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Impurities in Pharmaceutical Substances

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ABSTRACT: The quality, safety, and effectiveness of pharmaceutical products are significantly impacted by impurities in active pharmaceutical ingredients (APIs). During the synthesis, production, and storage processes, these impurities may originate from a number of sources, such as pollutants, reagents, residual solvents, and degradation products. International regulatory bodies including the FDA, EMA, and ICH strictly control the presence of impurities in APIs and offer detailed recommendations on permissible impurity levels and testing procedures. For the detection and measurement of contaminants, analytical methods like mass spectrometry (MS), gas chromatography (GC), and high-performance liquid chromatography (HPLC) are frequently used. During API development and manufacture, strict impurity control methods are required due to the safety issues associated with impurities, which include toxicity, mutagenicity, and immunogenicity. While efforts like Quality by Design (QbD) seek to proactively address impurity issues across the drug development lifecycle, new developments in purification technologies and green chemistry concepts have helped to minimize impurity generation. This study highlights the significance of efficient impurity management in guaranteeing drug quality and patient safety by going over the origins, types, regulatory guidelines, analytical techniques, and safety concerns pertaining to impurities in APIs.

Keywords: FDA, EMA, ICH, QbD

I. INTRODUCTION:

Impurity:

Impurity any entity of the drug substance or drug product that is not the chemical entity defined as the drug substance, an excipient, or other additives to the drug product. [1,2,]

Impurities in APIs can be broadly categorized into three main types: Organic impurities, inorganic impurities, and residual solvents.

Starting materials, reagents, intermediate compounds, by-products, degradation products, and impurities from the manufacturing process are some of the sources of organic contaminants in APIs. These impurities fall into one of three categories: degradants, process impurities, or related chemicals.

Unreacted starting materials, impurities from side reactions, and transformation products created throughout the production process are a few examples of organic impurities. The primary sources of inorganic impurities in APIs are either the manufacturing method or the raw materials employed in the synthesis. They may consist of inorganic substances like metal salts or catalyst residues, as well as heavy metals like lead, mercury, or arsenic. [3]

Inorganic impurities need to be carefully managed within reasonable bounds because they can present major health hazards. Volatile organic substances known as residual solvents are utilized in the production process but are not entirely eliminated from the finished API. These solvents can belong to a variety of chemical classes, including hydrocarbons, alcohols, and chlorinated solvents. The quality and safety of pharmaceutical products might be impacted by the presence of residual solvents in excess, which are subject to strict regulations.[4]

Pharmaceutical goods' efficacy, safety, and quality can all be impacted by impurities in APIs. Certain contaminants can seriously endanger consumers' health, particularly heavy metals, genotoxic contaminants, or recognized toxic substances. They could result in toxicity, negative reactions, or long-term health issues. To guarantee safety, these contaminants must be strictly controlled.

Furthermore, contaminants may have an impact on the stability of APIs and their formulations, which may result in deterioration or a shorter shelf life. The pharmacological characteristics of the API may be changed by degradation products, making it less useful or possibly hazardous. The effectiveness and potency of APIs can be impacted by impurities, especially related compounds or degradants. They may potentially change the pharmacokinetics, cause

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undesirable side effects, or obstruct the intended therapeutic impact.[5,6,7]

Identification

Impurities present at 0.10% or higher levels should be identified and characterized.

Qualification threshold

For drugs with a maximum daily dose of less than 2 grams per day, the qualification threshold is 0.1% or 1 milligram per day, whichever is lower. For drugs with a maximum daily dose of more The ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) provides comprehensive guidelines for the analysis and control of impurities in drug substances produced by chemical synthesis. These impurities can be broadly classified into three categories:

1. **Organic Impurities**: These include impurities related to the synthesis process, such as:
   - **Starting materials**: Raw materials that are used in the initial stages of synthesis.
   - **Process-related products**: By-products or unreacted intermediates that result from the chemical manufacturing process.
   - **Intermediates**: Compounds formed during the steps of the synthesis but are not the final drug substance.
   - **Degradation products**: Compounds that form when the drug substance degrades under normal storage or usage conditions.
2. **Inorganic Impurities**: These include contaminants that are typically associated with the manufacturing process, such as:
   - **Salts**: Inorganic salts that may remain in the drug substance after synthesis or processing.
   - **Catalysts**: Residual catalysts that were used to facilitate chemical reactions during production.
   - **Ligands**: Metal-binding molecules that may be part of the catalytic process.
   - **Heavy metals or other residual metals**: These may come from catalysts, reagents, or equipment used during production and could be harmful if present in excessive amounts.
3. **Residual Solvents**: These are organic or inorganic solvents that may remain in the final product after processes like recrystallization or during the drug's manufacturing process. Solvents such as ethanol, acetone, or chloroform are common examples, and their levels must be carefully controlled to avoid toxicity.[8,9,10]

