

GENOTOXIC IMPURITIES IN PHARMACEUTICALS: ADVANCES IN RISK ASSESSMENT, ANALYTICAL STRATEGIES, REGULATORY PERSPECTIVES, AND CONTROL APPROACHES

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ABSTRACT

Genotoxic impurities (GTIs) are trace-level contaminants capable of damaging DNA and increasing the potential for mutation and carcinogenesis. They may arise from starting materials, reagents, catalysts, intermediates, by-products, degradation pathways, manufacturing operations, or packaging interactions. Their control is therefore a critical component of pharmaceutical quality assurance. This review summarizes the major sources and classes of GTIs, mechanisms of DNA damage, toxicological risk-assessment approaches, regulatory expectations, in silico prediction, analytical strategies, method validation, genotoxicity testing, and practical control measures. Particular attention is given to ICH M7(R2), the Threshold of Toxicological Concern (TTC), Acceptable Intake (AI), (Q)SAR, read-across and weight-of-evidence approaches. Modern analytical platforms such as LC-MS/MS, GC-MS/MS, high-resolution mass spectrometry, ICP-MS and ICP-OES

provide sensitive detection, while optimized sample preparation and analytical quality by design improve method performance. Quality by Design (QbD), Process Analytical Technology (PAT), impurity purge studies, green chemistry and continuous manufacturing support prevention rather than relying only on end-product testing. Nitrosamines, including

drug substance-related nitrosamines, remain an important area because of their very low acceptable exposure levels and their occurrence through synthesis, degradation and storage. Emerging approaches involving artificial intelligence, digital laboratories, chemometrics, metabolomics, portable devices and real-time release testing are expected to strengthen lifecycle impurity control.

KEYWORDS: Genotoxic impurities; ICH M7(R2); nitrosamines; risk assessment; LC-MS/MS; HRMS; (Q)SAR; Quality by Design; Process Analytical Technology.

1. INTRODUCTION

Pharmaceutical impurities are unwanted chemical substances present in an active pharmaceutical ingredient (API) or finished product as a consequence of synthesis, purification, formulation, storage or degradation. Even at low concentrations, impurities can influence quality, stability, efficacy or safety. Genotoxic impurities are of particular concern because some can react with genetic material and produce mutations or other forms of DNA damage at very low exposure levels. Consequently, identification, qualification, quantification and control of impurities form an important part of pharmaceutical development and quality assurance.

GTI evaluation is integrated across the drug-development lifecycle. ICH M7 provides a science-based framework for the assessment and control of DNA-reactive mutagenic impurities, supported by analytical validation and toxicological evaluation. The source document emphasizes that risk management should combine route selection, process understanding, toxicological prediction, sensitive analysis, purification and lifecycle monitoring rather than depending on a single control step.

Pharmaceutical impurities may be grouped as organic impurities, inorganic or elemental impurities, residual solvents and genotoxic impurities. GTIs overlap with process- and degradation-related impurities but require special attention because their acceptable levels may be substantially lower than conventional impurity limits.

2. Sources and Classification of Genotoxic Impurities

The principal sources identified in the review are starting materials, reagents, catalysts, intermediates, by-products, degradation products and packaging materials. Starting materials with structural alerts, reactive reagents, incompletely removed intermediates and side-

products can introduce or generate DNA-reactive substances. Degradation caused by heat, moisture, oxygen, light or pH changes may create new impurities during storage. Packaging components such as plasticizers, adhesives, inks and polymers may also contribute through extractables, leachables or chemical interactions.

Table 1: Common Sources of Contamination, Typical Concerns, and Key Control Measures.

Source	Typical concern	Key control
Starting materials	Reactive structural alerts or contaminated raw materials	Supplier qualification, testing and route selection
Reagents/catalysts	Genotoxic reagent residues or side reactions	Process optimization and validated purge
Intermediates/by-products	Reactive intermediates and unwanted reaction products	Reaction control, impurity profiling and purification
Degradation products	Formation during heat, light, moisture, oxygen or pH stress	Stability studies and suitable storage
Packaging	Migration, extractables/leachables and interactions	Compatibility assessment and packaging control

2.1 Major Classes

Important classes discussed in the source include alkylating agents, nitrosamines, epoxides, alkyl sulfonates, hydrazines, aromatic amines, azides and halo compounds. Alkylating agents can transfer alkyl groups to nucleophilic sites in DNA. Nitrosamines are commonly associated with nitrosation of amines under suitable conditions and may also arise during degradation or storage. Epoxides possess strained electrophilic rings and can form DNA adducts. Alkyl sulfonates are strong alkylating species that can arise from sulfonic-acid-based chemistry. Hydrazines and some aromatic amines may undergo metabolic activation to reactive species. Azides and halo compounds require careful control because reactive residues or derivatives may contribute to genotoxic risk.

