

## Nitrosamine impurities analysis solution guide

- **Find the right analytical solution** for each stage of nitrosamine impurity analysis
- **Confidently detect and quantify** genotoxic impurities in active pharmaceutical ingredients and finished drug products

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# Monitoring genotoxic impurities in pharmaceutical products



Since elevated levels of nitrosamines were detected in certain pharmaceuticals as first reported in July 2018, finding the right solutions have become the major focus for many pharmaceutical manufacturers. Thermo Fisher Scientific™ as a trusted partner for pharmaceutical analysis and quality control offers several solutions to fit your needs. We are your partner to:

- Monitoring the levels of class 1 genotoxic impurities, which are known mutagenic carcinogens according to IARC and ICH M7(R1) regulatory guidelines
- Avoid any risks of recalls of your drug products
- Effortlessly follow and satisfy regulatory guidelines



# Why is nitrosamine impurity analysis in drugs important?

Nitrosamines are small molecular weight chemical substances that are probable human carcinogens, and their presence in medicines is considered unacceptable by regulators. They are organic compounds featuring a nitroso group and amino group. They have the generic formula  $R_2N-N=O$  where the R groups are typically alkyl in nature, they may be formed during API manufacturing—from starting materials, intermediates, reactants, recycling of solvents and the presence of nitrites and secondary amines.

In 2018, nitrosamine impurities, including NDMA, were discovered in Valsartan, an Angiotensin II receptor blocker (ARB) medication used to treat high blood pressure and heart failure. This led to a global recall of Valsartan and several other ARB drugs.

First mostly N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA), two carcinogenic impurities were the target of careful monitoring efforts. Since then, several other N-nitrosamines have also been identified and are being investigated by regulators: N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), N-Nitrosodibutylamine (NDBA), and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA).

The outcome that all events has made clear—there's a recognized need for a risk assessment strategy for potential nitrosamines in any pharmaceutical product at risk for their presence.



# Requirements for nitrosamine analysis

Nitrosamine impurity analysis requires robust and sensitive analytical methods to ensure confidence in the obtained results.

The wide Thermo Scientific™ portfolio is proven to be best in class for nitrosamine analysis, ensuring your exploratory and routine methods are performed as accurately and reliably as possible while maintaining requirements from regulatory bodies worldwide.

## Our major products for the analysis of nitrosamines include:

- Liquid, gas, and ion chromatography for robust separation
- High resolution, accurate mass (HRAM) mass spectrometry for ultimate confidence avoiding false positive results
- Tandem mass spectrometry, the best tool in routine analysis
- Single, compliance-ready software solution for all our technology solutions

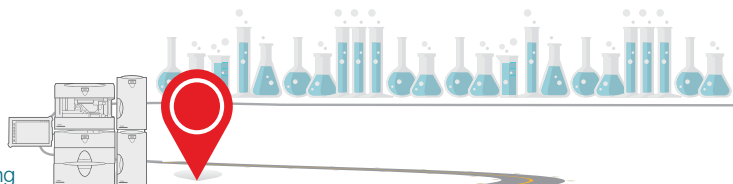


# Enabling analytical tools for each stage of nitrosamine impurity analysis



## Ingredient and product monitoring

- Monitor nitrite and amine levels during manufacturing process and storage
- Risk monitoring



## Highly confident detection

- High resolution accurate mass detection
- Impurity assessment and exploratory analysis
- Confident confirmation
- Routine assay capable

