



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Guidance 18: Impurities in drug substances and drug products

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TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

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Introduction

This guidance provides sponsors with the information requirements relating to impurities in prescription medicines entered in the [Australian Register of Therapeutic Goods](#) (ARTG).

18.1 Impurities in drug substances and drug products

Identifying and describing the impurities that are present in prescription medicines is important for safety reasons, since some impurities can be hazardous to the health of the person using the medicine.

Impurities can arise during the process of manufacturing or storage of medicines.

They can be either:

- related to the [drug substance](#) (e.g. starting materials, by-products, intermediates that arise during synthesis, degradation products)
- unrelated to the drug substance (e.g. residual solvents, residual metal catalysts, reagents used during synthesis, chemicals that leach from the container).

18.2 Related impurities in drug substances and drug products

18.2.1 Guidelines adopted by the TGA

For impurities in new chemical entities produced by chemical synthesis and their resultant [drug products](#), the TGA has [adopted the following European Union/International Conference on Harmonisation \(EU/ICH\) guidelines](#):

- [Note for guidance on specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances](#) ICHQ6A (CPMP/ICH/367/96 Corr)
- [Note for guidance on impurities testing: impurities in new drug substances](#) ICHQ3A(R) (CPMP/ICH/2737/99)
- [Note for guidance on impurities in new drug products](#) ICHQ3B(R2) (CPMP/ICH/2738/99)
- [Guideline on the limits of genotoxic impurities](#) (CPMP/SWP/5199/02)
- [Question & answers on the CHMP guideline on the limits of genotoxic impurities](#) (EMA/CHMP/SWP/431994/2007 Revision 2).



Note

Although the guidelines, ICHQ3A(R) and ICHQ3B(R2), do not specifically refer to impurities in existing [drug substances](#) and their drug products (e.g. generic products), the principles in these guidelines are still applicable.

The [qualification thresholds](#) given in ICHQ3A(R) and ICHQ3B(R2) do not apply to enantiomeric impurities. Nonetheless, the principles established in those guidelines are relevant to the toxicological qualification of enantiomeric impurities.

18.2.1.1 Qualification of limits for impurities

Limits for levels of impurities in an existing drug substance and/or an associated drug product are considered qualified if impurity levels are not more than the limits in a transparent official monograph. If there is no transparent official monograph one or more of the following criteria are met:

- Levels of impurities are not more than the applicable ICH qualification thresholds.
- Any new product does not contain impurities in levels that exceed those in a market leader (the Australian reference product).
- The impurity is shown to be a significant metabolite in animal or human studies.
- Appropriate toxicological data have been submitted demonstrating the safety of the impurity at the proposed levels.



Note

The use of quantitative structure–activity relationships (QSAR) programs is not considered appropriate or conclusive to qualify impurities above ICH limits.

Monographs can be transparent or [nontransparent](#).

Transparent monographs

A [transparent monograph](#) lists the impurities controlled by that monograph by name and/or chemical structure. In a transparent monograph, a statement such as '*No individual impurity is greater than 0.5 per cent*' means that none of the individual impurities listed in the monograph is greater than 0.5 per cent.

Any related substance (identified or unidentified) that is not listed in the monograph is expected to comply with the relevant ICH threshold, or be otherwise qualified.

Newer European Pharmacopoeia (Ph. Eur.) monographs include two separate lists of impurities: *qualified* and *other detectable*.

Only those impurities designated as *qualified* in such monographs are subject to the limits specified in the monograph. *Other detectable* impurities are detectable using the prescribed analytical procedure, but are subject to relevant ICH limits.

Nontransparent monographs

A nontransparent monograph does not list the specific impurities controlled by that monograph by name and/or chemical structure.

A nontransparent monograph cannot be used for the qualification of individual impurities. All impurities are subject to relevant ICH limits (as per the Ph. Eur. general monograph 'Substances for pharmaceutical use', the Ph. Eur. general chapter 'Control of impurities in substances for pharmaceutical use' and the European Union [Guideline on control of impurities of pharmacopoeial substances: compliance with the European Pharmacopoeia general monograph](#)

["Substances for pharmaceutical use" and general chapter "Control of impurities in substances for pharmaceutical use"](#)[CPMP/QWP/1529/04]).

