Technical Paper
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Impurities in pharmaceutical ingredients: an overview

Abstract

The impurity content in active pharmaceutical ingredient (API) is of critical importance because a high level of impurities can be harmful to the patient, mainly due to their potential toxicity. The formation of these impurities is sometimes related to insufficient control of the reaction. Since there are several types of impurities, it is essential to understand their classification. The origin of these impurities involves different formation pathways, and by taking these pathways into account, it is possible to develop effective purification methods. Analytical methodologies are key tools for determining impurity structures and, consequently, for developing mitigation strategies. Impurities also have other uses, such as serving as standards in analytical methods and in establishing process limits. This article provides an overview of impurity management, including their origins within synthetic pathways, their classification, and potential purification approaches to ensure compliance with stringent quality standards for pharmaceutical substances and other uses of impurities.

Keywords: pharmaceutical ingredients, impurities, classification, purification

Volume 11 Issue 1 - 2026

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Received: March 14, 2026 | **Published:** March 27, 2026

Abbreviations: APIs, active pharmaceutical ingredients; ICHQ3A, international council for harmonization. impurities in new drug substances; ICHQ3B, international council for harmonization. impurities in pharmaceutical dosage forms; ICHQ3C, international council for harmonization. guideline for residual solvents; ICHQ3D, international council for harmonization. guideline for elemental impurities; ICHQ7, good manufacturing practice guide for active pharmaceutical ingredients; ICHM7, international council for harmonization. assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk M7(R2); NDMA, N-nitrosodimethylamine.

Introduction

Medicines are designed to treat illnesses across the entire population, and for this reason significant investment is dedicated to the development of new active pharmaceutical ingredients (APIs). However, an equally important aspect of manufacturing is the purification process, whose objective is to isolate the main compound with high purity, since impurities may pose safety risks to patients.

Before addressing purification in detail, it is useful to examine the structural complexity of the molecules involved. Many APIs require multi-step synthetic routes, where at each stage new impurities may be formed some easy to remove, others far more challenging. For illustration, Figure 1 shows the structure of Odevixibat, a pharmaceutical ingredient approved for the treatment of various cholestatic diseases.[1] The synthesis of this molecule involves 12 steps, reflecting its structural complexity.

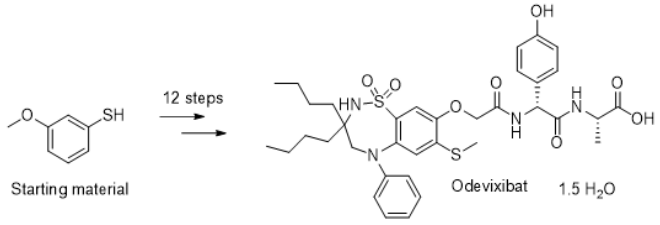

Figure 1 Example of complexity in the synthesis of a pharmaceutical ingredient.

The molecule contains two chiral centers, a deprotected phenol, a free carboxylic acid, and a sulfonamide moiety within a heterocyclic ring. During each of these steps, by-products are generated, and depending on their structural similarity to the desired intermediate or final product, purification can range from relatively straightforward to extremely difficult. This complexity underscores the importance of developing robust purification strategies throughout the entire synthetic sequence (Figure 1).

As previously mentioned, this molecule has a specific manufacturing procedure, and in every step of the synthesis, various byproducts are generated. What does this mean? Essentially, at each stage of the synthesis, it is necessary to develop purification methods to obtain the main compound with high purity. For example, imagine a one-step synthesis in which raw material 1 reacts with raw material 2; as a result, product 1 is generated (ideal generation). (Figure 2).

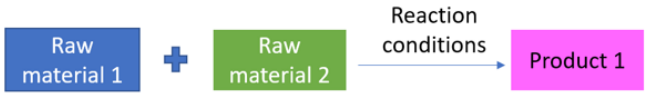

Figure 2 Ideal generation of a product in a chemical reaction

Now, imagine that the reaction is not stopped and continues progressing. In that case, the product may react with the raw materials in different ways. For example, raw material 1 could react with Product 1 (via B) or with raw material 2 (via C). Additionally, the product may react with another molecule of the same product, forming a dimer (via D). This dimer could continue reacting with raw materials, generating additional impurities (vias G and H). Furthermore, other impurities may arise as over-reaction products (vias E and F). All these potential impurity generation pathways are illustrated in Figure 3. And it is important to note that this scenario represents only *one* step of a synthesis yet many manufacturing processes may involve more than twenty steps (Figure 3).

Another type of impurity includes unreacted raw materials. If a starting material does not completely react, it will remain in the final product, thus becoming an impurity itself. Although this scheme may seem somewhat exaggerated, it accurately reflects what occurs in real chemical manufacturing. For this reason, it is essential to develop

robust control strategies, effective purification methods, and strict specifications to limit and ideally prevent the formation and carryover of impurities throughout the entire synthesis.

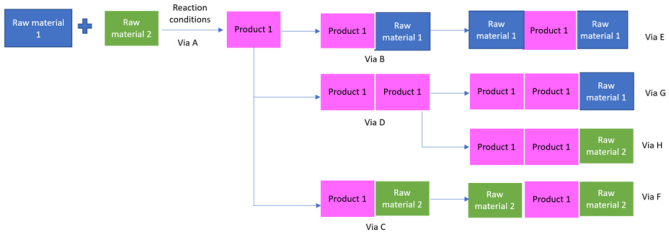

Figure 3 Possible generation of by products in a chemical reaction (non-exhaustive).

Importance of the impurities

The importance of controlling impurities in pharmaceutical ingredients is critical because they can directly impact patient safety. Several examples reported in the literature illustrate this point clearly. The first example involves valsartan (angiotensin receptor blocker), where some formulations were found to contain the genotoxic impurity N-nitrosodimethylamine (NDMA).

This compound is extremely toxic and classified as a probable human carcinogen. Due to its presence, numerous batches of valsartan were recalled, and the issue eventually extended to other pharmaceutical ingredients contaminated with nitrosamines, triggering worldwide regulatory actions.[2] The second case concerns ritonavir (antiviral), where dissolution testing revealed results that did not meet specifications during product launch. Investigation showed that the failure was caused by the appearance of a new polymorphic form of the active ingredient. This incident marked a turning point in the systematic study of polymorphism in pharmaceutical substances and demonstrated how solid-state forms can drastically affect product performance.[3]

The third case demonstrates even more profoundly the critical impact of impurities. In the 1970s, thalidomide was marketed as a racemic mixture to alleviate morning sickness in pregnant women. The therapeutic effect was attributed to the *R*-enantiomer, whereas the *S*-enantiomer exhibited severe teratogenic properties. Therefore, thousands of newborns developed phocomelia, a condition characterized by severely underdeveloped limbs. This tragedy underscored the necessity of controlling stereochemical purity in drug substances.[4] These examples collectively demonstrate the essential need to manufacture pharmaceutical ingredients with high purity, or stated differently, free from impurities that may compromise safety or efficacy. In the figure 4 the molecules of these historical cases associated to impurities in pharmaceutical ingredients are showed (Figure 4).

