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Review Article

Impurities in Drug Substance-An Overview of ICH Q3A, Q3C and M7 Guidelines

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ABSTRACT

Impurities are undesired chemical substances found in pharmaceutical drug products with no therapeutic benefits and, in some cases, can pose a risk to patient safety if their levels exceed a certain limit. Impurities present in the drug substance can affect quality, safety and efficacy of pharmaceutical products causing serious health hazards. Generally, when the pharmaceutical products are free from impurities, they would exert the intended therapeutic response. International Council for Harmonization (ICH) has provided guidelines for impurities in new drug substance (ICH Q3A) that provides guidance on the qualification and control of impurities in new drug substance using different thresholds for their evaluation. The current study provides an overview of ICH Q3A, 3C and M7 guidelines applicable for impurities in drug substances. All these guidelines focuses on safeguarding the safety and quality of drug substances by providing recommendations that address the particular type of impurities involved. The study concludes that by understanding regulations for classification and control of impurities in drug substance it gives an idea for the regulators to prepare and compile the documents required in compliance with standard guidelines.

Keywords: Impurities, ICH guidelines, Drug substance, ICH Q3A guidelines.

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INTRODUCTION

As per ICH impurity is "any component of the new drug substance which is not the chemical entity defined as the new drug substance".[1] As per the definition provided, these impurities are inevitable and will exist in small amounts. Therefore, various regulatory bodies follow guidelines which allow permissible limits to these impurities in order to bring pharmaceuticals into the market. Even in trace amounts, the impurities can impact the quality, safety, and efficacy of the drug product.[2,3]

Various pharmacopoeias have set limitations on the acceptable quantities of impurities contained in Active Pharmaceutical Ingredients (APIs) or formulations. The presence of impurities in drug substance may be due to various reasons. These impurities may be identifiable or unknown, volatile or nonvolatile, organic or inorganic. Since different regulatory standards and management strategies must be established and followed, sources of impurities must be properly classified before proceeding.[4]

Impurities in drugs can be derived from a variety of sources, including starting materials, reagents, solvents, catalysts, and intermediates formation. Impurities can arise during the manufacturing of any drug substance or drug product. API can be incompatible with excipients, or can interact with packaging material. Therefore quantifying, qualifying, identifying, and controlling impurities have become crucial in the drug development process as they determine the final drug product's safety and purity.

Impurities in drugs can be determined using a various analytical technique such as gas liquid chromatography, High performance liquid chromatography (HPLC), Capillary Electrophoresis (CE), Supercritical fluid chromatography with UV detectors or mass spectroscopy, and so on.[5]

Different Pharmacopoeias, such as British Pharmacopoeia (BP), European Pharmacopoeia (EP), Indian Pharmacopoeia (IP), Japanese Pharmacopoeia (JP), and the United States Pharmacopoeia (USP) update their monographs periodically, setting limits for different impurities. Identifying and managing impurity sources are a major concern for drug manufacturers. It has been found that the presence of a single unknown impurity in the final stage of production might have a negative impact on the entire batch, causing it to be rejected based on quality criteria.

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ICH recommends identifying and describing all impurities present at a level of 0.1% or higher.

ICH Q3A guidelines for organic and inorganic impurities

According to ICH Q3A guidelines, impurities in drug substance are mainly classified into 3 types they are organic impurities, inorganic impurities and residual solvents as shown in Figure 1.[6,7]

Organic impurities (process-and drug-related)

They mainly arise during the process of manufacturing and storage of new drug substance. They can be volatile or non-volatile, identified or non-identified. Organic impurities are further classified as:

- Starting materials,
- By-products,
- Intermediates,
- Degradation products,
- Reagents, ligands and catalysts.

Inorganic impurities

They result from manufacturing process. They are generally identified and known. Inorganic impurities are further classified as:

- Reagents, ligands and catalysts,
- Heavy metals or other residual metals,
- Inorganic salts,
- Other materials (e.g., filter aids, charcoal).

