INTRODUCTION:

Impurity structural elucidation or impurity profiling (determination and characterization of impurities associated with drugs or drug products) is increasingly viewed as a valuable and essential part of quality requirements. Impurity (1,4) can be defined as any component of the drug substance which is not the chemical entity of the drug substance. It can also be defined as any material that affects the purity of the material of interest like active ingredient or drug substance.

A key component of the overall quality of a pharmaceutical is control of impurities, as their presence, even in small quantity, may affect drug safety (2,3) and efficiency. Impurities decrease the quality of APIs because they might not have the same level of pharmacological activity and can be harmful to the patients. As per ICH guidelines unknown impurities associated with bulk drug and dosage form, greater than the identification threshold should be identified. It is hence one of the most important responsibilities of the pharmaceutical industry to give quality products of the highest standards which are proven in terms of their efficiency and safety. In this respect the pharmaceutical industry needs to go hand in hand with analytical chemistry.

Presence of impurities in trace quantity in drug substance or drug products is inevitable. Therefore their level should be controlled and monitored. The effect produced by impurities can be teratogenic, mutagenic or carcinogenic. It can jeopardize the human health by affecting the Quality, Safety, and Efficacy (QSE) of the product. Hence API impurity profiling (identification, isolation and characterization) is required. Their limits and threshold values should comply with the limit set and specified by official bodies legislation (Pharmacopoeias and International Conference on Harmonization (ICH) Guideline). It is very important when company files Investigational New Drug Application (AND) or Abbreviated New Drug Application (ANDA).

ICH has published guidelines for validation of methods for analysis of impurities in new drug substances, new drug products, residual solvents and microbiological impurities (5-9) for registration of pharmaceuticals for human use. ICH defines impurities as “substances in the API that are not the API itself”. For pharmaceutical products, impurities defined as “Substances’ in the product that are not the API itself for the recipients used to manufacture it” That is impurities are unwanted chemicals that remain
within the formulation or API in small amounts which can influence QSE, thereby causing serious health hazards. Hence impurity profiling is a major concern in drug developing and processing (10-11).

Impurities have been classified sometime commonly or as specified by ICH guideline.

1. common terminology:
   
a. Intermediate – The compound produced during synthesis of the desired material or as part of the route of synthesis.

b. Penultimate intermediate – It is the last compound in the synthesis prior to the production of the final desired compound.

c. Byproduct—The compound produce in the reaction other than the required intermediate.

d. Transformation product --- They are theorized and nontheorized products, which produced in the reaction.

e. Interaction products --- It is formed by the interaction of chemicals in reaction either intentionally or unintentionally.

f. Related products – It is chemically similar to drug substances and may even possesses biological activity.

g. Degradation Products—Compounds produce due to degradation by the effect of external factors like light, heat and moisture.

2. Official compendial terminology: According to USP impurities are discussed as:

   - Impurities in official articles described as foreign substances, toxic impurities and concomitant compounds.
   - Ordinary impurities
   - Organic volatile impurities (OVI) or residual solvents.

ICH terminology:

As per the ICH guideline impurities in the new drug substances and formulations classified as,

1. Organic impurities

2. Inorganic impurities

3. Residual solvent
Sources of Impurities:

The impurities can be originated from several sources: such as a) Crystallization related impurities, b) Stereochemistry related impurities, c) Residual solvent, d) Synthetic intermediates and by-products, e) Formulation related impurities, f) Impurities arising during storage, g) Method related impurities, h) Mutual interaction amongst ingredients, i) Functional group related typical degradation (12)

a) Crystallization-Related impurities:

Based on the realization that the nature of the structure adopted by a given compound upon crystallization could exert a profound effect on the solid-state properties of the system, the pharmaceutical industry is required to take a strong interest in polymorphism and solvatomorphism as per the regulation laid by the regulatory authorities. Polymorphism is the term used to indicate crystal system where substances can exit in different crystal packing arrangements, all of which have same element composition. Whereas, when the substances exits in different crystal packing arrangements, with a different elemental composition; the phenomenon is known as Solvatomorphism (13)

b) Stereochemistry-related impurities:

Compounds have similar chemical structure but different spatial orientation, these compounds can be considered as impurities in the APIs. The single enantiomeric form of chiral drug is now considered as an improved chemical entity that may offer a better pharmacological profile. The pharmacokinetic profile of levofloxacine (S-isomeric form) and ofloxacine (R-isomeric form) are comparable (14). The single isomer drugs are being marketed as levofloxacine (S-ofloxacine), lavalbuteral (R-albuterol), and esomeprazole (S-omeprazole).

c) Residual solvent:

Residual solvents are organic volatile chemicals used during the manufacturing process or generated during the production. Depending on possible risk to human health, residual solvents are divided into three classes (15). Solvent in Class1 (benzene,
carbontetrachloride, methylenchloride, methanol, pyridine.). Class-II solvent,(N,N dimethyl formamide, acetonitrile.). Class-III solvent (acetic acid, ethanol, acetone). (16)

d) Synthetic intermediates and by-products:
   Impurities in pharmaceutical compounds or a new chemical entity (NCE) can originated during the synthetic process from raw materials, intermediates and/or by-product (17).

e) Formulation related impurities:
   Many impurities in a drug product can originate from excipients used to formulate a drug substance. Drug substance is subjected to a variety of condition in the process of formulation that can cause its degradation or have other undesirable reaction. Solutions and suspensions are inherently prone to degradation due to hydrolysis or solvolysis (18). Microbiological growth resulting from the growth of bacteria, fungi, and yeast in a humid and warm environment may result in unsuitability of an oral liquid product for safe human consumption. Microbial contamination may occur during shelf life and subsequent consumer use of a multiple-dose product, either due to inappropriate use of certain preservatives in the preparation, or because of the semi-permeable nature of primary containers (19).

f) Impurities arising during storage:
   A number of impurities can originate during storage or shipment of drug products. It is essential to carry out stability studies to predict evaluation and ensure drug product safety (20).

g) Method related impurity:
   A known impurity, 1-(2,6-dichlorophenyl) indolin-2-one is formed in the production of a parenteral dosage form of Diclofenac sodium (21).

h) Mutual interaction amongst ingredients:
   Most vitamins are very labile and on aging they create a problem of instability in different dosage forms, especially in liquid dosage form. Degradation of vitamins does not give toxic impurities; potency of active ingredient drops below pharmacopoeial specification (22).

i) Functional group-related typical degradation:
Hydrolysis of ester can be explained with a few drugs, Aspirin, Benzocaine, Ethyl paraben.(23). Hydrolysis is the common phenomenon for ester type of drugs, water that can hydrolyze some drugs or affect the dosage from performance. Small electrophiles-like aldehydes and carboxylic acid derivatives. Peroxides-that can oxidize some drugs. Metals which can catalyze oxidation of drugs and the degradation pathway. Leachable or Extractable- Can comes from Glass, Rubber stopper, Plastic packing materials. (24).
Flow chart depicting various kinds of impurities