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Impurities in drug substances and drug products: A regulatory CMC perspective

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This article is the first of a series focused on regulatory management of impurities, introducing the topic of impurities in both drug substances and drug products from a regulatory chemistry, manufacturing, and controls (CMC) perspective. In this article, the main international guidelines, with a specific focus on mutagenic, nitrosamine, and elemental impurities, are discussed. Risk-based approaches for regulatory management of impurities and simulated case studies for impurity management in drug substances and drug products are discussed in the subsequent articles of the series, published separately.

Keywords – CMC, guidelines, ICH, impurities, regulatory

Introduction

When discussing impurities in medicinal products, it is important to note that active pharmaceutical ingredients (APIs) and medicinal products are seldom without any trace of impurities – there is always a minute amount of contamination. Impurities are described by the ICH guidelines as "any component of the new drug substance that is not the chemical entity defined as the new drug substance"[1] and as "any component of the new drug product that is not the drug substance or an excipient in the drug product."[2] Drug substances can be defined as any substances used in the manufacturing of a drug product and responsible for the pharmacological activity of the drug product itself. Drug products can be defined as finished products, developed for administration, which contain one or more drug substances and any other substances without pharmacological action (i.e., excipients). The nature and the quantity of the impurities are governed by a number of different factors, including the synthetic route of the drug substance, reaction conditions, quality of the starting materials of the drug substance, reagents, solvents, purification steps, excipients, drug product manufacturing process, packaging, and storage of the final product.[3] Impurities may impact product quality, influencing the efficacy and the safety profile; in the worst-case scenario, the impurities may have carcinogenic, mutagenic, or teratogenic effects. As the presence of impurities at

trace levels is inevitable, these levels should be controlled and monitored. Furthermore, as detection limits in analytical chemistry decrease, the number of impurities detected tends to increase.[4] The interest in controlling the levels of impurities has grown over the years, along with the progress of scientific knowledge and technologies and with the general awareness of how impurities can affect the overall quality of pharmaceutical products as well as people's quality of life.

Control of impurities is one of the major challenges facing the pharmaceutical industry and regulatory agencies today.[4] Regulatory bodies have issued several guidelines to regulate and harmonize the approaches to controlling different types of impurities. Different pharmacopeias – such as the British, European, Indian, and Japanese versions and the US Pharmacopeia – are also regularly revising their monographs for drug substances and drug products to introduce limits for the different types of impurities.[5-7] An important and recent example of the monitoring and control of impurities by regulatory bodies is the case of nitrosamines.[8] Within recent years, a considerable number of drug product lots containing APIs – for example, valsartan, irbesartan, losartan, ranitidine, nizatidine, and metformin – have been withdrawn or recalled from the market due to the presence of carcinogenic N-nitrosamine impurities (e.g., N-nitrosodimethylamine [NDMA], N-nitrosodiethylamine [NDEA], and N-nitroso-N-methyl-4-aminobutyric acid [NMBA]).[9] Consequent interruption or discontinuation of the manufacturing and distribution has culminated in shortages of marketed drugs, including the antidiabetic drug metformin and the potentially life-saving drug rifampin for the treatment of tuberculosis.[10] Following analyses and discussion, regulatory guidance has been issued in which marketing authorization holders have been asked to review all chemically synthesized commercial drug substances and drug products for the presence of N-nitrosamine impurities.[11,12]

No company can avoid addressing the issue of impurities. The regulatory management of impurities requires a strong understanding of the product, supply chain, and regulatory guidelines and regulations. Knowledge of these aspects must be integrated into a quality design approach that enables consistent management of impurities from early development stages through to the postmarket stage.

Impurities

In chemistry, *impurity* refers to a chemical substance inside a confined chemical phase that differs from the chemical composition of that phase.[4] Regulatory definitions are provided by ICH Q3A, ICH Q3B, and the US Pharmacopeia.[1,2,13] Apart from formal definitions, impurities are any unwanted chemicals that remain with the APIs or develop during formulation or upon aging of both APIs

and formulated APIs in medicines.[5] Although there are different ways to group impurities, the ICH classification is the most widely recognized. The ICH Q3A(R2) guideline defines three broad categories: organic impurities, inorganic impurities, and residual solvents.[1] Each category is in turn divided into subcategories. Knowing how impurities are classified and their main characteristics and sources is the first step in managing risk and predicting potential impurities in products, from both technical and regulatory standpoints.

