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# PHARMACEUTICAL IMPURITIES: A MULTIFACETED REVIEW OF ORIGINS, CLASSIFICATION, ANALYSIS AND CONTROL

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## ABSTRACT

Pharmaceutical impurities pose significant challenges to drug safety, efficacy, and quality. This comprehensive review provides an in-depth examination of the origin, classification, analysis, and control of pharmaceutical impurities. We discuss the sources of impurities, including synthetic pathways, degradation products, and contaminants, and classify them based on their chemical nature. Various analytical techniques for detecting and quantifying impurities are reviewed, including chromatography, spectroscopy, and mass spectrometry. Additionally, we explore regulatory guidelines and strategies for controlling impurities in pharmaceutical products. This review aims to provide a thorough understanding of pharmaceutical impurities, enabling researchers and industry professionals to develop effective methods for minimizing their impact on drug development and ensuring the safety of pharmaceutical products.

**KEYWORDS:** Impurity, Pharmaceuticals, sources, detection, chromatography, spectroscopy, regulatory guidelines, control.

## INTRODUCTION

Pharmaceutical impurities refer to unwanted chemical substances that are present alongside active pharmaceutical ingredients (APIs), either as residual compounds from the manufacturing process, or as a result of degradation during formulation, storage, or aging of both APIs and finished pharmaceutical products. Even trace amounts of these impurities can potentially impact the effectiveness and safety of the medication, making their detection and control crucial in pharmaceutical development and quality assurance.[1]

Impurities are defined as any unwanted chemical substances that can compromise with the safety and efficacy of pharmaceutical products.[2]

Food and drug administration (FDA) describe an impurity as, "Any component present in the drug substance or drug product that is not the desired product, a product-related substance, or an excipient including buffer component. It may be either process-or-product related".

International conference on Harmonization (ICH) has defined impurity is "Any compound of the medicinal product which is not the chemical entity defined as the active substance or as an excipient in the product".[3] According to ICH guidelines, impurities below 0.1% do not require identification unless their potency and genotoxicity must be evaluated. If relevant data is unavailable, further studies are needed to qualify the specified impurity level. According to it, the qualification threshold for maximum daily dose is set at ≤2g/day for impurities at 0.1% or 1mg/day intake, and ≥2g/day for impurities at 0.05%.[4]

Impurities can impact efficacy, bioavailability, or adverse consequences through detrimental pharmacological or toxicological effects that may outweigh the advantages of the parent drug or formulation. Chiral impurities are especially dangerous since one isomer may have the intended therapeutic effect while the other is inert or even dangerous. One well-known instance is the racemic medication Thalidomide, which was sold as a sedative. While the R- (+) - enantiomer of the medicine had therapeutic effects, the S- (+) - enantiomer was later found to be teratogenic, resulting in hundreds of birth deformities.[5]

## SOURCES OF IMPURITIES

Impurities in drug substances can arise from diverse sources and stages of the synthesis process, including intermediates and by-products that may be carried over into the final product.[3] Additionally, impurities can form during aging or storage[4] and those present in starting

materials can also be transferred to the drug substance. They are as follows,

- Starting materials and intermediates
- Impurities in the starting material
- Reagents, ligands and catalysts
- By-products of the synthesis
- Products over reaction
- Products of side reactions
- Impurities originating from degradation of the drug substances.[3]

**TYPES OF IMPURITIES**

According to ICH guidelines, impurities in drug substances produced through chemical synthesis can be broadly categorized into the following three groups.

- Organic impurities
- Inorganic impurities
- Residual solvents[6]

**1. ORGANIC IMPURITIES**

The impurities occurs during the manufacturing process or during the storage of the drug substances or chemicals are known as organic impurities.

- Starting Materials or Intermediate Impurities

APIs are often contaminated with residual solvents and other impurities, unless manufacturers implement rigorous quality control measures at every step of the synthesis process to prevent their introduction.

- By-products

In synthetic organic chemistry achieving a single product with 100% yield is highly unlike as a formation of by-products along the desire product is a common occurrence.[7]

- Degradation Products

Product degradation happens during the synthetic process, storage, formulation of dosage form and aging.[8]

**Other Types of Organic Impurities**

- Synthesis Related Impurities

The formation of new chemical entities during synthesis can be compromised by impurities present in raw materials, solvents, intermediates, or by-products, underscoring the need for meticulous attention to detail and rigorous quality control to minimize impurity levels and ensure a high-quality final product.

