

## IMPURITIES AND ITS IMPORTANCE IN PHARMACY

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### ABSTRACT

The current practice of characterization and control of impurities in pharmaceutical substances and products are reviewed with emphasis on issues specific to the active pharmaceutical ingredient and pharmaceutical formulations. The control of pharmaceutical impurities in the pharmaceutical industry is an important task to the formulator. The International Conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities in pharmaceutical drug substance as well as formulations. In this review article, impurities, its different types and origin of impurities have been discussed briefly.

**Keywords:** Impurities, ICH, pharmaceutical substance, pharmaceutical products

### INTRODUCTION

An impurity in a drug substance as defined by the International Conference on Harmonisation (ICH) Guidelines<sup>1</sup> is any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances. 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<sup>2</sup>. Therefore any extraneous material present in the drug substance has to be considered an impurity even if it is totally inert or has superior pharmacological properties.

The impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention from the public and from the media. Several recent books<sup>3,4</sup> and journal reviews<sup>5,6</sup> address this topic and guidelines are available from US and international authorities<sup>7</sup>.

Most active pharmaceutical ingredients (API) are produced by organic chemical synthesis. Various components, including residual solvents, trace amounts of inorganic, and organic components can be generated during such a process. Those components remaining in the final API are considered as impurities.

The sources and routes of formation of impurities in generics are special case<sup>8,9</sup>, they are the same as those in the reference drug product: starting materials, by-products and residual solvents from the API synthesis; degradants formed during the process and long-term storage; contaminants from packaging components and other drug products manufactured in the same facility. Impurities could be forming from the impact of heat, light, and oxidants (including air) on the drug product and might be catalyzed or accelerated by trace metal impurities, changes in the pH of the formulation, interactions with packaging components, excipients and other active ingredients, in the case of combination products.

Therefore, identification, quantification, and control of impurities in the drug substance and drug product, are an

important part of drug development and regulatory assessment.

### Common terms for Impurities<sup>10</sup>

1. Intermediate, Penultimate intermediate and By-products
2. Transformation products
3. Interaction product
4. Related product
5. Degradation product

#### 1. Intermediate, Penultimate Intermediate and By-products

The compounds produced during synthesis of the desired material are called intermediates, especially if they have been isolated and characterized. The penultimate intermediates are the last compound in the synthesis chain prior to the production of the final desired compound. By-products are unplanned compounds produced in between the reaction. It may or may not be possible to theorize all of them.

#### 2. Transformation Products

They are very similar to by-products which relates to theorized and non-theorized products that may be produced in the reaction.

#### 3. Interaction products

Interaction products that could occur between various involved chemicals intentionally or unintentionally.

#### 4. Related Products

These products have similar chemical structure and potentially similar biological activity.

#### 5. Degradation products

These compounds are products due to decomposition of the active ingredient or the material of interest.

## CLASSIFICATION

Impurities in drug substance can be classified into the following categories<sup>4,11</sup>

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

### Organic impurities

This type of impurities in bulk pharmaceutical chemicals those are innocuous by virtue of having no significant undesirable biological activity in the amounts present. Organic impurities can arise during the manufacturing process and/or storage of the drug substance. They can be identified or unidentified, volatile or nonvolatile, and include:

### Starting materials or intermediates

These are the most common impurities found in every API unless a proper care is taken in every step involved throughout the multi-step synthesis. Although the end products are always washed with solvents, there are always chances of having the residual unreacted starting materials may remain unless the manufacturers are very careful about the impurities.

### Degradation products

Impurities can also be formed by degradation of the end product during manufacturing of bulk drugs. However, degradation products resulting from storage or formulation to different dosage forms or aging are common impurities in the medicines.

### Reagents, ligands, and catalysts

These chemicals are less commonly found in APIs; however, in some cases they may pose a problem as impurities.