Organic impurities

Organic impurities can arise during the manufacturing process or during storage and are also referred to as process- or drug-related impurities. This category includes starting materials, by-products, intermediates, and degradation products. These impurities can be identified (known) or unidentified (unknown). Although the end products are always washed with solvents and purification steps are performed, there is still the potential for residual unreacted starting materials in the final product.[6] In synthetic organic chemistry, incomplete reactions, overreactions, isomerization, dimerization, rearrangement, or unwanted reactions between starting materials or intermediates with chemical reagents or catalysts are always a possibility. This is why by-products are quite common impurities. Furthermore, it may not be possible to theorize all of them.[14]

Some organic impurities may be formed during storage or may increase over time. Such impurities are called degradation products and are another common subcategory of organic impurities. Penicillins and cephalosporins are classic examples of impurities from degradation products.[15]

Inorganic impurities

Inorganic impurities can result from the manufacturing process. Their main difference from organic impurities is that they are usually known and identified. Inorganic impurities include reagents, ligands, catalysts, heavy or other residual metals, and inorganic salts. The main sources of heavy metals are the water used in the processes and the reactors, if stainless steel reactors are used, where acidification or acid hydrolysis takes place.[6] Heavy metals contamination is largely covered by the ICH Q3D guideline, as explained later in this article. Inorganic impurities can also form as a result of leaching from the equipment used in the process, such as from reactors, micron filters, transfer lines, centrifuges, and dryers.[16] Other sources of inorganic impurities are the primary packaging materials, especially for liquid pharmaceutical forms. Provided that the materials used for primary packaging comply with current legislation, extractable impurities are compounds that can be removed from the coating of elastomeric components, plastic components, or containers and closure systems.[16] A classic example is the glass container, in which oxides such as NO_2, SiO_2, CaO, and MgO are major components leached or extracted from glass.[15]

The evaluation of leachable and extractable impurities is important especially for liquid formulation, where the risk for contaminant extraction is higher. Reagents, ligands, and catalysts are generally consumed or removed during the purification steps, so the likelihood of having these impurities is minimal.[6]

Residual solvent

Residual solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a drug substance or a drug product. The solvents are never completely removed by common manufacturing techniques.[17] Not only may they be hazardous to human health, but they can also affect physicochemical properties of the bulk drug substances, such as crystallinity of the bulk drug, which in turn may affect the dissolution properties, odor, and color changes in finished products.[15] Therefore, their use is strictly regulated as described in ICH guideline Q3C. This ICH guideline defines four classes of solvents according to the impact on human health, from Class 1 with major or severe impact to Class 4 with less impact, as follows:[18]

- **Class 1 solvents** (i.e., carbon tetrachloride, dichloroethane, and trichloroethane) should be avoided in any pharmaceutical manufacturing process due to their high carcinogenicity and toxicity to human health and the environment.
- **Class 2 solvents** (e.g., methanol, acetonitrile, cyclohexane, and others) are regulated by precise limits expressed for each solvent by the ICH Q3C guideline, both for content in the drug (as ppm) and for relevant permitted daily exposure (PDE); it is suggested that the more restrictive limit, generally corresponding to the maximum ppm content of the solvent in the drug, is used.
- **Class 3 solvents** are identified with low toxicity, and a common wider limit in ppm (5,000 ppm) is defined for all the Class 3 solvents listed in the ICH Q3C guideline.
- **Class 4 solvents** are solvents for which no adequate toxicological data was found. In this case, limits should be proposed and justified by the manufacturer.

The list of the solvents belonging to each class is reported in the ICH Q3C guideline.

Regulatory landscape

Knowledge of regulatory guidelines is an essential requirement to properly manage impurities. An overview of the main regulatory guidelines on impurities is provided in **Table 1** (pp. 5-6). Thresholds for reporting, identification, and qualification of impurities are provided for drug substances[1] (**Table 1**, p. 6) and drug products[2] (**Table 2,** p. 7).