## Routine Screening

- Sensitive, high throughput assays
- Complementary analysis
- LC and GC-MS/MS



## High throughput assay automation and optimization

- To enable fast and reproducible
- Less hands-on
- Efficient monitoring



GMP compliant software for all analysis

## Featured nitrosamine solutions

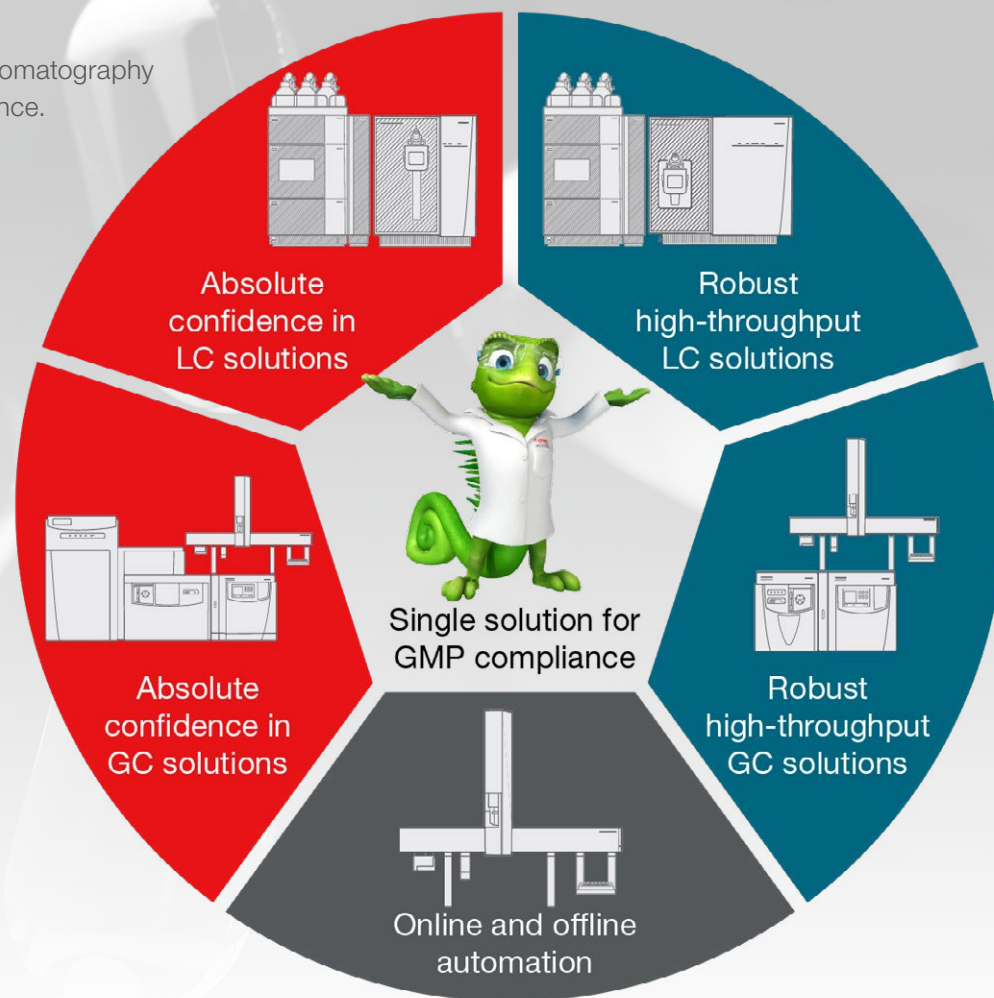
We're here for you each step of the way...

# Compliance for all analytical solutions

No matter which solution fit your needs, Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) is going to be there to assure confidence in your compliance.

## Powerful, compliance-ready single solution platform for:

- Instrument control
- Data analysis and reporting
- In a secure, audit-trailed space
- LC-HRAM
- LC-MS/MS
- GC-HRAM
- GC-MS/MS
- IC
- Automation
- Fit within existing laboratory infrastructure of chromatographic systems



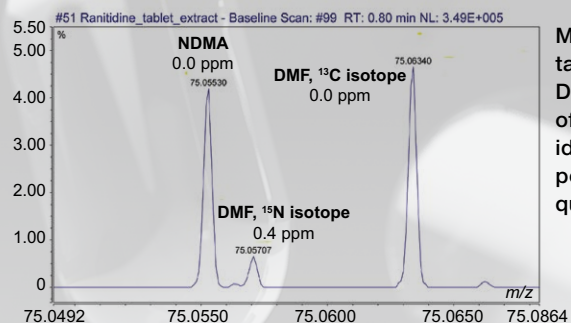
 **Stay up-to-date, join our community.**

# Absolute confidence with High Resolution Accurate Mass

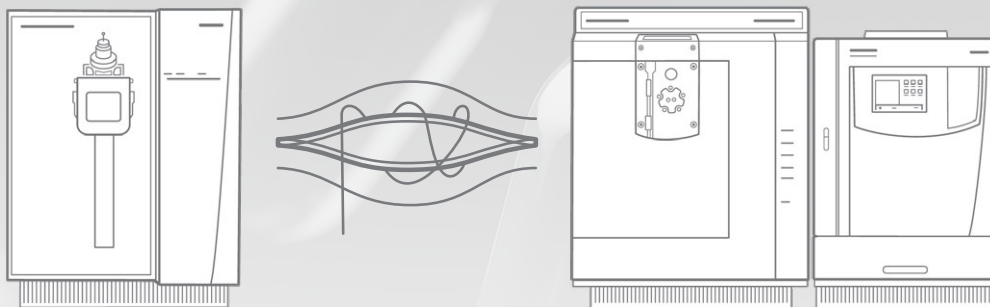


Matrix interferences and or common solvents, such as DMF, from the manufacturing process can lead to false-positive results with unit mass resolution mass spectrometry. This is especially true if the interfering compounds aren't separated chromatographically.

We recommend Thermo Scientific™ Orbitrap™ technology as the gold standard mass spectrometry technique as a minimum of 45k resolution is critical to eliminate false-positive results. Whether you want to perform fast and confident nitrosamine impurity screening and or peace-of-mind confirmatory analysis in combination with triple quadrupole MS, HRAM MS should be a corner stone in your workflow.