ICH Q3C guidelines for Residual solvents

According to the ICH guideline Q3C, residual solvents are organic volatile chemicals that can be present in pharmaceutical products. These solvents are either used or produced during the manufacturing process of drug substances or excipients. Residual solvents can remain in the final drug product if not removed through purification processes. Residual solvents in pharmaceutical products can pose potential risks to patients if not adequately controlled. To protect patient safety, guidelines have been proposed to classify these solvents based on their toxicity level. Additionally, ICH Q3C provides guidance on controlling these residual solvents in pharmaceutical products. This guideline classifies the solvents into three different categories on the basis of their toxicity and risks associated with human health. Class 1 residual solvents are highly toxic and require strict control and monitoring due to their significant health risks.[8]

The Permitted Daily Exposures (PDEs) for Class 1 Residual solvents were shown in Table 1. On the other hand, Class 2 residual solvents have moderate toxicity, necessitating appropriate measures to ensure consumer safety. Table 2 presents the PDEs for Class 2 residual solvents. The concentration limits for these solvents are established to minimize potential health hazards and comply with regulatory requirements. The classification system of residual solvents along with indications, claim, toxicity levels, PDE and remark is represented in Figure 2.

ICH M7 guidelines for mutagenic and carcinogenic impurities

ICH M7 guideline provides guidance on the control of genotoxic impurities in drug substances. It emphasizes the need for thorough risk assessment and appropriate measures to mitigate the potential risks associated with genotoxic impurities. The control of genotoxic impurities involves several steps. Initially, a comprehensive risk assessment should be conducted to identify and characterize potential genotoxic impurities present in the drug substance. Figure 3 represents the classification of these impurities. This assessment includes evaluating the structure-activity relationship, available toxicological data, and establishing acceptable exposure limits. Based on the risk assessment, control strategies are implemented to limit the presence of genotoxic impurities. These strategies may include process optimization, selection of alternative synthetic routes, and rigorous purification techniques. These guidelines play a crucial role in ensuring the safety of pharmaceutical products by assessing and controlling potential genoto-toxic risks associated with impurities.[9]

The ICH M7 classification of mutagenic and carcinogenic impurities was illustrated in Figure 3.

Sources of impurities

The impurities can originate from different sources. The most important source of impurities is during synthesis, where the intermediates and by-products can be carried into the API or become the source of other impurities produced from them.[10,11]

There are different sources of impurities include starting materials, intermediates, byproducts of the synthesis, products of over-reaction, byproducts of reactions and also impurities can originate from the degradation of the drug substance, enantiomeric impurities, reagents, ligands, and catalysts.[12]

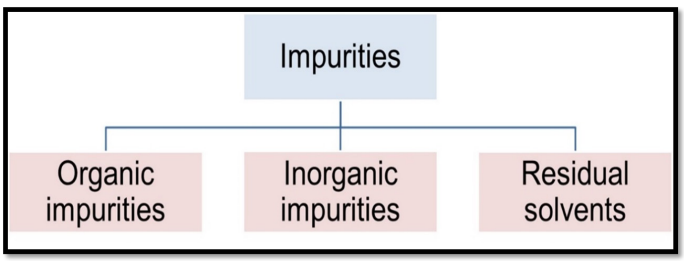

Figure 1: Classification of impurities in drug substance.

Impurity Evaluation studies

Forced degradation studies

These studies are conducted to evaluate the stability of the drug substance and how it degrades under different stress conditions. The drug substance is exposed to factors like heat, humidity, light, acid/base hydrolysis, oxidation, and photolysis. By subjecting the drug substance to these conditions, researchers can identify any degradation products or impurities that may form. These studies provide information about the stability of the drug substance, which helps to determine its shelf life. The results of these studies contribute to understanding the behavior of the drug substance and ensure that the final drug product is of high quality and remains stable over time. When compared to stability studies, these studies accelerate the generation of degradants in a shorter time.[13]

Stability studies

Stability testing aims to determine how environmental factors such as temperature, light, and humidity can affect the quality of drug substances or products over time. The information collected from stability studies also enables us to develop the suggested storage conditions. More research is being done on pharmaceutical chemical stability, since it impacts the safety and effectiveness of drugs. Before registering a dossier, stability tests of novel drug are required. It includes accelerated stability study and long-term study both of which can be conducted under conditions that are more tolerable than those employed in accelerated or forced deterioration experiments.[14]