Table 2: Classification of Potentially Genotoxic Impurities and their Major Concerns.

Class	Examples from source	Main concern
Alkylating agents	MMS, EMS, DMS, DES	DNA alkylation and adduct formation
Nitrosamines	NDMA, NDEA, NEIPA, NDIPA, NDBA	Mutagenic/carcinogenic potential; ultra-trace limits
Epoxides	Ethylene oxide, propylene oxide, glycidol, epichlorohydrin	Electrophilic DNA reaction
Alkyl sulfonates	MMS, EMS, MPTS, EPTS	Strong alkylating activity
Hydrazines	Hydrazine, methyl hydrazine, phenyl	Reactive intermediates and DNA

	hydrazine	damage
Aromatic amines	Aniline, o-toluidine, p-phenylenediamine	Metabolic activation and DNA binding
Azides	Sodium azide, alkyl/aryl azides	Reactive residues/by-products
Halo compounds	Methyl chloride, benzyl chloride, ethylene dibromide	Alkylating/reactive behavior

3. Factors Influencing GTI Formation

GTI formation is strongly influenced by chemical structure and process conditions. The source review identifies starting-material quality, synthetic route, reaction mechanism, temperature, pressure, pH, reaction time, solvent, concentration, catalyst selection, purification efficiency, storage conditions, packaging, cross-contamination and scale-up or process-transfer changes as relevant factors.

- Starting materials and reagents containing structural alerts can directly introduce GTIs or generate them during reaction.
- Multistep routes involving reactive intermediates and harsh conditions may increase by-product formation.
- Temperature, reaction time, pH, solvent and reagent concentration can shift impurity formation pathways.
- Catalysts may promote desired reactions but can also facilitate unwanted side reactions.
- Insufficient crystallization, filtration, extraction, washing or chromatography can allow GTI carry-over.
- Storage-related oxidation, hydrolysis, photolysis and thermal degradation can generate new impurities.
- Cross-contamination during manufacture and changes during scale-up or technology transfer require lifecycle monitoring.

4. Mechanisms of Genotoxicity

GTIs can damage genetic material directly through chemical reaction with DNA or indirectly through metabolic activation and formation of reactive oxygen species. DNA adducts may interfere with replication and transcription. If damage is not repaired correctly, permanent mutations can result. The review identifies base-excision repair, nucleotide-excision repair and mismatch repair as important cellular mechanisms, but persistent or extensive damage may overwhelm repair capacity.

Mutations may affect oncogenes, tumour-suppressor genes and DNA-repair pathways. GTIs can also produce structural or numerical chromosomal changes such as breaks, deletions, inversions, translocations and aneuploidy. The review describes carcinogenesis as a multistep process involving initiation, promotion and progression. Structural-alert analysis and (Q)SAR are useful for identifying chemical features associated with DNA reactivity, including alkyl halides, epoxides, nitroso groups, aromatic amines, hydrazines, azides, Michael acceptors and alkyl sulfonates.

5. Toxicological Risk Assessment

GTI risk assessment is based on the potential for DNA reactivity, mutagenicity and carcinogenicity together with patient exposure. Relevant factors include chemical reactivity, metabolic activation, DNA-binding potential, daily dose, frequency and duration of treatment, administration route, patient population and available toxicological evidence.

5.1 (Q)SAR and Structural-Alert Assessment

ICH M7 supports the complementary use of an expert rule-based model and a statistical-based model. Rule-based systems identify known structural alerts, whereas statistical models use experimental datasets to estimate mutagenic potential. Concordant results provide greater confidence; discordant or out-of-domain predictions require expert review and, where appropriate, experimental testing.

5.2 TTC and Acceptable Intake

The Threshold of Toxicological Concern (TTC) is a risk-assessment concept used when compound-specific toxicological data are limited. The source document describes the commonly applied TTC value of 1.5 µg/day for DNA-reactive impurities and notes that particularly potent chemical classes may require compound-specific assessment. Acceptable Intake (AI) represents an exposure level considered acceptable based on toxicological and carcinogenicity information, exposure duration, route and population factors.

