Waters™

Forward-thinking CDMO Tackles the Dynamic Challenge of N-nitrosamines Control with High Performance Analytical Instrumentation

Poland based Polpharma API relies on Waters analytical instrumentation for impurities method development and testing to meet the ever-evolving regulatory guidance around N-nitrosamines (nitrosamines) control in Active Pharmaceutical Ingredients (API).

API METHOD DEVELOPMENT AND TESTING AT POLPHARMA

Leader of the Polish pharmaceutical market and one of the leading drug manufacturers in the region of Central and Eastern Europe, Polpharma exports medicinal products to 35 markets and active pharmaceutical ingredients (APIs) to more than 60 countries. Polpharma API manufacturing facilities are therefore subject to rigorous inspections by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and other regulatory authorities. As the largest Polish manufacturer of APIs, Polpharma holds a broad and varied portfolio of pharmaceutical products and CDMO solutions that are offered worldwide. The organization offers a full range of services from initial development (for early stages of new chemical entities [NCEs]), process development, validation, and commercial manufacturing of APIs.

Focused on method development and testing, Polpharma API constantly works to stay ahead of ever-evolving regulatory guidelines on contaminants, most recently the detection of nitrosamines in pharmaceutical products. The analytical team is a part of the R&D Department at Polpharma API. They work as an integral part of the 'control strategy' group, in conjunction with other sections and departments in Polpharma API departments. The company has capitalized on the capabilities of advanced analytical instrumentation, particularly liquid chromatography coupled with mass spectrometry (LC-MS) for this purpose.

Polpharma API uses Waters UPLCs with tandem mass spectrometry for method development, identification of impurities, and other trace level applications.

WORKING WITH WATERS

While Polpharma has relied on Waters™ analytical instrumentation for many years, it's the long relationship with the Waters Support and Service team that has truly made the difference in managing the CDMO's rapid growth and innovative approach. Dr. Paweł Olszowy, Head of Analytical Development Section at Polpharma API, explains:

"We know the Waters Support and Service team is very experienced, and they're more than happy to help us or look for answers. We rely not only on their technical support to keep our instrumentation working, but also the analytical support that Waters provides. When we need them, they are there for us."

Dr. Olszowy explains how the CDMO's expansive experience has helped the company and its customers work through the global crisis:

"As an API producer, we were exceptionally well-prepared when regulatory agencies began expressing concerns. We had conducted thorough research on nitrosamines long before any rumors surfaced. API producers consistently find themselves at the forefront of adapting to evolving regulations due to our extensive client base and diverse range of drug products. Leveraging our core competency and extensive experience, we gained a significant advantage in addressing these concerns."

Backed by a long history of support from Waters, Polpharma has continued to upgrade its Waters analytical instruments to achieve the sensitivity and robustness necessary for impurity analysis.

MEETING GLOBAL NITROSAMINE REQUIREMENTS

Polpharma API offers products in the most restrictive global markets, particularly the United States, Europe, Korea and Japan, among many others. These products include baclofen, aripiprazole, tadalafil, vardenafil, alendronate, risedronate, sildenafil, and hydrochlorothiazide. Additionally, 19 substances are vertically integrated to produce ready-made pharmaceutical forms including sildenafil citrate, piracetam, pentoxifylline, metronidazole, and hydrochlorothiazide. This extensive portfolio requires high-end analytical instrumentation to support the company's R&D, quality control, and method development efforts.

"Within our comprehensive end-to-end CDMO services, our clients rely on us for insights into impurities, including nitrosamines. As we cater to a global clientele subject to diverse regulatory frameworks, we must meticulously navigate the nuances of each. Notably, the U.S. FDA and the EMA employ distinct approaches. While we endeavor to establish a universal methodology encompassing all requirements, occasionally achieving this harmonization proves challenging."