Addressing Impurities: A Unified Approach

ICH Guidelines for Impurity Analysis

ICH has published several key guidelines relevant to the control of impurities in pharmaceuticals, including:[11,12,13]

- **ICH Q3A (R2)**: This guideline covers the **impurities in new drug substances**. It provides recommendations for the identification, qualification, and reporting of impurities in the drug substance, with a focus on organic impurities, inorganic impurities, and residual solvents.
- **ICH Q3B (R2)**: This guideline provides similar guidance for **impurities in new drug products**.[14]
- **ICH Q3C**: This guideline addresses **residual solvents** and provides safety-based limits for residual solvents in drug substances and products.[15]
- **ICH Q3D**: This guideline deals with **elemental impurities** and offers recommendations on the permissible limits for metals and other inorganic impurities in drug products. [16,17]

The guidelines also emphasize the importance of validating analytical methods to detect and quantify these impurities accurately and reliably. The validated methods should be capable of ensuring that the impurity levels in the drug substance and drug product are within acceptable limits, as defined by regulatory agencies.[18,19]

Analytical procedures

For analytical methods, the quantitation limit should not exceed the reporting threshold.

Reference standards:

It is important to assess and describe the reference standards that are utilized in analytical methods.

Analytical results:

For every batch used for clinical, safety, and stability testing, analytical findings must be supplied.

Impurities in APIs can be a quality issue, as they can impair the drug's efficacy and lead to safety issues. However, some impurities are unavoidable and will be present in trace amounts

1. Impurity types include:

Process-related Impurities: These occur when APIs are synthesized or manufactured. They consist of leftover chemicals, solvents, and

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intermediates from the process of chemical synthesis.

Degradation Products: These contaminants develop as the API deteriorates over time, either as a result of the drug's metabolic processes or during storage.

During manufacturing, contaminants may be introduced through equipment, raw materials, or packaging. Particulate pollution, microbiological contaminants, and heavy metals are a few examples.

Impurities connected to excipients: Because of their own degradation or interactions with the API, excipients employed in the formulation process may also contribute to impurities. [20]

