

USP Science

New nitrosamines research featured in special cluster issue of *Journal of Pharmaceutical Sciences*



When unsafe levels of nitrosamine impurities were first detected in medicines in 2018, the focus was on small di-alkyl nitrosamines (e.g., NDMA) in sartans. Regulators around the world issued recommendations for risk assessment and mitigation, while they faced the unenviable challenge of balancing the public health risk of exposure to nitrosamines against the impact of disruptions to supplies of lifesaving drugs. Little data was available for determining acceptable intake limits for nitrosamines. The sources of the impurities were unclear. Analytical methods for assessing and mitigating risk were scarce. In short, there were many questions and few answers.

Since then, the emergence of a subcategory of nitrosamine impurities – nitrosamine drug substance related impurities (NDSRIs) – has further complicated the issue. NDSRIs are drug-specific nitrosamine impurities whose chemical structure is similar to the active pharmaceutical

ingredient (API) of a drug. Estimating the carcinogenic potential of nitrosamines is especially difficult for NDSRIs because robust experimental data are not available.

The challenges associated with the emergence of NDSRIs are a useful example for demonstrating the moving target nitrosamines have posed – as we've learned more, new questions have emerged. The situation is evolving rapidly, and the stakeholder community has responded accordingly. The speed with which progress has been made in understanding and guarding against unsafe levels of nitrosamine impurities in drugs has been possible, in large part, because scientists in industry, regulatory agencies and academia have been pooling their collective knowledge. Through written publications and direct interactions – both in-person and online – scientists from around the world have connected to share scientific and regulatory information about nitrosamines, helping one another understand and address the challenges of these impurities in medicines.

[USP's Nitrosamines Exchange](#) online community has provided a much-needed platform for this crucial, expedited information sharing. Recently, an idea that began as a discussion item in the USP



Nitrosamines Exchange community resulted in the collaboration between USP, LHASA Limited, AstraZeneca, Sai Life Sciences and Merck. Their in-silico analysis of more than 12,000 APIs and API-related impurities and degradants found that 40% of the APIs and 30% of API impurities are potential nitrosamine precursors. These higher-than-expected percentages suggest that the potential problem of nitrosamine impurities in medications may be more widespread than initially thought.

Ongoing research into the sources of nitrosamine impurities in drugs revealed that nitrosamines can potentially form from any drug ingredient (API or excipient), intermediate or impurity that contains a vulnerable amine group as part of its chemical structure. This, coupled with the relatively simple chemical conditions required for nitrosamines to form, underscores the urgent need for in-depth understanding of manufacturing processes. Pinpointing when and where nitrosamines are likely to form is the first step towards process modifications to control them.

The sensitivity of analytical test methodologies has improved since 2018, but a challenge that continues to hamper the pace of risk assessments is the inability to test for multiple nitrosamine impurities simultaneously. Significant progress on this front has recently been published in the *Journal of Pharmaceutical Sciences* and included in its [special cluster edition on nitrosamines](#). Scientists in USP's state-of-the-art laboratories in Hyderabad, India have developed a new, direct-injection GC-MS/MS method for detecting and quantifying six different nitrosamines simultaneously in four commonly used solvents. More of these multi-purpose analytical methods will streamline and accelerate detection and subsequent mitigation of nitrosamine impurities, making more medicines safe sooner.

Nearly five years have passed since nitrosamine impurities in medicines first gained public attention. Since then, recalls of a wide variety of drugs due to



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potentially unsafe levels of nitrosamines hinted at how pervasive the problem might be. Nitrosamines do not discriminate between medicines that are brand vs. generic, prescription vs. over the counter, pre- or post-approval.

It's likely that more evidence of nitrosamines in drugs will be found as analytical testing methods continue to improve. Such events should be considered successes – proof points that analytical methods and regulatory processes are effective at detecting potentially unsafe levels of nitrosamine impurities, enabling correction of the problems leading to their presence and removing affected products from the market.

The problem of nitrosamine impurities in medicines is too complex and too big for any single group to have all the knowledge and resources needed to fully address it. Regulators and industry, with support from government, pharmacopoeias, academia, and other stakeholders, must continue their collaboration on this evolving challenge, exchanging information and working together to protect patients and help ensure their continued access to the safe and effective medicines they need. ▲