MR. MARIUSZ KUROWSKI
Analytical Expert at Polpharma API Business Unit

Like all pharmaceutical companies around the world, Polpharma API was impacted by the regulatory guidance that followed the 2018 discovery of nitrosamines in pharmaceutical products, which potentially pose a significant health risk to patients. Nitrosamines are potentially carcinogenic mutagenic impurities found in groundwater, treated water, foods, beverages, and consumer products. When nitrosamine impurities were detected in specific drug products, it led to the recall of affected batches with excessive levels of these impurities. Regulatory agencies have since produced guidance on recommended steps that manufacturers of APIs and drug products should take to prevent the risk of above regulatory threshold levels of nitrosamine impurities in pharmaceutical products.

This potential presence of nitrosamine impurities is attributed to the utilization of certain processes and materials that have the capacity to generate nitrosamine impurities. Nitrosamine formation during API synthesis is a consequence of numerous factors like chemistry selection for synthesis, contaminated solvents, and water. Furthermore, apart from APIs, nitrosamines have also been found to be present in the final product due to degradation during formulation processing or storage through contaminated excipients and printing inks (simple alkyls such as NDMA, NDEA and complex API nitrosamines)[1] as shown in figure 1.

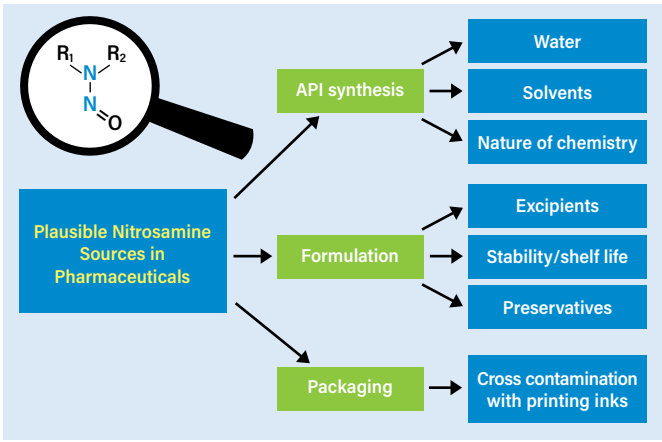

Figure 1. Possible sources of nitrosamine contamination in the pharmaceutical manufacturing process.

As concerns grew about nitrosamine impurities in pharmaceutical products, regulatory agencies have imposed stringent limits on their presence in medications. However, Polpharma clientele are located around the world, and the regulatory landscape can differ greatly between countries. It was the CDMO's global experience that enabled it to meet new regulatory questions head-on, irrespective of jurisdiction.

"Adapting to evolving regulatory requirements is an intrinsic part of our journey. With a rich history of engagement in nearly every corner of the globe, we have amassed invaluable expertise in API development and testing, successfully navigating shifting regulatory landscapes. A decade ago, our focus was on genotoxic impurity testing, whereas today, we must diligently monitor a spectrum of contaminants, including nitrosamines. Change is the constant in our domain, and we remain steadfast in our commitment to addressing emerging challenges as they arise."

DR. PAWEŁ OLSZOWY
Head of Analytical Development Section at Polpharma API

Polpharma follows a reactive approach based on risk assessment for nitrosamines control, as per regulatory guidance. When an external authority has questions or sends a letter, the team must react appropriately. These interactions with regulatory agencies are common in the API development and testing field, and the CDMO's extensive experience serves as an advantage when they need to respond quickly. Mr. Kurowski explains:

"Using risk analysis, we know the general possibility of forming an impurity. Our first workflow focuses on testing and proving the absence of contamination, which is relatively easy. However, if a regulatory agency has a question, our second workflow requires developing a method and analyzing batches of API samples to answer those questions, usually in a relatively short timeframe of 50–90 days. That's where our experience really helps us support our customers."

