Available online on 15 Sep, 2026 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article **Open Access**

Regulatory Trends and Challenges in Pharmaceutical Submissions: A Critical Analysis of Health Authority Requirements on Nitrosamine Impurities, Elemental Impurities, Forced Degradation and Genotoxicity

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Abstract

As the control of pharmaceutical impurity directly influences the patient safety and quality of the product, it has become a part and parcel of the contemporary drug regulation. Regulatory agencies worldwide have responded to recent outbreaks of nitrosamine contamination and increased scientific understanding of the genotoxic and elemental impurities by increasing the demands on impurity testing. This paper evaluates regulatory anticipations of impurity management within pharmaceutical submissions in terms of elements of nitrosamine impurities, genotoxic impurities, forced degradation, and elemental impurities. Some of the major health authorities that have put regulatory frameworks in place include the United States Food and Drug Administration (USFDA), the European Medicine Agency (EMA), and the Central Drugs Standard Control Organization (CDSCO). A comparative study of these frameworks was carried out based on harmonized guidelines that were released by the International Council for harmonization (ICH). Some of the practical case studies conducted were the assessment of elemental impurities in Atracurium Besylate in line with the ICH Q3D, the risk assessment of nitrosamine impurities in Minocycline Hydrochloride and forced degradation studies of Prednisolone under different stress conditions. The analysis was performed by the analytical procedures such as inductively coupled plasma mass spectrometry (ICP-MS) and high-performance liquid chromatography (HPLC). The results revealed that elemental impurities and detected nitrosamine were within regulatory level and were not in the tested batches. According to the results, regulatory harmonization and risk-based impurity control methods are important in the safety and compliance of pharmaceutical products.

Conclusion: Pharmaceutical safety and regulatory compliance require the effective management of impurities. This paper shows that the compliance with harmonized ICH requirements and regulatory frameworks (USFDA, EMA, CDSCO) allows managing impurities reliably. The analytical findings indicated that the levels of nitrosamine and elemental impurities were not beyond acceptable levels. Also, forced degradation tests were used to aid in stability testing and methodology development. In general, the risk-based and science-driven strategy is a necessary method to sustain the quality of the product.

Keywords: Nitrosamine Impurities; Elemental Impurities; Genotoxic Impurities; Forced Degradation Studies; ICH Guidelines; Pharmaceutical Regulatory Affairs; USFDA; CDSCO; EMA; NDMA; NDEA; toxicological concern (TTC) concept; QSAR.

Article Info: Received 21 Mar 2026; Review Completed 24 Jun 2026; Accepted 29 Jun 2026

Cite this article as:
Mistrya D, Patel Z, Movaliya V, Kanaki N, Kharidia S, Zaveri M. Regulatory Trends and Challenges in Pharmaceutical Submissions: A Critical Analysis of Health Authority Requirements on Nitrosamine Impurities, Elemental Impurities, Forced Degradation and Genotoxicity. Int. J. Drug Reg. Affairs [Internet]. 2026 Sep 15 [cited 2026 Sep 15]; 14(3):56-60. Available from:
http://ijdra.com/index.php/journal/article/view/890

DOI: https://doi.org/10.22270/ijdra.v14i3.890
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1. Introduction

Regulation of the pharmaceuticals is critical to ensuring that pharmaceuticals are always of high quality, safe and effective before the pharmaceuticals are administered to patients. All pharmaceutical products are subject to regulatory systems in product development, manufacturing, quality control, approval, as well as post-marketing surveillance. Scientific and legal demands set by regulatory bodies are rather strict to ensure pharmaceutical products meet the set standards of safety and quality as the impact of drugs directly affects people. **(Error! Reference source not found.)**

Some of the health authorities that perform the pharmaceutical regulation in the world include the United States Food and Drug Administration (USFDA), the European Medicines Agency (EMA), and the Central Drugs Standard Control Organization (CDSCO). Although these agencies may be working under different national laws, the International Council for Harmonization (ICH) is currently leading the way in international

harmonization efforts that are alignment of the regulatory expectations of these agencies.**(Error! Reference source not found.)** The ICH guidelines offer a uniform scientific framework of pharmaceutical development and regulatory submissions in many different regions.