- Formulation Related Impurities

The formulation of drugs in solutions or suspensions can lead to instability due to hydrolysis, introducing impurities and creating conditions that promote catalytic reactions, ultimately affecting the drug's quality and efficacy. The formulation of drugs in solutions or suspensions can lead to instability due to hydrolysis, introducing impurities and creating conditions that promote catalytic reactions, ultimately affecting the drug's quality and efficacy.

Factor affecting Organic impurities

- Functional Group Related Impurities
- Ester hydrolysis
- Hydrolysis
- Photolytic cleavage
- Decarboxylation[7]

**2. INORGANIC IMPURITIES[9]**

Inorganic impurities can originate from the manufacturing processes employed in bulk drug production. Although typically identifiable, these impurities can pose challenges if not properly managed.

- Reagents, ligands, and catalysts

The production of bulk can involve the introduction of inorganic impurities through manufacturing process which are normally identified and include the following examples.

- Heavy metals

Heavy metal impurities mainly originate from process water and stainless steel reactors, especially during acidification or acid hydrolysis, however, switching to demineralized water and glass-lined reactors can prevent these impurities.

- Other materials (e.g, filter aids, charcoal)

The filters such as centrifuge bags are frequently used in the pharmaceutical industries and in many cases activated carbon is also preferred. The regular monitoring of such fibers and black particles in the pharmaceuticals or bulk drugs prepared is essential to avoid contaminations.

**3. RESIDUAL SOLVENT**

Solvents, which are organic and volatile in nature, are utilized in various manufacturing processes or generated during production. Although complete removal of solvents through work-up processes is difficult, it's essential to reduce their presence as much as possible, adhering to safety data guidelines. The use of toxic solvents should be avoided, particularly those that pose significant risks to human health. Solvents are classified into three categories based on their potential health impacts.

**Class I solvents** - The use of these solvents is either prohibited or tightly controlled in the production of active pharmaceutical ingredients (APIs) and drug substances, given their potentially harmful and unpredictable toxic effects, as well as their classification as carcinogens.

| Residual solvent | Concentration limit (ppm) |
|---|---|
| Benzene | 2(carcinogenic) |
| Carbon tetrachloride | 4(toxic) |
| 1,1 Dichloro ethane | 8(toxic) |
| 1,2 Dichloro ethene | 5(toxic) |
| 1,1,1 trichloro ethane | 1500(environmental hazard) |

**Class II solvents** - Due to their inherent toxicity and potential as carcinogens and neurotoxicants, the use of Class II solvents in pharmaceutical manufacturing should be carefully controlled and limited to minimize exposure risks.[10]
E.g. Acetonitrile(410ppm), N, N-Dimethyl formamide (880ppm).[6]

**Class III Solvents** - Class III solvents are considered to be of lower toxicity and pose a reduced risk to human health compared to Class I or Class II solvents. Based on available data, they are not associated with significant health hazards, and long-term exposure is generally not a concern. Therefore, residual solvent levels of 50 mg or less are typically considered acceptable. E.g. Acetic acid, Acetone, Anisole, 1-Butanol.[10]

## DETECTION AND QUANTIFICATION OF PHARMACEUTICAL IMPURITIES

"For accurate estimation, sample validation is vital. The FDA mandates reporting of impurities exceeding 0.1%. In the preliminary stages of contaminant characterization, identifying and quantifying these impurities is essential to meet regulatory standards."[11]

## ANALYTICAL TECHNIQUES

- **Spectroscopic techniques**: "A range of spectroscopic measurement techniques have been employed to characterize impurities, with many serving as effective detectors for chromatographic methods, including.

1. Ultraviolet (UV).
2. Infrared (IR).
3. Raman spectroscopy.
4. Mass spectrometry (MS).
5. Nuclear magnetic resonance (NMR).[12]

- **Chromatographic / Separation methods:** Various methods are available for separating impurities and degradation products, including

1. Capillary electrophoresis (CE).
2. Chiral separations.
3. Gas chromatography (GC).
4. High-pressure liquid chromatography (HPLC).
5. Supercritical fluid chromatography (SFC).
6. High performance thin-layer chromatography (HPTLC).[4]

