Toxicological Approaches to Deal with Out-of-specification Impurities



When impurities exceed specification limits, manufacturers face the dual challenge of regulatory compliance and patient safety concerns. These out-of-specification impurities require systematic assessment through identification, characterisation, and toxicological evaluation against established thresholds. While ICH guidelines provide frameworks, each situation demands expert judgment to navigate successfully. Effective management isn't just about compliance—it's about ensuring patient safety while maintaining product availability. Through structured risk assessments and scientific justification, a concerning deviation can transform into a manageable solution with appropriate specification adjustments. A systematic approach turns potential manufacturing crises into opportunities to demonstrate scientific rigor and Regulatory intelligence.

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The pharmaceutical industry is a pillar of hope for millions of people, providing medications that alleviate pain, cure diseases, and save lives. From discovery to development and eventual patient use, every step of a drug's journey is meticulously regulated to ensure its safety, efficacy, and quality. Among the numerous quality assurance challenges the industry faces, managing impurities is one of the most formidable challenges faced by the industry. Among this, the out-of-specification (OOS) impurities present altogether a different challenge. These impurities, when exceeding acceptable limits, can pose serious toxicological risks and must be addressed through well-defined and scientifically grounded approaches. This editorial intends to explore the toxicological strategies deployed to manage OOS

impurities, ensuring that patient safety remains uncompromised and regulatory expectations are met.

Pharmaceutical impurities can arise from a variety of sources, including:

- Residual raw materials
- Reaction intermediates
- By-products of synthesis
- Degradation products from storage

To streamline impurity identification and control, the International Council for Harmonisation (ICH) has developed key guidelines—ICH Q3A and Q3B—outlining impurity classification, thresholds, and control strategies. These guidelines help define acceptable limits and emphasise risk-based approaches for managing the impurities in new drug substances and drug products.

However, when impurities exceed their predefined thresholds, they are considered as OOS. This triggers a comprehensive investigation to determine the root cause and define appropriate corrective actions. Whether the issue stems from a deviation in manufacturing, unexpected degradation, or contamination, identifying the cause is essential for selecting the most suitable mitigation strategy. Toxicological risk assessments of the specific OOS impurity is one of the most adopted approaches in the qualification process.

Toxicological risk assessment aims to evaluate the health hazards associated with specific impurities, with a particular focus on genotoxicity, mutagenicity, carcinogenicity, and systemic toxicity. The first step in toxicological assessment is impurity characterisation, including structural elucidation and estimation of potential biological activity. If the impurity has known toxicological data, it can be compared directly to established thresholds. However, in the absence of empirical data, QSAR predictive models are employed. In absence of genotoxicity data, the OECD validation principles for (Q)SAR models (statistical and expert rule-based prediction models) should be applied to predict mutagenicity. For (Q)SAR analyses, there are several software tools built on the principles of ICH M7 requirements that are readily available. These models help predict whether an impurity is likely to be genotoxic or non-genotoxic. If (Q)SAR prediction coupled with expert toxicologist's judgment concludes an impurity as mutagenic, a control strategy must be implemented in line with the Threshold of Toxicological Concern (TTC), usually set at 1.5 µg/day for lifetime exposure. This conservative threshold reflects the minimal level at which a genotoxic impurity might pose a minimum or negligible risk to human health.

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For impurities predicted to be non-mutagenic and that fall within specified limits, no further action is typically required. However, for OOS cases, more comprehensive toxicological assessments or experimental studies become necessary. When non-mutagenic impurities exceed the accepted limits, two main strategies can be employed for qualification:

1. Data-Based Qualification: This approach utilises existing non-clinical or clinical data, including:

Toxicokinetic and ADME (Absorption, Distribution, Metabolism, and Excretion) profiles identification for the impurity.

Hazards Identification: The first step involves a comprehensive search of scientific literature and databases to identify any existing toxicological data for the specific OOS impurity. This includes information on:

- Acute Toxicity: Effects following a single or short-term exposure.
- Repeat-Dose Toxicity: Effects following prolonged or repeated exposure.
- Genotoxicity: Potential to damage DNA and cause mutations.
- Carcinogenicity: Potential to cause cancer.
- Reproductive and Developmental Toxicity: Effects on fertility and fetal development.
- Local Toxicity: Irritation or sensitisation at the site of contact.

