

# Ensuring Industry Compliance in Identifying Genotoxic Impurities in APIs

Despite medical advances and innovative new drug therapies that are treating dreadful diseases, ensuring patient safety still must be the number-one goal of Contract Manufacturing Organizations (CMOs) and other drug manufacturers.

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For CMOs like PCI Synthesis, the control and characterization of drug substances and their impurities is not only a necessary step, but an essential and highly regulated aspect of the drug development process. This article, the second in a series on impurities (the first can be found [here](#)) provides insights and tips to improve the understanding of known and unknown components within your product which will ultimately help mitigate impact on patient safety, and minimize the likelihood of potential delays in commercialization, drug shortages or product recalls.

Genotoxic impurities are essentially reactive compounds that can induce genetic mutations when they react with DNA. Genotoxic impurities are not always a bad thing, and can sometimes be useful in chemical synthesis. Yet for the most part, if a genotoxic impurity is present in an active pharmaceutical ingredient (API), it could potentially cause cancer in a patient.

Yet it's almost impossible to eliminate all genotoxic impurities during API synthesis. Our scientists are always on the lookout for structural alerts but there's really no answer as to why one compound is genotoxic and another is not.

Identifying and controlling these impurities is extremely challenging because they have highly reactive, diverse properties, and must be controlled at levels much lower than what is typically found in traditional impurities.

## Industry and FDA Guidelines for Addressing Genotoxicity

To help drug manufacturers properly identify and address potentially genotoxic impurities in their chemicals, the international Conference of Harmonization (ICH) released [guidelines](#) in June 2014. "The Assessment and Control of DNA Reactive Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk," provides a practical framework for identifying, categorizing and qualifying genotoxic impurities to limit potential carcinogenic risk.

According to the guidelines, when genotoxic impurities are identified, an appropriate control strategy leveraging process understanding and/or analytical controls should be developed to ensure that the mutagenic impurity is at or below the acceptable cancer risk level. The impurity assessment is a two-stage process:

- Actual impurities that have been identified should be considered for their mutagenic potential.
- An assessment of potential impurities likely to be present in the final drug substance is carried out to determine if further evaluation of their mutagenic potential is required.

Potential impurities in the drug substance can derive from starting materials, reagents and other processes leading up to drug development. According to the ICH Guidelines, the risk of carryover into the drug substance should be assessed for identified impurities that are present in starting materials and intermediates, and impurities that are reasonably expected by-products in the route of synthesis from the starting material to the drug substance.

The FDA also released [guidance](#) on the ways CMOs can characterize and reduce the potential lifetime cancer risk associated with patient exposure to genotoxic and carcinogenic impurities both during clinical development and after approval. These approaches include:

- Changing the synthetic and/or purification routes to minimize the formation and/or maximize the removal of the relevant impurity.
- Allowing a maximum daily exposure target of 1.5 Iµg per day for the relevant impurity as a general target for marketed products, though higher levels may be acceptable during clinical development.
- Further characterizing the genotoxic and carcinogenic risk via mechanism of action or weight-of-evidence approaches, or through additional studies to better support appropriate impurity specifications.

## CMO Best Practices for Identifying and Addressing Genotoxic Impurities

When developing APIs, it is the primary responsibility of the CMO to identify the stages in which impurity can occur and work to control them at the stage of formation.

Additionally, toxicologists must perform safety evaluations of high-priority compounds, known API impurities, and impurities with a high probability of occurring, and they must classify these compounds as genotoxic or routine impurities. Various chromatography and spectroscopy methods can help identify genotoxic impurities in an APIs as well.

For CMOs like PCI Synthesis, it's imperative to identify genotoxic impurities at the source. Ensuring sound processes for identifying them, as well as having effective controls in place to address them are key to ensuring consistent and safe API manufacturing.

Because impurities during API manufacturing are a big problem, we will be writing more about impurities. The first article is, "[Identifying Impurities in APIs.](#)" Other relevant articles include: "[Filtration of APIs on a Basket Centrifuge: Key Process to Ensure Safe and Effective Drug Manufacturing and Delivery](#)" and "[Manufacturing APIs for Clinical Trials: How complexity impacts the timeline.](#)" For more information, consider subscribing to our [newsletter](#). Or call us at (978) 462-5555.