**UV-Spectroscopy:** UV spectroscopy, a technique within the realm of optical spectroscopy, leverages light across the visible, UV, and near-infrared ranges. The Beer-Lambert law dictates that absorbance is directly proportional to the concentration of the absorbing species and the path length. With a fixed path length, UV/VISIBLE spectroscopy can quantify the concentration of an absorber in a solution, given that the absorbance-concentration relationship is well understood.[13]

**IR-Spectroscopy:** IR spectrophotometry provides distinctive information on specific functional groups, allowing for quantification and selectivity. However, the detection of low-level concentrations can be a significant obstacle, requiring more advanced and complex approaches to improve sensitivity and overcome limitations.[14]

**NMR:** NMR or nuclear magnetic resonance spectroscopy is a versatile and informative analytical tool for elucidating the structural details of pharmacologically important compounds, including their precise stereochemistry and bonding arrangements. Research has validated the use of NMR-based diffusion coefficient determination to differentiate between monomeric and dimeric compounds. Nevertheless, NMR's relatively lower sensitivity compared to other techniques, such as MS, which can analyse samples smaller than 1 mg, whereas NMR typically requires around 10 mg, can be a limitation.[11]

**MS:** Mass Spectrometry (MS) has had a profound impact on pharmaceutical advancements over the decades. Improvements in interface design and efficiency have enhanced the ability of MS to monitor, characterize, optimize, and quantify active pharmaceutical ingredients (APIs) in various formulations. When a single method fails to provide adequate selectivity, orthogonal coupling of chromatographic techniques like HPLC, TLC, HPLC, and HPLC-CE provides comprehensive spectroscopic analysis. Techniques like HPLC-NMR and HPLC-MS offer rich information for authenticating the quality of finished products, making them indispensable tools in pharmaceutical development.[6]

**Gas Chromatography:** Gas Chromatography (GC) is a powerful analytical technique for identifying and separating volatile compounds, as well as non-volatile components that can be converted into volatile derivatives. To preserve the integrity of the samples, a non-destructive detector is essential. Today, GC is often paired with Mass Spectrometry (MS) to form a robust GC/MS system, enabling the sensitive detection and characterization of impurities with unparalleled accuracy.[15]

**TLC & HPTLC:** "Thin Layer Chromatography (TLC) is a versatile technique for identifying components at trace levels, widely used for developing stability-indicating analytical methods. While TLC offers ease, simplicity, and simultaneous determination of multiple components, its limitations include variability and non-quantitative results. However, when combined with densitometric detection, TLC evolves into High-Performance Thin Layer Chromatography (HPTLC), enabling quantitative analysis of challenging compounds lacking chromophores.[10] High-Performance Liquid Chromatography (HPLC) stands at the forefront of separation science, offering an unbeatable combination of speed, sensitivity, and specificity. Its exceptional

capabilities make it an indispensable tool for pharmaceutical analysis, allowing for the swift identification and purification of compounds with unprecedented precision.[13]

HPTLC surpasses conventional TLC in several aspects.

- ❖ Requires minimal sample amounts
- ❖ Allows simultaneous quantification of over ten spots
- ❖ Easily couples with various detectors
- ❖ Provides 3D imaging for enhanced quantitative estimation
- ❖ Reduces separation time

HPTLC's advantages have led to the publication of numerous stability-indicating methods for drugs like Telmisartan, Ramipril, Prasugrel, Drotaverine, and Acelofenac in tablet form. This technique plays a crucial role in initial degradation and stress studies, facilitating the analysis of degradation products.[10]