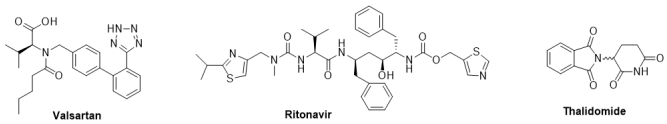

Figure 4 Examples of the importance of the impurities in pharmaceutical ingredients.

Classification

The presence of impurities in active pharmaceutical ingredients (APIs) is addressed through several regulatory guidelines, each focused on specific categories of impurities. First, the synthesis of APIs must comply with ICHQ7, the Good Manufacturing Practices (GMP) guideline for active pharmaceutical ingredients. This guideline establishes the minimum requirements for the safe and consistent production of APIs intended for human use.[5]

In addition, ICHQ3B regulates impurities in pharmaceutical dosage forms, covering impurities that may arise from both the API and the excipients involved in producing tablets, syrups, capsules, and other finished products.[6]

As mentioned previously, the synthesis of APIs can generate multiple organic and inorganic impurities. These are regulated by ICHQ3A, which focuses specifically on impurities in new drug substances. On the other hand, solvents used during manufacturing play an essential role in the synthetic process but must be removed because they provide no therapeutic benefit and may pose risks to patients. Their control is governed by ICHQ3C, which classifies solvents and sets permitted exposure limits.

Among all impurity types, some structural motifs are especially concerning because they may cause cellular or DNA damage. These mutagenic impurities are controlled by ICHM7, which provides classification, testing strategies, and limits to ensure patient safety. Furthermore, APIs are manufactured using equipment built from materials such as stainless steel, hastelloy, or glass-lined steel. These materials can introduce elemental impurities into the product. The limits for these metal contaminants are established in ICHQ3D, which defines permitted daily exposure levels and outlines risk assessment approaches. As shown, multiple impurity types must be controlled during the synthesis and manufacturing of pharmaceutical ingredients, each governed by a dedicated guideline. These guidelines will be discussed in more detail in subsequent sections and the interaction is showed in the next figure. The next figure illustrates the relationship among the different impurity-related guidelines (Figure 5).

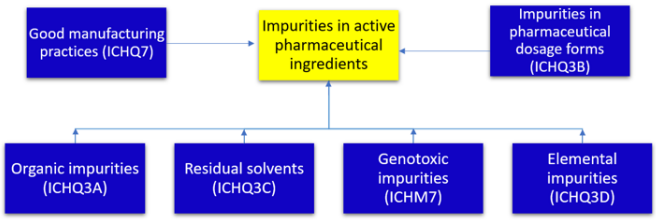

Figure 5 Guidelines associated to the control of impurities in pharmaceutical ingredients.

Impurity classification

ICHQ3A. Impurities in new drug substances: The ICHQ3A[7] guideline classifies impurities in new drug substances based on two key aspects: chemistry and safety. From the chemical perspective, impurities are divided into organic impurities, inorganic impurities, and residual solvents.

Organic impurities: Organic impurities receive an additional classification based on their origin or their role in the process. These include Starting materials, by-products, intermediates, degradation products, reagents, ligands, and catalysts. All these categories fall under the umbrella of organic impurities, regardless of whether they are intentionally used or unintentionally generated during synthesis.

Inorganic impurities: Inorganic impurities typically originate from the manufacturing process. They may include reagents, ligands, and catalysts, heavy metals, inorganic salts, processing aids, such as filter materials or activated charcoal.

Residual solvents: While solvents are considered impurities, their control is governed by a separate guideline, ICHQ3C, which provides detailed toxicological classification and permitted exposure limits.

Additional components of the ICHQ3A guideline: The guideline also includes rationale for impurity control, ICHQ3A describes the principles used to justify impurity limits based on chemistry, manufacturing process understanding, and safety considerations. Reporting thresholds for new drug applications. It establishes the impurity levels that must be reported, identified, and qualified, depending on the maximum daily dose of the drug substance. The guideline defines an impurity profile as the complete list of identified and unidentified impurities that may be present in the drug substance. This profile must reflect the consistency of the manufacturing process and is essential for regulatory submissions.

Qualification of impurities: Qualification refers to the biological studies demonstrating that a given impurity is safe at a specified concentration. If an impurity exceeds identification or qualification thresholds, appropriate toxicological assessments must be conducted. The classification of these impurities is illustrated in the next (Figure 6).

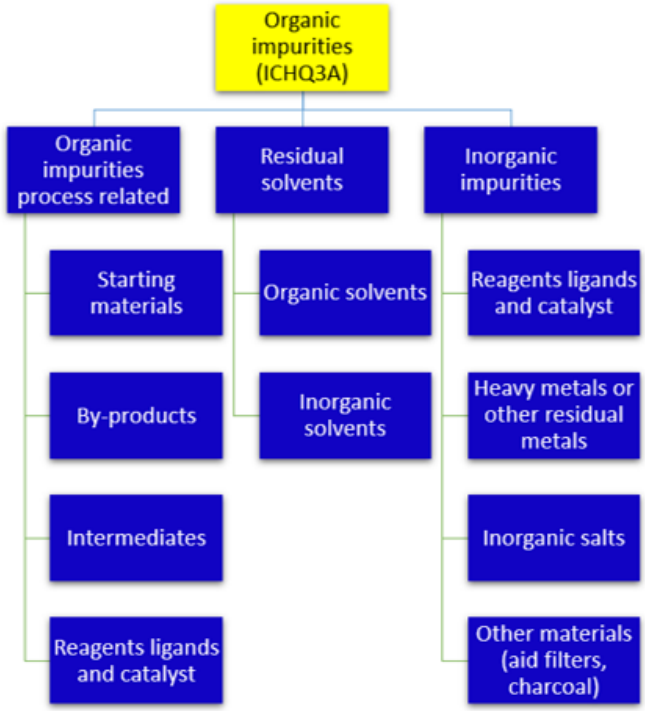

Figure 6 ICHQ3A Impurity classification.

ICHQ3C. Guidelines for residual solvents: The manufacture of pharmaceutical ingredients requires the use of appropriate solvents. Solvents are essential for achieving a suitable impurity profile during chemical reactions and, consequently, for maintaining good control of process-related impurities. However, once the product is formed and isolated, these solvents must be removed, since they do not provide any therapeutic benefit and may be harmful to patients. Solvents are typically used during reaction steps and then removed after the reaction, often through centrifugation. Following this operation, the level of residual solvent is reduced, but additional drying is required to eliminate the remaining traces. After drying, the residual solvent levels are quantified using analytical methods to ensure they fall within safe limits. Figure 5 illustrates the solvent elimination process (Figure 7).