18.2.1.2 Data requirements for qualification

If a new generic product contains impurities at levels greater than those allowed by ICH guidelines or by a relevant transparent monograph, the impurities need to be otherwise qualified. To achieve this:

- Compare the impurity profile of the product with the Australian reference product.
Note: Comparisons with reference products obtained in countries such as the United Kingdom, Sweden, France, Germany, the United States of America or Canada may be acceptable, if adequately justified; or
- Provide appropriate toxicological data to demonstrate that the impurities are also significant metabolites in appropriate animal and/or human studies which may include literature references.
- Provide appropriate toxicological data, as described in ICHQ3A(R) and ICHQ3B(R2), to demonstrate the safety of the impurities at the levels proposed.
Note:
 - Impurity limits should be set according to the principle of reducing levels to as low as reasonably practicable (ALARP)
 - Although higher levels may be justified by toxicological data, ALARP considerations will take precedence.

Note for all impurities

- All impurities should be subject to computational analyses for potential mutagenicity.

If there is a structural alert:

- ensure the limits for the impurities are below the Threshold of Toxicological Concern (TTC) as outlined in [Guideline on the limits of genotoxic impurities](#) (CPMP/SWP/5199/02) and [Question & answers on the CHMP guideline on the limits of genotoxic impurities](#) (EMA/CHMP/SWP/431994/2007 Revision 2); or
- provide data to indicate that it is not mutagenic.

European Certificates of Suitability

The TGA accepts Certificates of Suitability of a Monograph of the European Pharmacopoeia ([CEP](#)) issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM) in lieu of drug master files for certain categories of drug substances controlled according to monographs in the Ph. Eur. or the British Pharmacopoeia (BP).

Further justification is not required for impurity limits specified in these certificates. The TGA may request additional information from you or either:

- the drug substance manufacturer
- the EDQM.

Related information and guidance

- [Note for guidance on impurities testing: impurities in new drug substances](#) ICHQ3A(R) (CPMP/ICH/2737/99)
- [Note for guidance on impurities in new drug products](#) ICHQ3B(R2) (CPMP/ICH/2738/99)
- [Drug master files and Certificates of Suitability of a Monograph of the European Pharmacopoeia for drug substances](#)

18.2.1.3 Synthetic impurities versus degradants

The BP states (in Supplementary Chapter IA, 'Control of impurities', paragraph 24) that:

"Tests for impurities in monographs for formulated preparations are used to control not only degradation products but also by-products of the synthetic route used for the manufacture of active ingredients".

The above principles are equally applicable to drug products for which there is no current monograph.

In these cases provide details of the synthetic impurities that are detectable, including their relative retention times in the description of the test method for the drug product. Otherwise, a peak due to a synthetic impurity might be interpreted as an unidentified degradation product.

18.2.2 Impurities in combination products

If a drug product contains two or more drug substances, the limit for any [identified impurity](#) applies to the particular drug substance from which it is derived.

The limit for an [unidentified impurity](#) should normally apply to whichever drug substance leads to the more stringent limit for the impurity, unless it can be clearly demonstrated that the unidentified impurity was derived from a specific drug substance.

The limit should take into account:

- the maximum daily dose of each drug substance in the combination product
- the likely overall patient exposure to the substance
- the associated ICH limit for unidentified impurities
- the content of each drug substance in the combination product.

18.2.3 Impurities in synthetic peptides

The Ph. Eur. monograph 'Substances for pharmaceutical use' specifies identification and qualification thresholds for synthetic peptides.

The qualification thresholds given in ICHQ3A(R) and ICHQ3B(R2) do not apply to synthetic peptides. However, the principles established in the guidelines are relevant to the toxicological qualification of product-related impurities in these types of drug products. Specific genotoxic qualification is generally not required.