Exposure Assessment: Accurate determination of the concentration of the OOS impurity in the affected batch is critical. Additionally, the intended dose of the drug product and the duration of patient exposure and route of administration need to be considered. Based on detailed information, the Margin of safety (MOS) is calculated by dividing the identified safe threshold limit/PDE by the estimated maximum impurity exposure level. A larger MOS generally indicates a lower level of concern. Acceptable MOS are typically established based on the severity of the potential hazard and the uncertainty in the data.

The potential risks associated with the OOS impurity need to be weighed against the therapeutic benefits of the drug product. This assessment considers the severity of the potential adverse effects, the intended use of the drug, and the availability of alternative treatments.

2. Experimental Testing: If in silco mutagenicity prediction results in inconclusive results, or if existing data is insufficient, experimental validation becomes necessary. This typically involves: ▶

Ames test: The gold-standard genotoxicity assay for determination of mutagenic potential

Repeat-dose toxicity studies in rodent models, tailored to match the intended duration of human exposure. These studies help understand any systemic toxicity concerns and determine a No-Observed-Adverse-Effect Level (NOAEL), which can be used to calculate acceptable impurity levels/PDE using health agency recommended safety factors.

Pharmaceutical companies must decide the next course of action for the affected batches. Regulatory and quality teams typically consider the following outcomes:

- Reprocessing: This involves re-treating the batch to remove or reduce the impurity to acceptable levels in case the impurity exposure does not meet the safety standards and having impact on quality of the product.
- Release with Justification: If risk assessments demonstrate that the impurity poses negligible risk to patient health, companies may choose to release the batch with appropriate justification. Detailed toxicological evaluation, exposure data, and rationale must be documented and submitted to regulatory authorities.
- Rejection: If an impurity presents a significant health risk and cannot be mitigated, the batch must be discarded to ensure patient safety.

Each of these decisions must be thoroughly documented, supported by scientific evidence, and made in collaboration with regulatory bodies. Transparency and adherence to guidelines, such as ICH Q3C (residual solvents), Q3D (elemental impurities), and M7 (mutagenic impurities), are essential to maintain regulatory compliance and uphold public trust. Addressing OOS impurities is far from a linear process. It requires collaboration across several disciplines, including:

- Analytical Chemistry: For precise impurity identification and quantification
- Toxicology: For health hazard/risk evaluations and qualification strategies

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- Regulatory Affairs: For alignment with global compliance standards
- Quality Assurance: For process control and documentation
- Process Development: For implementing manufacturing changes to prevent recurrence

This coordinated effort ensures that pharmaceutical products meet the highest standards of safety and quality. Advancements in toxicological sciences and analytical technologies continue to enhance impurity control strategies. Tools such as in silico modelling, high-resolution mass spectrometry, and non-animal testing platforms are becoming increasingly integral in impurity evaluation.

Moreover, a growing emphasis on science- and risk-based decision-making—a cornerstone of modern regulatory frameworks which encourages a more pragmatic and data-driven approach to impurity qualification. The industry must also stay agile in responding to evolving regulatory expectations. Agencies such as the FDA, EMA, and PMDA are placing greater emphasis on impurity profiles and toxicological justifications during drug approvals and post-marketing surveillance. Continuous learning, adaptation, and proactive risk management are therefore vital.

Impurities in pharmaceuticals are an unavoidable aspect of drug synthesis and storage. However, when these impurities exceed their acceptable thresholds, toxicological evaluation becomes essential to ensure patient safety. Through predictive modelling, experimental validation, and regulatory engagement, manufacturers can effectively address OOS impurities and make informed decisions regarding product disposition. Ultimately, the toxicological approach to managing OOS impurities is not merely a regulatory requirement—it is a commitment to public health. By integrating science, expertise, and vigilance, the pharmaceutical industry can continue to uphold its most critical promise: delivering safe, effective, and high-quality medicines to those who need them most. ■

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Dr. Bakul Datta, Manager in MPR–Nonclinical & Toxicology Services at Freyr Global Regulatory Solutions, brings over 17 years of experience in regulatory pharmacology, toxicology, and risk assessment. He has published widely in peer-reviewed journals and has expertise in HBEL (PDE/OEL), impurity and extractable risk assessments, environmental risk assessments, F-Value determination for child resistant packaging, regulatory toxicology studies, and preparation of nonclinical documentation for IND, NDA, and 505(b)(2) submissions.