Control of impurities in drug substance

ICH Q3A guidelines

The ICH Q3A guideline provides a framework for establishing the reporting thresholds, such as qualification thresholds and identification thresholds for impurities in drug substances. It helps to determine the level of impurity that should be reported, qualified, or identified during the drug development and manufacturing processes. The ICH Q3A guideline focuses specifically on organic impurities.[14,15]

Reporting Threshold

The reporting threshold refers to the minimum concentration of an impurity that needs to be reported in the documentation of a drug substance. It serves as a practical limit for identifying and monitoring impurities. Any impurity above this threshold must be identified and included in the impurity profile. The reporting threshold is typically set at a level that ensures the ability to detect impurities accurately and assess their potential risks.[16]

Identification Threshold

The identification threshold represents the concentration at which an impurity needs to be identified. It is typically higher than the reporting threshold and helps to establish a limit for analytical methods sensitivity. When the concentration of an impurity exceeds the identification threshold, efforts are made to characterize and identify the impurity through various analytical techniques. Identification involves comparing the impurity's characteristics with known standards or reference materials to determine its identity.

Qualification Threshold

The qualification threshold is the concentration limit at which an impurity requires further assessment for its potential impact on patient safety. Impurities exceeding the qualification threshold are subjected to a comprehensive evaluation of their toxicological properties and potential risks. This evaluation helps to determine the need for additional control measures, such as establishing specific limits or implementing appropriate manufacturing process modifications to minimize the impurity levels.

The reporting, identification, and qualification thresholds are established based on scientific knowledge, available analytical methods, and toxicological considerations. These thresholds assist in evaluating impurity profiles, setting acceptance criteria, and ensuring that impurity levels in drug substances remain

Table 1: Permitted Daily Exposures (PDEs) for Class 1 Residual solvents.

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard.
1,2-Dichloroethane	5	Toxic
1,1-Dicholoroethane	8	Toxic
1,1,1-trichloroethane	1500	Environmental hazard

Table 2: Permitted Daily Exposures (PDEs) for Class 2 Residual solvents.

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene1	0.7	70
Cyclohexane	38.8	3880
Cyclopentyl methyl ether	15.0	1500
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600

Class of residual solvent	Indication	Claim	Toxicity Level	Permitted Daily Exposure (PDE)	Remark
Class 1	Solvents to be avoided	Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.	High	Low	If unavoidable, then their levels should be restricted as per the limits given by ICH guidelines
Class 2	Solvents to be limited	Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity	Moderate	Medium	PDEs are given to the nearest 0.1 mg/day.
Class 3	Solvents with low toxic potential	No health-based exposure limit is needed	Low	High	Less toxic in acute or short-term studies; 50mg/day (5000 ppm) or less was found acceptable.

Figure 2: Classification of Residual Solvents.

Class	Definition
1	Known mutagenic carcinogens
2	Known mutagens with unknown carcinogenic potential
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity

Figure 3: Classification of mutagenic and carcinogenic potential impurities.

within acceptable limits. By following the guidelines provided in ICH Q3A, manufacturers can effectively monitor and control impurities throughout the drug development and manufacturing processes, ultimately ensuring the safety and quality of pharmaceutical products.[16,17]

ICH Q3A impurity thresholds for the tolerance levels of impurities in drug substances are depicted in Figure 4.

The decision tree approach

The ICH Q3A guideline provides a decision tree approach to assess and control impurities in drug substances. The decision tree assists pharmaceutical manufacturers in determining the need for identification and qualification of impurities based on their levels and toxicological properties. The ICH Q3A enabled decision tree for control of impurities in drug substances is depicted in Figure 5.

The decision tree provides a systematic approach for the identification and qualification of impurities in drug substances. It helps pharmaceutical companies to take the necessary actions based on the impurity levels and characteristics. The decision tree steps are described as follows:

Identification Threshold

The first step is to check if the impurity level is greater than the identification threshold. If the impurity is below this threshold, no further action is required. However, if the impurity level exceeds the identification threshold, further evaluation is needed.

Structure Identification

If the impurity is above the identification threshold, the next step is to determine if the structure of the impurity is known. If the structure is identified, additional considerations come into play.