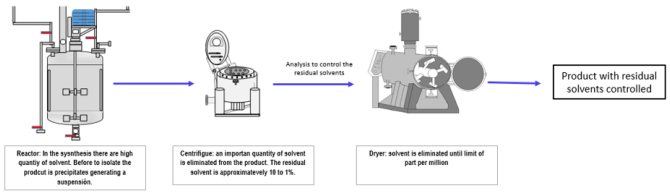

Figure 7 Elimination of residual solvents during the manufacturing process.

The **ICHQ3C**[8] guideline classifies solvents used in the synthesis of pharmaceutical ingredients into four groups:

Class 1. Solvents to be avoided: These solvents are highly toxic and known or suspected human carcinogens. Many also pose significant environmental hazards. Examples include benzene and carbon tetrachloride.

Class 2. Solvents to be limited: These solvents have lower toxicity compared to Class 1 but may cause neurotoxicity, teratogenicity, or other potentially reversible toxic effects. Examples include: acetonitrile, chlorobenzene, cumene.

Class 3. Solvents with low toxic potential: These solvents present minimal risk to human health, and for them, no health-based exposure limit is required. Examples include acetic acid, acetone, anisole, 1-butanol.

Solvents lacking adequate toxicological data: The guideline also identifies a group of solvents for which insufficient toxicological information is available. These solvents are typically used in the manufacture of excipients rather than active pharmaceutical ingredients. Examples include: 1,1-diethoxypropane, isooctane, isopropyl ether, trifluoroacetic acid.

ICHQ3D, elemental impurities: The synthesis of intermediates and active pharmaceutical ingredients is carried out using a variety of equipment, including reactors, centrifuges, dryers, mills, and other processing units. These pieces of equipment may be constructed from materials such as stainless steel, hastelloy, or glass-lined steel, among others. The construction materials themselves can become sources of contamination, introducing elemental impurities into intermediates or final products. In addition, the manufacture of active substances may involve metals as reagents or catalysts, which can contribute to residual elemental impurities. Other potential sources of contamination include raw materials, process catalysts, water used in manufacturing, utilities, and even storage containers. Given these possible contamination pathways, the **ICHQ3D**[9] guideline established a comprehensive classification system for elemental impurities. This classification provides a framework to evaluate risk, set appropriate control limits, and ensure patient safety through effective monitoring and mitigation strategies. The ICHQ3D guideline classifies elemental impurities into several groups based on toxicity and probability of occurrence. Each class includes recommended control approaches and analytical requirements.

Class 1: Elements in this class are highly toxic and should be strictly limited or avoided during the manufacture of active pharmaceutical ingredients. Their presence usually originates from excipients or environmental contamination. The Class 1 elements are: Arsenic (As), Cadmium (Cd), Mercury (Hg), Lead (Pb). Because of their high toxicity, these elements must be analyzed in the final product.

Class 2: This class includes route dependent human toxicants. It is divided into two subclasses depending on the likelihood that the impurity may be present.

Class 2A: These elements have a high probability of occurrence in pharmaceutical ingredients. A full risk assessment must be performed for all potential sources (raw materials, water, catalysts, equipment) and for all routes of administration. The elements in this group are Cobalt (Co), Nickel (Ni), Vanadium (V). These elements must also be tested in the product.

Class 2B: These elements have a lower probability of occurrence due to their low natural abundance and reduced likelihood of co-isolation during processing. The Class 2B elements are: Silver (Ag), Gold (Au), Iridium (Ir), Osmium (Os), Palladium (Pd), Platinum (Pt), Rhodium (Rh), Ruthenium (Ru), Selenium (Se), Thallium (Tl). Even though they are less likely to occur, these elements must be monitored when used as catalysts or when present in starting materials.

Class 3: These elements exhibit low toxicity by the oral route, although risk assessment is required for inhalation and parenteral routes for oral drug products, even if these elements are intentionally added, they do not need to be included in the risk assessment. Elements in this class include Barium (Ba), Chromium (Cr), Copper (Cu), Lithium (Li), Molybdenum (Mo), Strontium (Sr), Tin (Sn).

Other elements: An additional category includes elements with very low inherent toxicity, for which no PDE limits are established. These elements are Aluminum (Al), Boron (B), Calcium (Ca), Iron (Fe), Potassium (K), Magnesium (Mg), Sodium (Na), Tungsten (W), Zinc (Zn). The guideline also includes detailed risk assessment procedures, potential sources of elemental impurities, classification and permitted limits, control strategies, analytical considerations, and a glossary of relevant terms.

ICHM7: The ICHM7[10] guideline focuses on the control of mutagenic impurities, which are compounds demonstrated to cause DNA damage through appropriate mutagenicity testing. This guideline classifies mutagenic impurities into five categories. The classification was established based on extensive database and literature searches related to carcinogenicity and bacterial mutagenicity, and each class is associated with specific control limits.

Class 1. Known mutagenic carcinogens: These impurities are both mutagenic and carcinogenic. They must be controlled at or below a substance-specific acceptable limit.

Class 2. Known mutagens with unknown carcinogenic potential: These impurities are demonstrated mutagens, but their carcinogenicity is not established. They are controlled at or below the compound-specific acceptable limit.

Class 3. Alerting structures: These impurities contain structural alerts for mutagenicity. They must be controlled below the acceptable limits, or alternatively, a bacterial mutagenicity assay (e.g., Ames test) can be conducted to clarify their biological relevance.

Class 4. Alerting structures present in the drug substance or in related compounds: These alerts are shared with the active pharmaceutical ingredient or closely related structural analogues. They may be controlled using the same limits applied to non-mutagenic impurities, as supporting data mitigate the initial concern.

Class 5. No structural alerts or sufficient data to demonstrate lack of mutagenicity or carcinogenicity: These impurities are treated as non-mutagenic impurities and follow the standard impurity qualification thresholds.

In addition to classification, the guideline provides detailed recommendations on: acceptable control limits for mutagenic impurities, assessment and control strategies, considerations during clinical development, definitions and glossary of key terms, and practical decision-making scenarios for implementation. It is important to highlight the role of structural alerts mentioned in Classes 3 and 4, which serve as triggers for further evaluation or testing.

Some functional groups found in pharmaceutical ingredients can be harmful to humans, and these structural motifs may occasionally appear as impurities. In 2006, Müller et al. reported several "structural alerts," grouped into three categories of concern.[11]

Group 1: Includes aromatic structures such as: N-hydroxyaryls, N-acylated aminoaryls, Aza-aryl N-oxides, Alkylated aminoaryls.

Group 2: Includes highly reactive or electrophilic functional groups such as: aldehydes, epoxides, N-methylols, Aziridines, N-nitrosamines, other related electrophiles.