Mass spectrum of ranitidine drug tablet when co-elution of NDMA and DMF happens, with a resolution setting of 120,000 confident and accurate identification of isotope masses possible and allows for accurate quantitation.

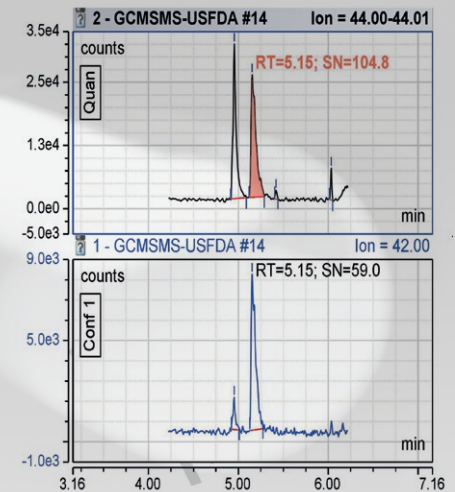
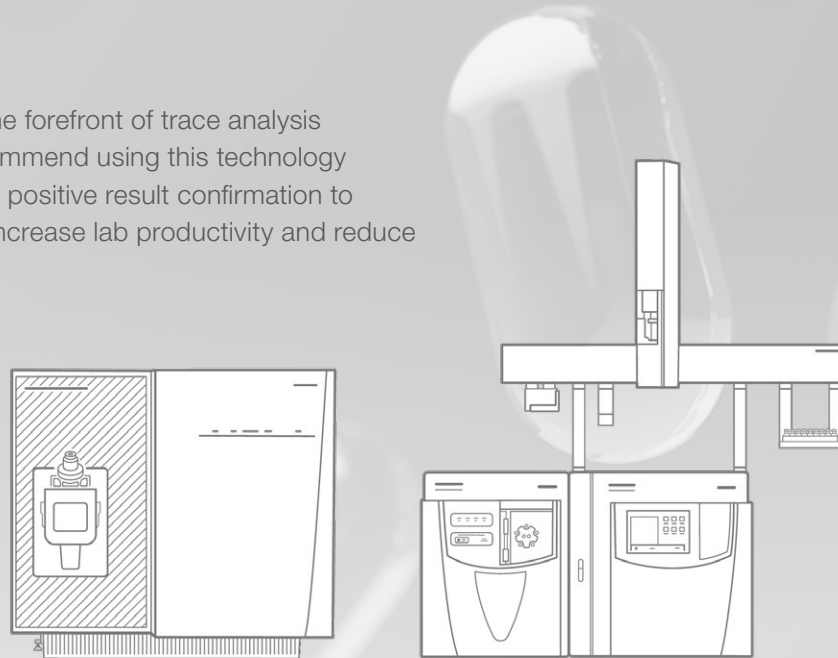


**Ultimate confidence—eliminate false positive results with HRAM.**



# Cost effective nitrosamine screening with MS/MS

Triple quadrupole mass spectrometry is at the forefront of trace analysis of nitrosamines in pharmaceuticals. We recommend using this technology for screening and in harmony with HRAM for positive result confirmation to eliminate false positive results. MS/MS can increase lab productivity and reduce workload on your HRAM systems.



Chromatograph of valsartan extract with NDMA spiked at 5 ppb (ng/mL) on column

**Increase your productivity with the analytical workhorse MS/MS and screen hundreds of samples per day.**

“Did you know that this strategy is currently used in the same manner for dioxin analysis in food and feed? Why? This is an established solution for maximal productivity and ultimate confidence in results.”

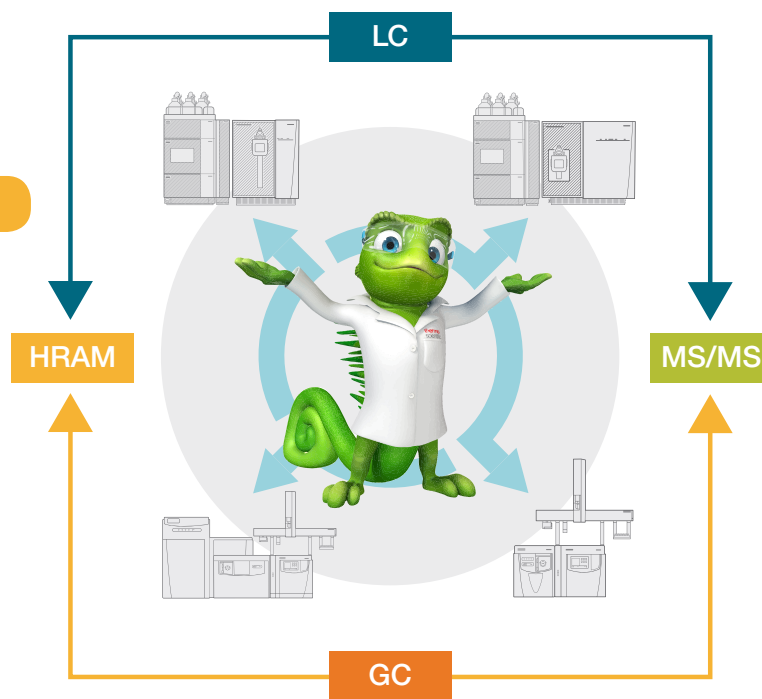
# Are you at a cross-roads in choosing your nitrosamine analysis strategy?