Human Relevance

Once the structure of the impurity is identified, the decision tree considers whether the impurity poses a known human relevant risk. If there is evidence of a potential risk, efforts should be made to reduce the impurity level to minimize its presence in the drug substance.

Qualification Threshold

If the impurity does not pose a known human relevant risk, the decision tree moves on to evaluate whether the impurity level exceeds the qualification threshold. If the impurity level is below this threshold, no further action is required. However, if the impurity level exceeds the qualification threshold, qualification efforts should be considered.

Toxicity Studies

When the impurity cannot be reduced to a level below the qualification threshold, toxicity studies should be conducted to assess its potential adverse effects on patients. These studies help to determine if the impurity poses a clinically relevant risk.

Safe Level

Based on the results of toxicity studies, if the impurity is found to have clinically relevant adverse effects, efforts must be made to reduce the impurity level to a safe level that does not pose harm to patients. On the other hand, if no adverse effects are observed, the impurity can be considered qualified.

It is important to note that the decision tree is a guideline and the specific actions may vary depending on the impurity and its characteristics. Pharmaceutical companies should consult with regulatory authorities to discuss and determine the appropriate actions for impurity control in their specific drug substances.[18]

ICH Q3C guidelines

The ICHQ3C provides a basis for the risk assessment that begins with the identification of the residual solvents used during the manufacturing and synthesis of the pharmaceutical product. For each class of residual solvent, the guidelines provide specific indications, claims, toxicity levels, PDE values, and remarks. Class 1 solvents, being highly toxic, should be avoided if possible. If their use is unavoidable, their levels should be restricted as per the limits outlined in the guidelines. Class 2 solvents, although less toxic, still require limitations. The guidelines recommend setting PDE values for these solvents to ensure their exposure remains within safe limits. The PDE values are calculated based on the toxicity level and the daily dose of the drug product. Class 3 solvents, having low toxic potential, are considered acceptable at levels of 50 mg/day (5000 ppm) or less. These solvents are generally considered safe for use in pharmaceutical products. The risk assessment process involves evaluating the toxicity levels of residual solvents, determining their potential risks to human health, and setting appropriate limits to ensure patient safety. The guidelines provide a systematic approach to assess and control the presence of residual solvents in drug substances and drug products.[19]

ICH M7 guidelines

These guidelines focus on evaluating the potential risks associated with mutagenic impurities and establishing appropriate limits to ensure the safety of the final drug product. These guidelines are intended to provide benefits to new drug substances and products throughout their clinical development and marketing applications. Furthermore, they can be applied to post-approval submissions of existing marketed products. In certain situations, the guidelines are also applicable to new marketing applications for products that contain a drug substance already approved in another product. The assessment of impurity can be divided into two different stages:

Threshold	Maximum drug daily doses	
	≤ 2 g/day	>2 g/day
Reporting Threshold	0.05 %	0.03 %
Identification Threshold	0.10 % or 1.0 mg per day intake (whichever is lower)	0.05 %
Qualification Threshold	0.15 % or 1.0 mg per day intake (whichever is lower)	0.05 %

Figure 4: Impurity Thresholds in Drug Substances according to ICH Q3A.

