td>
<td>0.10 per cent</td>
<td>0.15 per cent</td>
<td></td>
</tr>
<tr>
<td>Veterinary use</td>
<td>Not Applicable</td>
<td>0.3 per cent(^1)</td>
<td>1.0 per cent(^1)</td>
<td>1.0 per cent(^1)</td>
</tr>
</tbody>
</table>

\(^a\) whichever is lower, calculated value or TDI (in parentheses).

\(^1\) Higher threshold should be scientifically justified.

In cases of complex impurity profiles, limits may be established based on the grouping of impurities, if appropriate and scientifically justified. 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.

For DNA reactive impurities, the requirements of ICH guideline M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk must be complied with for active substances to be used in medicinal products for human use, in cases defined in the scope of the guidelines.

The entire procedure for decision on Identification and Qualification of an Impurity in drug substance or a Degradation Product in drug product is shown in Fig. 5.5-2.
Fig. 5.5-2: Procedure for decision on Identification and Qualification of an Impurity in drug substance or a Degradation Product in drug product:

1. Is impurity or degradation product greater than identification threshold $c^*$?
   - Yes → Structure identified?
   - No → No action

2. Structure identified?
   - Yes ➔ Any Known human relevant risks?
     - Yes ➔ Reduce to safe level
     - No ➔ No further action
   - No ➔ Reduce to not more than (<) identification threshold?
     - Yes ➔ No further action
     - No ➔ Consider patient population and duration of use and consider conducting:
       - Genotoxicity studies (point mutation, chromosomal aberration)$^a$
       - General toxicity studies (one species, usually 14 to 90 days)$^b$
       - Other specific toxicity endpoints, as appropriate
     - Reduce to safe level

3. Greater than qualification threshold?
   - Yes ➔ No action
   - No ➔ Any clinically relevant adverse effects?
     - Yes ➔ Qualified
     - No ➔ No action
Note: a) If considered desirable, a minimum screen (e.g., genotoxic potential), should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are considered an appropriate minimum screen.

b) If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximise the potential to detect the toxicity of an impurity or degradation product. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

c) Lower thresholds can be appropriate if the impurity or degradation product is unusually toxic.

d) For example, do known safety data for this impurity or degradation product or its structural class preclude human exposure at the concentration present?

<table>
<thead>
<tr>
<th>Definition of Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any secondary peak</strong></td>
</tr>
<tr>
<td><strong>Degradation Product</strong></td>
</tr>
<tr>
<td><strong>Degradation Profile</strong></td>
</tr>
<tr>
<td><strong>Drug substance process-related impurity</strong></td>
</tr>
<tr>
<td><strong>Enantiomeric Impurity</strong></td>
</tr>
<tr>
<td><strong>Identification threshold</strong></td>
</tr>
<tr>
<td><strong>Identified impurity/ Degradation Product</strong></td>
</tr>
<tr>
<td><strong>Impurity profile</strong></td>
</tr>
<tr>
<td><strong>Impurity</strong></td>
</tr>
<tr>
<td><strong>Nominal concentration</strong></td>
</tr>
<tr>
<td><strong>Other detectable impurities</strong></td>
</tr>
<tr>
<td><strong>Potential impurity</strong></td>
</tr>
<tr>
<td>Term</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Qualification threshold</td>
</tr>
<tr>
<td>Qualification</td>
</tr>
<tr>
<td>Related substances</td>
</tr>
<tr>
<td>Reporting threshold or disregard limit</td>
</tr>
<tr>
<td>Specified impurity/ Degradation Product</td>
</tr>
<tr>
<td>Total impurities/ total degradation product</td>
</tr>
<tr>
<td>Unidentified impurity/ unidentified degradation Product</td>
</tr>
<tr>
<td>Unspecified impurity/ Degradation Product</td>
</tr>
</tbody>
</table>