

# Nitrosamine Impurity Detection and Quantification in Sartans and Ranitidine



## **Quantification of nitrosoamine impurity (NDMA) using LC-HRMS (orbitrap) and LC-MS at 'PPB' levels**

In July 2018, the FDA reported that some generic versions of the Angiotensin II Receptor Blocker (ARB) medicines contain nitrosamine impurities that don't meet the agency's safety standards. ARBs, including valsartan, irbesartan, losartan and others, are a class of medicines used to treat high blood pressure and heart failure. Nitrosamine impurities, including N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) are probable human carcinogens. The FDA issued a guidance for manufacturers that lays out risk assessments, which the manufacturers can use to evaluate the presence of genotoxic impurities. As this incident continues to evolve, it has resulted in numerous recalls and ARB drug shortages in the US.

To determine if ARB medicines contain these impurities, FDA developed three testing methods. These include the GC/MS headspace method, the combined headspace method, and the combined direct injection method. These testing methods can be used for evaluating both drug substances (API) and finished drug products.

Recently, FDA has found NDMA impurity in Ranitidine and asked the suppliers to ensure and report the quantities of these impurities in the API.

## Our Solution

- Aragen has successfully developed and implemented GC/MS methods to quantify N nitrosodimethylamine (NDMA) and Nnitrosodiethylamine (NDEA) at trace levels and has validated the method for Valsartan API which was provided by USFDA.
- Aragen Analytical solutions lab can perform the NDMA impurity in Ranitidine exactly as per USFDA published method using LC-HRMS orbitrap instrument under R&D (non-GMP) conditions. The sensitivity of the method is at 2 PPB Level.
- We have also developed an alternate method using LCMS for NDMA impurity in Ranitidine.
- The above LCMS method can be used for all SARTANS, STATINS for six impurities at same sensitivity level.
- We also have analytical methods for Sartans using GCMS and validated.

Name of Impurity		Technique	LOD (ppm)	LOQ (ppm)
NDMA	N-Nitrosodimethylamine	GCMS/LCMS	0.05	0.15
NDEA	N-Nitrosodiethylamine	GCMS/LCMS	0.03	0.08
NEIPA	N - Nitroso ethyl iso propylamine	GCMS/LCMS	0.02	0.05
NDIPA	N- Nitroso di isopropylamine	GCMS/LCMS	0.03	0.08
NDBA	N-nitrosodibutylamine	GCMS/LCMS	0.03	0.08
NMBA	N Nitroso N Methyl' 4' Aminobutyric Acid	LCMS/HPLC	0.01	0.03

Aragen has implemented the USFDA method using HRMS as well for both Sartans and Ranitidine. The instrument is under R&D and can support R&D sample data generation.

## About Aragen Analytical Solutions Lab

- Chromatographic & Spectroscopic Analysis
- Genotoxic & Elemental Impurities Analysis
- Physico-chemical characterization
- Microbiological and Environmental Analysis
- ICH Stability Studies
- Extractable & Leachable Studies



## Key Techniques

HPLC, ICPMS, GCHSMS, LCMSMS, GCHS, XRD, DSC, TGA, CHNS, PSA and Microbiology

## About Aragen

ARAGEN, a Contract Research & Development Organization that services the global Pharmaceutical industry is headquartered in Hyderabad, India and has five sites across the globe. Established in 2001, ARAGEN serves large and small pharma clients across the R&D value chain with a focus on speed and quality, ensuring safety and compliance. ARAGEN's team of over 2400 scientists, are supported by a no-conflict business model, modern facilities, strong customer-centric culture, and focus on bringing their customers' products to market rapidly and cost effectively

Let's begin the  
Conversation

E: [bd@aragen.com](mailto:bd@aragen.com)

W: [aragen.com](http://aragen.com)

[in /company/aragen-life-sciences](https://www.linkedin.com/company/aragen-life-sciences)

[f /AragenLifeSciences](https://www.facebook.com/AragenLifeSciences)



India • USA • UK • Netherlands • Japan • Italy