Group 3: Contains motifs capable of undergoing Michael addition or other undesired covalent reactions, such as: Michael acceptors, alkyl ester phosphonates and sulfonates, haloalkenes, halides. Among these groups, nitrosamines have become particularly relevant in recent years because they have been detected as impurities in several active pharmaceutical ingredients, creating significant regulatory and manufacturing challenges across the pharmaceutical industry (Figure 8).[12]

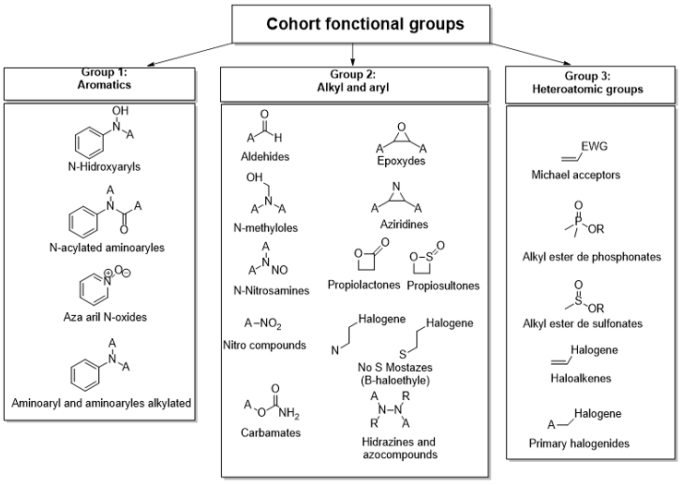

Figure 8 Alert groups in pharmaceutical ingredients.

Other classifications

One of the most common types of impurities is the dimeric impurities which are formed when the reagents concentration in the reaction is high, mainly because there are a lot of reagents and few groups to react, so the reaction is with same molecule is a possibility. A dimer formation was reported for the Elitriptan hydrobromide (antimigraine).[13] Other kind of impurities are tautomers, which are isomers that can interchange a hydrogen in the molecule, this migration includes some cycles and open chains. Some pharmaceutical ingredients that present this type of behavior are Cefotetan (antibiotic) and Lapatinib (anticancerogenic).[14]

Since the Thalidomide case the authorities are more cautious with the effect of the enantiomers in a drug. Some differences in activity, toxicity, metabolism, elimination, distribution can be observed. In general, one enantiomer has activity in the human body and the other is considered as an impurity. The chirality is associated to an atom that has attached different groups, more commonly a carbon, although other groups like nitrogen, sulfur of phosphor can have this property. The mirror image to this molecule is called enantiomer.

Some examples of active pharmaceutical ingredients which are enantiomeric pure are, Ibuprofen (anti-inflammatory), tramadol (analgesic), esomeprazole (proton pump inhibitor), levodopa (anti Parkinson disease), propranolol (treatment for hearts conditions), escitalopram (antidepressant).[15]

The impurity in pharmaceutical ingredients is an interesting topic for the Academy and the industry, in this context several authors have demonstrated their interest in this topic.[16–24] In this tessitura, Wadekar et al. reported additional classifications such as rearrangement impurities, which can be generated when reaction conditions are drastic (e.g., toluene at reflux). Sometimes, processes are designed to carry out several reactions in a single vessel; this process is called *telescoping*. The problem with this methodology is that multiple impurities can be formed in the same reactor. Consequently, the authors refer to these byproducts as in situ generated impurities.[25]

Transformation products is other category of byproducts; these can be theoretical or non-theoretical and are closely related to other byproducts. Interaction products are generated through the interaction of different chemical substances. The scope of these impurities is broader than that of conventional byproducts. Examples include interactions between the pharmaceutical ingredient itself, and in some cases, interactions between the pharmaceutical ingredient and the container.[26]

In the second part of these articles, interesting examples of impurities are discussed, including polymorphic impurities, which refer to the ability of a molecule to exist in several crystalline forms. A classic example is carbon, which can exist as graphite, diamond, fullerene, or nanotubes. In the third part, additional types of impurities are described, such as metabolic impurities, method-related impurities, and impurities resulting from interaction with the environment.[27] Ghosh et al. by his side reported a compilation of more than thirty impurities described in the literature. This wide range of examples provides an exceptional source of information on this topic.[28]

Finally, although this is not within the scope of this review, formulated impurities are also very important, because these types of by-products are generated through interactions with excipients and under specific storage conditions.[29] In the same context, an article presenting several cases of interactions between pharmaceutical ingredients and excipients can also be consulted.[30] Finally, in the Figure 9 all the potential impurities are compiled (Figure 9).

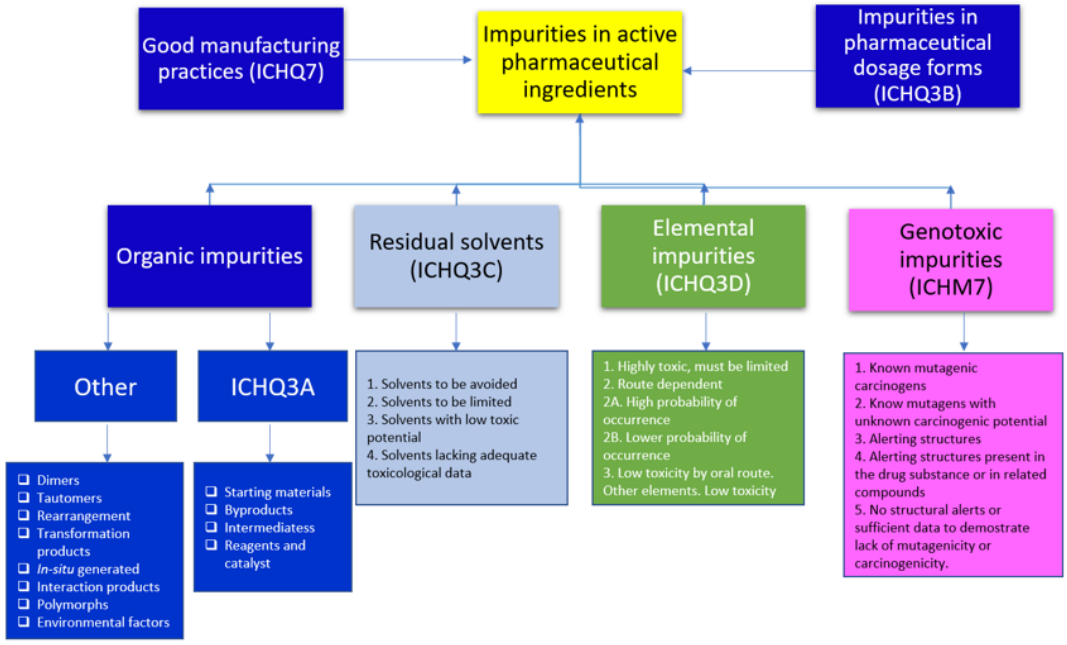

Figure 9 Compilation of potential impurities presented in active pharmaceutical ingredients.

