SCENARIO SHEET

Sterling

Genotoxic method development

THE SITUATION

Amid an evolving regulatory landscape and an increased industry-wide focus on genotoxic impurities, a proactive approach to genotoxic method development is critical in API development.

Genotoxic impurities are exceedingly important to detect because of their mutagenic and carcinogenic properties. As a result, it is critical to affirm that genotoxic impurities remain below dangerous levels using a thorough analytical approach.

THE CHALLENGES

Low detection levels

Since genotoxic impurities react with DNA, they can be detrimental to human health. Impurities are classified based on their level of risk, with class 1 presenting the most serious risk.[1] **With the potential to cause mutations and cancer, these impurities can be harmful even in very small amounts.** As a result, genotoxic impurities require very low levels of detection, typically based on the product's maximum daily dose (MDD). This necessitates a sensitive analytical approach that can identify impurities even in small concentrations.

Varying structures

Genotoxic impurities can vary in structure and solubility, and these properties have important implications for the most appropriate analytical method. The structure of an impurity can provide insight into whether it will ionise in any given manner. To adhere to project timelines and optimise the analytical approach, it is important to identify the ideal testing methodology early on. Liquid-chromatography mass spectrometry (LCMS), gas chromatography mass spectrometry (GCMS) and other sensitive analytical techniques are commonly used in genotoxic impurity analysis.

Iterative testing

The initially chosen analytical method may not always achieve the desired or anticipated results. **As a result, genotoxic method development can be an iterative process, requiring multiple rounds of testing and changes to the methodology to properly isolate and measure the impurity.**

Impurity sources

Genotoxic impurities can arise from various sources at different stages of development. They may come from starting materials, catalysts, reagents and even degradation of a finished drug product due to shipment and storage conditions. **Because these impurities can surface across a product's lifecycle, they can be notoriously difficult to pinpoint.** As a result, a proactive approach to genotoxic impurity analysis is important to set a project up for success.

The Sterling solution

At Sterling, our extensive analytical chemistry expertise, experienced team of analysts and range of specialised analytical equipment enable us to identify and mitigate harmful impurities. In addition, we closely collaborate with customers to determine the best analytical approach and maximise their project's success.

"Genotoxic impurities have become a key focus in the industry and for our customers in recent years, particularly with extensive conversation around nitrosamines. We're committed to detecting impurities even at very low levels to help our customers eliminate risk in their products."

- Richard Bates,
Senior Development Analyst, Sterling Pharma Solutions

Specialised equipment and teams

Specialised, high-sensitivity analytical equipment is critical for identifying impurities that are present at low levels. At Sterling, our range of analytical capabilities and equipment, including triple quadrupole mass spectrometry (TQMS) and headspace gas chromatography mass spectrometry, enable us to perform robust testing for our customers utilising the analytical approach that is best suited to the structure of each molecule and impurity. By using highly specialised equipment, we can test even very large samples with increased sensitivity.

Proven approach

Since genotoxic impurities can be challenging to identify, we leverage a proven, data-driven approach to method development. Typically, a customer affirms that an impurity is present using structural alerts. Then, we begin by evaluating the impurity's structure and determining whether it will ionise on certain instruments, enabling us to tailor our approach to the specific impurity. If the impurity does not ionise as anticipated, we then alter parameters and run the process again. If an impurity is present above the acceptable level based on toxicology studies, we collaborate with the customer to align on the best approach to mitigating the impurity, such as through recrystallisation.

Regulatory expertise

Regulatory agencies like the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Council for Harmonisation (ICH) place limits on genotoxic impurities and provide guidelines for testing.[2] **Our deep understanding of the regulatory landscape enables us to prevent harmful levels of impurities from ending up in customers' products.** In addition, we put safety first, working with fume hoods and gloves when handling potentially carcinogenic or mutagenic materials.

Are you ready to elevate genotoxic method development?

Visit **sterlingpharmasolutions.com** to learn more.

1 Gosar, A.; Sayyed, H.; Shaikh, T. Genotoxic Impurities and Its Risk Assessment in Drug Compounds. Drug Des Int Prop Int J [Online] Oct. 23, 2018, 227-232. Lupine Publishers. https://lupinepublishers.com/drug-designing-journal/pdf/DDIPIJ.MS.ID.000143.pdf (accessed May 3, 2021).

2. Bobst, S. Genotoxic impurities in pharmaceutical products. European Pharmaceutical Review, December 20, 2019. Retrieved from https://www.europeanpharmaceuticalreview.com/article/108031/genotoxic-impurities-in-pharmaceutical-products/.

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