SOURCES OF IMPURITIES:

Impurities can originate from several sources

1. Crystallization-related impurities
2. Stereochemistry-related impurities
3. Residual solvents
4. Synthetic intermediates and by-products
5. Formulation-related impurities
6. Impurities arising during storage
7. Method related impurity
8. Mutual interaction amongst ingredients
9. Functional group-related typical degradation

a. Crystallization-related impurities

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 take a strong interest in polymorphism and solvatomorphism as per the regulations laid down by the regulatory authorities. Polymorphism is the term used to indicate crystal system where substances can exist in different crystal packing arrangements, all of which have the same elemental composition. Whereas, when the substance exists in different crystal packing arrangements, with a different elemental composition, the phenomenon is known as Solvatomorphism.

b. Stereochemistry-related impurities

It is important to look for stereochemistry related compounds; that is, those compounds that have similar chemical structure but different spatial orientation, these compounds can be considered as impurities in the API's. Chiral molecules are frequently called enantiomers. The single enantiomeric form of chiral drug is now considered as an improved chemical entity that may offer a better pharmacological profile and an increased therapeutic index with a more favorable adverse reaction profile. However, the pharmacokinetic profile of levofloxacin (S-isomeric form) and ofloxacin (R-isomeric form) are comparable, suggesting the lack of advantages of single isomer in this regard. The prominent single isomer drugs, which are being marketed, include levofloxacin (S-ofloxacin), lavalbuterol (R-albuterol) and esomeprazole (S-omeprazole).

c. Residual solvents

Residual solvents are organic volatile chemicals used during the manufacturing process or generated during the production. Some solvents that are known to cause toxicity should be avoided in the production of bulk drugs. Depending on the possible risk to human health, residual solvents are divided into three classes.

Class I: benzene (2 ppm limit), carbon tetrachloride (4 ppm limit), methylene chloride (600 ppm), methanol (3000 ppm, pyridine (200 ppm), toluene (890 ppm) should be avoided.

Class II: N, N dimethyl formamide (880 ppm), acetonitrile (410 ppm).

Class III: acetic acid, ethanol, acetone has permitted daily exposure of 50 mg or less per day, as per the ICH guidelines.

A selective gas chromatography (GC) method has been developed to determine the purity of acetone, dichloromethane, methanol and toluene. Using this method, the main contaminants of each organic solvent can be quantified. Moreover, the developed method allows the simultaneous determination of ethanol, isopropanol, chloroform, benzene, acetone, dichloromethane, methanol and toluene with propionitrile as the internal standard.

d. Synthetic intermediates and by-products

Impurities in pharmaceutical compounds or a new chemical entity (NCE) can originate during the synthetic process from raw materials, intermediates and/or by-product. For example, impurity profiling of ecstasy tablets by GC-MS and MDMA samples, produced impurities in intermediates via reductive amination route.

e. Formulation-related impurities

Many impurities in a drug product can originate from excipients used to formulate a drug substance. In addition, a drug substance is subjected to a variety of conditions in the process of formulation that can cause its degradation or have other undesirable reactions. If the source is from an excipient, variability from lot to lot may make a marginal product, unacceptable for reliability. Solutions and suspensions are inherently prone to degradation due to hydrolysis or Solvolysis.

Fluocinonide Topical Solution USP, 0.05%, in 60-mL bottles, was recalled in the United States because of degradation/impurities leading to sub- potency. In general, liquid dosage forms are susceptible to both degradation and microbiological contamination. In this regard, water content, pH of the solution/suspension, compatibility of anions and cations, mutual interactions of ingredients, and the primary container are critical factors.

Microbiological growth resulting from the growth of bacteria, fungi, and yeast in a humid and warm environment may results in unsuitability of an oral liquid product for safe human consumption. Microbial contamination may occur during the shelf life and subsequent consumer-use of a multiple-dose product, either due to inappropriate use of certain preservatives in the preparations, or because of the semi-permeable nature of primary containers.

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, evaluate, and ensure drug product safety.

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, if it is terminally sterilized by autoclave. The conditions of the autoclave method enforce the intramolecular cyclic reaction of diclofenac sodium forming an indolinone derivative and sodium hydroxide. The formation of this impurity has been found to depend on initial pH of the formulation.

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 forms. Degradation of vitamins does not give toxic impurities; however, potency of active ingredients drops below Pharmacopoeial specifications. Because of mutual interaction, the presence of nicotinamide in a formulation containing four vitamins (nicotinamide, pyridoxine, riboflavin, and thiamine) can cause the degradation of thiamine to a sub-standard level within a one year shelf life of vitamin B-complex injections.

i. Functional group-related typical degradation

Ester hydrolysis can be explained with a few drugs aspirin, benzocaine, cefotaxime, ethyl paraben and cefpodoxime proxetil. Hydrolysis is the common phenomenon for ester type of drugs, especially in liquid dosage forms benzylpenicillin, oxazepam and lincomycin. Oxidative degradation of drugs like hydrocortisone, methotrexate,hydroxyl group directly bonded to an aromatic ring (phenol derivatives such as catecholamines and morphine), conjugated dienes (vitamin A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives and aldehydes (especially flavorings) are all susceptible to oxidative degradation.

In mazipredone, the hydrolytic and oxidative degradation pathway in 0.1 mol/Lt hydrochloric acid and sodium hydroxide at 80^0C were studied. Ergometrine, nifedipine, nitroprusside, riboflavin and phenothiazines are very liable to photo-oxidation. In susceptible compounds, photochemical energy creates free radical intermediates, which can perpetuate chain reactions. Most compounds will degrade as solutions when exposed to high-energy UV exposures. Fluroquinolone antibiotics are also found to be susceptible to photolytic cleavage.

In ciprofloxacin eye drop preparation (0.3%), sunlight induces photo cleavage reaction producing ethylenediamine analog of ciprofloxacin.

Decarboxylation of some dissolved carboxylic acids, such as p-aminosalycylic acid, shows the loss of carbon dioxide from the carboxyl group when heated.

An example of decarboxylation is the photoreaction of rufloxacin. As seen earlier, impurities in drug products can come from the drug or from excipients or can be brought into the system through an in process step by contact with the packaging material.

For most drugs, the reactive species consist of:
1. Water (can hydrolyze some drugs or affect the dosage form performance)
2. Small electrophiles (like aldehydes and carboxylic acid derivatives)
3. Peroxides (can oxidize some drugs)
4. Metals (can catalyze oxidation of drugs and the degradation pathway)
5. Leachable or Extractable (can come from glass, rubber stoppers, and plastic packaging materials. Metal oxides such as NaO2, SiO2, CaO, MgO, are the major components leached/extracted from glass).

Generally most synthetic materials contain leachable oligomers/monomers, vulcanizing agents, accelerators, plasticizers and antioxidants. Some examples of leachable / extractable from synthetic materials include styrene from polystyrene, diethylhexylphalate (DEHP, plasticizer in PVC), dioctyltin isooctylmercaptoacetate (stabilizer for PVC), zinc stearate (stabilizer in PVC and polypropylene), 2-mercaptobenzothiazole (accelerator in rubber stopper) and furfural from rayon.