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# IMPURITY PROFILING: A RECENT TREND IN PHARMACEUTICAL MANUFACTURING

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**Keywords:**

Impurity profiling, impurities, identification, analytical, Elucidation

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## ABSTRACT

In the Pharmaceutical field the word impurity refers to any unwanted chemical or extraneous substance that remains in API during synthesis or processes associated with formulation. A description of the identified and unidentified impurities present in a new drug substance is called as impurity profile. Impurity profiling is very important in the field of pharmaceutical analysis. Unidentified and potentially toxic impurities are health hazards and in order to increase safety, impurity should be identified .The present review focus on study of impurity profiling in API using various analytical techniques such as chromatographic (HPLC, CE, GC) and spectroscopic technique (UV, NMR, FTIR) by isolation and characterization of impurities.

## INTRODUCTION

There are increases the importance of Impurity profiling in modern pharmaceutical word because unidentified and toxic impurities are hazardous to the human health in order to increases the safety drug therapy impurity should be identifying by using selective method. Impurities are organic, inorganic material or residual solvent other than drug product arise out from synthesis or unwanted chemicals remains in API's Recently not only purity but impurity is also important according to various regulatory authorities. Presence of impurity in bulk drug or pharmaceutical formulation even in small amount affect on safety and efficacy of drug product. Impurity profiling involves identification, structural elucidation and quantitative determination of impurity and degradation product in bulk as well as pharmaceutical product. The impurity may be developed either during formulation or upon aging of both API's and formulated API's in medicines. The control of impurities in Formulated products and Active Pharmaceutical ingredients were regulated by various regulatory authorities like, ICH, USFDA, Canadian Drug and Health Agency. Identification of impurities is done by variety of Chromatographic and Spectroscopic techniques there are different methods for detecting and characterizing impurities with TLC, HPLC, HPTLC, and AAS.[1-21]

### Background of Study

The actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance should be summarized ,based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the drug substance. The spectroscopic studies (NMR, IR, MS etc. ) conducted to characterize the structure of actual impurities present in the drug substance above an apparent level of 0.1% (e.g., calculated using the response factor of the drug substance) should be described. All recurring impurities above an apparent level of 0.1% in batches manufactured by the proposed commercial process should be identified of these studies. According to I.C.H., the maximum daily dose qualification threshold to be considered is as follows; ≤ 2g/day 0.1 % or 1 mg per day intake (whichever is lower) ≥2g/day 0.05% Inorganic impurities are normally detected and quantified using Pharmacopoeia or other appropriate standards. Carryover of catalysts to the drug substance should be evaluated during development.[9-30]

**Regulatory Guidelines on Impurities in an Active Pharmaceutical Ingredient**

Ethical, economic and competitive reasons as well as those of safety and efficacy support the need to monitor impurities in drug products. However monitoring impurities and controlling these impurities mean different things to different people or to the same people at different times, even those in the pharmaceutical sciences and industry2. A unified terminology is necessary to assure that everyone uses the same vocabulary when addressing questions related to impurities. The United States Food and Drug Administration (US FDA) have endorsed the guidance prepared under the guidance of the International Conference of harmonization (ICH). The ICH guideline for impurities in pharmaceuticals was developed with joint efforts of regulators and industry representatives from the European Union (EU), Japan and United States and it has helped to ensure that different regions have consistent requirements for the data that should be submitted to various regulatory agencies. The guidelines not only aid the sponsors of New Drug Applications (NDA) or Abbreviated New Drug Application (ANDA) with the type of information that should be submitted with their applications, but also assist the FDA reviewers and field investigators in their consistent interpretation and implementation of regulations1-2. The various regulatory guidelines regarding impurities are as follows:

1. ICH guidelines “stability testing of new drug substances and products"- Q1A
2. ICH guidelines “Impurities in New Drug Substances”- Q3A
3. ICH guidelines “Impurities in New Drug Products”- Q3B
4. ICH guidelines “Impurities: Guidelines for residual solvents”- Q3C
5. US-FDA guidelines “NDAs -Impurities in New Drug Substances”
6. US-FDA guidelines “ANDAs - Impurities in New Drug Substances”
7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.[5-11,14,15,18-22]