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Table 1. Overview of the main international regulatory guidelines on impurities

Guideline	Brief description
ICH Q3A(R2) – Impurities in new drug substances[1]	The guideline addresses the chemistry and safety aspects of impurities, including the listing of impurities in specifications. The guideline defines the thresholds for reporting, identification, and qualification of impurities in drug substances.[a]
ICH Q3B(R2) – Impurities in new drug products[2]	The guideline complements the ICH Q3A guideline and provides advice regarding impurities in drug products containing new, chemically synthesized drug substances. The guideline specifically deals with those impurities that might arise as degradation products of the drug substance or arise from interactions between the drug substance and excipients or components of primary packaging materials. Thresholds for reporting, identification, and qualification are defined.[b]
ICH Q3C(R8) – Impurities: Guideline for residual solvents[18]	The guideline provides recommendations on the use of solvents in the manufacture of drug substances and dosage forms and setting pharmaceutical limits for residual solvents.
ICH Q3D(R2) – Guideline for elemental impurities[19]	The guideline provides information about the control of elemental impurities in medicinal products, and it establishes PDEs for the most common elemental impurities.
ICH Q3E – Guideline for extractables and leachables (E&L)[20,c]	The guideline provides indications about the assessment and control of extractables and leachables in medicinal products.
ICH M7(R1) – Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk[21]	The guideline provides information regarding the acceptable limits of known mutagenic and carcinogenic impurities. It is intended to provide guidance for the assessment and the control of mutagenic impurities that reside or are reasonably expected to reside in a final drug substance or product, taking into consideration the intended conditions of human use.
EMA/425645/2020 European Medicines Regulatory Network approach for the implementation of the CHMP opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines[11]	These guidelines recommend approaches that should be taken to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products.
[FDA guidance] Control of nitrosamine impurities in human drugs[12]	
EMA/409815/2020 Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products[22]	

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Table 1 (cont.) Overview of the main international regulatory guidelines on impurities

Guideline	Brief description
[FDA guidance] ANDAs: Impurities in drug substances[23]	The guidance provides recommendations on the information to include regarding the reporting, identification, and qualification of impurities that are classified as degradation products in drug substances when submitting original ANDAs or a drug master file.
[FDA guidance] ANDAs: Impurities in drug products[24]	The guidance provides recommendations on the information to include regarding the reporting, identification, and qualification of impurities that are classified as degradation products in drug products when submitting original ANDAs.
EMA/CHMP/QWP/545525/2017 Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials[25]	The guideline provides information about the CMC quality of investigational drug products, including advice on impurities monitoring and management.

ANDA, abbreviated new drug application; **CMC,** chemistry, manufacturing, and controls; **CHMP,** Committee for Medicinal Products for Human Use; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **ICH,** International Council for Harmonisation; **PDE,** permitted daily exposure.

[a]See Table 2 for the thresholds for reporting, identification, and qualification of impurities in drug substances. [b]See Table 3 for the thresholds for reporting, identification, and qualification of impurities in drug products. [c]ICH Q3E is currently under revision and not available on the ICH website.

Table 2. Thresholds for reporting, identification, and qualification of impurities in drug substances defined by ICH Q3A(R2)[1]

Maximum daily dose, g/day[a]	Threshold		
	Reporting[b,c]	Identification[c]	Qualification[c]
≤ 2	0.05%	0.10% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake (whichever is lower)
> 2	0.03%	0.05%	0.05%

[a]The amount of the drug substance administered per day. [b]Higher reporting thresholds should be scientifically justified. [c]Lower thresholds can be appropriate if the impurity is unusually toxic.

Table 3. Thresholds for reporting, identification, and qualification of impurities in drug products defined by ICH Q3B(R2)[2]

Maximum daily dose[a]	Threshold
Reporting[b,c]	
≤ 1 g	0.1%
> 1 g	0.05%
Identification[b,c]	
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1-10 mg	0.5% or 20 µg TDI, whichever is lower
> 10 mg-2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%
Qualification[b,c]	
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10-100 mg	0.5% or 200 µg TDI, whichever is lower
> 100 mg-2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

TDI, total daily intake

[a]The amount of the drug substance that is administered per day. [b]Thresholds for degradation products are expressed either as a percentage of the drug substance or as TDI of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic. [c]Higher thresholds should be scientifically justified.