18.2.4 Impurities in fermentation products and semisynthetic derivatives

The adopted EU/ICH guidelines exclude drug substances that are manufactured by fermentation and drugs that are chemically synthesised from fermented starting materials ([semisynthetic drug substances](#)). However, impurities in these substances still need to be qualified as above.

The European Union [Guideline on setting specifications for related impurities in antibiotics](#) (EMA/CHMP/CVMP/QWP/199250/2009 Corr) should be considered. Thresholds are given in the guideline for reporting, identification and qualification of [related impurities](#) for antibiotic drug products whose drug substance is produced by fermentation or semisynthesis.

18.2.5 Impurities in biological medicines

[Biological medicines](#) (biotechnology products) include vaccines (that do not contain viable human cells), recombinant products and plasma-derived products (or medicines that contain plasma-derived products). Biological medicines are regulated as therapeutic goods but not as biologicals, as defined by the [Therapeutic Goods Act 1989](#) (the Act).

Identify and characterise major product-related impurities including:

- aggregates
- subunits
- fragments
- truncated proteins
- deamidated, oxidised, phosphorylated, sulfated or *N*-terminally cyclised products.

The manufacturing process and subsequent use should be demonstrated to be adequately controlled so that product-related impurities remain within justified limits, both at time of release and at the end of the [shelf life](#).

Degradants related to the product (e.g. chemical changes to protein structure such as aggregates, deamidation and oxidation) should also be monitored to justify the shelf life of the drug substance and the drug product. In some cases (e.g. deamidation, oxidation of methionine), the same degradation process requires monitoring in both materials (substance and product).

In general, the acceptance criteria for product-related impurities should be based on data obtained from lots used in nonclinical and clinical studies, and manufacturing consistency lots, or covered by relevant product-specific monographs.

Related information and guidance

- [Note for guidance on specifications: test procedures and acceptance criteria for biotechnological/biological products](#) ICHQ6B (CPMP/ICH/365/96)
- [Guideline on development, production, characterisation and specifications for monoclonal antibodies and related products](#) (EMA/CHMP/BWP/157653/2007)

18.2.6 Impurities relating to mesilates, tosilates, (di)isetionate and besilates

For medicines containing the drug substance as a mesilate, tosilate, besilate or (di)isetionate salt, or another sulfonate, or if an aryl/alkyl sulfonate was used in the synthesis of the drug substance, the presence of contaminating aryl/alkyl sulfonic esters should be investigated, due to the known genotoxicity of these compounds.

These contaminants should be controlled based on thresholds outlined for genotoxic impurities ([Guideline on the limits of genotoxic impurities](#) [CPMP/SWP/5199/02]). Higher levels may be acceptable if adequately justified.

Refer to the letter from the European Medicines Agency (EMA) entitled: [Request to assess the risk of occurrence of contamination with mesilate esters and related compounds in pharmaceuticals](#) (EMA/44714/2008).

18.3 Unrelated impurities in drug substances and drug products

18.3.1 Residual solvents

Levels of residual solvents in [drug substances](#) and derived [drug products](#) should be reduced as much as possible, and should meet product specifications, good manufacturing practices or other quality-based requirements.

The limits should comply with those in the EU/ICH guideline on residual solvents ([Impurities: guideline for residual solvents](#) ICHQ3C(R5) [EMA/CHMP/ICH/82260/2006]).



Note

This guideline does not address solvents deliberately used as [excipients](#), or solvates.

For residual solvents for which no ICH limit has been provided, permitted daily exposures can be calculated as outlined in the guideline, using adequate toxicological data. These data should be generated using appropriate protocols, such as those described by:

- the Organisation for Economic Co-operation and Development (OECD)
- the United States Environmental Protection Agency
- the United States Food and Drug Administration ([FDA](#)) Redbook - *Guidance for industry and other stakeholders – toxicological principles for the safety assessment of food ingredients*.