What are the advantages of each approach?

- Universal applicability
- Common availability
- All FDA nitrosamines are LC amenable

## THE GOLD STANDARD

- Maximum selectivity
- Zero false positives
- Ultimate confidence
- Unknown screening



- High throughput targeted screening
- Support of a HRAM confirmatory strategy
- Cost effectiveness and commonality


- Ultimate sensitivity
- Excellent peak shape
- Highest column efficiency, best separation

Compliance is at the center  
whichever route you choose!

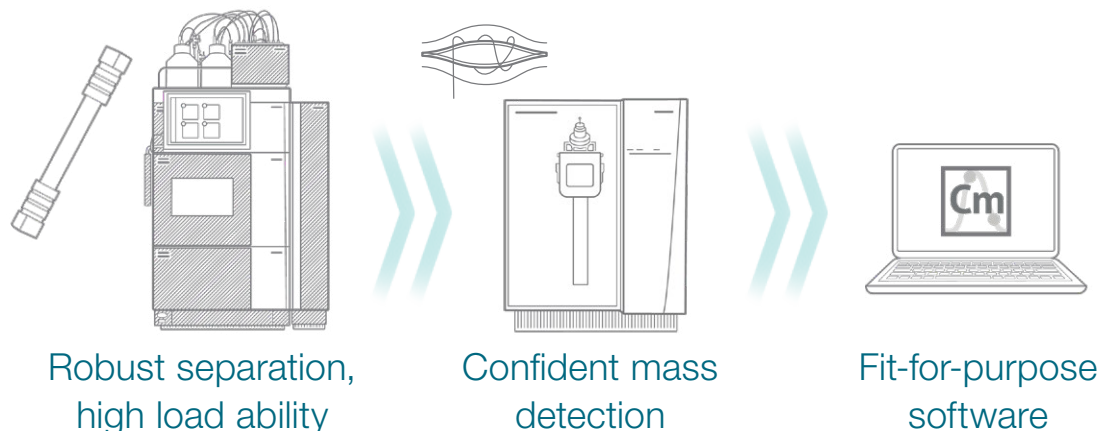
# Solution summary

Nitrosamine analysis	LC-MS	GC-MS	IC
Highly confident identification, quantitation, and monitoring	Orbitrap Exploris 120 LC-HRAM	Orbitrap Exploris GC-HRAM	—
Robust, high throughput routine screening	TSQ Quantis LC-MS/MS	TSQ 9000 GC-MS/MS	—
Laboratory workflow automation	TriPlus RSH	TriPlus RSH	—
Single compliance-ready software	Chromeleon CDS Software	Chromeleon CDS Software	Chromeleon CDS Software
Nitrite and nitrate assessment	—	—	HPIC System

[Click on each listing for more information](#)

 **Would you like to learn more?  
Contact a specialist now.**

# LC-HRAM MS Solution for absolute mass confirmation



- Stable chromatography over extended period and hundreds of injections
- Confidence in analytical results allowing exceptional screening or confirmatory analysis
- Ease-of-use and compliance-ready software

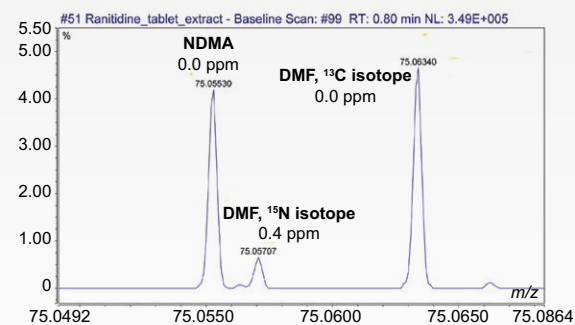
The Thermo Scientific™ Orbitrap Exploris™ 120 mass spectrometer system provides high resolution accurate mass assuring absolute identification and quantitation of nitrosamines.

## Featured Application Note

HRAM LC-MS method for the determination of nitrosamine impurities in drugs



- Chromatographic co-elution of NDMA and DMF may cause over-estimation (false positive) if mass resolution is not sufficient
- The mass difference between NDMA and DMF <sup>15</sup>N isotope is only 21 ppm, 0.002 amu difference—requires minimum 45K resolution and 3 ppm mass accuracy



Mass spectrum of ranitidine drug tablet when co-elution of NDMA and DMF happens, with a resolution setting of 120,000 confident and accurate identification of isotope masses possible and allows for accurate quantitation.

