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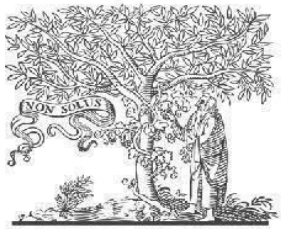

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REVIEW OF IMPURITY PROFILING IN PHARMACEUTICAL PRODUCTS

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Abstract:
The term "impurity" often raises concerns within the pharmaceutical industry due to its direct impact on product quality. This article explores the diverse types of impurities that may be found in Active Pharmaceutical Ingredients (API's) formulations. Comprehensive guidelines from regulatory bodies such as ICH, WHO, and pharmacopoeias play a crucial role in continuously monitoring and regulating these impurities. Given that impurities can significantly influence the quality and efficacy of drugs, understanding their nature is essential. This paper outlines different terms, regulatory frameworks, and fundamental analytical techniques like HPLC, LC-MS, and TLC, which are pivotal for beginners to comprehend, identify, and quantitatively assess impurities, facilitating their profiling. The focus is primarily on the identification and control of organic, inorganic, and genotoxic impurities. Ultimately, the pursuit of quality remains paramount in pharmaceutical substances, underscoring the importance of managing impurities to ensure high-quality product outcomes.

Keywords: Impurity Profiling, Impurities, Organic Impurity, Inorganic Impurity, International Conference on Harmonization, Identification.

Introduction:

Medicine, as a field of science, encompasses the identification, treatment, and prevention of diseases, with a history dating back to ancient times when remedies were extracted from plants containing active compounds. Over the years, drug development has evolved to include compounds sourced from animals, microorganisms, and through chemical synthesis, thereby enhancing drug efficacy by refining active ingredients and removing unnecessary components. A typical drug comprises two main components: the active ingredient, a chemical compound that exerts therapeutic effects, and inactive ingredients like excipients, binders, colors, and flavors, added for specific purposes.

During drug manufacturing or storage, another element, known as an impurity, can inadvertently become part of the drug substance. Understanding the origin, control, and measurement of these impurities is crucial for ensuring the production of high-quality drug substances. Impurity profiling, therefore, involves the analytical processes of detection, identification, and quantitative determination of impurities present in drug substances.

Impurities, even in trace amounts, can significantly impact the safety and efficacy of drug products.

Analyzing impurities is a rigorous task involving method development, impurity synthesis, isolation, and various analytical techniques to precisely identify impurities of interest. There is a continuous need for developing new analytical methods to evaluate the quality of emerging drugs effectively. Impurity profiling demands high-resolution chromatography systems capable of reliably separating and detecting both known and unknown impurities associated with active compounds. Methods developed for impurity determination in raw materials, intermediates, and finished product samples must be stability-indicating and well-validated according to guidelines set forth by the International Council for Harmonisation (ICH) and Pharmacopoeias.

Impurities in Pharmaceuticals:

Definition of Impurities: Impurities in pharmaceuticals are defined by various authoritative bodies and guidelines:

- The United States Pharmacopeia (USP), in chapter <1086>, defines impurity as any component in a drug substance that is not the chemical entity defined as the drug substance. For drug products, it includes any component that is not a formulation ingredient.
- The European Pharmacopoeia (EP) chapter 5.10 defines impurity as any component in a substance for pharmaceutical use that is not the defined chemical entity.
- The International Council for Harmonisation (ICH) defines impurity as any component of the drug substance that is not the defined chemical entity.
- The Food and Drug Administration (FDA) describes impurity as any component in the drug substance or drug product that is not the desired product, a product-related substance, or an excipient, including buffer components. These impurities may be process or product related.
-

Classification of Impurities: Impurities in pharmaceuticals are classified into several categories:

- **Organic (process and drug related):** These impurities arise during the synthesis of active and inactive materials and may occur during manufacturing or storage. They include intermediates, by-products, reagents, ligands, and catalysts used in chemical synthesis.
- **Inorganic:** This category includes impurities such as filter aids, color-removing agents like charcoal, reaction rate modifiers (catalysts), ligands, and heavy metals. Inorganic impurities can have toxic effects and must be controlled to minimal levels.
- **Residual Solvents:** These impurities are solvents used in the manufacturing process that remain in the final drug product.
- **Polymorphic:** Impurities that arise due to different crystalline forms of the same substance.