Continued from p. 4

An impurity is reported when it is detected as an impurity, but no studies or analyses are performed to investigate its nature. Impurity identification is the process of understanding and elucidating the nature of the impurity, with a specific focus on the chemical structure, formula, and main chemical properties. Qualification is the step of acquiring and evaluating data that establish the biological safety of an impurity at the level at which it is observed.

Mutagenic impurities, nitrosamines, and elemental impurities are the three most critical categories of impurities, as they can significantly impact the final quality of the product and its safety; for this reason, they are strictly controlled by regulatory bodies, with increased attention in recent years. A focus on the reference guideline requirements for these impurities is provided below; regulatory strategies for the control of these impurities are discussed later in the article.

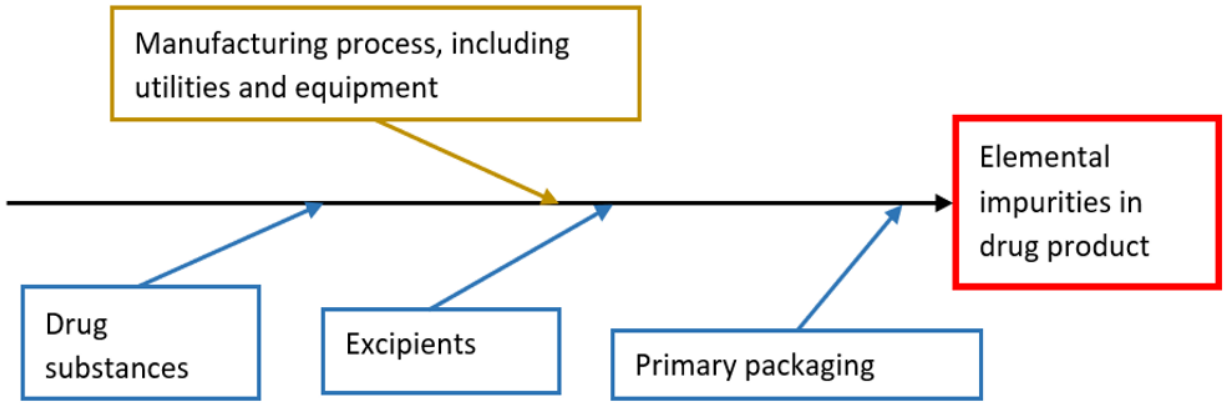
ICH Q3D

The ICH Q3D guideline defines principles for controlling the level of elemental impurities in drug products via risk assessment.[26] The guideline classifies the elemental impurities based on their known toxicity to humans and the likelihood of occurrence in drug products.

- **Class 1 –** Elemental impurities known to be seriously dangerous for human health. These elements require evaluation during the risk assessment, across all potential sources of elemental impurities and routes of administration.[27]
- **Class 2 –** Elemental impurities with a route-dependent toxic effect on humans. Based on likelihood of occurrence, this class is further divided into Class 2a (high probability of occurrence) and Class 2b (low probability of occurrence).
- **Class 3 –** Elemental impurities with low or no toxic effect by oral administration route but that may have safety concerns for parenteral and inhalation routes.
- **Class 4 –** All the elemental impurities not included in the other classes due to their low toxicity or because they are addressed by other guidelines and regional regulations.

The PDE limits of 24 individual elemental impurities are provided in the ICH Q3D, together with suggestions and guidance on how to determine the elemental impurities to be considered in the risk assessment. According to the guideline, the elemental impurities evaluation should consider the administration route of the drug product, composition (drug substances and excipients), manufacturing equipment and manufacturing process (e.g., metal catalysts intentionally added and utilities), and the primary packaging materials. The components with the greatest contribution of elemental impurities to the drug product are likely to be the drug substance and the excipients used in the drug product formulation.[28]

Figure 1. Fishbone diagram for sources of elemental impurities



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The company should describe in a dedicated risk assessment:

- How the impurities to be considered are defined (e.g., evaluation of the manufacturing process and of the supply chain);
- How the expected amount of each elemental impurity is defined (e.g., by retrieving information about drug substances, excipients, and packaging materials from the suppliers, results of dedicated laboratory tests, and results of literature research);
- The comparison of the expected or measured levels of elemental impurities in the drug product with the PDE foreseen by the guideline; and
- Any potential risks, relevant mitigation strategy, and actions (e.g., establishing specifications for drug substances or drug products, change in the packaging material, and inclusion of in-process controls). Notably, the guideline defines a control threshold of 30% of the established PDE to determine if additional controls may be required.