5.3 Compound-Specific, Read-Across and Weight-of-Evidence Approaches

When adequate data exist, compound-specific assessment may incorporate genotoxicity and carcinogenicity studies, metabolic activation, pharmacokinetics, dose-response modelling and benchmark-dose analysis. Read-across uses information from structurally similar compounds, considering functional groups, metabolic pathways, physicochemical properties and mechanisms of action. A weight-of-evidence approach integrates Ames results, mammalian-

cell assays, in vivo studies, (Q)SAR predictions, mechanistic information, literature, exposure data and other relevant evidence rather than relying on a single result.

6. Regulatory Perspectives

The review identifies ICH M7(R2) as the central framework for assessment and control of DNA-reactive mutagenic impurities. ICH Q3A addresses impurities in new drug substances, ICH Q3B addresses degradation products in new drug products, ICH Q3D addresses elemental impurities, and ICH Q2(R2) addresses analytical procedure validation. The source also discusses EMA, US FDA, WHO, PMDA and CDSCO/India expectations, emphasizing risk-based impurity assessment, validated analytical methods, GMP and lifecycle control.

Table 3: Regulatory Guidelines and Their Relevance to Genotoxic Impurity (GTI) Control.

Guideline/Authority	Primary focus	Relevance to GTI control
ICH M7(R2)	DNA-reactive mutagenic impurities	(Q)SAR, classification, risk assessment, AI/TTC and control
ICH Q3A(R2)	New drug substances	Identification, reporting and qualification of impurities
ICH Q3B(R2)	New drug products	Degradation-product control
ICH Q3D	Elemental impurities	Risk-based elemental impurity limits
ICH Q2(R2)	Analytical validation	Specificity, accuracy, precision, LOD/LOQ, robustness and related parameters
EMA / US FDA	Regional regulatory control	Risk assessment, process changes and exposure minimization
WHO / CDSCO	GMP and quality assurance	Impurity profiling, validated testing and manufacturing controls

7. In Silico Prediction and Computational Toxicology

(Q)SAR tools provide early assessment of mutagenic potential from molecular structure. The source describes DEREK Nexus as an expert rule-based system and Sarah Nexus as a statistical model trained using experimental mutagenicity data. The OECD QSAR Toolbox supports structural grouping and read-across. These tools can reduce unnecessary laboratory testing and prioritize analytical or toxicological investigations, but predictions require expert interpretation, particularly for chemicals outside the applicability domain.

Artificial intelligence and machine learning extend computational prediction by integrating chemical descriptors, reaction conditions and large experimental datasets. Algorithms discussed in the source include Random Forest, Support Vector Machine, Decision Tree, Artificial Neural Network, Gradient Boosting and Deep Neural Networks. Their usefulness

depends on the quality, diversity and annotation of training data, and experimental confirmation remains important when predictions have significant implications.

8. Analytical Strategies for GTI Determination

GTIs are frequently present at very low concentrations, creating stringent requirements for sensitivity and selectivity. Complex matrices containing APIs, excipients, degradation products and process impurities can cause ion suppression, enhancement, co-elution and recovery problems. Consequently, analytical methods should be designed around specificity, accuracy, precision, linearity, range, recovery, robustness, LOD and LOQ in accordance with applicable validation expectations.

8.1 Sample Preparation

Liquid-solid extraction is simple and suitable for many solid pharmaceutical materials. Liquid-liquid extraction separates analytes between immiscible phases and can concentrate trace impurities. Solid-phase extraction provides selective clean-up, reduced matrix effects and improved sensitivity. Derivatization can enhance volatility, stability or detector response for poorly responding analytes. Microextraction minimizes solvent consumption and can enrich trace analytes. QuEChERS combines extraction with dispersive clean-up and may be useful for complex matrices.

8.2 Chromatographic and Mass-Spectrometric Techniques

LC-MS/MS and GC-MS/MS are important platforms for trace GTI analysis. LC-MS/MS is particularly useful for compounds with suitable ionization characteristics and polar or thermally labile analytes, while GC-MS/MS is useful for volatile or derivatized compounds. HRMS, Orbitrap-MS and QTOF-MS provide accurate-mass information and support non-targeted screening and structural characterization.

