VIEW POINT

Detection and quantitation of process-related impurities

in biopharma manufacturing

Syngene

Putting Science to Work

Introduction

Detection and quantitation of process-related impurities is an important part of quality control in biopharma manufacturing. Process-related impurities can significantly impact a pharmaceutical product's quality, safety, and efficacy. These impurities may get generated during the manufacturing process, degradation, starting materials and reagents, by-products, storage conditions, or contamination. If not properly detected and quantified, these impurities can lead to adverse effects on patients.

For this reason, ICH guidelines make quality by design (QbD) an essential requirement during pharmaceutical development. The ICH Q8, Q9, and Q10 outline a systematic approach to pharmaceutical development, emphasizing the critical importance of understanding product and process parameters to ensure product quality.

In this article, we discuss the challenges in the detection and quantitation of process-related impurities including nitrosamine impurities and Syngene's capabilities and solutions to address them.

Challenges in the detection and quantification of process-related impurities

Several challenges can arise in the detection and quantification of process-related impurities using analytical techniques.

1 Sensitivity

Some impurities may be present at very low concentrations, making detection and quantification challenging. Specialized analytical techniques, pre-concentration or derivatization, may be necessary to improve sensitivity.

2 Selectivity

Analytical techniques must be selective enough to distinguish the impurities from other components in the sample matrix.

3 Matrix effect

The sample matrix, such as drug substance or formulation, can affect the performance of the analytical method. Matrix effects can interfere with separating or detecting impurities and may require additional steps to overcome them.

4 Identification

Identifying impurities can be challenging, especially if the impurity is unknown or has a complex structure. The use of multiple analytical techniques is required to identify the impurity .

5 Standardization

The lack of standardized methods for detecting and quantifying process-related impurities can make comparing results between different laboratories or studies difficult. Establishing standardized procedures and reference materials can help improve consistency and accuracy.

6 Validation

Analytical validation methods must be corroborated to ensure accuracy, precision, and reliability. Validation can be time-consuming and resource-intensive and may require the use of reference materials or standards.

7 Cost

Some analytical techniques can be expensive or require specialized equipment or expertise, making them inaccessible to some laboratories or companies. This can limit the ability to characterize the impurities in a drug substance or product fully.

Syngene's solutions for addressing process-related impurities

The detection and quantitation of process-related impurities are typically accomplished using high-end analytical techniques. These techniques are used to separate, identify and quantify impurities in the drug substance.

Our services include providing the framework to identify the critical quality attributes (CQAs) to finalize the relevant process parameters during product development. During this process, the emphasis is on using risk management tools such as failure-mode effect analysis and DoE to identify and control potential sources of variability in the manufacturing process. This, in turn, facilitates the analytical justification of specifications.

Analytical method development: Syngene can help pharmaceutical and biopharma companies develop analytical methods to detect and quantify impurities in drug substances or products. We have expertise in various analytical techniques, including HPLC, GC, NMR, and high-resolution mass spectrometry.

Identification of unknown impurities: We use various techniques, such as mass spectrometry, NMR spectroscopy, and IR spectroscopy, to identify unknown impurities in drug substances and drug products.

Impurity profiling: We offer impurity profiling services to fully characterize the impurities in the drug substance or product. This includes identifying impurities, quantifying impurities, and assessing the impurity profile over time.