## SIGNIFICANCE OF IMPURITY DETECTION[13]

- ➢ **Optimizing Storage and Shelf Life:** Impurities can compromise the stability and shelf life of pharmaceutical products. By understanding the types and levels of impurities, manufacturers can design optimal storage conditions and accurately determine product expiration dates, ensuring the longevity and effectiveness of their medications.
- ➢ **Advancing Analytical Capabilities:** The detection of impurities pushes the boundaries of analytical techniques and methods. Developing cutting-edge analytical methods for impurity analysis is crucial for achieving precise and reliable results, driving innovation in pharmaceutical quality control.
- ➢ **Streamlining Production and Reducing Impurities:** Identifying impurities offers valuable insights into the manufacturing process, enabling pharmaceutical companies to refine production methods, minimize impurity levels, and boost overall efficiency, ultimately leading to higher-quality products.
- ➢ **Informing Early-Stage Drug Development:** Characterizing impurities during the initial stages of drug development provides critical information for refining formulations and production processes. This insight is instrumental in shaping the eventual success of pharmaceuticals, ensuring they meet the highest standards of quality and efficacy.
- ➢ **Ensuring Therapeutic Integrity:** Impurities can compromise the safety and efficacy of pharmaceuticals, underscoring the need for rigorous identification and analysis to guarantee high-quality final products that meet stringent regulatory requirements.
- ➢ **Navigating Regulatory Landscapes:** Pharmaceutical manufacturers must adhere to exacting regulatory standards, as mandated by authorities like the FDA, to ensure the approval and commercialization of their products, necessitating comprehensive impurity analysis.
- ➢ **Protecting Patient Well-being:** Impurities pose a significant threat to patient safety, making it imperative for manufacturers to detect and characterize these substances, thereby mitigating potential health risks associated with impure or contaminated drugs.

**Maintaining Product Consistency**: Continuous impurity monitoring and control are vital components of quality control, enabling pharmaceutical companies to produce dependable and effective medications that meet the highest standards of excellence.

## REGULATORY GUIDELINES

The United States Food and Drug Administration (FDA) has adopted the International Conference on Harmonization (ICH) guidelines to ensure the safety and efficacy of pharmaceuticals.[8] These guidelines provide a framework for managing impurities in drug substances and products.

The key regulatory guidelines for impurities are.

1. ICH Q1A: "Stability Testing of New Drug Substances and Products"
2. ICH Q3A: "Impurities in New Drug Substances"
3. ICH Q3B: "Impurities in New Drug Products"
4. ICH Q3C: "Impurities: Guidelines for Residual Solvents" [4,8]
5. US-FDA Guidance for New Drug Applications (NDAs): Impurities in New Drug Substances.
6. US-FDA Guidance for Abbreviated New Drug Applications (ANDAs): Impurities in New Drug Substances
7. Therapeutic Goods Administration (TGA) Australia: Regulatory Guideline for Prescription Medicines.[10]

Additionally, the ICH Q6A guideline outlines specifications, test procedures, and acceptance criteria for new drug substances and products, focusing on chemical substances.[4]

The USFDA has adopted the groundbreaking guidance developed by the International Conference on Harmonisation (ICH)for a significant move towards regulatory alignment, a pioneering collaboration between regulatory authorities and industry experts from the European Union, Japan, and the United States. This landmark ICH guideline on impurities has achieved a major milestone in global regulatory harmonization, ensuring that pharmaceutical companies submit consistent, high-quality data to regulatory agencies worldwide, thereby streamlining the approval process and facilitating the safe delivery of medicines to patients globally.[6]

### ICH Harmonized Guidelines on Impurities

**Q3A (R2): Comprehensive Framework for Drug Substance Impurities**

This guideline establishes a robust framework for managing impurities in drug substances, encompassing specification listing, reporting thresholds, identification,

and qualification, to ensure the safety and quality of pharmaceuticals.

**Q3B (R2): Focused Approach to Impurities in New Drug Products**

This guideline targets specific impurities in new drug products, namely degradation products and reaction products with excipients or container closure systems, providing clarity on their evaluation and control.

**Q3C (R6): Mitigating Risks from Residual Solvents**

This guideline advocates for the use of safer solvents in drug manufacturing and sets stringent pharmaceutical limits for residual solvents in drug products, safeguarding patient health and ensuring environmental sustainability.[16]

## CONTROL AND MINIMIZATION OF IMPURITIES

Impurities can significantly reduced by applying good manufacturing procedures in pharmaceutical industries and pharmacies during their production and handling.

According to the WHO, GMP "is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization".[17]

GMP is a vital component of Quality Assurance that guarantees the consistent production and control of medicinal products, aligning with their intended use, marketing authorization, and product specifications. By integrating production and quality control, GMP minimizes inherent risks in pharmaceutical manufacturing, ensuring.

- Consistent product quality
- Adherence to regulatory requirements
- Patient safety and trust

GMP's primary objective is to mitigate risks and ensure the reliability of pharmaceutical products, fostering a culture of quality and excellence in the industry.[18]

Regular GMP audits are essential to minimizing the risk of adulteration and misbranding, ensuring the integrity of pharmaceutical products. These audits comprehensively evaluate various systems, including.