### Enantiomeric impurities

The single enantiomeric form of a 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

### Inorganic impurities

Inorganic impurities may also derive from the manufacturing processes used for bulk drugs. They are normally known and identified and include the following

### Reagents, ligands, and catalysts

The chances of having these impurities are rare: however, in some processes, these could create a problem unless the manufacturers take proper care during production.

### Heavy metals

The main sources of heavy metals are the water used in the processes and the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place. These impurities of heavy metals can easily be avoided using demineralized water and glass-lined reactors.

### Other materials (eg. filter aids, charcoal)

The filters or filtering aids such as centrifuge bags are routinely used in the bulk drugs manufacturing plants, and, in many cases, activated carbon is also used. The regular monitoring of fibers and black particles in the bulk drugs is essential to avoid these contaminations.

### Organic Volatile Impurities

Organic Volatile Impurities relates to residual solvents that may be found in the drug substance.

## OTHERS<sup>10</sup>

### Chiral Impurity

Compounds having similar chemical structure but different spatial orientation leading to different optical rotation are of great importance because of the resulting optical isomers. The undesired optical isomer is considered as a chiral isomer.

### Synthesis Related Impurities

Impurities in a pharmaceutical compound or a new chemical entity originate mainly during the synthetic process from raw materials, solvents, intermediate and by-products. The raw materials are generally manufactured to much lesser purity requirements than a drug substance. Similarly solvents used in the synthesis are likely to contain a number of impurities that may range from trace levels to significant amounts that can react with various chemicals used in the synthesis to produce impurities.

### Formulation related impurities

Number of impurities in a drug product can arise out of inert ingredients used to formulate a drug substance. In the process of formulation, a drug substance is subjected to a variety of conditions that can lead to its degradation or other deleterious reaction.

Solutions and suspensions are potentially prone to degradation due to hydrolysis. The water used in the formulation cannot only contribute its own impurities; it can also provide a ripe situation for hydrolysis and catalysis. Similar reactions are possible in other solvents that may be used.

### Impurity forms during formulation

#### a) Method related

#### b) Environmental related

The primary environmental factors that can reduce stability include the following

- Exposures to adverse temperatures
- Light-especially UV light
- Humidity

#### c) Formation of impurities on ageing

- a. Mutual interaction amongst ingredients
- b. Functional group- related typical degradation
  - Ester hydrolysis
  - Hydrolysis

- Oxidative degradation
- Photolytic cleavage
- Decarboxylation

### ISOLATION AND CHARACTERIZATION<sup>10</sup>

It is frequently necessary to isolate and characterize impurities in order to monitor them accurately, because approximate estimations of impurities are generally made against the material of interest (i.e. drug substance) and can be incorrect. These estimations are based on the assumption that impurities are structurally related to the material of interest and thus have the same detector response. It is important to test this assumption because impurities frequently have different structures with significantly different detector responses. Most of the time it is difficult to ensure that the assumption stated above is correct.

Number of methods can be used for isolation and characterization of impurities. But the application of any method depends on the nature of impurity (i.e.) its structure, physicochemical properties and availability. The following methods are commonly used for the isolation, they are

1. Extraction
2. Column Chromatography
3. Preparative Separations

#### Extraction

1. Liquid-Solid extraction
2. Liquid-Liquid extraction

### LIQUID-SOLID EXTRACTION

To simplest form, a solvent is selected that would dissolve the impurity of interest but not the solid matrix. If compound contains more than one impurity means, in that case desirable to use an organic solvent for extraction because of its unique properties. It is generally easier to volatilize the organic solvent at low temperatures in order to concentrate the impurity. Commonly using various organic solvents are enlisted in Table No. 1 with boiling point and dielectric constant.