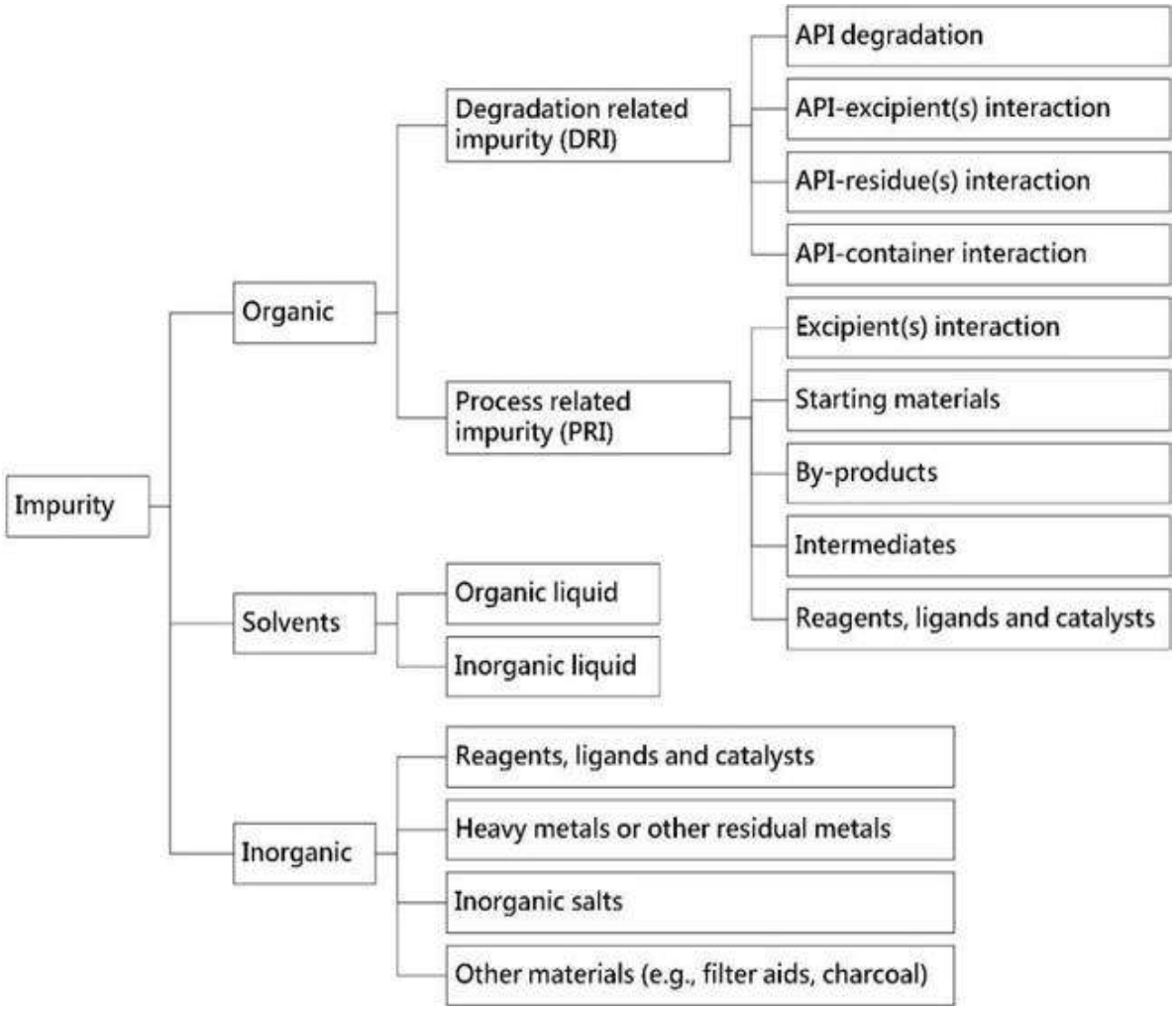

Figure 1. Classification of impurities[21,22,23]

2. Sources of Impurities

It is obvious that contaminants can come from a variety of sources. The synthesis is the most evident source of impurities, as intermediates and by-products can either enter the API as contaminants or contribute to the formation of more impurities. The active ingredient of interest may contain any impurities that may have been present in the beginning material. Additionally, it is necessary to take into account the contaminants associated with the solvents and inert substances (excipients) utilized in the synthesis process. Several stages in the formulation of a medicinal product can result in the production of impurities. The finished pharmaceutical product may contain these contaminants. It is also necessary to assess potential reaction products associated with these contaminants. [24,25]

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Raw Materials: During the synthesis process, contaminants from the initial materials, including chemicals or reagents, may be transferred.
Manufacturing Process: Impurities may be introduced into the finished product due to inadequate purification, incomplete reactions, or inadequate storage conditions.
Packaging and Storage: When items are exposed to light, moisture, or oxygen during packaging or storage, degradation products may develop or contaminants may adsorb.

3. Impurity Profiling

- **Identification and Quantification:** To identify and measure contaminants in the API, a variety of analytical methods are employed, including mass spectrometry, spectroscopy (NMR, MS), and chromatography (HPLC, GC).
- **Threshold Levels:** Depending on the toxicity of the impurities and the intended therapeutic application, regulatory bodies such as the FDA and EMA offer guidelines on allowable levels of impurities in APIs.
- **Stability Studies:** Depending on storage circumstances, stability testing is done to determine how contaminants may build up over time. [26,27,28]

4. Regulatory Guidelines

- **ICH Q3A recommendations:** These recommendations, which specify the permissible limits and testing procedures for contaminants in APIs, were released by the International Council for Harmonization (ICH).
- **Regulations of the FDA and EMA:** The FDA and EMA have particular rules pertaining to the documentation and management of impurities in the production of APIs.
- **Impurity Control:** Guidelines offer comprehensive guidance on permissible limits for various impurity types and strategies for controlling them, such as employing verified analytical procedures.[29,30]

5. Safety Concerns

At low amounts, certain pollutants can be hazardous, causing negative effects in patients. Their levels are therefore strictly controlled, and risk analyses are carried out to guarantee patient safety.
Carcinogenicity and Mutagenicity: Impurities that have the potential to cause cancer or mutagenesis are very dangerous and need to be closely watched and managed.[31]
Immunogenic impurities: Some impurities, especially those found in biologics or peptide APIs, might cause an immunological reaction and have negative effects.

6. Techniques for Impurity Control and Removal

6.1 Purification Methods: Techniques like recrystallization, chromatography, and filtration are used to purify APIs and reduce the level of impurities.

6.1.1 Extraction:

Liquid-solid extraction: A solvent is chosen that will dissolve the target impurity. When a compound comprises more than one kind of impurity, an organic solvent blend is utilized for extraction. At low temperatures, these solvents have a tendency to volatilize, which makes impurity concentration easier. Common solvents used in liquid-solid extraction include cyclohexane, water, methanol, and toluene, among others.
Soxhlet extraction: This method uses a little amount of solvent that is repeatedly syphoned through a product to create a concentrated extract. It is used to extract compounds of interest from crude medicinal formulations, etc. This technique is used to separate natural chemicals, such as curcumin from turmeric rhizomes. Soxhlet extraction is used in impurity profiling when the impurity is insoluble in a solvent and the target chemical has limited solubility in that solvent. Simple filtering can be used to separate the desired component from the insoluble substance if it is highly soluble in a solvent. This system's benefit is that, rather than passing numerous portions of warm solvent through the sample, a single batch of solvent is recycled.
Liquid-liquid extraction: It entails the extraction of two liquids, one of which is aqueous and the other organic, both of which are mutually incompatible. [32,33]

6.1.2 Gas chromatography:

It is helpful for separating and characterizing volatile contaminants or substances that derivatization can volatilize. For example, gas chromatography identified ethanol and acetone as contaminants during the manufacturing of doxorubicin hydrochloride.