Impact of environmental factors

It is important to note that environmental factors can also affect the stability of intermediates or pharmaceutical ingredients. For example, ambient moisture can degrade water-sensitive compounds. Visible light is another critical factor, as it can induce isomerization in certain molecules. Temperature plays a crucial role as well, since elevated heat may generate byproducts for instance, through dehydration reactions. Finally, oxygen is one of the most challenging factors to control because it can cause oxidation of labile compounds.

To illustrate these concepts, the literature describes montelukast sodium as being sensitive to all four factors: water, light, temperature, and oxygen. Regarding moisture, the compound absorbs water and undergoes degradation, resulting in a yellowish coloration (author's experience). Montelukast contains a double bond that can isomerize upon exposure to visible light; therefore, light filters must be used to avoid photodegradation. Oxygen exposure may lead to oxidative degradation; for example, the sulfoxide impurity can be further oxidized to sulfones.

To minimize this, a continuous nitrogen stream must be maintained throughout the manufacturing process. Temperature is another critical variable: excessive heat can lead to dehydration of the tertiary alcohol present in the molecule, so reaction conditions must be carefully controlled. Considering all these factors, controlling impurities in an active pharmaceutical ingredient becomes a highly specialized practice almost an art. The impurity generation pathways of montelukast are illustrated in the following (Figure 10).[31]

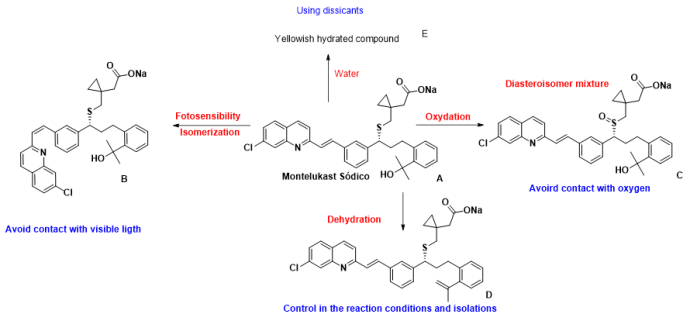

Figure 10 Example impact of environmental conditions in the impurity generation.

Degradation of functional groups

Pharmaceutical ingredients, like any organic molecules, contain several functional groups that can undergo transformations induced by their surrounding environment. Some of these degradation pathways can be predicted; for example, an ester will typically hydrolyze to yield an acid and an alcohol. In this context, Kumar et al. compiled the degradation mechanisms associated with the most common functional groups (Table 1).[32] For his part, Li has published a book on drug degradation that serves as an excellent source of information and a valuable tool for predicting or even determining the potential structure of impurities.[33] Taking in account this information it is possible predict some possible degradation and in consequence mitigates the potential source of degradation (Table 1).

Table 1 Degradation of most common functional groups in pharmaceutical ingredients

Functional group	Degradation reaction	Product	Example
Ester, Lactones	Acid hydrolysis	Alcohol + acid	Aspirine, Ciclandate
Amides, Lactames	Acid or basic hydrolysis	Acide + amine	Acetaminophen, Cloranphenicol
Carbamic ester	Acid hydrolysis + decarboxylation	Amine + CO2	Loratadine, Pipazetate
Imidas	Acid or basic hydrolysis	Amide + acid	Glutetimide
Cetones y Aldehydes	Acid or basic catalysis	Condensation products Gemdiol. Tautomerization	Haloperidol, Triamcinolone
Nitriles	Acid hydrolysis + decarboxylation	Base + CO2	Cimetidine, Diphenoxylate
Amines	Oxidation	N-oxide	Dibucaine, Dorzolamine
Imine	Basic hydrolysis	Amine + cetone	Diazepam
Hidrazine	Acid or basic hydrolysis	Base + hidrazone	Isoniacide
Nitro	Fotooxidation + oxidation	Aromatization	Nifedipine
Sulfonamides	Acid hydrolysis	Sulfonamide + hydrolysis product	Brinzolamide
Sulfonilureas	Acid hydrolysis	Sulfonamide + amine	Glibenclamide
Tiol, eter, tioeter	Oxidation or hydrolysis	Oxidation / Hydrolysis products	Cefamandol
Epoxides, Aziridines	Basic hydrolysis	Hydrolysis product	Mitomycine C
Alcohol	Dehydration	Alken, rearrangement	Butorfanol, Lovastatine
Phenols	Oxidation	Rearrangement	Epinefrine
Alkyl halides	Hydrolysis	Alcohol	Melfalan
Benzyl	Oxidation	Cetone	Cyclandelate
Olefines	Isomerization, oxidation	Geometric isomers, oxidation products	Tioxiphen, Montelukast

Purification methods

The previous arguments demonstrate that several impurities can originate from the synthetic process, environmental conditions and as well as from equipment and catalysts. This leads to the key question: how can we purify these intermediates and final products? Before addressing this, it is necessary to describe some basic concepts regarding solid forms in pharmaceutical ingredients.

A pharmaceutical ingredient can exist as different solid-state forms, each of which may exhibit distinct physicochemical properties relevant to purification, manufacturability, stability, and bioavailability:

1. **Polymorphs**: These are different crystalline arrangements that the same molecule can adopt at the microscopic level. Each polymorph has a unique crystal lattice and therefore different properties.
2. **Salts**: When the molecule contains ionizable functional groups, it can form pharmaceutical salts through acid–base reactions, generating an ionic structure that often improves solubility or stability.
3. **Cocrystals**: These are crystalline solids composed of the active pharmaceutical ingredient (API) and a neutral coformer, held together by non-covalent interactions—primarily hydrogen bonding and van der Waals forces.
4. **Amorphous forms**: In this state, the API lacks long-range molecular order. Amorphous solids often exhibit higher solubility but lower physical stability.
5. **Solvates** (and hydrates): These are crystalline forms in which solvent molecules are incorporated into the lattice of the API. When the included solvent is water, the form is known as a hydrate.
6. **Mixtures of solid forms**: In some cases, the material may consist of a combination of the above states (e.g., polymorphic mixtures, amorphous–crystalline blends, or partially solvated crystals).

These different solid-state alternatives are illustrated conceptually in (Figure 11).[34]

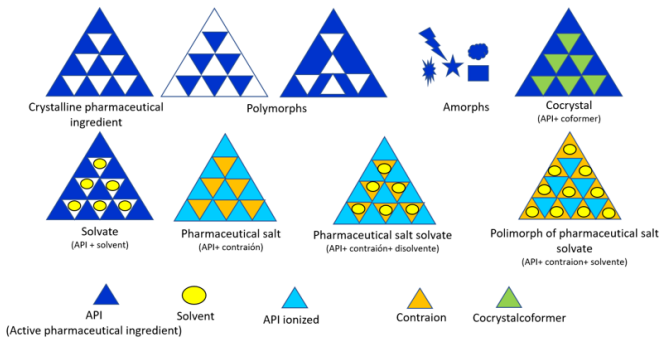

Figure 11 Some solid forms in active pharmaceutical ingredients.

