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A Review of Impurity Profile in Pharmaceutical Substances

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Palve Rohit[1]*, Gaikwad Annasaheb[2], Mandale Komal[3], Pawar Reshma[4]

Loknete Shree Dadapatil Pharate College of Pharmacy, Mandavgan Pharata, Pune. Maharashtra, India 412211.

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ABSTRACT

A quality drug when marketed has various factors associated with it one of the crucial factors being impurities identification, quantification, and removal of impurities at each stage of its development. Impurity is any substance coexisting with the original drug such as starting material or intermediates or that is formed due to any side reaction. Impurity plays a major role in pharmaceuticals; therefore, profiling of impurity is very important. Recently there has been increased stress on impurity profiling of APIs and formulation. Impurity profiling includes identification, structure elucidation and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulations. Isolation, identification, and quantification of impurities help us in various ways to obtain a pure substance with less toxicity and safety in drug therapy. Impurity profiling study has been in the limelight in the recent pharmaceutical scenario and its importance is increasing day-by-day. This review provides the valuable information about the impurities, its classification, and sources of impurities and various techniques of isolation and characterization, analytical techniques for the determination, qualification of impurities have been described. Guidelines and limit for impurity present in the pharmaceutical and impurity profiling as per ICH is discussed.

INTRODUCTION

IMPURITY

Impurity is something that is impure or makes something else impure.[3] Pharmaceutical impurities are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs) or are developed during formulation or upon aging of both API and formulated APIs to medicines.[1] The presence of these impurities even in minor amounts can influence the efficacy and safety of the drug.[6] Impurities present in excess of 0.1% should be identified and quantified by selective methods. Isolation, identification, and quantification of impurities help us in various ways to obtain a pure substance with less toxicity and, safety in drug therapy.[8] Impurities in new drug substances can be addressed from two perspectives 1) The chemical aspect which includes classification and identification of impurities, report generation, a listing of impurities in specifications and a brief discussion of analytical procedures. 2) The safety aspect which includes specific guidance for quantifying impurities, present, substantially at lower levels in a drug substance used in clinical studies.[5,7]

How Can Impurities Be Controlled?[18]

- By understanding the formation, fate, and purge of the impurities during the manufacturing process.

- By setting up appropriate controls at places where they either enter or form during the manufacturing process of drug substance and/ or drug product.

- Based on the knowledge of the types of impurities and their potential sources, a comprehensive control strategy is designed via material quality control and process control steps and ultimately by drug substance/product specifications.

IMPURITY PROFILING

Impurity plays a major role in pharmaceuticals; therefore, profiling of impurity is very important. Impurity profiling is the common name of a group of analytical activities the aim of which is the detection, identification/structure elucidation and quantitative determination of organic and inorganic impurities as well as residual solvents in bulk drugs and pharmaceutical formulations.[2] The impurity profile of a drug is defined as “A description of the identified and unidentified impurities present in a new drug product”. It is the best way to

characterize the quality and stability of bulk drugs and pharmaceutical formulations. It helps in identifying and quantifying the impurities present in drug substance (API) or pharmaceutical formulation.[1]

SOURCES OF IMPURITIES IN DRUG PRODUCTS

The various sources of impurity in pharmaceutical products are reagents, heavy metals, ligands, catalysts, other materials like filter aids, charcoal, and the like degraded end products obtained during or after manufacturing of bulk drugs from hydrolysis, photolytic cleavage, oxidative degradation, decarboxylation, enantiomeric impurity and so on.[2] In general, the types of impurities that may be present in pharmaceutical substances can come from the following sources.[8,17]

1. The raw materials used.
2. The method of manufacture adopted.
3. Due to the instability of the product.
4. From the atmospheric contaminants.
5. Crystallization-related impurities e.g. Polymorphism.