Due to the potential sources of impurities, which may be the raw materials, intermediates, or processing, or degradation in storage, impurity management has become a critical aspect of pharmaceutical quality assurance. The level of identification, qualification, and control of impurities in drug development and regulatory development is intensely requested by regulatory bodies since some impurities may be toxicologically hazardous even when present in very low amounts. (3) CH guidelines such as Q3A, Q3B, Q3D and M7 are international standards of risk assessment and impurity assessment of pharmaceutical product. (4)

Nitrosamine contaminants in recent years were found in various pharmaceutical products and this has increased regulatory interest around the world in the control of impurities. In some manufacturing circumstances, nitrosamines such as NDMA and NDEA that are believed to be potential carcinogens can develop in the process of synthetic chemicals. The stricter requirements set by regulatory organizations to ensure pharmaceutical industries conduct risk assessment and analysis testing of nitrosamine impurities were introduced against the background of widespread recalls of certain medications. (5)

Along with nitrosamine impurities, regulatory assessment focuses on elemental impurities, genotoxic impurities and degradation products caused during stability tests e.g. in the course of those stability tests. Whereas the ICH M7 introduces the ways of assessing genotoxic impurities based on the toxicological level of toxicity and predictive instruments, such guidelines as ICH Q3D introduce risk-oriented approaches to elemental impurity control.(7) Also, forced degradation tests are often conducted to identify the stability-indicating methods of analytical analysis to be made in regulation applications and to understand degradation mechanisms.(8) The paper at hand evaluates the present-day trends in regulations concerning impurity control and its importance with respect to risk-based impurity management plans in a pharmaceutical submission in respect to the evolving regulatory expectation.(9)

2. Objective of Study

2.1 Regulatory Framework Analysis

Global rule international regulations on controllability of pharmaceutical impurities were revisited. The regulatory documents of the International Council of harmonization (ICH) and other key health bodies such as the US Food and Drug Administration, European Medicines Agency and the Central Drugs Standard Control Organization were consulted to understand the changing requirements on regulations of impurity management. This was tested against the regulatory demands in organic impurities, elemental impurities, genotoxic impurities and degradation products with consideration to analyzing key guidelines on ICH of Q3A, Q3B, Q3D, M7(R2) and Q1A. This regulatory review provided the scientific background of the comparative study conducted in this paper.

2.2 Nitrosamine Risk Assessment Approach

The theoretical presence of nitrosamine toxicants in the active pharmaceutical ingredient (API) minocycline hydrochloride was assessed. According to the international regulations on nitrosamine, specifically the ICH Q9, the assessment was conducted through quality risk management concepts. All the sources of nitrosamine production were assessed as raw materials, solvents, reagents, catalysts, conditions of the process of manufacture, equipment, packaging materials, and outsourced activities. Three successive commercial batches were analyzed in order to identify the potential nitrosamine contaminants including N-nitrosodimethylamine (NDMA) and N-nitrosodiethyl - amine (NDEA).

2.3 Elemental Impurity Assessment

Atracurium Besylate drug substance was tested with regard to elemental impurity as outlined in the risk-based approach in the ICH Q3D guideline. Possible elements contamination sources such as starting materials, catalysts, manufacturing equipment, container closure systems and water were evaluated. Inductively coupled plasma-mass spectrometry (ICP-MS) was used to quantify the amount of elemental impurities in three production batches to determine the presence of metals arsenic, cadmium, mercury, lead, cobalt, nickel, vanadium, palladium, lithium, antimony, and copper in the samples.

2.4 Forced Degradation Study

The forced degradation tests were done on prednisolone BP to determine the ability of the analyzed method to show stability. Drug samples were exposed to stress conditions which included, acidic hydrolysis, alkaline hydrolysis, oxidative degradation, thermal degradation and photolytic degradation. The samples containing the degradation products were analyzed through high-performance liquid chromatography (HPLC) so as to trace the evolution of the degradation products and the stability profile of the medicinal substance.

2.5 Genotoxic Impurity Evaluation

The method of genotoxic impurity analysis of losartan potassium on an in-silico toxicological evaluation was performed. Quantitative structure-activity relationship (QSAR) approaches were applied to detect structural alerts and predict mutagenicity in obedience to the principles that are offered in the ICH M7(R2) guideline. The primary objectives of the assessment were finding potential contaminants of DNA-reactin with possible mutagenic risk and assessing the potential risk of those contaminants with the concept of the threshold of toxicological concern (TTC).