# Learn more about our LC-HRAM MS Solution

## Products and resources

Click on each listing for more information

### Products



#### Robust separation, high load ability

##### Impurity separation with (U)HPLC platforms

- Thermo Scientific™ Acclaim™ PALL Columns
- Thermo Scientific™ Vanquish™ Flex UHPLC System
- Thermo Scientific™ Vanquish™ Core HPLC System



#### Confident mass detection

##### Mass detection

- Thermo Scientific™ Orbitrap Exploris™ 120 Mass Spectrometer
- Thermo Scientific™ Q Exactive™ Plus Mass Spectrometer



#### Fit-for-purpose software

##### Software

- Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) Software



Would you like to learn more?  
Contact LC-HRAM specialist now.

### Resources



#### Literature

- Application Note: HRAM LC-MS method for the determination of nitrosamine impurities in drugs
- Application Note: High-resolution accurate-mass liquid chromatography methodology
- Article: How to comply with FDA imposed nitrosamine impurity testing
- Brochure: Vanquish Core
- Brochure: Orbitrap Exploris 120
- Brochure: Chromeleon CDS software
- Brochure: Consumables



#### Web tools

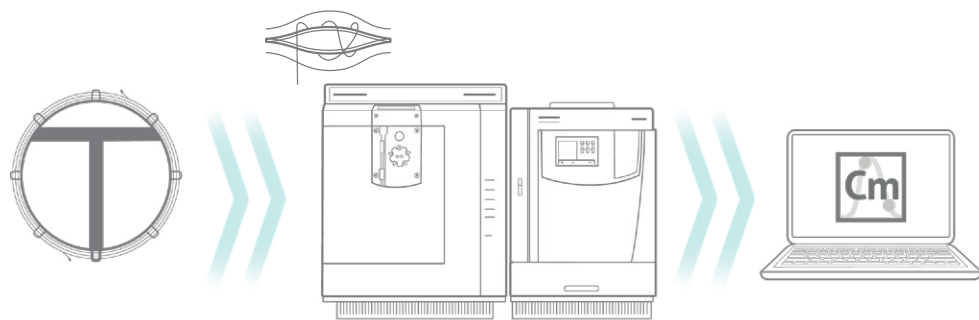
- Vanquish Selection tool
- Nitrosamine impurity analysis
- Orbitrap LC-MS
- HPLC and UHPLC platforms



#### Webinars

- Nitrosamine analysis; a leading CDMO's perspective
- Virtual seminar: Nitrosamine analysis

# GC-HRAM MS Solution for nitrosamine analysis gives ultimate sensitivity and confidence



Robust separation,  
high load ability



Confident mass  
detection



Fit-for-purpose  
software



- Ultimate sensitivity
- Eliminate false positive results
- Ease-of-use and compliance-ready software

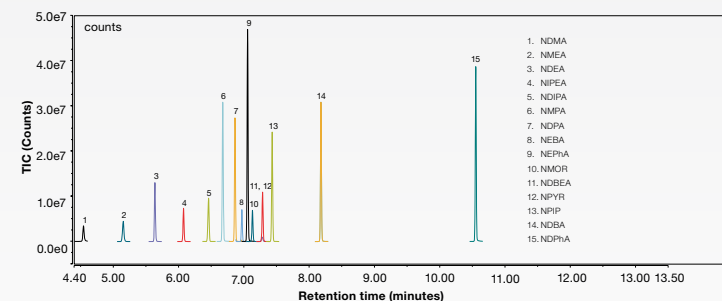
The Thermo Scientific Orbitrap Exploris GC-MS system provides high resolution accurate mass confirmation while beating LOQ requirements.

## Featured Application Note

A validated method for the rapid determination of fifteen nitrosamines in metformin drug substance



- Rapid separation of 15 nitrosamines in <12 minutes
- 10x <FDA regulatory limits of 30 ppb (ng/g) <2 ppb
- Excellent robustness over 2 weeks continual analysis



XIC of nitrosamine quantifier ions in a 50 ppb spiked sample.

# Learn more about our GC-HRAM MS Solution

Products and resources

[Click on each listing for more information](#)

## Products



### Robust separation, high load ability

#### Impurity separation with GC platforms

- Thermo Scientific™ TraceGOLD TG-1701 MS Column



### Confident mass detection

#### Mass detection

- Thermo Scientific™ Orbitrap Exploris™ GC Mass Spectrometer



### Fit-for-purpose software

#### Software

- Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) Software

## Resources



### Literature

- Application Note: GC Exploris HRAM validation of 15 nitrosamines in metformin drug substance
- Article: How to comply with FDA imposed nitrosamine impurity testing
- Case Study: GC solutions for nitrosamines
- Brochure: Orbitrap Exploris GC
- Brochure: Chromeleon CDS software
- Brochure: Consumables



### Web tools

- Orbitrap GC-MS



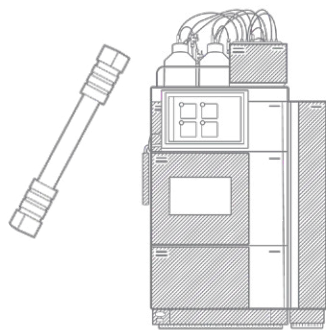
### Webinars

- Nitrosamine analysis; a leading CDMO's perspective
- Virtual seminar: Nitrosamine analysis

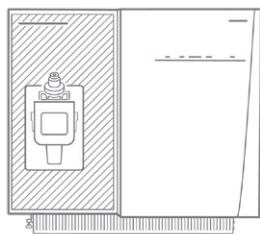


Would you like to learn more?  
Contact GC-HRAM specialist now.

