# NITROSAMINE IMPURITY ANALYSIS (NDMA, NDEA AND NMBA) IN ARB MEDICINES

Detection and quantification of nitrosamine impurities, found in some ARB medicines, according to the FDA headspace gas chromatography-mass spectrometry (GC/MS-HS) method

**There is a current focus by the FDA on three nitrosamine impurities (NDMA, NDEA or NMBA) which have been found in some angiotensin II receptor blocker (ARB), such as valsartan, active pharmaceutical ingredients (APIs) and drug products. Robust analysis to determine if these are present and at what levels they are present is critical to ensuring that these potentially harmful impurities do not enter the market in the future.**

**Our experts detect and quantify nitrosamine impurities in APIs and finished drug products. Data can be used to support regulatory submissions or quality assessments**

## Impurity risk

Nitrosamine impurities N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA) and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA), found in some angiotensin II receptor blocker (ARB) medicines, have been the driver for recent product recalls and the subject of a US Food and Drug Administration (FDA) focus to ensure products entering the market do not contain NDMA, NDEA or NMBA impurities in the future whilst establishing suitable analytical methods to determine levels of these impurities and establish interim limits for nitrosamine impurities.

## NDMA and NDEA impurities

NDMA is an impurity found in valsartan APIs and products and was the driver for a product recall by the FDA in July 2018. Since then the European Medicines Agency (EMA) and the FDA have reported the presence of a second impurity, NDEA, also found to be present in valsartan products. Both NDMA and NDEA are classified as a probable human carcinogens. The presence of NDMA and NDEA in finished pharmaceutical products is thought to be the result of the manufacturing process of the drug substance and drives the need for robust analysis to detect and quantify these substances in ARB products.

## Nitrosamine impurity analysis services

The FDA Office of Testing and Research have developed a combined NDMA and NDEA impurity assay by GC/MS-Headspace chromatography- mass spectrometry (GC/MS-HS) method to detect and quantify the presence of NDMA (LOD 0.005ppm, LOQ 0.1ppm) or NDEA (LOD 0.02ppm, LOQ 0.05ppm) in drug substance samples (Figure 1). Intertek has established this FDA GC/MS-HS method within our GMP laboratory services to assist clients in performing the required method validations where the data can be used to support regulatory submissions or quality assessment of the API or drug product.

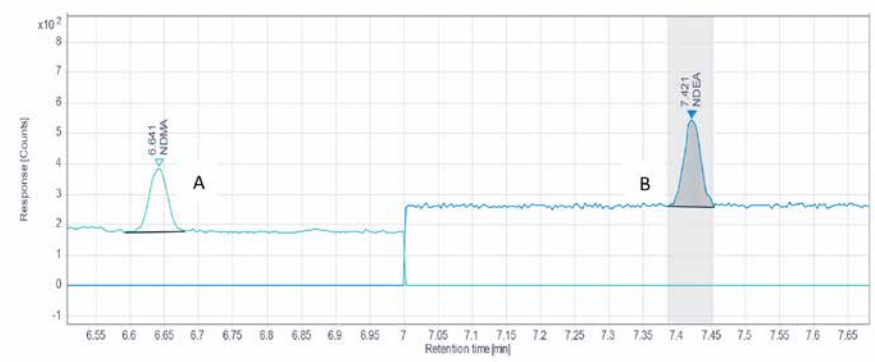


Figure 1: Chromatogram of NDMA/NDEA working standard. Peak A) NDMA and peak B) NDEA, equivalent to 150ppb and 300ppb respectively relative to a 350mg sample.

## Toxicological risk assessment

In addition to experienced pharmaceutical impurity analysis, we can support with toxicological risk assessments.
Our experienced consultants conduct risk assessments to address the impact associated with exposure to residual solvents, process impurities, extractables & leachables, elemental impurities (ICH Q3D) and other substances that may find their way into a pharmaceutical product.

## Total Quality Assurance

Intertek's network of GMP compliant laboratories provide compliant data to support regulatory requirements or product development activities of our global clients. Bringing quality and safety to life, we help you bring your product to market quickly, responsibly, and economically, ensuring Total Quality Assurance.


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