LIMITS FOR IMPURITIES

According to the ICH guidelines on impurities in new drug products, identification of impurities below 0.1% level is not measured to be necessary unless otherwise potential impurities are expected to be unusually potent or toxic. [10] ICH has given following limits for impurities:

- When the dose is less than 2 gm/day impurity present should be less than 0.1 % or 1 mg/day intake, whichever is lesser.
- When the dose is more than 2 gm/day impurity present should be less than 0.05 % of intake.[16]

Limits for impurities in drug substances are shown in table 1 while limits for impurities in degraded products of drugs are shown in table 2.

Table No. 1: Limits for impurities in the drug substance.[1]

Drug Substance Impurity	Limits
Each identified specified impurity Each unidentified impurity Total impurities	Not more than 0.5 percent Not more than 0.3 percent Not more than 1.0 percent

Table No. 2: Limits for impurities in the degradation products of drugs.[1,7]

Degradation Product Impurity	Limits
Each identified degraded product Each unidentified degraded product Total degraded products	Not more than 1.0 percent Not more than 0.5 percent Not more than 2.0 percent

CLASSIFICATION OF IMPURITIES

Authorities classify impurities differently.

As per ICH [3,6,7,9]

In the chemical synthesis, the impurities produced can be classified into three classes are as follows:

a. Organic impurity (process- and drug-related)

b. Inorganic impurity

c. Residual solvents

a. Organic Impurity: These impurities may arise during the manufacturing process or storage of the new drug substances, which includes starting materials, by-products, intermediates, degradation products, intermediates, degradation products, reagents, ligands, and catalysts.

Fig. 1: Classification of Organic Impurity[3]

b. Inorganic Impurity: These impurities include reagents, ligands and catalysts, heavy metals or other residual metals, inorganic salts, filter aids, charcoal etc.

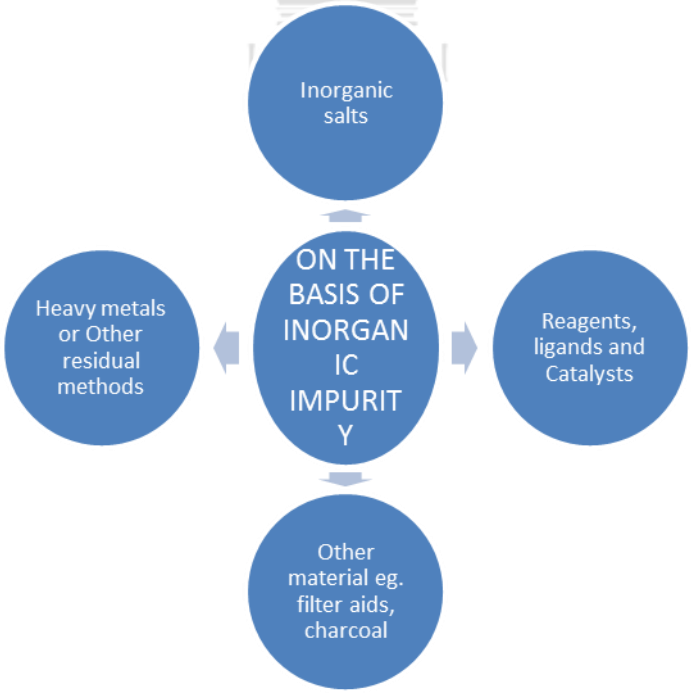

Fig. 2: Classification of Inorganic Impurity [3]

c. Residual Solvents: These solvents are organic or inorganic liquids used during the manufacturing process. Since these are generally of known toxicity, the selection of appropriate controls can be accomplished easily.[7] For the detection of residual solvent, gas chromatography is used because they are most volatile in nature. Nonvolatile solvents are converting to volatile solvents by chemical derivatization.[6]

Table No. 3: Classification of residual solvents [10]

Solvent	Risk assessment	Example
Class I	Solvents to be avoided	Benzene (2ppm), Carbon tetrachloride (4ppm), Methylene chloride (600ppm), Methanol (3000ppm), Pyridine (200ppm), Toluene (890ppm)
Class II	Solvents to be limited	N, N- dimethylformamide (880ppm), acetonitrile (410ppm)
Class III	solvents with low toxic potential	Acetic acid, Ethanol, Acetone has permitted daily exposure of ≤50mg/day.