Additionally, regulatory agencies often change their requirements over time, even when a product is already on the market. Dr. Olszowy provides a recent example:

"Even now, the regulatory agencies can surprise us. We've worked in Brazil for many years, and usually we can predict what they will ask and be prepared with the answers. However, we have a product on the market that we developed 5–6 years ago when the requirements were different. Now they are reviewing that product based on current requirements, so we may need to do something a little differently now."

LC-MS/MS FOR IDENTIFICATION AND QUANTIFICATION OF NITROSAMINES

One of the preferred analytical techniques for quantifying nitrosamines is LC-MS/MS because the technique allows for the separation of complex mixtures of impurities from the API itself, excipients, and other matrix components present in the drug formulation, followed by the sensitive detection and robust quantification of trace impurities to beyond regulatory required levels.

To manage the control of nitrosamines impurities in both API and final drug product, regulatory bodies assign a range of Acceptable Intake (AI) limits for N-nitrosamine impurities in the final drug product, which can be challenging. In most cases, limits that required a level of sensitivity that only a triple quadrupole instrument could deliver. Procuring such advanced instrumentation and acquiring the necessary expertise to operate them can be challenging for most companies but at Polpharma, making the investment in more sensitive and robust instrumentation to meet these limits and support their supply chain was an easy decision to make. Mr. Kurowski describes the impact:

"As an API producer, we must always prove that our products are free of contaminants – not only nitrosamines, but all kinds of genotoxins, carcinogens, and other impurities. About 10 years ago, we were focused on testing for genotoxic impurities, which could be done on a single quadrupole mass spectrometer. Nitrosamines require more sensitivity, so when we brought our analysis in-house, we moved to triple quads and MS/MS techniques. These MS systems have become more robust and more precise in terms of the sample integration, injection, and other factors, which offers the capabilities we need for these types of analyses."

Mr. Mariusz Kurowski, Analytical Expert at Polpharma API Business Unit, uses Waters instrumentation to prove that products are free of contaminants, including nitrosamines.

The shift from outsourced analysis to the creation of their in-house center of excellence for impurity analysis brought positive results for the team at Polpharma API. In the past, the company outsourced part of genotoxic impurity testing as well as some method development but, as the nitrosamine situation developed, a strategic decision was made to bring all testing in house. The expertise that the Polpharma team has built up is now relied on by customers in their supply chain. Mr. Kurowski explains:

"We simply cannot afford any delays. Not just in answering regulatory queries regarding nitrosamine or other contaminants, but also because even a short delay in getting a result can mean an API or a finished product not being able to be released for sale."

Polpharma API also invested in two Waters Xevo™ TQ-S micro Mass Spectrometers, adding the ability to deliver consistent low levels of quantitation with a wide dynamic range to the CDMO's other Waters instrumentation. The CDMO also uses MassLynx™ Security to provide the tools for maintaining 21CFR11 compliance, safeguarding data, and documenting audit trails from acquisition through archiving.

The Xevo TQ-S micro robustly demonstrates high-quality analytical performance injection after injection, with the most complex sample matrices. In addition to these capabilities, however, it was also Polpharma's positive experiences working with Waters' broader portfolio of instrumentation that supported their decision for in-house expansion. Since the CDMO was particularly pleased with the performance of its Waters ACQUITY™ UPLC™ I-Class PLUS Systems, the team decided it was beneficial to stay with the same vendor to achieve the results they wanted.

"I think 50% of success in LC-MS is due to the chromatography. The quality of the peaks gives you an advantage right from the start. The compatibility of the Waters Xevo TQ-S micro with our Waters ACQUITY UPLC I-Class PLUS Systems was very appealing. Of course, the performance of the mass spectrometer also provides a lot of benefits in the heavily regulated environment of pharma testing, particularly compared to instruments from some other vendors."

