Impurity and Stability Studies

Dr. Y .Padmavathi

What is an impurity……

As per dictionary impurity is “something that is impure or make something impure.

A simple definition of impurity is any material that affects the purity of the material of inertest, drug substance or drug product.

In the pharmaceutical world, an impurity is considered as any other organic material, besides the drug substance, or ingredients, arise out of synthesis or unwanted chemicals that remains with API’s.

The following definition of impurity is currently under consideration by the regulatory bodies …..

Impurity:

Any entity of the drug substance (bulk material) or drug product(final container product) that is not the chemical entity defined as the drug substance or excipients or other additives to the drug product.

This definition of impurity include degradation products as impurities.

According to International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use(ICH), the degradation products are defined as…..

“ A molecule resulting from a change in the drug substance brought about over time. Such changes could occur as a result of processing or storage”

(Ex: oxidation, aggregation deamidation and proteolysis)

- The impurity may be developed either during formulation, or upon aging of both API's and formulated API's in medicines.

- Impurity profiling (i.e., the identity as well as the quantity of impurity in the pharmaceuticals), is now gaining critical attention from regulatory authorities.

- The different Pharmacopoeias, such as the British Pharmacopoeia (BP), United States Pharmacopeia (USP), and Indian Pharmacopoeia (IP) are slowly incorporating limits to allowable levels of impurities present in the API's or formulations.

- The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has also published guidelines for validation of methods for analysing impurities in new drug substances, products, residual solvents and microbiological impurities.

Designations of Impurities

- Impurities have been named differently by various groups of scientists who deal with them.

- Described here are commonly used terms and those terms that are used by official bodies such as compendia or that have been found acceptable by ICH and various regulatory bodies.

A . Common Names

Various terms that have been commonly used to describe impurities are listed alphabetically below.

- By-product
- Degradation product
- Interaction product
- Intermediate
- Penultimate intermediate
- Related product
- Transformation product

- **By-products:** The unplanned compounds generated in the reaction to produce API are generally called by-products. Because it might not be possible to theorize all of them, they present a significant challenge to the analytical chemist.
- **Degradation products:** The compounds produced as a result of decomposition of the material of interest or API are often called degradation products (or degradants). It is necessary to be concerned with these products as well as those brought about by degradation of other compounds that may also be present as impurities in the drug substance.
- **Interaction products:** This term is slightly more inclusive and more difficult to evaluate than the two previously described, i.e., by-products and degradation products, in that it takes into account interactions that could possibly occur between various involved chemicals purposely or inadvertently.

- **Intermediates:** The planned compounds produced during synthesis of the desired substance are called intermediates, especially if they have been isolated and characterized.

  The most important requirements are isolation and characterization, i.e., they cannot be just potential reaction products that may be produced theoretically. The theorized products are best designated as “Potential intermediates”.

- **Penultimate intermediate:** As the name implies, this is the last compound in the synthetic chain just preceding the production of the ultimate desired compound. Confusion sometimes occurs when the desired material is a salt of a free base or acid. It is not appropriate to label the free acid or base as the penultimate intermediate if the drug substance is a salt.

- **Related products:** As suggested previously, the term ‘‘related products’’ tends to imply that the impurity is similar to the drug substance, and it thus tends to downplay the negativity frequently attached to the term ‘‘impurity.’’
- These products may have similar chemical structures and potentially similar biological activities; however, we know that the structure alone does not provide any surety about biological activity.

Description of impurity types and their sources:

Impurity type	Impurity source
Process related drug substance	-organic -starting material -Intermediate -By-product
Process related drug product	-Impurity in starting material -Organic or In organic -Reagents, catalysts etc
Degradation drug substance or drug product	-Organic -Degradation products
Degradation drug product	-Organic -Excipient interaction

B) United State Pharmacopeia

- The United States Pharmacopoeia (USP) classifies impurities in various sections;

  Impurities in Official Articles

  Ordinary Impurities

  Organic Volatile Impurities

- The pharmacopeia states that our nations about purity are likely to change with time and that purity is closely related to current developments in analytical chemistry.
- Therefore, what we regard as pure today may be considered impure at some future time if methods are found that can determine other components in a particular compound.