Purification is easy or not?

When a process generates impurities, two scenarios are possible. In the first scenario, the impurity is structurally very similar to the target molecule (the product). In the second scenario, the impurity is notably different in structure. If the impurity is not structurally like the target molecule, purification is normally feasible because the two compounds exhibit sufficiently different physicochemical properties. These differences enable separation through conventional purification methods. However, when the impurity is very closely related in structure to the product, purification becomes extremely difficult, as both molecules behave similarly during the process. In such cases, the impurity may pass through the same purification steps as the desired product for example, a crystallization resulting in poor or ineffective separation.

The following conceptual figure illustrates this idea:

I. The **red triangle** represents an impurity.

II. The **green rectangles** represent the target molecule (product).

III. The orange rectangle represents impurity with a structure similar to the product

IV. The blue box represents the purification process

In the first case, where the impurity differs significantly from the product, purification is successful because the impurity does not behave like the product and is removed during the purification step. In the second case, where the impurity is structurally very similar (represented as a **green rectangle** versus an **orange rectangle**), both species behave almost identically and pass together through the purification process (blue box), making separation highly challenging (Figure 12).

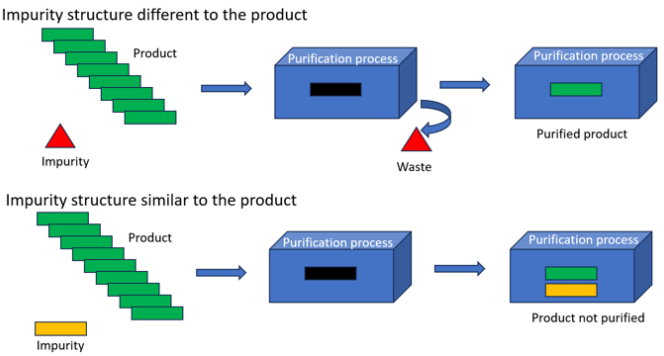

Figure 12 Easiness of impurities purification.

The most difficult impurities to purify are those that are structurally very similar to the target compound. These impurities are often found in starting materials. For example, in the synthesis of olmesartan medoxomil (angiotensin II receptor blocker), an analogue impurity containing an ethyl group instead of a methyl group was reported at the end of the process. This impurity originated from contamination of methylmagnesium chloride with ethylmagnesium chloride used in the first reaction step.[35]

This type of impurity is practically impossible to remove through purification, and therefore it becomes necessary to tighten and control the specifications of the starting materials to prevent its formation (figure 13). For impurities that differ more significantly from the target molecule, the purification processes described in the next sections can be applied.

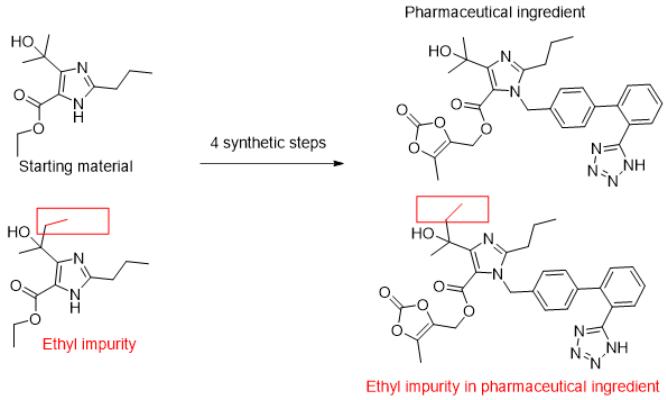

Figure 13 Example of impurities in raw materials.

Study cases

During the final steps of the process development of Olanzapine (an antipsychotic drug), several impurities were detected by high-performance liquid chromatography (HPLC) at levels ranging from 0.05% to 0.15%. The compound was analyzed using liquid chromatography coupled to a mass detector. The generated data were associated with proposed structures, which were later confirmed through laboratory synthesis. Regarding impurity content, current guidelines establish a limit of 0.15% for known related compounds, meaning impurities whose structures have been elucidated. In contrast, unknown impurities (i.e., those with structures not yet identified) are subject to 0.10%.[36] The standard procedure for the synthesis of Olanzapine (last three steps) focuses on the reaction of compound 1 with piperazine 2.

The intermediate is then reacted with dimethyl sulfate to generate Olanzapine. It is worth mentioning that in these three steps, six impurities are generated. To explain these byproducts, the starting material **1** can be hydrolyzed to form impurity 6. Regarding the piperazine derivative, two impurities were observed, both resulting from overreactions. On one hand, impurity 7 is an overreaction product formed during the quenching step with acetic acid. On the other hand, impurity 8 is a dimer generated due to a high concentration of molecules at a specific stage of the process. In the last step of the synthesis, intermediate 5 undergoes an overreaction resulting in an additional N-alkylation, forming impurity 9. Furthermore, an N-oxidation was observed, probably caused by insufficient blanketing in the reactor. Finally, an unexpected reaction between the solvent and the final intermediate was also detected. After determining the molecular masses, the six structures were confirmed through experimental work in the laboratory (Figure 14).

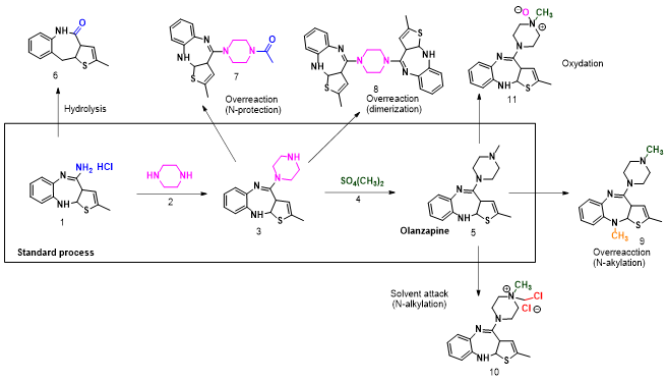

Figure 14 Related impurities to Olanzapine.

The second example concerns Baloxavir Marboxil and Baloxavir acid, an antiviral drug. In the literature, five metabolites, twelve degradation products, fourteen chiral impurities, and forty process-related impurities have been reported, in addition to five stable isotopes (Figure 15). This work discusses the formation pathways and analytical methods used to characterize these impurities. The description of all degradation pathways can serve as a reference when reviewing the impurity profile of a drug (Figure 15).[37]

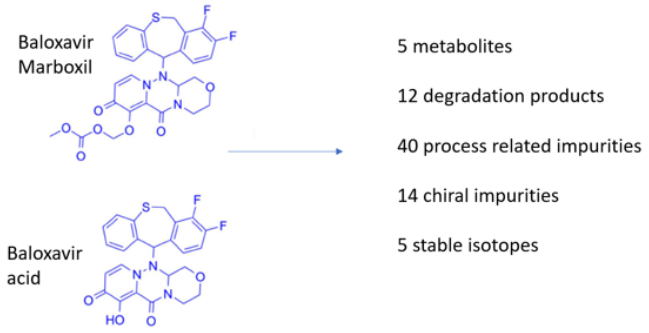

Figure 15 Related impurities to Baloxavir Marboxil and Baloxavir acid.