3. Risk Assessment and control Strategies for Impurities

3.1 Regulatory Comparison of Risk Assessment and Control Strategies for Major Pharmaceutical Impurities

Table:1 Comparative regulatory framework for risk assessment and control of all four impurities

Parameter	Nitrosamines	Genotoxic Impurities	Elemental Impurities	Forced Degradation
Guideline Basis	EMA & FDA Guidance	ICH M7(R2)	ICH Q3D	ICH Q1A/Q3B
Toxicological Model	Acceptable Intake (AI)	TTC (1.5 µg/day)	PDE	Identification Threshold
Risk Assessment	Mandatory NRA	(Q)SAR + Toxicology	Risk-based evaluation	Stress testing
Analytical Approach	LC–MS/MS	In-silico / Ames	ICP–MS	HPLC/UPLC
Regulatory Sensitivity	Very High	Very High	High	Moderate
Post-2018 Impact	Significant expansion	Increased scrutiny	Stable harmonization	Routine requirement
Primary Regulatory Concern	Carcinogenicity	Mutagenicity	Systemic toxicity	Product stability

The comparative analysis in Table 1 shows the various regulatory provisions applied in controlling key impurities of pharmaceuticals that comprise nitrosamine impurities and genotoxic impurities and elemental impurities and degradation products recognized by forced degradation studies. Due to their potential genotoxicities, carcinogenicity and mutagenicity, nitrosamine and genotoxic impurities are the most sensitively regulated. In order to ensure that such contaminants can be kept within allowable intake rates, regulatory authorities require high levels of risk assessment, analytical testing as well as toxicological evaluation. (5)

Conversely, the ICH Q3D standard that set the allowed daily exposure (PDE) limits and risk-related assessment methods has taken the regulation of elemental impurities to a more elevated degree of global coordination. (7) Even though forced degradation studies are not involved with toxicological risk, they remain an important regulatory necessity to measure drug stability and generate stability-indicating assays. Looking at the overall picture, the comparative analysis indicates that the modern regulatory frameworks focus on the risk-based, toxicologically justifiable impurity management methods throughout the pharmaceutical product lifecycle. (8)

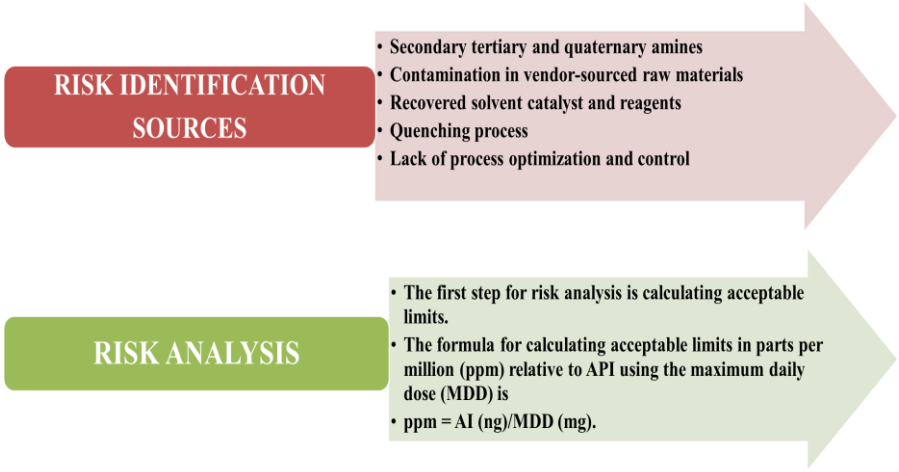

Figure 1. Nitrosamine impurity identification and analytical assessment

3.2 Nitrosamine Risk Assessment of Minocycline HCl

The principal purpose of the minocycline hydrochloride risk assessment was to find the potential sites of nitrosamine impurity formation throughout the manufacturing process. All the raw materials, solvents, reagents, catalysts, manufacturing machine conditions, and packaging materials were considered. Close attention was paid to the presence of amines and nitrite materials, which could potentially help in the formation of nitrosamine under acidic reaction conditions.

Analytical testing of three successive batches of commercial product confirmed that no measurable amounts of nitrosamine impurities were present despite the theoretical processes of the formation of nitrosamine through the use of material sources capable of forming amines and nitrite reagents. The non-detectability of contaminants in the form of NDMA and NDEA indicates that the controls and temperature control processes (manufacturing), as well as the purification process implemented to eliminate the formation of nitrosamines, are effective. These findings underscore the importance of preventive risk evaluation and process management practices in control of regulatory risks of nitrosamines.

