

# Almac Voice

## Conducting Nitrosamine impurity identification and quantification on drug substance and drug product



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Using mass spec analysis techniques to quantify low levels of NDMA and related substances during the manufacture of medicines containing chemically synthesised active substances.

Nitrosamines are organic compounds that we are commonly exposed to. They exist in low levels in our water and foods, including meat, vegetables, and dairy products. They originate from chemical reactions and can form in drugs during manufacturing. Nitrosamines are classified by the ICH M7(R1) Guideline as Class 1 impurities, “known mutagenic carcinogens”<sup>(1)</sup>, and may increase the risk of cancer if people are exposed to them above acceptable levels over a significant time period.

Medicine regulatory authorities first became aware of these impurities in July 2018 when N-Nitrosodimethylamine (NDMA) was detected in some angiotensin II receptor blocker (ARB) medicines and were immediately recalled by the US Food and Drug Administration (FDA). Over-the-counter medicines used in the treatment of heartburn, such as ranitidine, were recalled in 2019 by the Health Sciences Authority in Singapore, and Swissmedic (OMCL) also detected NDMA contamination in particular metformin preparations which are used in the treatment of type 2 diabetes. More recently, regulatory agencies have identified additional related impurities as causes for concern. Updated guidance from September 2019 includes 5 other nitrosamine compounds to be included in risk assessments and analytical programmes.

Manufacturers must be aware of the potential source of nitrosamine formation in their manufacturing processes and take comprehensive measures to

reduce the possibility of any formation. In addition, robust analytical methods must be implemented to determine not only the presence of the impurities, but the levels, to ensure compliance in accordance with industry guidelines. To aid this, the FDA has published testing methods that can be used to detect nitrosamine levels. These methods include:

- GC/MS headspace chromatography-mass spectrometry (GC-MS)
- Liquid chromatography-high resolution mass spectrometry (LC-HRMS)
- Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

In conjunction, the Official Medicines Control Laboratories (OMCLs) Network of the Council of Europe has also published several methods that may be used when testing for nitrosamines.

Links to all these methods can be found at the end of this document.

The FDA, in collaboration with regulatory counterparts worldwide, has also determined acceptable daily intake limits for nitrosamines based on its established published methods. It should be noted that a person taking a drug that contains nitrosamines at or below the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer.<sup>(2)</sup>



Within the EU, since September 2019, the European Medicines Agency (EMA) has requested that all EU Marketing Authorization Holders (MAH) include a new requirement to review their drug products for the possible presence of nitrosamines on their human medicinal drug products containing chemically synthesized APIs.<sup>(3)</sup> Although these impurities are not expected to form during the manufacture of the majority of medicines containing chemically synthesised APIs, recommended steps are:

- Risk evaluation
- Confirmatory testing and notification to relevant authorities
- Change of marketing authorisation

The EMA has requested that MAHs complete this review within 6 months.

All regulatory authorities are continuing to work with their national and international counterparts to ensure compliance in preventing nitrosamine presence in their products. There are various reasons why nitrosamines can be present in medicines, but the regulatory authorities will communicate new findings and guidance as it becomes available. This includes retrospective analysis on marketed products and control on new products in clinical trials.

*In the meantime, how can Almac's expert team help resolve your challenges in nitrosamine detection and analysis?*

Our mass spectrometry laboratory in Almac Sciences has successfully performed testing on a number of APIs and Finished Products as per FDA method FY20-006-DPA-S\_LCMSMS 10/17/2019 to establish levels of NDMA. We understand the challenges this analysis presents, particularly considering ion suppression, but we have met these and clean-up has been successful. Almac routinely work on products in development and have significant experience in mitigating risks relating to impurities as well as our experience in nitrosamines. Our experience also extends to potential genotoxic impurities found in novel compounds and can detect and quantify these to low levels. With our experts each holding over 20 years' experience in mass spectrometry, developing and validating methods for 100's of compounds in multiple matrices, we would be delighted to hear from you to discuss your requirements.

<https://www.USFDA.gov/media/124025/download>

<https://www.USFDA.gov/media/115965/download>

<https://www.USFDA.gov/media/130801/download>

<https://www.USFDA.gov/media/131868/download>

<https://www.edqm.eu/en/ad-hoc-projects-omcl-network>

(1) International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; "ICH Harmonised Guideline - Assessment And Control Of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7(R1)"; March 31, 2017, [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Multidisciplinary/M7/M7\\_R1\\_Addendum\\_Step\\_4\\_2017\\_0331.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_2017_0331.pdf)

(2) <https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>

(3) <https://www.ema.europa.eu/en/news/ema-advises-companies-steps-take-avoid-nitrosamines-human-medicines>

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