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6.2 Separation method:

Following isolation, contaminants from a mixture of chemicals are separated into their constituent parts using a variety of methods.

Thin layer chromatography: It operates on the adsorption principle and is a useful method for chemical separation. In general, silica gel plates are recommended for doing separation. UV is typically used for detection. The adsorbent from plates is scraped off and then extracted using the appropriate solvents to elute the desired substance.

Column chromatography: Impurities ranging in size from milligrams to kilograms can be quantitatively separated using this method. By periodically observing the fractions that are taken from a particular sample, UV spectrophotometry is used to detect the eluent. For instance, the column approach can be used to separate the mirabegron impurity, which is linked to many impurities. [34,35]

6.3 Advanced Analytical Technologies:

Low-level impurity identification and quantification are improved by newer technologies like LC-MS/MS and high-resolution mass spectrometry (HRMS).

The following techniques can be used to find contaminants in active pharmaceutical ingredients (APIs):

Reversed phase high performance liquid chromatography (RP-HPLC) with UV detection: The most used technique for monitoring impurity profiles is this one. It entails adjusting the mobile phase's pH, screening various stationary phases, and experimenting with different organic modifiers.

NMR: It can offer details on the compound's stereochemistry and molecular structure. Analysing multicomponent mixtures is simple. For instance, NMR is used to analyse contaminantsin dehydro-apixaban, mirabegronarecan,and benzoyl(4-morpholinophenyl) carbamate.

MS: It is the most precise method for figuring out the target compound's molecular mass and elemental makeup. Additionally, drug-related compounds in API are monitored, characterized, and quantified using it. Rich information can be obtained by pairing this technique with GC, HPLC, and LC if a single method is unable to give the required selectivity. For instance, MS has detected and measured the des-fluoro impurities of linezolid and sertraline.

GC-MS:GC and MS can be used together to identify several chemicals in a test sample, giving reliable information that is challenging to answer with just one technique. In this combination, MS offers comprehensive structural information while GC separates volatile and semi-volatile components. GC analyses a variety of residual solvents, including carbon tetrachloride, ethanol, hexane, and benzene.[36-40]

7. Impact of Impurities on Drug Development and Manufacturing

- **Formulation Issues:** Impurities may impact the final drug product's performance and physical characteristics (such as stability and solubility), necessitating formulation modifications.
- **Cost Implications:** Finding and managing impurities can raise the price of developing new drugs, particularly if more complex purification procedures or analytical methods are required.

8. Emerging Trends

- **Quality by Design (QbD)**: The QbD approach emphasizes the identification of potential impurities during the early stages of drug development and designing processes to minimize their presence. This concept should be present through the whole pharmaceutical product lifecycle to ensure product quality and GMP compliance. This includes the management of (among others) environment, equipment, procedures and staff, as well as all kinds of materials/reagents/references or data and deliverables. [41-43]

The QbD concept, initially introduced for manufacturing processes, can be described in four steps:

1. Determination of patient requirements, namely the Quality Target Product Profile (QTPP)
2. Design and development of manufacturing process
3. Risk assessment and definition of the manufacturing Design space (DS)

- Implementation of a control strategy
- **Green Chemistry**: As part of environmental sustainability, green chemistry approaches focus on minimizing the environmental impact of pharmaceutical manufacturing, including the reduction of impurity formation.
- **Biopharmaceuticals**: Impurity control in biopharmaceuticals (e.g., monoclonal antibodies) requires specific attention to host-

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cell proteins, endotoxins, and other biological impurities.[44,45]

Importance of impurity profiling:

Impurity profiling plays a crucial role in drug development, as the formation of a drug is incomplete without identifying and managing impurities. For a drug to gain market approval, it is essential to identify, quantify, and control its impurities. Quantifying impurities is vital for validating the drug's quality and safety. By elucidating the structure of impurities, these can be synthesized and used as impurity standards, which are valuable for developing selective analytical methods for accurate impurity quantification. Regulatory authorities require the submission of impurity data, which they use as standards for official drug analysis. Impurity profiling is also important in understanding the degradation pathways of various substances, including amines, alkaloids, analgesics, steroids, anticancer drugs, and tranquilizers. A robust control system for impurities is necessary to ensure they do not interfere with the final desired compound, and impurities must be managed effectively to secure market approval.[46]

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