

AIMS AND OBJECTIVES

Impurity is defined in a drug substance as any component of the drug substance which is not the chemical entity defined as the drug substance. Similarly any component which is not the chemical entity defined as the drug substance or an excipient in the drug product is considered as impurity in the finished dosage forms.

Impurities are classified into several groups based on the type and the source. They are broadly categorized as follows.

- Organic Impurities (Process and drug related)
- Inorganic Impurities
- Residual solvents (organic volatile impurities)
- Polymorphic forms
- Enantiomer Impurities
- Drug substance with particle size outside the specifications (presently not labeled as impurity by the ICH or any other regulated body, but soon we can expect the same since the higher particle size component of the drug substance can lead to differences in the bio-availability which will have an impact on the safety and efficacy of the drug)

Impurities can originate from several sources. They are listed as follows:

- 1) Synthetic intermediates and by-products from the manufacturing process
- 2) Stereochemistry-related impurities from the manufacturing of the API's with chiral configurations
- 3) Residual solvent usage in the manufacturing process of the API (Active Pharmaceutical Ingredient) and drug products of all kinds of dosage forms

- 4) Residual solvent usage in the raw material manufacturing which are used in the manufacturing process of the API
- 5) Residual solvent usage in the packaging components manufacturing which are used to pack the drug substances and drug products
- 6) Residual solvent impurity in the originator solvent (as in benzene as a impurity in the toluene solvent)
- 7) Residual solvent arising from the drug solvates, which eventually loses the solvate bonding giving rise to the solvents as impurities and the free drug.
- 8) Impurity generation during the formulation of the drug products
- 9) Impurity arising during storage
- 10) Mutual interaction between the drug component and the excipients
- 11) Mutual interaction of the drug to drug in combination drug products due to catalysts like water, oxygen etc.
- 12) Functional group related typical degradation
- 13) Extraneous contaminants from within the facilities used for manufacturing operations
- 14) Transformation or migration to a new polymorphic form during manufacturing operations and/or storage of the API's and drug products
- 15) Particle agglomeration leading to increased particle size during storage of API's in presence of any atmospheric moisture available in the head space of the packaging bags or drums or inherent moisture content in the API itself.

If the above mentioned sources are appraised and evaluated during the development process then the control of the impurities can be achieved to a greater extent. The above list is not the complete possibilities for the source of the impurities but constitutes a majority of the possible sources.

Organic Impurities

Organic impurities can arise during the manufacturing process and/or storage of the API and drug products. They can be identified or unidentified, volatile or non-volatile.

Example:

- ❖ 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.

Example:

- ❖ Reagents, ligands, catalysts
- ❖ Heavy Metals or other residual metals
- ❖ Inorganic salts
- ❖ Other materials like filter aids, charcoal etc.

Residual Solvents

Residual solvents are organic volatile chemicals used during the manufacturing process or generated during the production and cleaning of the equipments used in manufacturing operations. Depending on the possible risk to human health the residual solvents are divided into three classes.

Class I: Solvents to be avoided in the drug manufacturing processes

Solvents listed in this Class as per ICH Q3C Impurities: Residual Solvents, are considered as known human carcinogens or strongly suspected human carcinogens and environmental hazards Benzene, Carbon tetrachloride, 1, 2-dichloroethane, 1, 1-dichloroethene, 1, 1, 1-trichloroethane

Class II: Solvents to be limited in the drug manufacturing processes

Solvents listed in this class are Non-Genotoxic animal carcinogens or possible causative agents of other irreversible toxicity. These solvents are suspected of other significant but reversible toxicities.

Acetonitrile, Chloroform, Cyclohexane, Dioxane, Methanol, Methylbutylketone, tetrahydrofuran and Toluene

Class III: Solvents with low toxic potential

These solvents are the ones with low toxic potential to humans; no health based exposure limit is needed during the submission of the drug applications

Acetone, Butanol, Butylacetate, DMSO, Ethanol, Ethyl Acetate, Ethyl ether, Heptane, Isopropanol, Methyl ethylketone etc.

Polymorphic forms

Polymorphic form impurities are those which are having the same chemical structure and formula of the drug but having different crystal form than the form which is considered as required form to have similar bio-availability as per the brand product when evaluated during the bio-equivalency study.

Based on the realization that the nature of structure adopted by a given compound upon crystallization, could exert a profound effect on the solid-state properties of that system. The Pharmaceutical industry is required to invest significant resources to this area in polymorphism and solvatomorphism as per the regulations.

Polymorphism is the term used to indicate a crystal system where substances can exist in different crystal packing arrangements, all of which have same elemental composition. Whereas, when the substance exists in different crystal packing arrangements, with a different elemental composition, the phenomenon is known as solvatomorphism.

Enantiomeric Impurities

It is of paramount importance to look for stereo-chemically related compounds as these compounds are considered as impurities in the API's. Potentially these are process related impurities but in some instances depending on the drug, these impurities could be degradation impurities as well, which can generate during the accelerated stability studies.