Inorganic, organic, biochemical, isomeric, or polymeric components may all be considered impurities. The following terms have been used to describe impurities:

- Concomitant components
- Foreign substances
- Ordinary impurities
- Organic volatile impurities
- Signal impurities
- Toxic impurities

- **Concomitant components:** Bulk pharmaceutical chemicals (frequently referred to as API in the pharmaceutical industry) may have concomitant components, e.g., geometric and optical isomers and antibiotics that are mixtures.
- **Foreign substances:** These are materials that are introduced by contamination or adulteration, and not as a result of formation or preparation; they are classified as foreign substances, e.g., pesticides in oral analgesics.
- **Ordinary impurities:** The types of impurities in bulk pharmaceutical chemicals that are harmless by virtue of having no serious undesirable biological activity in the amounts present are specified as ordinary impurities.

C. ICH Terminology

- According to ICH guidelines (on the Internet, see http://www.fda.gov/cder/guidance), impurities can be broadly classified into the following three categories for the drug substance produced by chemical synthesis:

- ❑ Organic impurities (starting materials, process-related products, intermediates, and degradation products).
- ❑ Inorganic impurities (salts, catalysts, ligands, and heavy metals or other residual metals).
- ❑ Residual solvents (organic and inorganic liquids used during production and/or recrystallization).

Impurities can be classified into the following categories

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

Organic impurities

These can arise during the manufacturing process and/or storage of the new drug substance.

They can be identified or unidentified, volatile or nonvolatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands, and catalysts

Inorganic impurities

They can result from the manufacturing process.

They are normally known and identified and include:

- Reagents, ligands and catalysts
- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance.

Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Q3C on Residual Solvents).

Excluded from this document are:

(1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as good manufacturing practice (GMP) issues,

(2) polymorphic forms, and

(3) enantiomeric impurities.

The Need to Isolate and Characterize Impurities

- Impurities are generally assumed to be inferior to API because they might not have the same level of pharmacologic activity. However, they are not necessarily always inferior. From the standpoint of its usage, the drug substance is compromised in terms of purity even if it contains another material with superior pharmacologic or toxicologic properties.
- At first pass this may not be readily apparent; however, on further thought it will become clear that if we are to ensure that the accurate amount of the drug substance is being administered to the patient, we must assess its purity independent of the extraneous materials.

- Therefore, any extraneous material present in the drug substance or active ingredient must be considered an impurity even if it is totally inert or has superior pharmacologic properties, so that an appropriate evaluation of its content in the drug product can be made.
- The control of low-level impurities is of great importance when a drug is taken in large quantities; for example, the use of methotrexate (10–20 g) to treat neoplasia or the use of vitamins, notably vitamin C.

- It is necessary to isolate and characterize a number of impurities and degradation products mentioned because it is not always possible to unambiguously characterize them with the widely used hyphenated methods that are frequently the first line of defense.

- These methods utilize detectors such as diode array UV detector (DAD), nuclear magnetic resonance spectrometer (NMR), and mass spectrometer (MS) with separation methods such as gas chromatography (GC), high-pressure or high-performance liquid chromatography (HPLC), supercritical fluid chromatography (SFC), and capillary electrophoresis (CE).

- Methods such as gas chromatography-mass spectrometry (GC/MS), high-pressure or high-performance liquid chromatography–mass spectrometry (HPLC/MS, or simplyLC/MS), GC or LC/MS/MS, LC/DAD/MS, LC/NMR, LC/DAD/MS/NMR, SFC/MS, or CE/MS and various other combinations are extremely useful and can shorten the time needed for characterization of impurities.

Qualification of Impurities in Drug Substances and Drug Products

- U.S. and international guidance, especially International Conference on Harmonization (ICH) Q3A(R2), ICH Q2B(R2), Q3C(R4) and VICH GL10R1 require that drug manufacturers identify, quantify and qualify real or potential impurities in drug substances and drug products.
- These regulations apply to both human and veterinary drugs and are further delineated in terms of organic or inorganic materials and solvents. Identification and quantification are, generally, achieved with analytical methods.

- Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product, impurity or metabolite at the level(s) specified. The rationale for establishing impurity acceptance criteria must include safety considerations.

Quantification of impurities in drug substance and drug products

Impurity quantification in pharmaceutical dosage forms
Identification and quantification of impurities in drug compounds is a crucial task in pharmaceutical process development for quality and safety.

Related components are the impurities in pharmaceuticals which are unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during stability testing, or develop during formulation or upon aging of both API and formulated APIs in medicines

- The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products.