18.3.2 Ethylene oxide and chlorohydrins

If the product or container is sterilised by treatment with ethylene oxide, the residue level for ethylene oxide and chlorohydrin should be controlled by the limits specified in the Committee for Proprietary Medicinal Products (CPMP)/ICH guideline on the use of ethylene oxide ([Note for](#)

[guidance on limitations to the use of ethylene oxide in the manufacture of medicinal products](#) [CPMP/QWP/159/01]).

18.3.3 Metals

Residual metals used as process catalysts do not provide any therapeutic benefit and should therefore be restricted to meet safety-based and quality-based criteria.

The adopted guideline, [Guideline on the specification limits for residues of metal catalysts or metal reagents](#) (EMA/CHMP/SWP/4446/2000), recommends maximum acceptable limits of metal residues (irrespective of their source) in drug substances and excipients. Guidance is also given on testing strategies, analytical procedures and reporting levels in excipients and drug substances.

18.3.4 Leachables and extractables

Chemicals leached from glass, plastic, metal or rubber components of medicine containers may cause adverse effects.

For applications to register a prescription medicine:

- identify the material, formulation code and manufacturer
- provide evidence of physicochemical and biological safety tests, and an assessment of the risks associated with patient exposure to the chemicals that may leach.

Where this evidence refers to a monograph of a recognised pharmacopoeia (e.g. United States Pharmacopoeia (USP) <87>, Ph. Eur. 3.2.9):

- provide test certificates or reports to demonstrate compliance.

If a toxicological [qualification](#) of the leachables/extractables is required to be included in the dossier:

- provide full study reports or literature references.

18.3.5 Impurities in biological medicines

For [biological medicines](#) (biotechnology products), the residual level of process-related impurities and contaminants should be minimised and controlled.

Two components that should be considered for safety and tolerance reasons are residual host-cell deoxyribonucleic acid (DNA) and residual host-cell proteins.

18.3.5.1 Residual host-cell DNA

The level of cell-derived and plasmid-derived DNA should be not more than 10 ng per purified dose, in accordance with the recommendation from the World Health Organization (WHO) Expert Committee on Biological Standardization ([Position statement on the use of tumourigenic cells of human origin for the production of biological and biotechnological medicinal products](#) (CPMP/BWP/1143/00)).

18.3.5.2 Residual host-cell protein

For biological medicines used chronically over a lifetime (e.g. human insulin, erythropoietin or factor VIII), the level of host-cell proteins should be not more than 10 parts per million.

For other biological medicines, the permissible level of host-cell proteins should be justified by:

- the minimum achievable level within methodological and statistical variation
- data from product manufactured for use in nonclinical and clinical studies.

A risk assessment of the effect of the proposed level may be required to justify the limit.

18.3.5.3 Other process-related impurities

The levels of other process-related impurities should be considered, as outlined in:

- [Note for guidance on specifications: test procedures and acceptance criteria for biotechnological/biological products](#) ICHQ6B (CPMP/ICH/365/96)
- [Guideline on development, production, characterisation and specifications for monoclonal antibodies and related products](#) (EMA/CHMP/BWP/157653/2007).

18.4 Measuring impurities - rounding

In many pharmacopoeial tests for impurities, compliance (or otherwise) with the test is determined by direct comparison of high-performance liquid chromatography (HPLC) peak areas of impurities with those of standards.

The limit is the peak area of the standard; if a numerical limit is given in parentheses, it is only an approximate limit, for information.

Where a numerical limit is specified as the primary decision criterion, the calculated result of the test is first rounded to the number of significant figures given in the limit before the decision criterion is applied.

If the number of decimal places is greater than the number specified in the limits, the data should be rounded in accordance with the BP. If the last figure is 0–4, it is rounded down; if the last figure is 5–9, it is rounded up.

For example: A result of 0.14 per cent complies with a specified limit of not more than 0.1 per cent, but would not comply with a limit of 0.10 per cent.

Note



- An HPLC limit for an [identified impurity](#), expressed as a percentage, generally means percentage by weight (% w/w) relative to the nominal content of [drug substance](#), unless otherwise specified.
- For an [unidentified impurity](#), it generally means percentage by area (% a/a).

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