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# International Conference on Harmonisation Guidelines for Regulation of Pharmaceutical Impurities in New Drug Substances

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## ABSTRACT

*Pharmaceutical impurities regulation is very important for reduction the risk by evaluation and control of impurities and establishment of acceptance criteria for both drug substance and drug product. Impurities should always be reduced to the lowest levels that are reasonably practical, it is acknowledged that impurities cannot be reduced to zero and specifications for impurities need to be established.*

**Key words:** Impurity, Authorities Abbreviated Registration Application, Residual solvent, Drug product, Drug substance.

## INTRODUCTION

An impurity in a drug substance as defined by the International Conference on Harmonisation (ICH) is any component of the drug substance that is not the chemical entity defined as the drug substance. Similarly, an impurity in a drug product is any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product. Impurities can be classified into the following categories:

### Relevant Substances

***Organic Impurities*:** Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include - starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts.

***Inorganic Impurities*:** Inorganic impurities can result from the manufacturing process. They are normally known and identified and include - reagents, ligands, catalysts**,** heavy metals or other residual metals**,** inorganic salts and other materials (e.g. filter aids, charcoal).

**Residual Solvents**

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacturing of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance.

**Classification of Residual Solvents by Risk Assessment**

***Class 1 solvents: Solvents to be avoided***

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards. Solvents in this class should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect.

***Class 2 solvents: Solvents to be limited***

Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities. PDEs (permitted daily exposure) are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm.

***Class 3 solvents: Solvents with low toxic potential***

Solvents in Class 3 may be regarded as less toxic and of lower risk to human health. It includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in this class. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5%) would be acceptable without justification [1,2].

## EXPERIMENTAL SECTION

The secondary data used in the study was obtained from various official reports and guidelines published by International Conference on Harmonisation and regulatory bodies of Canada and Japan. The study is of descriptive type and method used is the description.

**Analytical Procedure**

The nature and quantity of these impurities is governed by a number of factors, including the synthetic route of drug substance, reaction conditions, quality of the starting material, reagents, solvents, purification steps, and storage of the end product. As the structure of impurities is sometimes unknown, several spectroscopic and micro-chemical techniques have been developed which require minute quantities of material and readily enable the structural elucidation of the impurity. Versatile analytical methods are also available for the detection and monitoring of impurities in drug substances and drug products. The primary criterion of analytical methodology is the ability to differentiate the compounds of interests. The commonly used methods are separation (isolation), detection and quantification (spectroscopic) in tandem. The separation methods include thin layer chromatography (TLC), high performance liquid

chromatography (HPLC), gas chromatography (GC), and capillary electrophoresis (CE). HPLC is the most commonly used method for impurity monitoring in an inexpensive way. TLC can be used to separate a broad range of compounds. Capillary electrophoresis is a useful technique when very low quantities of samples are available and high resolution is required. The spectroscopic methods include ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS). Ultraviolet spectroscopy at a single wavelength provides minimal selectivity of analysis while the availability of diode array detectors offers much more information at various wavelengths to ensure greater selectivity. Infrared spectroscopy provides specific information on some functional groups that may allow quantisation and selectivity. Nuclear magnetic resonance spectroscopy offers fairly detailed structural information on molecules and is a very useful method for characterization of desired product and associated impurities. Mass spectrometry which requires minute amounts of sample provides excellent structural information based upon mass ion fragmentation patterns. Thus, UV, IR, NMR, and MS are excellent techniques for characterization and analysis of pharmaceutical compounds and impurities [3].

**Control of impurities**

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval [6].

**Impurities testing guidelines in new drug substance**

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guideline: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived from herbal products, and crude products of animal or plant origin.

**Reporting and Control of Impurities:** The studies conducted to characterise the structure of actual impurities present in the new drug substance at a level greater than the identification threshold. Any impurity at a level greater than the identification threshold in any batch manufactured by the proposed commercial process should be identified. In addition, any degradation product observed in stability studies at recommended storage conditions at a level greater than the identification threshold should be identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify impurities present at levels of not more than the identification thresholds, it is useful also to report the results of these studies. Identification of impurities present at an apparent level of not more than the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than the identification threshold. The quantisation limit for the analytical procedure should be not more than the reporting threshold [4].

**Setting acceptance criteria for impurities**

The acceptance criterion for impurities in the drug substance should be set no higher than the qualified level. In establishing impurity acceptance criteria, the first critical consideration is whether an impurity is specified in the compendial monograph. If there is a monograph in the compendial that includes a limit for an identified specified impurity, it is recommended that the acceptance criterion be set no higher than the official compendial limit.

However, if the level of the impurity is above the level specified in the compendial monograph, qualification would be recommended. Then, if appropriate qualification has been achieved, an applicant may wish to petition the compendial monograph for revision of the impurity's acceptance criterion. If the acceptance criterion for a drug substance impurity does not exist in the compendial monograph and this impurity can be qualified by comparison with an Health (FDA) approved human drug product, it is important that the acceptance criterion be consistent with the level observed in the approved human drug product. In other circumstances, the acceptance criterion may need to be set lower than the qualified level to ensure drug substance quality [5].

**Drug substance impurities threshold value**

| Maximum Daily Dose | Reporting Threshold | Identification Threshold | Qualification Threshold |
|---|---|---|---|
| ≤ 2g/day | 0.05% | 0.10% or 1.0 mg per day intake (whichever is lower) | 0.15% or 1.0 mg per day intake (whichever is lower) |
| > 2g/day | 0.03% | 0.05% | 0.05% |

**Qualification of impurities**

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) being considered. When appropriate, we recommend that applicants provide a rationale for establishing impurity acceptance criteria that includes safety considerations [7].

**Qualification Procedure**

The studies considered appropriate to qualify the impurity will depend on a number of factors, including the patient population, daily dose, route, and duration of drug administration. The following are descriptions of methods for qualifying impurities:

**Comparative Analytical Studies**

An impurity present in a drug substance covered by an ANDA(Abbreviated New Drug Application) can be qualified by comparing the analytical profiles of the drug substance with those in an approved human drug product using the same validated, stability-indicating analytical procedure (e.g. comparative HPLC studies). This approved human drug product is generally the reference-listed drug (RLD). However, the impurity profile of a different drug product, having the same drug substance, with the same route of administration and similar characteristics (e.g., tablet versus capsule) may also be used if samples of the reference listed drug are unavailable, or in the case of an ANDA submitted pursuant to a suitability petition.

**Scientific Literature and Significant Metabolites**

If the level of the identified specified impurity is adequately justified by the scientific literature, no further qualification is considered necessary. In addition, an impurity that is also a significant metabolite of the drug substance is generally considered qualified.

**Toxicity Studies**

Toxicity tests are the least preferred method to qualify impurities. The test is used only when impurities cannot be qualified by either of the above procedures. The tests are designed to detect compounds that induce general toxic or genotoxic effects in experimental systems. If performed, such studies should be conducted on the drug product or drug substance containing the impurities to be controlled, although studies using isolated impurities may also be used [5].

## RESULT AND DISCUSSION

It provides a perspective on Impurities in Drug Substance for Authorities Abbreviated Registration Application. In this we also propose pathway for determination of impurities and acceptance criteria based on general principles of ICH guidelines. Impurity Guideline in new drug substance is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guideline: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived from, herbal products, and crude products of animal or plant origin.

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