As per the United States Pharmacopeia [12]

The United States Pharmacopoeia (USP) classifies impurities into two sections i.e. ordinary impurities and organic volatile impurities.

a. Ordinary impurities.

b. Organic volatile impurities.

a. Ordinary Impurities: Ordinary impurities are found in bulk pharmaceutical chemicals that are innocuous by virtue of having no significance on the biological activity of the drug substance. These impurities may arise out of the synthesis, preparation or degradation of the chemical.

b. Organic volatile impurities: Organic volatile chemicals are produced in the manufacture of drug substances or excipients or in the preparation of drug products; they are volatile in nature and by themselves get removed out at time of storage or processing.

REGULATORY GUIDELINES ON IMPURITY [4, 6, 14]

The United States Food and Drug Administration (FDA) inscribe International Conference on Harmonization guidance of Technical Requirements for Registration of Pharmaceuticals for Human Use. The FDA has the assigned responsibility of ensuring the safety and efficacy of drugs. 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 of Medicines, Therapeutic Governance Authority (TGA), Australia.

ANALYTICAL METHOD DEVELOPMENT FOR IMPURITY PROFILE [1, 3, 17]

The impurities can be identified predominantly by following methods

1. Reference standard method
2. Spectroscopic method
3. Separation method
4. Isolation method
5. Characterization method.

1. Reference standard method[3,17]

The key objective of this is to provide clarity to the overall life cycle qualification and governance of reference standard used in the development and control of the new drug.

Reference standards serve as the basis for evaluation of both process and product performance and are the benchmarks for assessment of drug safety for patient consumption.

2. Spectroscopic method[3]

The following spectroscopic methods can be used

1. Ultraviolet (UV)
2. Infrared (IR)
3. Nuclear magnetic resonance (NMR)
4. Mass spectrometry (MS)

3. Separation method[3]

The following separation methods can be used

1. Thin-layer chromatography (TLC)
2. Gas chromatography (GC)
3. High-pressure liquid chromatography (HPLC)
4. Capillary electrophoresis (CE)
5. Supercritical fluid chromatography (SFC)

4. Isolation method[10,13,15]

A number of methods can be used for isolation and characterization of impurities. However, the application of any method depends on the nature of impurity i.e. its structure, physicochemical properties, and availability. Predominantly the chromatographic techniques are used for isolation of impurities along with non-chromatographic techniques are also rarely used. A list of methods that can be used for isolation of impurities is given below.

1. Solid-phase extraction method
2. Liquid-liquid extraction method

3. Accelerated solvent extraction method
4. Supercritical fluid extraction
5. Column chromatography
6. Flash chromatography
7. Thin layer chromatography (TLC)
8. Gas chromatography (GC)
9. High-performance liquid chromatography (HPLC)
10. High-performance thin layer chromatography (HPTLC)
11. Capillary electrophoresis(CE)
12. Supercritical fluid chromatography (SFC)

5. Hyphenated methods /characterized method[11]

There are several methods used for the identification of impurities in pharmaceuticals but the characterization of impurities is an important method of identification. Characterization includes nuclear magnetic resonance spectrometry (NMR) and mass spectrometry (MS). There are some recent hyphenated techniques for impurity profiling coupled with mass spectrometry like LC-MS, LC-MS-MS, GC-MS, HPLC-DAD-MS, HPLC-DAD-NMR-MS, capillary electrophoresis-mass spectrometry and tandem spectrometry.