3.3 Elemental Impurity Evaluation of Atracurium Besylate

The evaluation of Atracurium Besylate elemental impurity was conducted based on the risk approach as outlined in the ICH Q3D guideline. The assessment was based on the possible sources of contamination such as raw materials, catalysts, manufacturing equipment, container closure systems, and water that was employed during the manufacturing process. The hydrogenation step of

synthesis was also catalyzed by palladium and had to be specifically considered since it involves the elemental impurity that is potentially toxic.

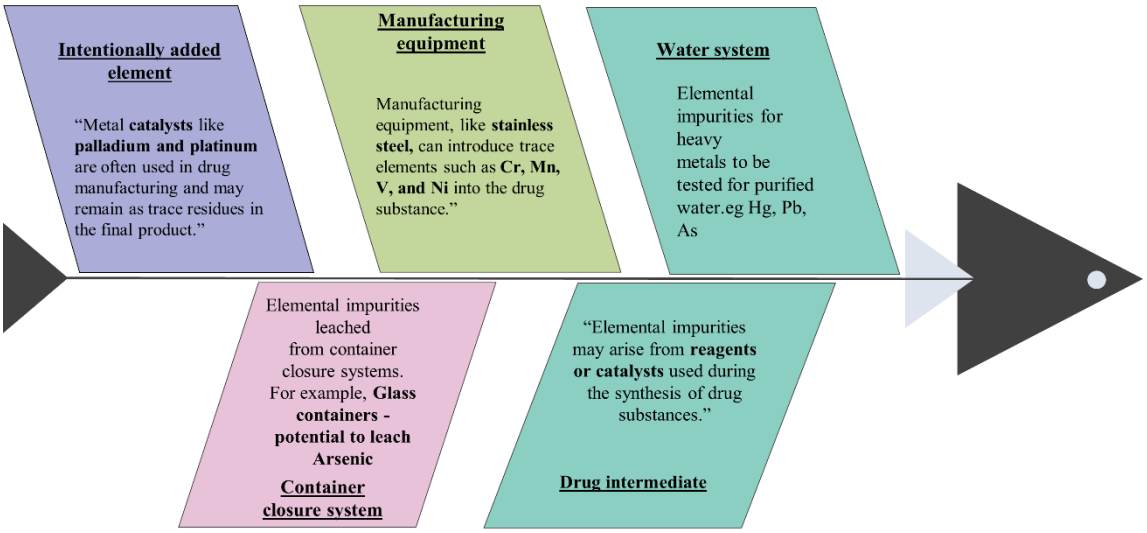

Figure 2. Potential sources of elemental impurities in drug substances illustrated using a fishbone diagram.

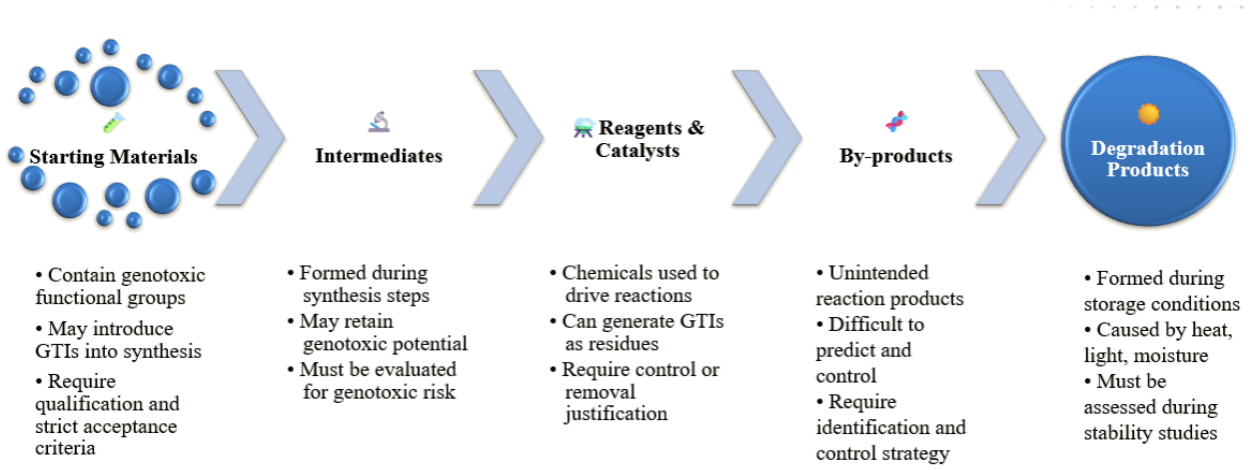

Figure 3. possible origins of genotoxic contaminants during the production of pharmaceuticals