**Table 1:** List of solvents for Liquid-Solid extraction

Solvents	Boiling Point	Dielectric constant
n-Hexane	190	1.9
Cyclo hexane	81	2.0
Carbon tetrachloride	77	2.2
Toluene	110	2.4
Ethyl ether	35	4.3
Chloroform	61	4.8
Methylene chloride	40	8.9
Ethanol	78	24.6
Methanol	65	32.7
Dimethyl formamide	153	36.7
Acetonitrile	82	37.5
Water	100	80
Formamide	210	111

#### Soxhlet Extraction

It is a popular method for extracting compounds of interest from solids. eg. Natural products are isolated by reputed

extraction with the suitable solvent. The main advantage of this method is that it allows utilization of a small volume of solvent to produce a fairly concentrated extract. The material to be extracted is placed in the Soxhlet extractor, the extraction vessel is heated adequately to ensure volatilization of solvent vapors, which are condensed in the top of the material to be extracted. The condensed solvent percolates through the material and drains back into the extraction vessel to repeat the process.

#### Steam Distillation

It is yet another method that can be used for extracting volatile components from natural materials and other matrixes of interest.

#### Supercritical fluid extraction (SFE)

Supercritical fluid extraction provides idealized means of extracting materials, since high solute diffusivity, lower viscosity and excellent solvating properties can be obtained with supercritical fluids, they provide excellent means of isolating impurities and other compounds of interest in a short period of time. The critical pressure, critical temperature and density of a few compounds used for SFE are given in Table No. 2. But carbon dioxide is most commonly used for SFE because of its availability, ease of use and disposition.

**Table 2:** List of solvents for SFE

Solvent	Pressure (ATM)	Temperature	Density (g/ml)
n-pentane	33.3	196.6	0.232
Carbondioxide	72.9		0.448
Ammonia	111.3	132.3	0.24

### LIQUID-LIQUID EXTRACTION

This simply entails extraction of one liquid with another generally one of those liquid is aqueous and other is organic. The primary requirement is that these liquids to be immiscible. This procedure is very useful when the liquid into which the material of interest is being extracted is easy to volatilize, thus permitting concentration of the material. Hence the choice of solvents must be made with that consideration in mind.

In this type of extraction process, a solute is distributed between two immiscible solvents. The extraction is controlled by distribution or partition co-efficient which defines the ratio of concentration of the solute in two solvents a and b

$$K_d = C_a / C_b$$

$K_d$  is the distribution co-efficient or partition coefficient.

The distribution co-efficient related to a single species and does not include possible products of side reactions.

#### Column Chromatography

This technique is commonly used for the separation of pharmaceutical compounds in preparative chemistry. The separation of quantities ranging from micrograms to kilograms, which depends on the size of the column.

Detection of the eluent is generally performed by UV-spectrophotometry, either continuously by using a flow cell or periodically by monitoring the collected fractions from a given sample that alerts the emergence of UV-active components. Commonly silica gel or alumina is used in classic adsorption chromatography. Ion exchange resins to chemically modified polydextran gels used primarily for the analysis of biological samples.

For liquid-liquid partition chromatography columns, inert carrier such as celite or kieselguhr is impregnated with an aqueous buffer or another polar solvent such as dimethyl formamide or dimethyl sulfoxide and elution is carried out with non-polar solvents.

### Thin Layer Chromatography

It is a valuable technique for isolation and purification of compounds. All the modes of chromatography including adsorption, partition, ion exchange and gel filtration can be utilized. In addition choosing a sorbent and an eluent for performing TLC it is necessary to select a suitable method for applying a sample to the plate. Silica gel plates with or without fluorescent indicator are frequently used for most application. Detection is frequently performed by UV eg. 366nm or Iodine vapors can help to detect most of the organic substance. To elute the material from the plates, the simplest method is scraping the sorbent containing the material of interest and it is extracted with a suitable solvent, followed by filtration or centrifugation. The solvent is removed to collect the desired substance. If aluminium plates are used means cut the sample and eluted.

### Gas Chromatography

It is very useful for isolation and characterization of volatile components or those components that can be made volatile by derivatization technique and the detector used should be non destructive. Now GC is more apt to be used in combination with mass spectrometry (GC/MS) for characterization of impurities.

### Analytical Methodology<sup>12</sup>

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 structures of impurities are 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.