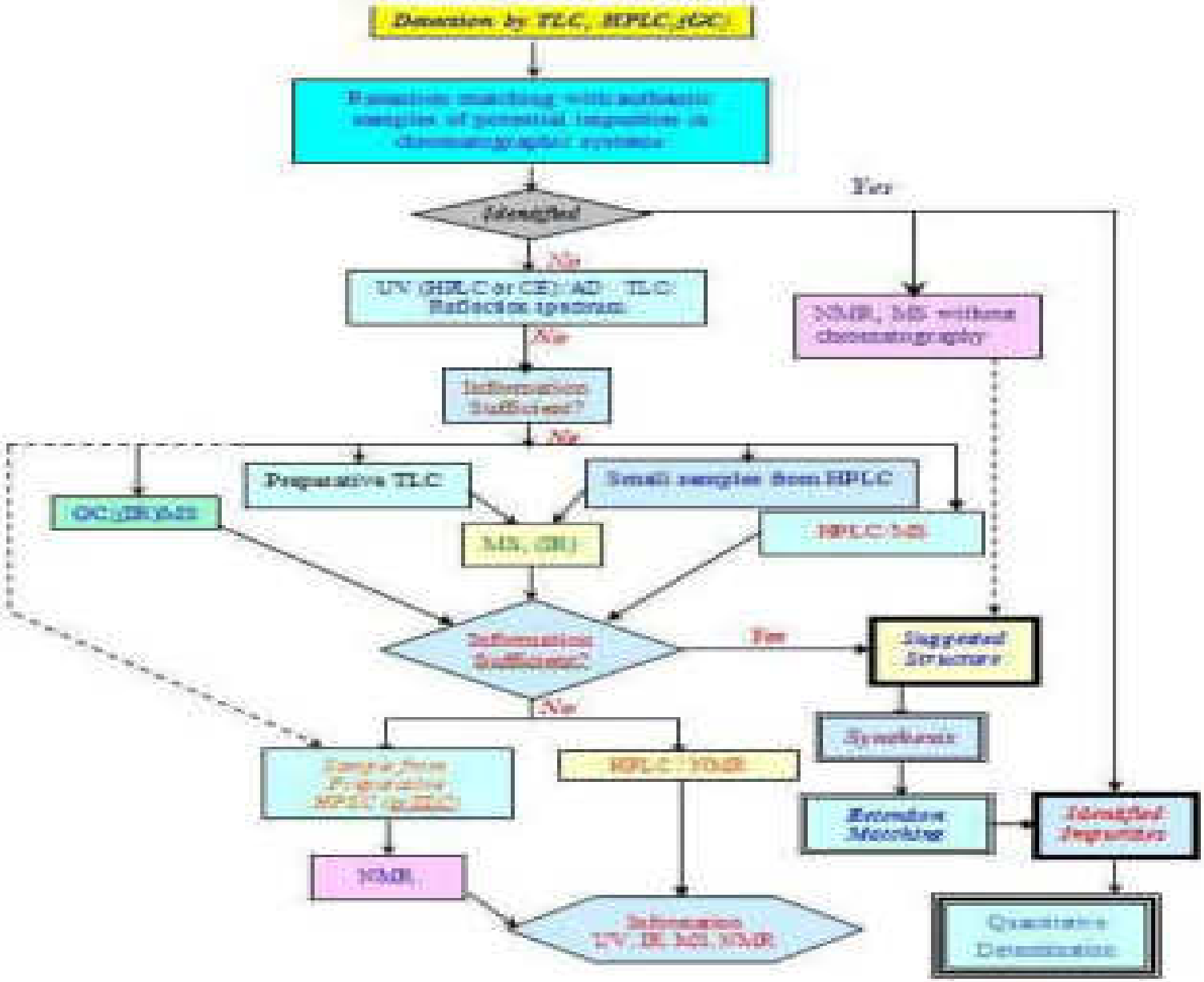
- Various analytical methodologies were employed for the determination of related components in pharmaceuticals.

- Analytical methods for impurities estimation should be stability indicating to monitor the stability of pharmaceutical dosage forms during the investigational phase of drug development, and once the drug is marketed, the ongoing stability studies must be conducted/ performed.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enables to establish a retest period/shelf life for a drug substance and a recommended storage condition.

Methods can be developed which measure the amount of drug remaining, the amount of drug lost (or the appearance of degradation products), or both.

The development of these methods for pharmaceuticals can be approached from several avenues. Related components, related substances, and related impurities are synonyms for the term impurities; the use of above terms at different phrases means one and the same (i.e. impurities).


Preparative TLC
Small samples from HPLC
Yes
No
Yes
No
No
Yes