Table 4: Recommended Analytical Techniques for Different Classes of Genotoxic Impurities (GTIs)

GTI group	Commonly preferred technique	Reason
Nitrosamines	LC-MS/MS or GC-MS/MS	High sensitivity and selectivity at ultra-trace levels
Alkyl halides	GC-MS / GC-MS/MS	Volatility and chromatographic suitability
Sulfonate esters	LC-MS/MS	Sensitive determination of relevant process impurities

Azides	Ion chromatography / LC-MS/MS	Suitable for ionic or reactive species
Unknown/degradation impurities	HRMS / QTOF / Orbitrap	Accurate mass and structural information

8.3 Spectroscopic Techniques

FTIR provides rapid functional-group identification and supports impurity characterization. NMR offers detailed structural information and can distinguish isomers and confirm structures suggested by mass spectrometry. Raman spectroscopy provides complementary vibrational information and can support direct or in-process analysis. UV-Vis is useful for chromophoric compounds and routine HPLC-UV impurity monitoring, although some GTIs lack suitable chromophores and therefore require derivatization or mass spectrometry.

8.4 Elemental Impurity Determination

Elemental impurities arise from raw materials, catalysts, equipment, process water, packaging and environmental sources. The review identifies ICH Q3D(R2) and USP <232>/<233> as important frameworks and describes ICP-MS and ICP-OES as preferred techniques. ICP-MS measures ions according to mass-to-charge ratio and provides very high sensitivity, whereas ICP-OES measures characteristic optical emission from excited atoms and ions.

Table 5: Comparison of ICP-MS and ICP-OES Techniques Based on Principle, Sensitivity, Multi-Element Analysis, and Major Strengths.

Parameter	ICP-MS	ICP-OES
Principle	Mass-to-charge measurement	Characteristic optical emission
Typical sensitivity	Very high; trace/ppt capability	High; generally ppb capability
Multi-element analysis	Yes	Yes
Major strength	Ultra-trace determination	Routine multi-element analysis

9. Analytical Method Development and Validation

A fit-for-purpose GTI method begins with defining the analytical target, understanding the matrix and selecting an appropriate separation and detection platform. Analytical Quality by Design (AQbD) can be used to identify critical method attributes and critical method parameters, evaluate risks and establish a robust analytical design space.

- Specificity: reliable discrimination of the GTI from API, excipients and related impurities.
- Accuracy and recovery: closeness of measured values to accepted values and adequate extraction recovery.
- Precision: repeatability and intermediate precision appropriate to the intended use.

- LOD and LOQ: sufficiently low to demonstrate control at the required impurity level.
- Linearity and range: suitable response across the intended concentration interval.
- Robustness and ruggedness: resistance to deliberate and normal variations in analytical conditions.
- Stability: demonstration that standards and prepared samples remain suitable during analysis.

10. Genotoxicity Testing

Analytical detection establishes the presence and concentration of an impurity, whereas toxicological testing addresses biological relevance. The source discusses the Ames bacterial reverse mutation test, micronucleus assay, mouse lymphoma assay, comet assay, chromosomal-aberration assay and in vivo genotoxicity studies.

Table 6: Comparison of Common Genotoxicity and Mutagenicity Tests Based on Primary Endpoints and Test Systems.

Test	Primary endpoint	Typical system
Ames test	Gene mutation	Salmonella/E. coli
Micronucleus assay	Chromosome damage	Mammalian cells/rodents
Mouse lymphoma assay	Gene mutation	L5178Y cells
Comet assay	DNA strand breaks	Rodent tissues/cells
Chromosomal aberration	Structural chromosome abnormalities	Mammalian cells
In vivo studies	Genetic damage in an organism	Mice/rats and other accepted models

11. Control Strategies for Genotoxic Impurities

The preferred approach is prevention or minimization of GTI formation wherever feasible. Route selection can avoid hazardous reagents or reactive intermediates. Process optimization reduces side reactions, while impurity purge studies demonstrate removal across downstream operations. Starting-material selection and supplier qualification reduce incoming risk. Green chemistry can reduce hazardous reagents, waste and solvent burden.

QbD integrates risk assessment and process understanding into development. PAT provides in-process monitoring of critical process parameters and quality attributes, supporting earlier detection of deviations. Continuous manufacturing can improve process control and reduce the time available for impurity accumulation. Together, these strategies shift GTI control toward proactive lifecycle management.