MR. MARIUSZ KUROWSKI
Analytical Expert at Polpharma API Business Unit

Waters Service and Support plays an important role in keeping things moving smoothly in both busy departments. Prompt and reliable service from Waters helps minimize downtime and ensures that the instruments are running at optimal performance. Dr. Olszowy continues:

"Service is vital. We only have two triple quads now, and we have many methods to be developed and validated. At the same time, our QC department is sometimes waiting to release the product, so with our regulatory time pressures we can't afford for our instrumentation to not be working. We need Waters to help us get up and running as soon as possible."

METHOD DEVELOPMENT AND TRANSFER BETWEEN R&D AND QC

Mr. Kurowski continues:

"The synergy between elements of the Waters systems is also clear when the API R&D team transfer methods to Polpharma's QC department. Currently we prepare every method to be run routinely, so it can be transferred and also performed by our QC team using the QDa."

Where sensitivity allows, they use the Waters ACQUITY™ QDa™ Mass Detector rather than a triple-quadrupole MS system (which we need for our API work). This creates an instrument combination that does not need the sample-specific or user adjustments typical of traditional mass spectrometers and, as a result, the QC team can consistently generate high-quality mass spectral data routinely without the need for any special training or expertise. Working in this way speeds up the process for both teams, as the QC workflow experiences fewer bottlenecks where they need assistance from R&D, Dr. Olszowy explains:

"MS is a sophisticated technique, but the QDa Mass Detector is easy to work with, and we see that as the future for us. It facilitates our departmental interface."

NEXT STEPS

With the API development and testing field always in flux, the Polpharma team continues to position itself for what's coming.

Recent developments from regulators have reframed the initial AI limits for some nitrosamines, known as NDSRIs, increasing the range of limits to be from ppb up to ppm levels in some cases. This change is supported by instrumentation that offers versatility of detection sensitivity, or scope for QDa or other single quadrupole MS where detection limits are higher. However, for Polpharma API, the role of UPLCs with tandem mass spectrometry systems remains clear in method development and identification of impurities, as well as for other trace level applications.

Dr. Paweł Olszowy, Head of Analytical Development Section at Polpharma API, works with the Waters Support and Service team to manage the CDMO's rapid growth.

Another significant change Mr. Kurowski sees for the CDMO's future is the increasing focus on Analytical Quality by Design (AQbD), a systematic approach favored by regulatory agencies that can be used in analytical method development to ensure that the quality of analytical results is consistently achieved and maintained throughout the life cycle of the method.

The Polpharma team is already working on the tools they'll need for AQbD, particularly regarding software. The goal is to make the development of an AQbD method as automated as possible.

Dr. Olszowy describes the importance of these solutions in their future work:

"We're preparing now for what we'll need, and we have many things that need to be done. We hope to work with Waters as they continue to develop the software tools that we'll need to support our efforts."

Of course, the CDMO's recent investments in the Waters analytical instrumentation will also play a role. The capabilities of the Waters Xevo TQ-S micro mass spectrometers will likely help the Polpharma team navigate the constant changes in API development and testing. Mr. Kurowski explains:

"We plan on using the Waters Xevo TQ-S micro mass spectrometer in future projects. The capabilities of the triple quad will be needed as we solve new problems. It will be one of our main R&D resources. In addition, designing methods that run on the simpler QDa detector systems for routine QC will remain a focus for our work too."

However, Polpharma's extensive experience, including navigating the evolving nitrosamines situation, makes them very confident that when new challenges emerge, the team will be prepared to meet them. Dr. Olszowy summarizes:

"In our field, we know that something else is always around the corner. I remember 10 years ago the focus was on genotoxic impurities and since 2018 we have been dealing with the challenges around nitrosamines. I don't have a crystal ball to see the future but, whatever emerges in the future we can be calm because we know we are ready."

polpharma API

References

1. Akkaraju, H., Tatia, R., Mane, S. S., Khade, A. B., & Dengale, S. J. (2023). A comprehensive review of sources of nitrosamine contamination of pharmaceutical substances and products. Regulatory Toxicology and Pharmacology, 139, 105355. https://doi.org/10.1016/j.yrtph.2023.105355.

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