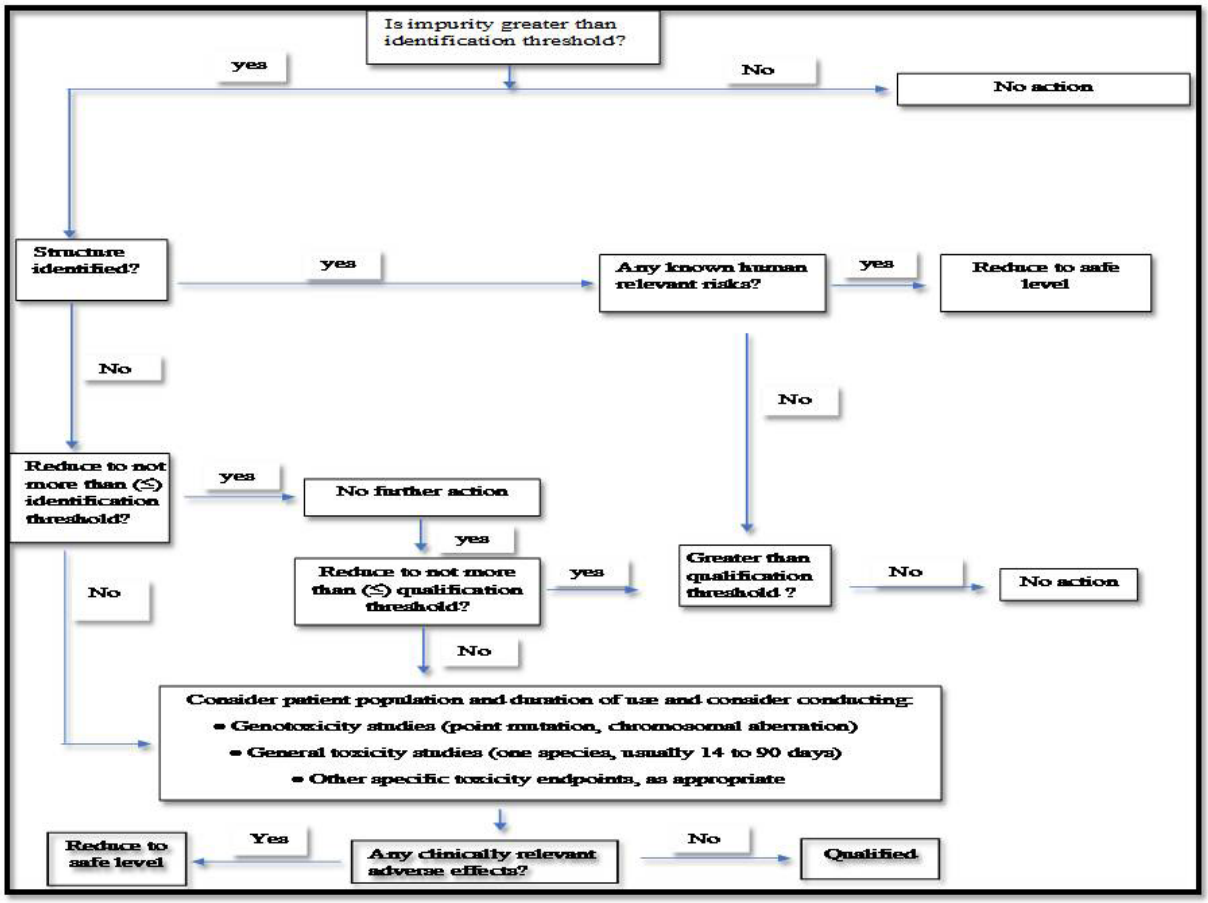

Figure 5: Decision tree for control of impurities in drug substances.

The mutagenic potential of actual impurities that have been discovered should be taken into account.

Potential impurities that are expected to be found in the finished medication material are evaluated to see if further research into their mutagenesis potential is necessary.[20,21]

CONCLUSION

This study provides a comprehensive overview of regulatory guidelines for controlling impurities in drug substances. The analysis emphasizes the importance of three key guidelines: ICH Q3A, Q3C, and M7 guidelines.ICH Q3A focuses on the classification of impurities and establishes thresholds for control of impurities in API. The ICH Q3C guideline addresses the control of residual solvents in drug substances and provides a list of solvents with their acceptable limits classified according to their toxicological properties. Furthermore, the ICH M7 guideline focuses on the identification and control of mutagenic impurities in drug substances. Manufacturers need to consult and adhere to these guidelines as per the specific impurity types and risks associated with their pharmaceutical products. The guidelines contribute to the overall control of impurities in drug substances based on the nature of the impurities. By categorizing impurities and implementing effective control measures, manufacturers can minimize risks, ensure product quality, meet regulatory requirements, and enhance operational efficiency. This study serves as a valuable resource for navigating impurity control in the pharmaceutical industry.

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CONFLICT OF INTEREST

The authors declare that there is no conflicts of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **DNA:** Deoxyribonucleic Acid; **GMP:** Good Manufacturing Practice; **ICH:** International Council for Harmonization; **PDE:** Permitted Daily Exposure; **PPM:** Parts Per Million; **mg:** Milligrams.

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