It is necessary for monitoring impurities in pharmaceutical by very selective analytical methodology. A good method should be able to reliably determine the impurity of interest at a 0.1% level means the methods must be developed to detect at least at 0.05% level to provide assurance for quantitation at the desired level.

### Strategy for Method Development

Method development strategy should have the following details.

1. Physico chemical data
  - Ionization constant
  - Solubility
  - Water absorption
  - Distribution co-efficient
  - Optical rotation
  - Crystal form

Impurities can be analyzed by the following instruments

1. Ultra Violet Spectroscopy
2. IR Spectroscopy
3. NMR Spectroscopy
4. Mass Spectrometry
5. Gas Chromatography
6. HPLC

### QUALIFICATION OF IMPURITIES<sup>12</sup>

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.

An impurity is considered qualified when it meets one or more of the following conditions:

- When the observed level and proposed acceptance criterion for the impurity do not exceed the level observed in an FDA approved human drug product.
- When the impurity is a significant metabolite of the drug substance.
- When the observed level and the proposed acceptance criterion for the impurity are adequately justified by the scientific literature.
- When the observed level and proposed acceptance criterion for the impurity do not exceed the level that has been adequately evaluated in comparative in vitro genotoxicity studies.

Recommended qualification thresholds based on the maximum daily dose as described in Table No. 3 for drug substance and Table No. 4 for drug product, are provided in ICH Q3A<sup>1</sup> and ICH Q3B<sup>2</sup>.

**Table 3:** Drug substance impurities thresholds

Maximum daily dose <sup>a+</sup>	Reporting threshold <sup>b,c</sup>	Identification threshold <sup>b,c</sup>	Qualification threshold <sup>b,c</sup>
≤ 2g/day	0.05%	0.10% or 1.0 mg/day intake (whichever is less)	0.15% or 1.0 mg/day intake (whichever is less)
≥ 2g/day	0.03%	0.05%	0.05%

a The amount of drug substance administered per day.

b Higher reporting threshold should be scientifically justified.

c Lower threshold can be appropriate if the impurities are unusually toxic.

**Table 4:** Thresholds for degradation products in drug products

Maximum daily dose <sup>a</sup>	Reporting threshold <sup>b,c</sup>
≤ 1 g	0.1%
> 1 g	0.05%
Maximum daily dose <sup>a</sup>	Identification threshold <sup>b,c</sup>
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg–10 mg	0.5% or 20 µg TDI, whichever is lower
> 10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%
Maximum daily dose <sup>a</sup>	Qualification threshold <sup>b,c</sup>
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg–100 mg	0.5% or 200 µg TDI, whichever is lower
> 100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

a The amount of drug substance administered per day.

b Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

c Higher thresholds should be scientifically justified

## CRITICAL FACTORS AFFECTS THE QUALITY OF BULK DRUGS

### Crystallization

Formation of the crystals during the crystallization which determines the quality and stability of the synthesized molecule. Trace of solvents can be entrapped during the formation of larger size crystals, which may cause the degradation of the drug. Hence, the manufacturers of bulk drugs should take care to produce finer crystals while isolating the products.

### Washing the wet cake

Washing the samples in wet cake condition can remove the unwanted chemicals and residual solvents thoroughly or unwanted chemicals and residual solvents can be thoroughly removed by washing the samples in the wet cake condition.

### Drying

Vacuum dryer or a fluid-bed dryer is preferable instead of tray dryer for the preparation of bulk drugs due to reduction of drying time and uniform drying; which is also useful for thermolabile substances.

### Appropriate packaging

The bulk drugs should be packed based on their nature to avoid the degradation during storage.

## CONCLUSION

This review provides a perspective on impurities in drug substance and drug product. Impurity profile of pharmaceuticals is an increasing importance and drug safety receives more and more attention from the public and from the media. This article provides the valuable information about the impurities types and its classification, various techniques of isolation and characterization, analytical techniques for the determination, qualification of impurities and critical factors to be considered while preparation of the bulk drugs.

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