Purification methods

As mentioned previously, it is necessary to eliminate all impurities from the product. This task is often challenging because impurities can differ significantly in structure; however, these differences can be advantageous, as they allow the product to be separated from its byproducts. In most cases, crystallization is the most effective method for purifying an organic compound. The purification process typically involves dissolving the organic material in a suitable solvent and then inducing slow crystallization. As a result, the compound can be isolated as a crystalline solid with high purity. A recent article on this topic was published by Northen providing further insight into advances and methodologies in crystallization-based purification.[38]

It is important to highlight the use of seeds among these purification methods, as they play a critical role in controlling crystal formation. A seed is a crystal that contains all the necessary structural information to direct the growth of a specific crystalline form. Seeds can influence properties relevant to intellectual property, manufacturability, and even absorption in the human body, since different crystal forms (polymorphs) may exhibit different behaviors. The use of seeding enables selective crystallization of a desired form, improving reproducibility and purity. An example of this methodology has been described for prasugrel (an antiplatelet agent), where controlled seeding was used to obtain the desired crystalline form.[39]

Precipitation is another isolation method and is sometimes useful for improving the purity of a product. The most common approach involves dissolving the product in a highly soluble solvent and then adding an antisolvent to induce precipitation. A classic example consists of dissolving the product in dimethylformamide (or similar) and subsequently precipitating it with water. Under these conditions, the product precipitates while most impurities remain in the mother liquors. Although precipitation is not as selective as crystallization, it is effective when the solvent used has a high boiling point and is miscible with both water and organic solvents such as dimethylacetamide, dimethylformamide, or dimethyl sulfoxide. Moreover, precipitation can also serve as an alternative route to obtain amorphous compounds. An example of this approach has been reported for montelukast (an anti-asthmatic agent).[40]

Salt formation[41] is a very common purification method. It consists of dissolving the product in an appropriate solvent and then adding a counterion. As a requirement, the organic molecule must contain at least one ionizable functional group, such as a carboxylic acid, amine, or phenol. To illustrate the purification by salt formation, the purification of 2,4-dichlorobenzoic acid contaminated with approximately 0.5% of its positional isomers has been reported. In this case, methylbenzylamine was used as the counterion. The corresponding salt was formed, and after hydrolysis, the impurity content decreased to less than 0.05% (Figure 16).[42] The greatest advantages of this method are its simplicity, its suitability for large-scale operations (even at the metric-ton level), and the generally low cost of the counterions used (Figure 16).

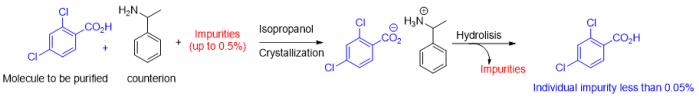

Figure 16 Example of purification with organic salts.

Salt formation followed by selective crystallization has also been described for solifenacin (an antagonist of muscarinic receptors). In this approach, several methodologies are combined, including salt formation, diastereomeric purification, and the use of seeding techniques.[43] Organic salts have long been used for chiral resolution. In this context, a variety of molecular systems such as coordination complexes, covalent derivatives, and organic salts have been applied. The methodology operates as follows: the racemic mixture of the compound to be resolved typically an amine or an acid is first reacted with an enantiomerically pure counterion. As a result, two diastereoisomeric salts are formed.

These salts generally exhibit different physicochemical properties, allowing them to be separated by crystallization or other purification techniques. This strategy continues to be widely used today. Commonly employed chiral acids for such resolutions include dibenzoyl tartaric acid, di-p-toluoyl tartaric acid, camphorsulfonic acid, and (S)-mandelic acid. Additional examples and a broader overview of the methodology can be found in the review by Fogassy et al.[44] Another interesting alternative is the Pope and Peachey method. This strategy uses a pair of acids one chiral and one achiral at a 1:1 ratio. This means that only half of the onerous chiral resolving agent is required, while the other half is substituted with an easily available and inexpensive achiral counterion. For example, tartaric acid can be used together with aqueous hydrochloric acid. The main advantage of this method is the reduced use of costly chiral resolving agents. Since the resulting diastereomeric salts often differ in solubility, effective resolutions can be achieved. A well-known example reported in the literature is the resolution of naproxen (an anti-inflammatory drug) using this procedure.[45]

The classical alternative mainly for colored impurities is the use of activated charcoal. Activated charcoal in the surface has a lot of functional groups as carboxylic acids, amides, amines, lactones, quinones among others (fig 17) these functional groups can react with impurities generating a product free of impurities. In the market there are a lot of options that can be useful, with some specification, however in the practice is necessary test the activated charcoal before to use at industrial level. The basics of the activated charcoal can be consulted in the book of Marsh and Rodriguez (Figure 17) .[46]

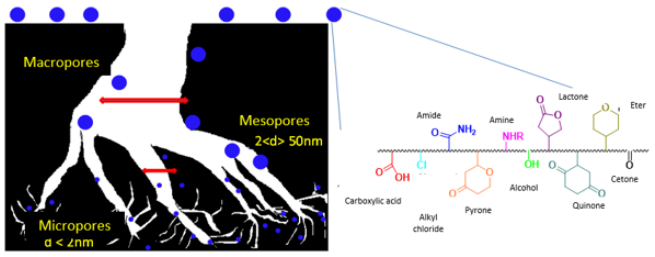

Figure 17 Functional groups over activated charcoal.

Washing cakes: In the synthesis of pharmaceutical ingredients, the reactions are carried out in a chemical reactor, after which the product is isolated by crystallization or precipitation. Inside the reactor, the product remains suspended, while the impurities remain dissolved in the mother liquors. The product is then isolated by centrifugation, and the resulting cake (isolated product) must be washed with an appropriate solvent to remove as many by-products as possible. This operation is critical, because if it is not performed properly, the impurities can contaminate the intermediate or final product. This step has also been recommended by Poojashree in his article.[47]

Finally, the least common method used to purify pharmaceutical ingredients is chromatography. At the industrial scale, it is generally considered too expensive and resource-intensive, which makes its routine use impractical. However, examples at the laboratory scale have been reported recently.[48] Additionally, an interesting review discussing the use of chromatography at the industrial level has also been published.[49] Finally, in the figure 18 the purification methodologies are complied (Figure 18).