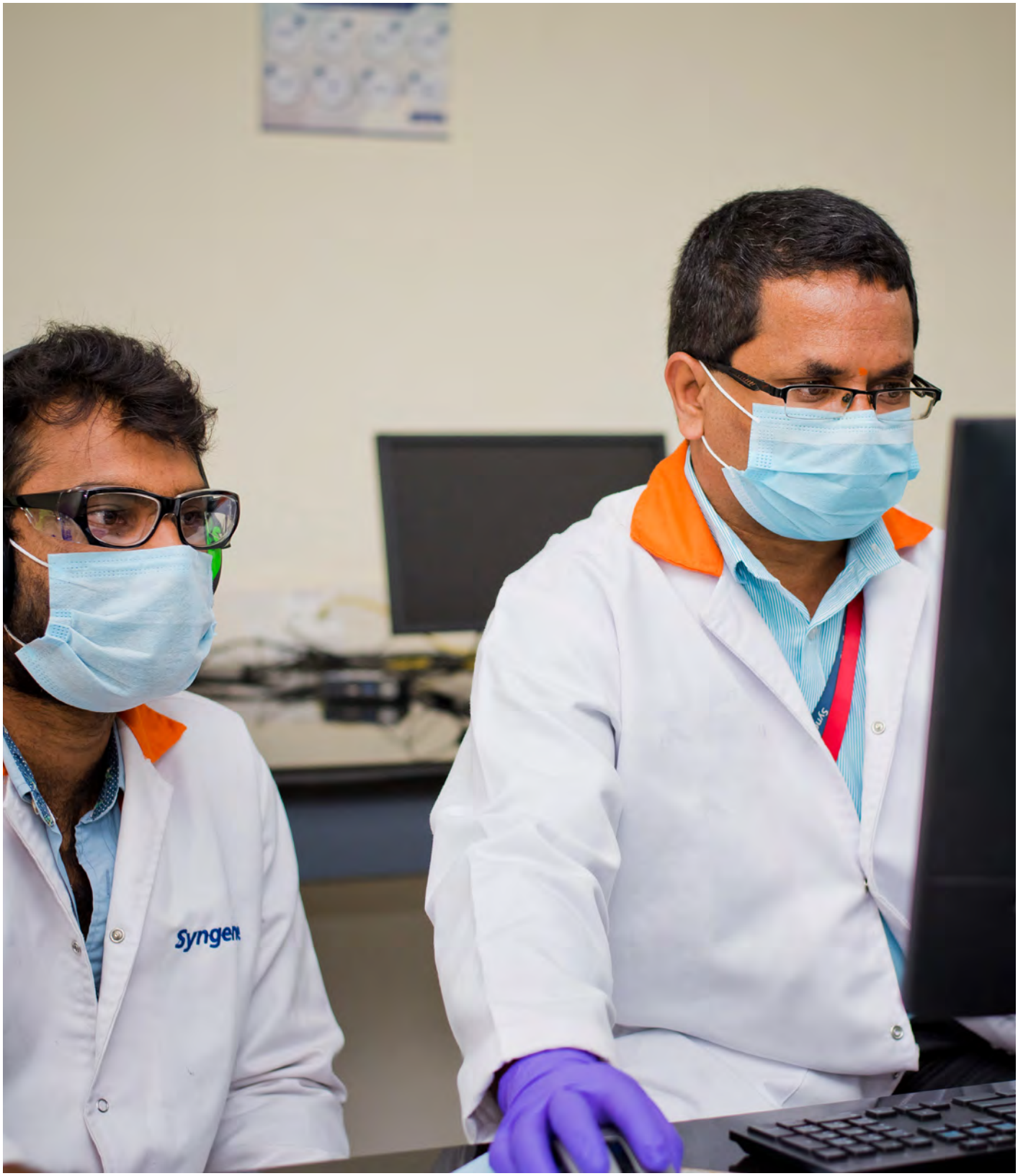
Validation and transfer of analytical methods: We can help to validate analytical methods to ensure they meet regulatory requirements in line with ICH Q2(R1). We can also transfer validated methods to client laboratories, providing a standardized approach to impurity testing.

ICH Stability testing: We can conduct pharmaceutical stability testing to identify impurities that may arise during the shelf-life of a drug substance or product.

Regulatory support: We offer regulatory support for impurity testing, including preparing regulatory submissions and interactions with regulatory agencies.

Nitrosamine impurities

The recent and unexpected finding of nitrosamine impurities (probable human carcinogens in pharmaceuticals), such as angiotensin II receptor blockers (ARBs), ranitidine, nizatidine, and metformin, resulted in a large-scale recall of these drugs. Consequent to this finding, the FDA, in collaboration with regulatory counterparts worldwide, issued guidance to API and drug product manufacturers. The guidance was on appropriate actions they need to take to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products *(Source: Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry)*.