# LC-MS/MS Solution for your targeted monitoring needs



Robust separation,  
high load ability



Robust and sensitive  
mass detection



Fit-for-purpose  
software



- Stable chromatography over extended period and hundreds of injections
- Great for screening or confirmatory analysis
- Ease-of-use and compliance-ready software

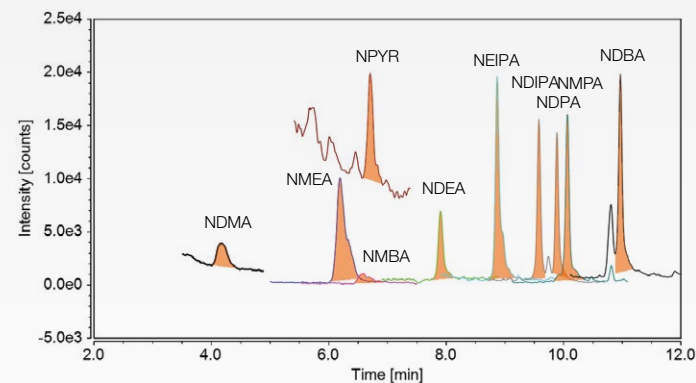
The Thermo Scientific Triple Quadrupole systems assure absolute confidence in results for any targeted quantitation needs.

## Featured Application Note

Highly sensitive and robust LC-MS/MS solution for quantitation of nitrosamine impurities in metformin drug products



- Vanquish Horizon UHPLC, Hypersil GOLD phenyl column coupled to a TSQ Quantis Chromeleon CDS
- LOQ 5 ppb using APCI and 10 ppb using HESI
- Excellent reproducibility for over 1,000 sample injections



XIC of nitrosamine quantifier ions in a 20 ppb spiked sample. APCI data are shown.



# Learn more about our LC-MS/MS Solution

## Products and resources

Click on each listing for more information

### Products



#### Robust separation, high load ability

##### Impurity separation with (U)HPLC platforms

- Thermo Scientific™ Acclaim™ PALL Columns
- Thermo Scientific™ Vanquish™ Flex UHPLC System
- Thermo Scientific™ Vanquish™ Core HPLC System



#### Robust and sensitive mass detection

##### Mass detection

- Thermo Scientific™ TSQ Altis Triple Quadrupole Mass Spectrometer
- Thermo Scientific™ TSQ Quantis Triple Quadrupole Mass Spectrometer
- Thermo Scientific™ TSQ Fortis Triple Quadrupole Mass Spectrometer



#### Fit-for-purpose software

##### Software

- Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) Software



Would you like to learn more?  
Contact LC-MS/MS specialist now.

### Resources



#### Literature

- Application Note: Highly sensitive and robust LC-MS/MS solution for quantitation of nitrosamine impurities in metformin drug products
- Application Note: TSQ Quantis application note
- Article: How to comply with FDA imposed nitrosamine impurity testing
- Article: Nitrosamine, a CDMO perspective
- Brochure: Chromeleon CDS software
- Brochure: TSQ Quantis
- Brochure: Consumables
- Brochure: Vanquish Core



#### Web tools

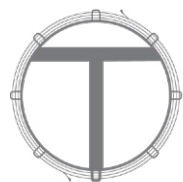
- Nitrosamine impurity analysis
- TSQ LC-MS/MS portfolio
- HPLC and UHPLC platforms



#### Webinars

- Nitrosamine analysis; a leading CDMO's perspective
- Virtual seminar: Nitrosamine analysis

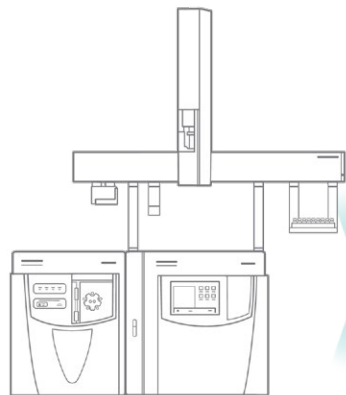
# GC-MS/MS Solution for volatile analysis needs with confident targeted approach



High efficiency separation



- Faster data evaluation and increased confidence with exceptional levels of selectivity, sensitivity, and linear dynamic range
- Versatility of full-scan, high-resolution accurate-mass data to screening and quantitation
- Intuitive instrument control and method templates