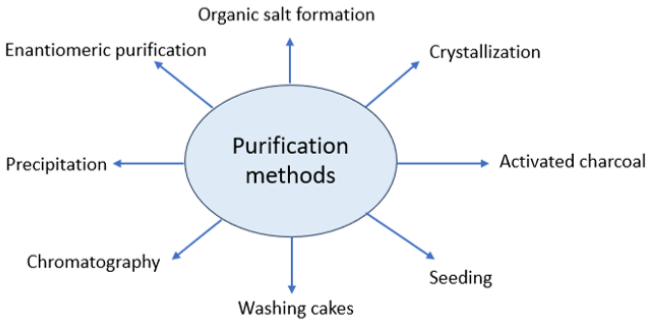

Figure 18 Purification method for impurities in active pharmaceutical ingredients.

Impurities in regular manufacturing

In the current manufacturing process, all impurities are theoretically controlled; however, in real-life operations, several issues may arise. For example, equipment may fail (such as a reactor, pump, or centrifuge), or there may be interruptions in electricity or gas supply to the heating systems. All these issues can generate an unexpected impurity during the process. When this occurs, manufacturing is halted until the root cause of the deviation is identified. Due to the process excursion, the product becomes contaminated with the impurity, leading to batch rejection. The production line remains stopped until the issue is fully understood.

In such cases, it becomes necessary to isolate the byproduct and subsequently perform structural elucidation using spectroscopic methods. After elucidation, the proposed structure must be confirmed in the laboratory. Once both the impurity structure and the root cause of the deviation are clarified, corrective and preventive actions are implemented to prevent recurrence. The process is then restarted, incorporating the new control activities (figure 19). It is worth mentioning that all these activities are governed by the quality system (including deviation management, change controls, etc.). This methodology was recently reported in the literature.[50]

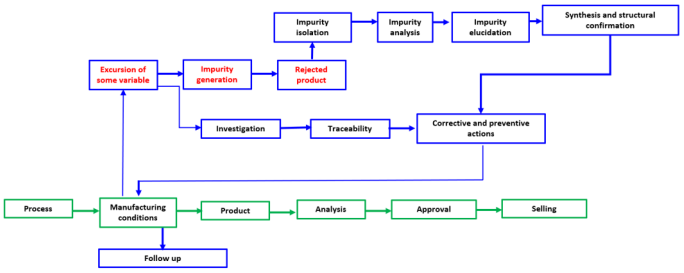

Figure 19 Scheme of solvent problems with an impurity in regular manufacturing.

Analytical methodologies

As illustrated throughout this manuscript, the impurities are closely related to the main compound in both structure and physicochemical properties. One of the major challenges in their analysis is achieving proper separation. In this context, advances in analytical technologies focus on facilitating separation and increasing detector sensitivity. In addition, hyphenated methods, which combine different analytical techniques, have been developed to first separate and then analyze the components to obtain structural information and characterize.

To characterize an impurity, it is necessary to isolate it. In this context, a complementary strategy must be implemented, and the use of hyphenated techniques is very useful to achieve this task. For example, chromatography followed by mass spectrometry or even nuclear magnetic resonance equipment can be used. With these tools, the molecule is separated from the matrix, and important data such as molecular mass or signal multiplicity are generated, making it easier to elucidate the structure. Hyphenated methods offer several advantages, including high sensitivity, short analysis time, high precision and accuracy, and the ability to isolate the required analyte from a complex matrix.

Several common techniques are used to elucidate impurities, such as liquid chromatography–mass spectrometry, gas chromatography–mass spectrometry, high-performance liquid chromatography–mass spectrometry, capillary electrophoresis–mass spectrometry, liquid chromatography–nuclear magnetic resonance, and gas chromatography–infrared spectroscopy. In addition to this, it is also possible to use combinations of three hyphenated techniques, for example: liquid chromatography–atmospheric pressure ionization mass spectrometry, electrospray ionization mass spectrometry, and large-volume injection gas chromatography–mass spectrometry, among others.[51]

The use of hyphenated methods are particularly useful in the case of genotoxic impurities, for which the acceptable limits are extremely strict. A recent and interesting article has been published on this topic,

where new methodologies, technological improvements and study cases are described and can be consulted for further detail.[52]

Other uses of the impurities

Impurities do not only carry a negative connotation; they also offer several positive uses. First, during the development phase, an impurity profile is generated. Most detected impurities are elucidated, meaning that their structures are determined using spectroscopic techniques such as X-ray diffraction, infrared spectroscopy, and mass spectrometry among others. Then impurities can be isolated from various sources, including starting materials, intermediates, or final products. They may also be obtained from reaction crudes or mother liquors, which theoretically contain higher levels of impurities. Additionally, separation through chromatographic columns can be employed. Alternatively, high-pressure chromatographic equipment offers another effective option for isolating impurities. Once isolated, impurities can be used to establish limits within the process.

For example, during development, the process may be intentionally contaminated with a specific amount of an impurity to observe its behavior and the extent to which it is purged by the system. This information is then used to define limits for in-process controls. In addition, Landge et al. describe several separation methodologies for the isolation and identification of impurities in drugs, including technical data on the equipment used. Among these methods, the authors mention flash chromatography, high-performance liquid chromatography, capillary electrophoresis, gas chromatography, supercritical fluid chromatography, solid-phase extraction, and various hyphenated techniques.[53]

Another important area in which isolated impurities are useful is analytical method development. The isolation of an impurity allows the generation of reference materials that can be used as standards for analytical methods, ensuring accurate quantification and identification.[47] Toxicological studies are also impacted by the presence of impurities. Process-related impurities must be evaluated to determine whether they pose a risk to patients, considering the corresponding cohort of concern.[54] Degradation studies are crucial for determining whether the active pharmaceutical ingredients and their impurities remain stable over time.

To assess this, accelerated conditions can be used to intentionally stress the molecules and identify potential degradation pathways. Some of these conditions expose the pharmaceutical ingredients to acid, basic, oxidation, thermal, humidity.[55] Cleaning procedures are likewise affected by impurities, as it is necessary to develop appropriate cleaning methodologies to prevent cross-contamination between products manufactured sequentially. In such cases, it is essential to verify that no residual compounds remain, as these could contaminate the subsequent process. Cleaning samples are then compared against a reference standard to ensure compliance.[56]

Conclusion

There are several guidelines that classify and establish the requirements and assessments for each type of impurity. Achieving high purity in pharmaceutical ingredients is the main goal for manufacturers, primarily because impurity content can compromise patient safety. Historical cases support these arguments. In this context, it is necessary to control manufacturing processes thoroughly because the impurities can be toxic for patients. In addition, understanding the pathways of impurity generation is critical to establish mitigation strategies and avoid product rejection or recall. Moreover, several approaches can be used to reach an acceptable impurity level; crystallization, salt formation, and activated carbon are some examples. Finally, although impurities often carry a negative connotation, their isolation is very useful for testing processes, analytical methodologies, and toxicological studies. In summary, the study of impurities is a fascinating field for developing new mitigation strategies to ensure pharmaceuticals are free of impurities and, consequently, maintain patient safety.

Acknowledgments

The authors thank the journal for it support in publishing this work.

Conflicts of interest

The authors declare that there are not conflict of interest.

Funding

None.

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