ICH M7

The ICH M7 guideline describes how to identify and control the exposure to impurities that could potentially have mutagenic or carcinogenic effects. Based on the known mutagenic or carcinogenic properties and on the presence of alert structures (i.e., chemical structures generally associated with mutagenicity), impurities are categorized into five classes:

- **Class 1 –** Known mutagenic carcinogens
- **Class 2 –** Known mutagens with unknown carcinogenic potential
- **Class 3 –** Impurities with alert structures but no mutagenicity or carcinogenicity data. These impurities need to be further investigated to better define the classification.
- **Class 4 –** Impurities with alert structures, or with the same alert structures that are present in compounds related to the drug substance (e.g., process intermediates), known to be nonmutagenic
- **Class 5 –** Known as nonmutagenic

Although 1.5 µg of mutagenic impurities per person per day is considered by the guideline to be an acceptable intake associated with a negligible risk (theoretical excess cancer risk of less than one in 100,000 over a lifetime of exposure), this limit is generally applied only for lifetime and long-term treatments or if no carcinogenicity data are available. If carcinogenicity data are available (i.e., Class 1 impurities), compound-specific limits should be determined based on carcinogenic potency and linear extrapolation or with published data taken into consideration. For Class 2 and Class 3 impurities, the ICH M7 guideline provides the acceptable daily intake based on the supposed treatment duration. As with the ICH Q3D, the ICH M7 guideline foresees a risk-based approach for the

management of the mutagenic impurities. The risk-based approach can be summarized as follows:

- Define the class of each impurity based on data from literature and databases (if any) or with the support of computational toxicology assessment using quantitative structure-activity relationship model methodologies to identify and evaluate alert structures. If needed, additional tests may be performed to further investigate Class 3 impurities.
- Define actions and strategies for controlling impurities. The most common action is the definition of specifications for drug substances or drug products, set according to the requirements of the guideline.

Nitrosamine guidelines

The main guidelines covering the topic of nitrosamine impurities are the EMA guideline on nitrosamine impurities in human medicines[11] and the US Food and Drug Administration guideline on the control of nitrosamine impurities in human drugs.[12] Nitrosamines are a group of organic compounds containing the nitroso functional group; among them, N-nitrosamines are such potent mutagenic carcinogens that they are referred to as the "cohort of concern" by the ICH guideline ICH M7.[21] For this reason, the regulatory approach for the management of nitrosamines recalls the approach described by the ICH M7 guideline for the management of mutagenic impurities. Companies are requested to perform a risk assessment to determine if there are risks of having nitrosamine in the drug substance or in the drug product. If risks, theoretical or confirmed by laboratory tests, of having nitrosamines in the final product or drug substance are identified, it is necessary to apply control strategies to limit these risks.

Conclusion

Impurities can negatively impact the final quality of the products, their safety, and their stability over time. The constant improvement of analytical techniques allows for the identification of impurities in ever lower quantities, and the advancement of scientific knowledge enables a clearer understanding of the impact of impurities on product quality and patient health. Over the years, companies and regulatory agencies have paid more attention to the management of impurities, and the current regulatory landscape is complex, with many guidelines to be considered. Knowledge of the guidelines is a crucial step in setting up processes and controls that facilitate the development of high-quality products and that align with the expectations of the regulatory authorities.

Abbreviations

API, active pharmaceutical ingredient; **CHMP,** Committee for Medicinal Products for Human Use; **CMC,** chemistry, manufacturing, and controls; **ICH,** International Council for Harmonisation; **NDEA,** N-nitrosodiethylamine; **NDMA,** N-nitrosodimethylamine; **NMBA,** N-nitroso-N-methyl-4-aminobutyric acid; **PDE,** permitted daily exposure

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