- Infrastructure and facilities
- Materials management and procurement
- Quality control and assurance processes
- Manufacturing and production operations
- Pack aging, labeling, and identification procedures
- Quality management systems and governance
- Personnel training and GMP compliance
- Purchasing and supplier management
- Customer service and support
- Sanitation, hygiene, and environmental control[19]

## CONTROLING METHODS OR REMEDIES TO AVOID IMPURITIES

- Rigorous monitoring and management of critical factors that can impact product quality.[19]
- To ensure the quality and safety of drug products, pharmacopoeias should establish and enforce stringent limits on impurities in raw materials used for production.
- The selection of an appropriate production method should be guided by comprehensive stability studies, which inform the development of optimal manufacturing processes that minimize impurities and ensure the consistency and efficacy of the final product.[4]
- Pharmaceutical products sensitive to light require specialized packaging to protect their integrity. A study on ergometrine ampoules, wrapped in either black carbon paper or aluminum foil, demonstrated remarkable resistance to degradation when exposed to direct sunlight during accelerated stability testing. This suggests that effective light-protective packaging can significantly minimize degradation and ensure the stability of light-sensitive pharmaceuticals.[1]
- Conducting stress studies to identify potential degradation pathways and mitigate transportation-related issues.
- Methodically analysing degradation products to understand their impact on drug safety and efficacy.
- Meticulously determining the shelf life of drug substances and products based on robust stability data.[20]
- Precise attention to operational details while handling equipment, machinery, reactors, and tools to prevent contamination and introduction of impurities
- Implementation of robust protocols to minimize the risk of operational errors and ensure the consistency of the final product.[10]

The pharmaceutical industry has a sacred responsibility to ensure the safety and quality of its products. To achieve this, manufacturers must implement and adhere to robust measures that prevent impurities and contamination in their products. Regulatory authorities must also conduct rigorous evaluations to guarantee compliance. By working together, the industry can uphold its commitment to and ensure provide public health and safety.[20]

## CASE STUDIES

**"Uncovering the Instability of Linagliptin: A Study on Degradation Products"[11]**

Ensuring the purity of Active Pharmaceutical Ingredients (APIs) is most important unit in pharmaceutical development, as it directly impacts the final product's quality, safety, and efficacy. Various factors, including environmental elements like heat, light, or moisture, can introduce impurities during the manufacturing process. These contaminants can compromise the medication's

therapeutic benefits, trigger unwanted side effects, or even jeopardize patient safety.

This study investigates the degradation landscape of linagliptin, intentionally inducing degradation to identify and characterize its breakdown products. Leveraging advanced mass spectrometry techniques - liquid chromatography coupled with high-resolution mass spectrometry and UPLC paired with a single quadrupole detector mass spectrometer researchers uncovered the drug's vulnerability to acidic and oxidative environments, while revealing remarkable stability in alkaline, thermolytic, and photolytic conditions.

**"The Hidden Danger: Azido Impurities in Pharmaceutical Production"**

Azido impurities can contaminate pharmaceuticals through various routes, including production processes, intentional addition, degradation, or cross-contamination. The manufacture of drug substances involves multiple components, increasing the risk of azido impurities. These impurities can be harmful, as they are metabolized into highly reactive intermediates that can damage DNA, leading to mutations and cancer. The International Agency for Research on Cancer classifies aziridine, a compound formed from azido impurities, as a known human carcinogen. Azide compounds can also disrupt DNA repair mechanisms and increase the frequency of mutations, further elevating cancer risk. Therefore, it's crucial to identify and mitigate sources of azido im8purities in pharmaceutical production to ensure drug safety.[21]

## CONCLUSION

In conclusion, the intricate landscape of pharmaceutical impurities necessitates a multifaceted approach to ensure the safety, efficacy, and quality of drug products. This review has elucidated the origins, classification, analytical techniques, and control strategies for impurities, highlighting the interplay between regulatory guidelines, industry practices, and technological advancements. By harnessing this knowledge, researchers and manufacturers can develop innovative solutions to mitigate impurity risks, optimize drug development, and enhance patient outcomes. Ongoing research should focus on refining analytical methodologies, exploring novel purification techniques, and fostering collaboration between industry, regulatory agencies, and academia to establish harmonized standards for impurity control. Ultimately, a proactive and comprehensive approach to managing pharmaceutical impurities is crucial for safeguarding public health and driving progress in pharmaceutical sciences.

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