**Systemic approach**

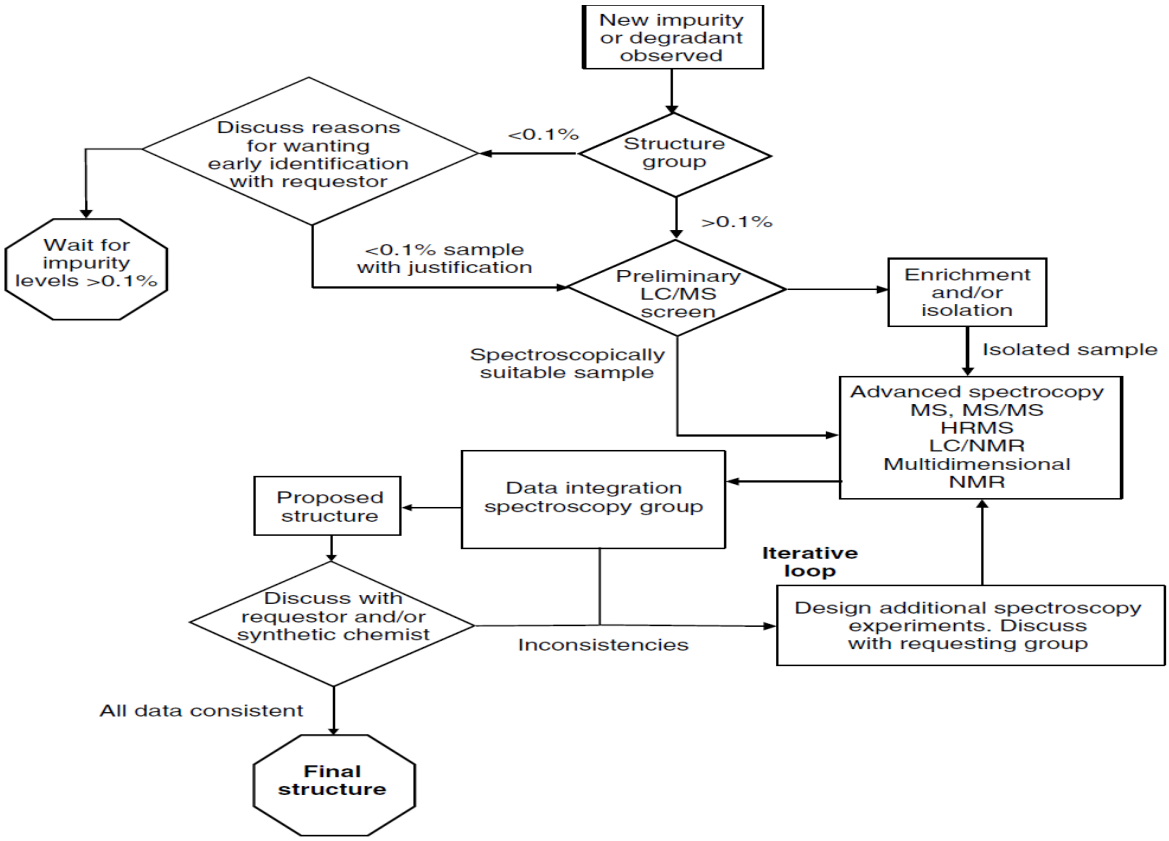


Fig-1: Steps in Impurity Profiling

**Common terms for Impurities**

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.[1-8, 14-22, 25, 28, 29, 30]

**Impurities can be classified as,**

- Organic Impurities (Process and drug-related)
- Inorganic Impurities (Reagent, ligands, catalysts)
- Residual Solvents (Volatile solvents)
- Polymorphic forms
- Enantiomeric impurities

**1) Organic impurities:**

Can arise during the manufacturing process and storage of the API. They can be identified or unidentified, volatile or non volatile

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

**2) Inorganic impurities:**

Can result from the manufacturing process, they are normally known and identified and include

- Reagents, ligands, catalyst
- Heavy metals or other residual metals
- Inorganic salts
- Other materials, e.g. filter aids, charcoal

**3) Residual Solvents (Volatile solvents)**

**Class 1 solvents (Solvents to be avoided):** Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

**Class 2 solvents (Solvents to be limited):** Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

**Class 3 solvents (Solvents with low toxic potential):** Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

**Solvents for which No Adequate Toxicological Data was found:** However, no adequate toxicological data on which to base a PDE was found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.[23, 24, 26, 37-43]

**4) Formulation related impurities (impurities in drug products)** 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. The formulation related impurities can be classified as follows:

**A) Method related**

Environmental related the primary environmental factors that can reduce stability include the following

I. Exposures to adverse temperatures

II. Light-especially UV light

III. Humidity

**B) Dosage form related**

I. Mutual interaction amongst ingredients

II. Functional group- related typical degradation

- Ester hydrolysis
- Hydrolysis
- Oxidative degradation
- Photolytic cleavage
- Decarboxylations

**The impurities can be identified predominantly by following methods**

- Reference standard method
- Spectroscopic method
- Separation method
- Isolation method
- Characterization method

**Reference standard method:**

The key objective of this is to provide clarity to the overall life cycle, qualification and governance of reference standards are used in the development and control of new drugs. Reference standards serve as the basis of evaluation of both process and product performance and are the benchmarks for assessment of drug safety for patient consumption. These standards are needed not only for the active ingredients in dosage forms but also for impurities, degradation products, starting materials, process intermediates and excipients.

**Spectroscopic methods:-**

The UV, IR, MS, NMR and Raman spectroscopic methods are routinely being used for characterizing impurities.

**Separation methods:-**

The Capillary electrophoresis (CE) Chiral Separations, Gas Chromatography (GC), Supercritical Fluid Chromatography (SFC), TLC, HPTLC, HPLC are regularly being used for separation of impurities and degradation products.

**Isolation methods**

A list of methods that can be used for isolation of impurities is given below. Solid-phase extraction methods, Liquid-liquid extraction methods,Accelerated solvent extraction methods, Supercritical fluid extraction, Column chromatography Flash chromatography, TLC, GC, HPLC, HPTLC, Capillary electrophoresis (CE)[5-7, 23, 25, 27-43]

**APPLICATIONS**

Numerous applications have been sought in the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods. The applications include alkaloids, amines, amino acids, analgesics, antibacterial, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids & miscellaneous.[8, 11-17]

## CONCLUSION

Impurity profiling study is very important during the synthesis and manufacturing of drug substances (API) and dosage forms, as it helps in providing crucial data regarding the safety limit, limits of detection, limit of quantification, limit of several organic and inorganic impurities along with their toxicity limit. Thus, by the help of impurity profile study, it become convenient to design such a method and product where in expected impurity cannot interfere.

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