Organic Impurities: Organic impurities are generated during the synthesis of active pharmaceutical ingredients (APIs) and can result from degradation reactions and ongoing

synthesis. They include intermediates, by-products, and contaminants such as herbicides and pesticides that may inadvertently be present in plant-derived drug substances.

Inorganic Impurities: Inorganic impurities encompass substances like catalysts used in synthetic processes, which can potentially leach into the final product from reaction vessels. Batch-to-batch variations in impurity levels underscore the importance of tightly controlled manufacturing processes to minimize impurity levels.

Understanding and managing impurities in pharmaceuticals are critical for ensuring the safety, efficacy, and quality of drug substances and products. Regulatory guidelines and advanced analytical techniques such as HPLC, LC-MS, and TLC play essential roles in identifying, quantifying, and controlling these impurities throughout the drug development and manufacturing process.

Residual Solvents:

Residual solvents in pharmaceuticals refer to volatile chemicals produced during side reactions in manufacturing APIs, excipients, or formulations [ICH Q-3C (R4) 2009]. While theoretically removable from the final product, practical constraints often prevent complete removal. Therefore, residual solvents represent a critical parameter in drug product manufacturing processes.

Polymorphic Forms:

Polymorphic forms denote solid materials existing in multiple crystalline structures. Organic and inorganic compounds can exhibit different polymorphs, each with distinct pharmacokinetic and material properties. Accurate identification and characterization of polymorphs are crucial, particularly for economic reasons. For instance, a new crystal form of maleic acid emerged from a solution of caffeine and maleic acid (2:1) in chloroform left to evaporate slowly in 2006 (Day et al. 2006).

ICH Guidelines for Impurity Profiling:

Regulatory authorities, notably the International Conference on Harmonization (ICH), emphasize impurities in drug substances and products, including residual solvents:

1. **Q1A - Stability Testing of New Drug Substances and Products**
2. **Q3A (R2) - Impurities in New Drug Substances**
3. **Q3B (R2) - Impurities in New Drug Products**
4. **Q3C (R5) - Impurities: Guidelines for Residual Solvents**

Regulatory Guidelines on Impurities:

The FDA, tasked with ensuring drug safety and efficacy, adheres to ICH guidelines and technical requirements for drug registration, including:

- **Stability Testing of New Drug Substances and Products (Q1A)**
- **Impurities in New Drug Substances (Q3A)**
- **Impurities in New Drug Products (Q3B)**
- **Impurities: Guidelines for Residual Solvents (Q3C)**

Sources of Impurities:

Impurities in pharmaceuticals stem from various sources throughout production and storage:

1. Raw materials used in formulation
2. Manufacturing processes of drug products

3. Product instability
4. Atmospheric contaminants
5. Starting materials and intermediates
6. Impurities within starting materials
7. Reagents, ligands, and catalysts
8. By-products and over-reactions during synthesis
9. Degradation products of drug substances

Understanding and controlling these sources are essential for maintaining high-quality pharmaceutical products, aligning with stringent regulatory standards and ensuring patient safety and efficacy.