12. Nitrosamine Impurities: Special Focus

Nitrosamines are an important GTI class because of their mutagenic and carcinogenic potential and their very low acceptable exposure levels. They may form from interactions between amines and nitrosating species during synthesis, processing, storage or degradation. The source describes increasing attention to nitrosamine drug substance-related impurities (NDSRIs), which may arise from the API itself under suitable chemical conditions.

Recent recalls described in the source illustrate several formation pathways, including manufacturing changes, contaminated solvents, API synthesis, degradation during storage and other process-related mechanisms. These events strengthened expectations for comprehensive nitrosamine risk assessment, improved supplier qualification, process controls, stability evaluation and sensitive analytical monitoring.

Table 7: Examples of Nitrosamine Impurities in Pharmaceutical Products and Reported Manufacturing or Storage-Related Actions.

Example	Impurity noted in source	Reported context/action
Valsartan	NDMA/NDEA	Process changes or contaminated solvents; global recall
Losartan	NDMA/NDEA/NMBA	API synthesis; recall
Ranitidine	NDMA	Storage degradation; withdrawal
Metformin ER	NDMA	Manufacturing contamination; affected-batch recall
Varenicline	N-nitroso-varenicline	Manufacturing/storage; voluntary recall
Quinapril	N-nitroso-quinapril	API degradation/storage; recall
Duloxetine	N-nitroso-duloxetine	NDSRI formation; Class II recall reported in source
Cinacalcet	NDSRI	Manufacturing-related; recall

13. Current Challenges

- Ultra-trace quantification at ppb or ppt levels requires highly sensitive instruments, optimized sample preparation and stringent validation.
- Complex pharmaceutical matrices can cause co-elution, ion suppression, enhancement and recovery problems.
- Many emerging GTIs lack universally standardized analytical procedures and certified reference standards.
- Regulatory implementation and product-specific expectations can differ across jurisdictions.

- Advanced instrumentation, isotopically labelled standards and trained personnel increase analytical costs.
- Large numbers of raw-material, process, release and stability samples create demand for automation and high-throughput workflows.

14. Emerging Trends and Future Perspectives

The source identifies several developments that may strengthen GTI control. AI-assisted method development can help optimize chromatographic conditions and predict impurity formation. Digital laboratories combine analytical instruments with LIMS, electronic laboratory notebooks, cloud computing and automated data processing. HRMS supports non-targeted screening and identification of previously unrecognized impurities. Green analytical chemistry aims to reduce solvent use and environmental burden.

Metabolomics and chemometrics can provide broader impurity profiling and interpretation of complex datasets. Portable Raman, NIR, FTIR and compact mass-spectrometric systems may support rapid on-site assessment. Real-Time Release Testing (RTRT) integrates PAT, sensors, multivariate models and automated control to evaluate product quality during manufacturing. Greater regulatory harmonization and improved reference standards for emerging NDSRIs are also identified as future priorities.

- AI-assisted analytical method development and computational toxicology.
- Expanded HRMS for non-targeted impurity screening.
- Machine-learning prediction of impurity formation and toxicity.
- Green analytical methods with reduced solvent consumption.
- Integration of metabolomics, chemometrics and digital laboratory systems.
- Portable analytical devices for rapid quality assessment.
- Wider implementation of RTRT, PAT and continuous manufacturing.
- International harmonization and development of validated methods/reference standards for emerging NDSRIs.

15. CONCLUSION

Genotoxic impurity control is a critical component of pharmaceutical quality because DNA-reactive impurities can present significant risk even at trace exposure levels. The source review demonstrates that effective management requires an integrated approach encompassing source identification, toxicological risk assessment, sensitive analytical

measurement, process understanding, validated purification and lifecycle monitoring. ICH M7(R2) provides the principal framework for DNA-reactive impurity assessment, supported by complementary impurity and analytical-validation guidelines.

Modern platforms such as LC-MS/MS, GC-MS/MS, HRMS, ICP-MS and ICP-OES have strengthened trace-level detection, while QbD, PAT and impurity purge studies support prevention and control. Nitrosamine and NDSRI concerns have reinforced the importance of proactive risk assessment and stability monitoring. Future progress is expected from AI, machine learning, digital laboratories, chemometrics, metabolomics, green analytical chemistry, portable devices and RTRT. Continued integration of analytical science, toxicology, process engineering and regulatory science will be important for maintaining safe, effective and high-quality pharmaceutical products.

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CONFLICT OF INTERESTS

Authors declare that there is no conflict of interest.

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