CASE STUDY 000227

Patheon: End-to-end pharma services solutions for every drug development journey

The road to successful nitrosamine impurity analysis begins with client collaboration and ends with fit-for-purpose methods

Patheon provides industry leading CDMO services as well as clinical trial solutions. With more than 55 locations around the world, we provide an end-to-end drug development offering to companies of all sizes including APIs, biologics, viral vector services, cGMP plasmids, early and late phase development, clinical trial solutions, logistics services, and commercial manufacturing. Patheon is a trusted partner for every step in the drug development journey with unrivalled quality, reliability, and expertise.

"Because we already perform extensive manufacturing and testing, we have the technology and expertise in place to take on additional services for our clients. We try to be as much as a one-stop-shop as possible and take as much of the burden as we can to streamline the experience."

– Allan Potts, Principal Leader PDS Analytical Development

Nitrosamines are a group of compounds that have potent genotoxic effects on humans, referred to by ICH M7 as a cohort of concern. This group has a mutagenetic effect on DNA as they are considered alkylating agents that can bind directly to DNA, leading to an increased lifetime risk of cancer. Because of the potential mutagenic and carcinogenic effects of these compounds, regulatory bodies such as USFDA and EMA recommend to control and monitor the levels in drug products to below published limits to minimize their impact on patient health.

On a broader perspective, the control of impurities in pharmaceuticals is important to ensure high efficacy of the final product. Impurities may be counterproductive, diminishing or negating the effect of the drug and/or increasing toxicity. The same care and end goal must be taken with the nitrosamine class of impurities as with all impurity classes—to reduce and control the levels as much as possible down to a toxicologically acceptable dose dependent intake level.

As part of making sure that Patheon is prepared for our client needs, we are always keeping up to date with current industry trends. Patheon primarily offers manufacturing and routine testing services, and so recognizes that our clients are trying to fulfil all the data requirements for registration and market approval of their drugs. Because we already perform extensive manufacture and testing, we have the technology and expertise in place to take on additional services for clients.

Optimizing methods to fit the client needs

Wael Elmasri, Staff R&D Manufacturing Scientist talks about the challenges faced with the first nitrosamine request:

"We started looking at nitrosamine impurities in Ranitidine drug product. At first the client request was to closely follow the methods based on FDA recommendations; one using high-resolution accurate mass (HRAM) mass spectrometry (MS), and another utilizing triple quadrupole mass spectrometry (QqQ). The latter we used as a starting point for our method development, optimizing as we went in order to satisfy the client requirements whilst utilizing the expertise and technology available to us in-house. We worked closely with the client to understand the needs and developed a method on our Thermo Scientific™ TSQ™ Fortis triple quadrupole mass spectrometer.

"We look for the instrumentation that will give us the most appropriate sensitivity and highest specificity, and then fully validate methods to make sure they are fit-for-purpose. For nitrosamines, there are published limits of detection and quantification, and we can achieve them with our in-house solutions rather than going strictly with the published methods. We have the expertise to make these suitable and fully validated."

"For specific classes of impurities where all clients are going to need the same service, we look to set up dedicated analytical capabilities to offer the best service we can with the right expertise and technology already in place, whether that's extractables and leachables, residual solvents, or anything new that comes along such as nitrosamine impurities."

– Allan Potts, Principal Leader PDS Analytical Development

Maximum productivity distinguishes the TSQ Fortis and TSQ Fortis Plus triple quadrupole mass spectrometers, thanks to robust design comprising the Matrix Separator Ion Guide and ion beam guide with neutral blocker, and simplified user maintenance. This system also offers intuitive, workflow-driven software platforms and solutions that support various applications, regardless of user or technical skill level. Its robust design ensures reliable and consistent results, whether the methods are single sample-based experiments or high-volume screenings and quantitation.

"The TSQ Fortis mass spectrometer is the entry level QqQ system in Thermo Fisher Scientific's triple quadrupole portfolio, designed for robustness and reproducibility. Despite this, we have not failed yet to determine any nitrosamine at or below the required levels. It has proven to be a very accurate and robust system providing excellent linearity across the range. The TSQ Fortis mass spectrometer in our routine monitoring lab makes sense. As a GMP lab, robust and repeatable systems are a must. Easy to use, it's not the most sensitive out of the product range but it is sensitive enough not to give issues with fouling or day-to-day variation. The TSQ Fortis mass spectrometer has proven itself capable for commercial and routine testing purposes."

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– Wael Elmasri, Staff R&D Manufacturing Scientist

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Not just robust, but easy to use and easy to maintain

“We have routine maintenance on the system every six months, which is more than enough. Ad-hoc cleaning of the ion source is sufficient to keep the sensitivity levels up. This can be performed without breaking vacuum, which is a simple procedure, and saves on downtime.”

"We have a need to regularly train new analysts and auditors on the system. Both the maintenance of the system and the ease of use of Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) software, used to control the system, process the data, and generate the reports, provides a positive first experience. The user-friendly interface makes routine work simple whilst maintaining confidence in data integrity.”

“Chromeleon CDS handles a lot of the detailed audit trail information behind the scenes for the day-to-day user; however, the audits are still accessible (only a click away) and satisfied our document auditors’ requirements, from making sure the correct user performs the correct actions to being able to see examples of the impact of any processing changes. Access and simplicity of the audit trail makes this software really pleasing to use in a GMP environment.”

Patheon prides itself in taking skills we already have and applying them to technology that exists to provide solutions, and we are ready to evolve again for future requirements.

Find out more at **thermofisher.com/nitrosamines**

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