Figure 1: Sources of impurities in drug substance and drug product

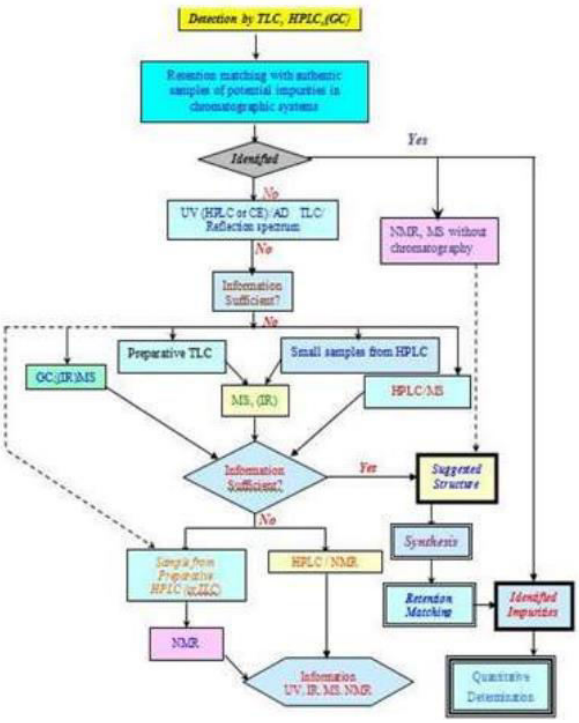

Figure 2: Schematic flowchart for detection, identification, structure elucidation

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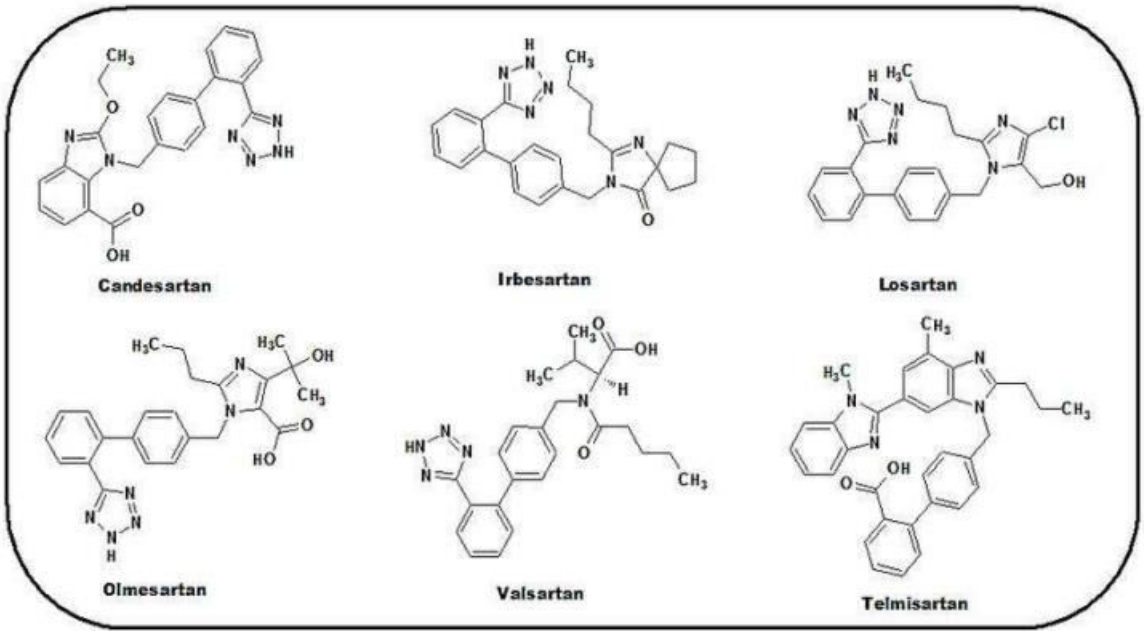

Figure 3: Structure of Sartans drug

Table 1: Limit for NDMA & NDEA in sartans drugs

Active substance (max daily dose)	NDMA		NDEA	
	AI ng/day	Limit (ppm)	AI ng/day	Limit (ppm)
Candesartan (32 mg)	96.0	3.000	26.5	0.820
Irbesartan (300 mg)		0.320		0.088
Losartan (150 mg)		0.640		0.177
Olmesartan (40 mg)		2.400		0.663
Valsartan (320 mg)		0.300		0.082

Conclusion:

Impurity profiling plays a critical role in the synthesis of drug substances and the manufacturing of dosage forms, providing essential data on toxicity, safety, detection limits, and quantification limits for various organic and inorganic impurities commonly found in bulk drugs and finished products. Method development and validation are crucial steps that facilitate accurate impurity profiling, thereby ensuring the integrity and compliance of pharmaceutical products.

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