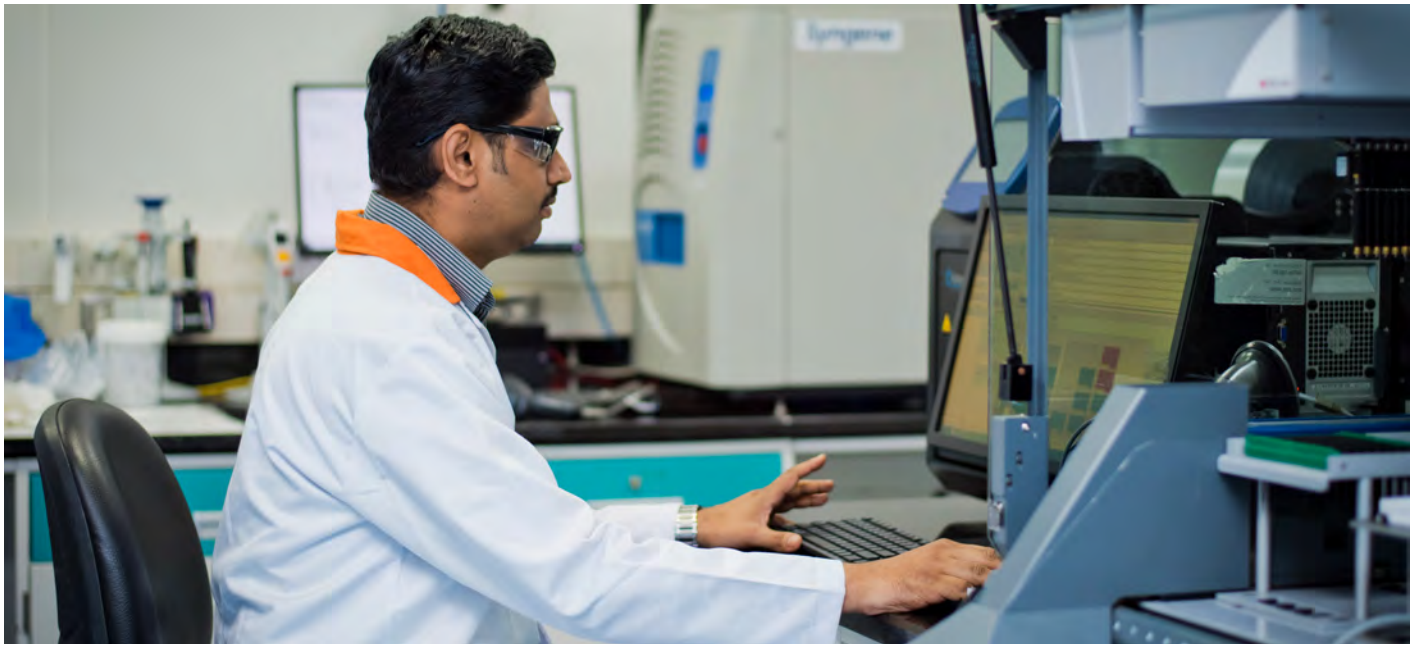


Syngene's Center of Excellence for nitrosamine impurity testing

Syngene offers a state-of-the-art facility for risk assessment, development, and validation of nitrosamine impurities in drug substances and drug products. The facility supports Nitrosamine testing in drug substances in line with formulation requirements for small molecule APIs, key sourcing materials (KSM), and intermediates. Its internationally accredited Analytical labs and highly skilled scientists ensure all the data generated complies with regulatory requirements.

Key Features

- Diverse experience in nitrosamine risk assessment, method development and validation, and testing of nitrosamine impurities in drug substances, drug products, key starting material, and intermediates
- All methods developed and validated according to USP General Chapter <1469> in line with current scientific and regulatory approaches. This ensures appropriate control over nitrosamine impurities in APIs and drug formulations
- Availability of skilled workforce, including those with expertise in nitrosamine impurity testing
- Dedicated area for nitrosamine and azido impurity testing; nitrosamine and azido impurity characterization
- Availability of sophisticated nitrosamine analysis instruments such as LC-MS/MS, GC-MS/MS, and HRMS to quantify impurities at the ppb level as per regulatory requirements
- All nitrosamine testing conducted in cGMP labs audited by multiple regulatory agencies



Conclusion

Syngene has the expertise and capabilities, including state-of-the-art instrumentation, to provide comprehensive solutions for the detection and quantitation of process-related impurities in pharma and biopharma products. We also offer a state-of-the-art facility for risk assessment, development, and validation of nitrosamine impurities in drug substances and products.

Our highly sensitive and selective methods allow for accurate identification and quantitation of impurities, even at low levels. The use of appropriate standards, controls, and validation procedures ensures the accuracy and reliability of our analytical results as per regulatory guidelines. This ensures the successful development and manufacturing of safe and effective pharmaceutical and biopharmaceutical products at all times.

About the author

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Jai Kumar Keshwan heads the Drug Substance Analytical function at Syngene that supports the three verticals of small molecules and macromolecules, oligonucleotides, and performance and specialty materials within Syngene. He has over 28 years of experience in API research and development (Analytical) ranging from generics to innovation, having worked in multiple roles in multinational companies. Jai Kumar's expertise lies in delivering drug substances that conform to GLP, and cGMP requirements of various drug regulatory authorities, characterizing APIs and related impurities, developing analytical methods, and technology transfer to commercial sites.

To know more about our Analytical services, contact our team

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About Syngene

Syngene International Ltd. (BSE: 539268, NSE: SYNGENE, ISIN: INE398R01022) is an integrated research, development and manufacturing services company serving the global pharmaceutical, biotechnology, nutrition, animal health, consumer goods and specialty chemical sectors. Syngene's more than 5200 scientists offer both skills and the capacity to deliver great science, robust data management and IP security and quality manufacturing at speed to improve time-to-market and lower the cost of innovation. With a combination of dedicated research facilities for Amgen, Baxter and Bristol-Myers Squibb as well as 2 Mn sq. ft of specialist discovery, development and manufacturing facilities, Syngene works with biotech companies pursuing leading-edge science as well as multinationals, including GSK and Merck KGaA.

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