1. GC–MS
2. LC-MS
3. LC–DAD–MS
4. LC–NMR
5. LC-MS-MS
6. HPLC-DAD-MS

7. HPLC-DAD-NMR-MS

IMPLEMENTATION OF QUALITY BY DESIGN APPROACH

Quality by Design (QbD) is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" and has the aim of improving product quality and of increasing regulatory flexibility. Impurity level is a critical quality attribute for a drug substance or a drug product because levels higher than the toxicologically qualified amount could affect the safety and efficacy of the product. [19]

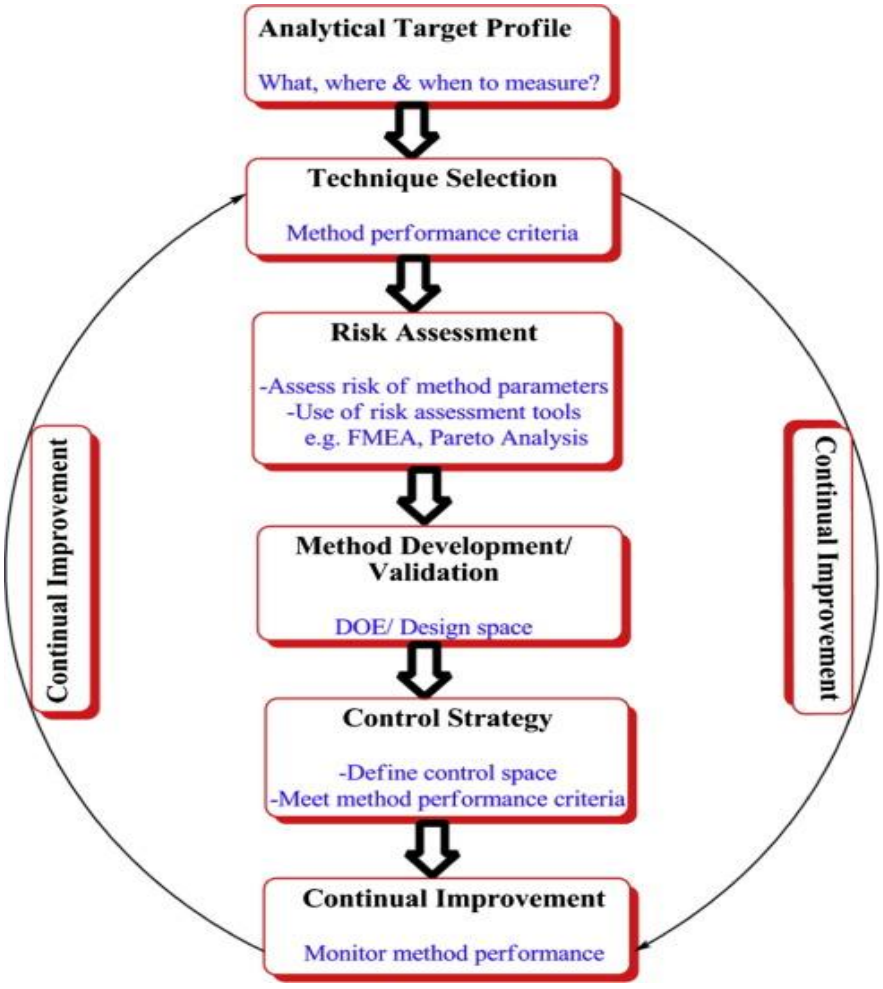

Fig. 3: Systematic implementation of QBD approach.

QBD APPROACH IN IMPURITY [18]

A systematic control of impurities via QBD approach has following benefits:

- **For Patients**: They receive the product of high quality.

- **For Regulators**: A clear control strategy from the manufacturers provides transparency and added assurance that risk of impurity has been adequately controlled.

- **Pharmaceutical companies**: A clear control strategy is identified which ultimately facilitates the successful launch of the product and various post-approval supplements like scale-ups, tech transfers etc.

SUMMARY

Impurity profiling in pharmaceuticals increases drug safety. Identification of impurities establishes an overall profile of a drug, which includes its toxicity and safety limits, limits of quantization and detection. It has received more attention from the public and social media. The present article provides detail information about pharmaceutical impurity, classification of impurity; a source of impurity, the recent technique used in the characterization of impurity and finally gives the various approaches of impurities control by QBD. Guidelines and limit for impurity present in the pharmaceutical and impurity profiling as per ICH is discussed.

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