Robust and sensitive mass detection



Fit-for-purpose software



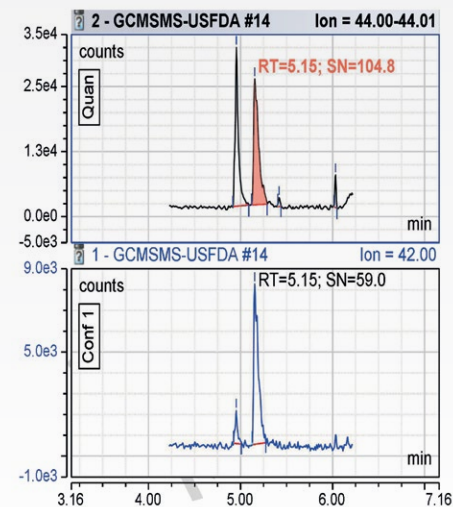
For high-throughput analytical laboratories, the Thermo Scientific TSQ 9000 GC-MS/MS system provides sensitive, specific quantitation of target compounds.

## Featured Application Note

Determination of genotoxic nitrosamines in Valsartan with gas chromatography and mass spectrometry



- Results that are compliant with the CFDA and U.S. FDA standard methods for nitrosamines detection and quantitation in Valsartan
- Three recommended instrumental approaches (GC-MS, HS-GC-MS, GC-MS/MS)
- The static headspace injection technique offers a simplified workflow for sample handling



Chromatograph of valsartan extract with NDMA spiked at 5 ppb (ng/mL) on column

# Learn more about our GC-MS/MS Solution

Products and resources

[Click on each listing for more information](#)

## Products



### High efficiency separation

#### Impurity separation with (U)HPLC platforms

- Thermo Scientific™ TraceGOLD TG-1701 MS Column



### Robust and sensitive mass detection

#### Mass detection

- Thermo Scientific™ TSQ 9000 GC-MS/MS System



### Fit-for-purpose software

#### Software

- Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) Software

## Resources



### Literature

- Application Note: Determination of genotoxic nitrosamines in Valsartan with gas chromatography and mass spectrometry
- GC Exploris HRAM validation of 15 nitrosamines in metformin drug substance
- Overcoming the challenges of nitrosamine impurities in drugs
- Brochure: Thermo Scientific TSQ 9000 Triple Quadrupole GC-MS/MS System
- Brochure: Chromeleon CDS software
- Brochure: Consumables



### Web tools

- Nitrosamine impurity analysis
- Triple Quadrupole GC-MS/MS



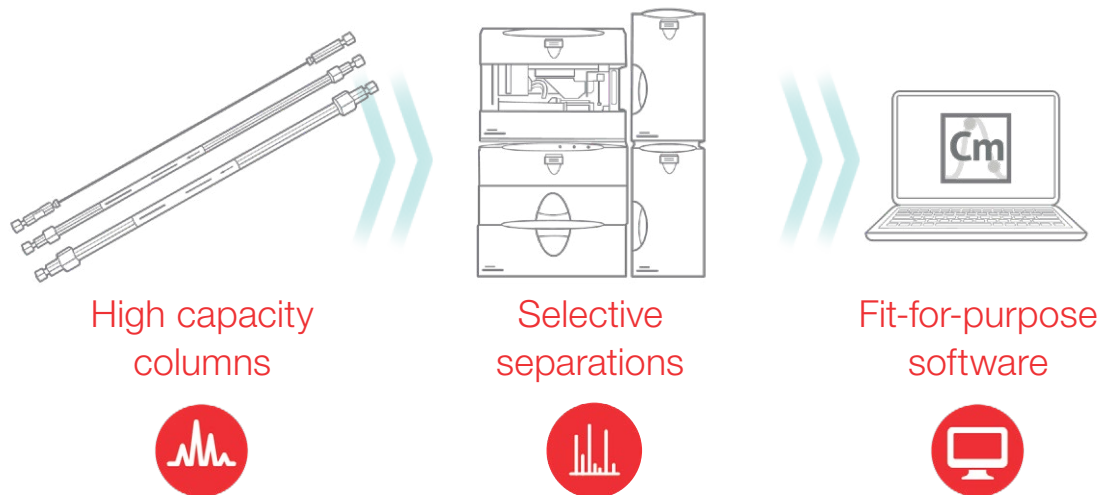
### Webinars

- Nitrosamine analysis; a leading CDMO's perspective
- Virtual Seminar: Nitrosamine analysis



Would you like to learn more?  
Contact a GC-MS/MS specialist now.