Nonetheless, only a few steps of purification, such as filtration, extraction, crystallization and drying, are involved in the manufacturing process and are able to eliminate any residual catalyst. Quantitative analysis utilizing an inductively coupled plasma-mass spectrometry (ICP-MS) showed that in three batches of elements analyzed all of the elemental contaminants augmented consisted of arsenic, cadmium, mercury, lead, cobalt, nickel, vanadium, palladium, lithium, antimony and copper characterized were below the method limits of detection. These results confirm the effectiveness of the implemented elemental impurity control measure and confirm that the manufacturing process complies with the limits that were established by the ICH Q3D guideline concerning the maximum daily exposure (PDE) to various elements.

3.4 Forced Degradation Study of Prednisolone

The forced degradation studies were done to determine the inherent stability of prednisolone in different stresses. In order to identify the potential degradation mechanisms and to confirm the stability-indicating capacity of the analysing procedure, the drug material was placed under acidic, alkaline, oxidative, thermal and photolytic stress conditions.

The results indicated very negligible variations in the degrees of impurities in the regions that were evaluated in the conditions of stress. The acidic and alkaline hydrolysis had only a minor difference in impurity profiles, whilst the global impurity levels remained within the pharmacopoeial acceptance range. Also, the values obtained in the assays remained within the established range and this is an indication that provided the drug substance is stable in terms of its chemical composition. As revealed in the ICH Q1A and Q3B guidelines, the results indicate that the analysis technique employed in the assessment is suitable to measure degradation products and helps to support the regulatory requirements on stability examinations.

3.5 Genotoxic Impurity Assessment of Losartan Potassium

Genotoxic impurities in losartan potassium were assessed using an in-silico prediction technique which is a quantitative structure-activity relationship (QSAR) toxicological prediction method. Structural alert identification and mutagenicity prediction were conducted in order to define the possibility of the presence of DNA-reactive contaminants during the synthesis of the drug substance. The QSAR analysis revealed that the potential contaminants that can be related to the production process do not present a significant mutagenic threat at the mentioned exposure levels. The expected exposures remained in acceptable safety limits based on the threshold of toxicological concern (TTC) concept. These findings indicate the usefulness of in-silico methods in the early warning and risk control of drug genotoxicants and the growing approval of the concept of computational toxicology instruments in regulatory risk assessment.

4. Conclusion

This paper examined the new international regulatory guidelines and scientific approaches to regulating pharmaceutical impurities, including nitrosamine impurities, elemental impurities, genotoxic impurities and degradation products. An analysis of the rules and regulations of the US Food and Drug Administration, European medicines agency, and Central drug standard control organization revealed that impurity control in pharmaceutical submissions is increasingly becoming scientifically stringent and regulatory in complexity. (4)

The case studies confirmed the fact that appropriate risk-based strategies and analytical methods are efficient in ensuring the management of impurity. The risk assessment of nitrosamine of Minocycline HCl showed that no purities are present in the batches that are analyzed. The elemental impurity test Atracurium Besylate complied with the exposure limits allowed on a daily basis, and so the purification and monitoring techniques were effective. The study of forced degradation of Prednisolone supported the validity of the analysis method in functioning as an indicator of stability under different stress factors, whereas Losartan Potassium was assessed in-silico to demonstrate the relevance of predictive toxicology instruments in predicting possible risks of genotoxic outcomes. (3)

In general, the results can be summarized as the modern regulation frameworks are more focused on science-based, risk-oriented impurity management on the lifecycle of the product. Such thin pharmaceutical submissions must, in turn, involve combination of quality risk assessment, toxicological analysis, and innovative methods of analysis to protect patient safety, regulatory interest, and universal acceptance of the drug products. (9)

Acknowledgement

I would like to express my sincere gratitude to my guide, mentor, and Head of the Department for their valuable guidance and support throughout this work. I also extend my heartfelt thanks to my colleagues for their encouragement and cooperation. Additionally, I would like to thank the International Journal of Drug Regulatory Affairs (IJDRA) for publishing my article.

Financial Disclosure statement:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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