# IC Solution for nitrite analysis needs with confident targeted approach



High capacity columns

Selective separations

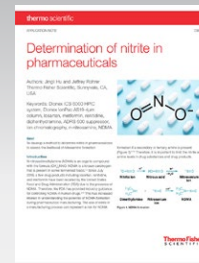
Fit-for-purpose software

- Little or no sample preparation is required
- Reagent-Free™ (RFIC™) ion chromatography system with electrolytically generated KOH eluent
- Multi drug product workflow

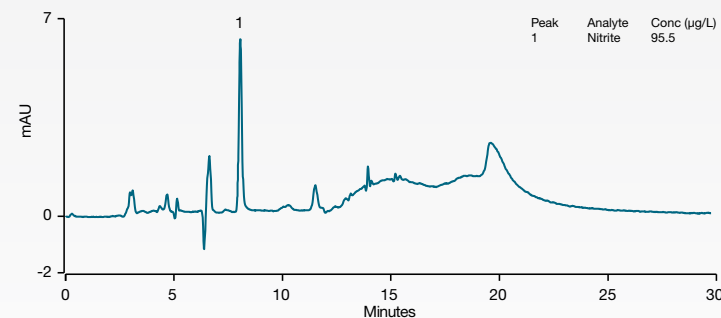
The UV absorbance detection allows the sensitive and selective detection of nitrite without interference from high amounts of chloride.

## Featured Application Note

### Determination of nitrite in pharmaceuticals



- The LOD of nitrite in a pharmaceutical sample is 0.918 ppm ( $\mu\text{g/g}$  API)
- The method is accurate and precise
- Applied to seven pharmaceutical samples, including metformin, losartan, ranitidine, and diphenhydramine



Nitrite in ranitidine drug product (S7) using a Dionex IonPac AS19-4 $\mu\text{m}$  column

# Learn more about our IC Solution

## Products and resources

[Click on each listing for more information](#)

### Products



#### High capacity columns

##### Impurity separation with (U)HPLC platforms

- Thermo Scientific™ Dionex IonPac™ AS19-4µm Column



#### Selective separation

##### Ion chromatography

- Thermo Scientific™ Dionex™ ICS-6000 Capillary HPIC™ System



#### Fit-for-purpose software

##### Software

- Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) Software

### Resources



#### Literature

- Application Note: Determination of nitrite in pharmaceuticals
- Brochure: Thermo Scientific Dionex ICS 6000 HPIC System
- Brochure: Chromeleon CDS software
- Brochure: Consumables



#### Web tools

- IC home page
- Nitrosamine impurity analysis



#### Webinars

- Nitrosamine analysis; a leading CDMO's perspective
- Virtual Seminar: Nitrosamine analysis



Would you like to learn more?  
Contact a IC specialist now.

## Solutions to help address regulatory needs

Requirement	Example approach	API	Separation	Detection	Download
<b>Fit-for-purpose, reliable quantitative screening</b>	Highly sensitive and robust LC-MS/MS solution for quantitation of nitrosamine impurities in metformin drug products	Metformin	LC	Triple quad MS	
	Determination of genotoxic nitrosamines in Valsartan	Valsartan	GC	Triple quad MS	
<b>Future proof your lab with absolute confidence and quantitation</b>	A validated method for the rapid determination of fifteen nitrosamines in metformin drug substance	Metformin	GC	High resolution MS	
	HRAM LC-MS method for the determination of nitrosamine impurities in drugs	Ranitidine	LC	High resolution MS	
	HRAM LC-MS methodology for the determination and quantitation of nitrosamine impurities in drug products	Ranitidine Valsartan	LC	High resolution MS	
	Overcoming the challenges of nitrosamine impurities in drugs: What Pharmaceutical QA/QC laboratories need to know	Metformin Valsartan	GC	High resolution MS Triple quad MS	
<b>Ingredient and product monitoring</b>	Determination of dimethylamine and nitrite in pharmaceuticals by ion chromatography to assess the likelihood of nitrosamine formation	Multiple	IC	UV / CD	

Stay up-to-date with latest releases on this topic.

Need more information? Contact a specialist

Find out more at [thermofisher.com/nitrosamine](https://thermofisher.com/nitrosamine)



### Technical and online support: peak performance for your instruments

Helping you keep your instruments running at peak performance is our goal. Whether you're looking for an instrument manual or spare parts, want to submit a repair request, or check on the status of your warranty or service contract, we have every support option you're looking for.

[thermofisher.com/technicalresources](https://thermofisher.com/technicalresources)



### The lab-forward trade-in program

A lab-changing experience. Our trade-in process is a highly personalized experience that starts with a conversation and doesn't end until your new instrument is successfully up and running. We help you assess your lab's needs and select a new system that is the best fit for your lab. We'll let you know the discounted, limited-time new system pricing you're eligible for based on your system trade-in.

If you need help with financing, we have a wide array of financing solutions available, but we don't stop there. Our service team will install your new system and arrange for the responsible disposal of your current one. Most importantly, our personalized support goes well beyond installation.

We'll also help you transfer methods and train your staff. Our goal is to ensure, from start to finish, your trade-in is a lab-changing experience for the better.

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