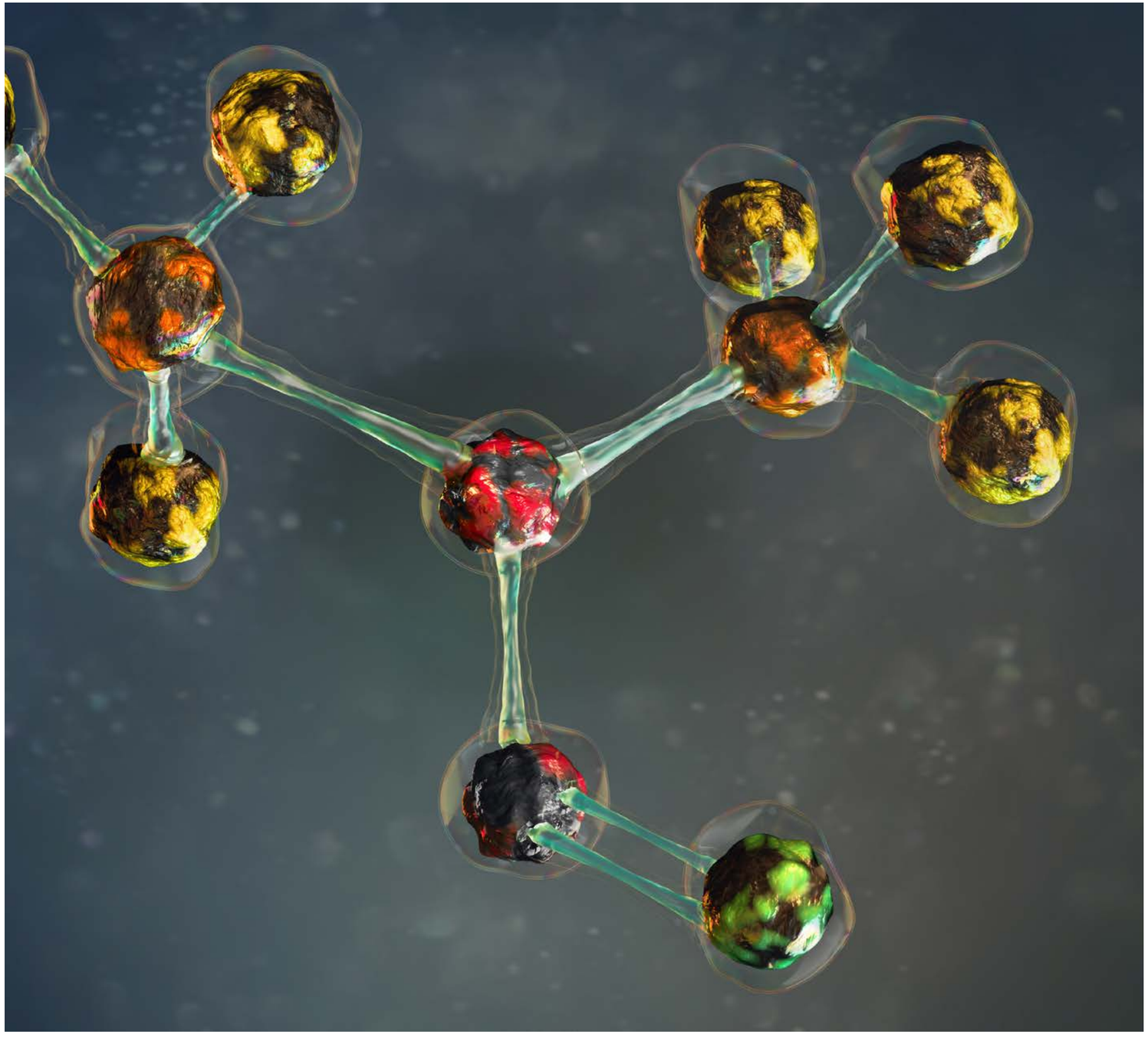
SCIEX impurities compendium

danaher

The power of precision



Contents

01

Thoughts from industry experts

Nitrosamines: history and background

Nitrosamines are carcinogenic compounds identified more than century ago, but their toxic potential got recognized from 1956 onwards. These compounds, formed by a nitroso group bonded to an amine, are by-products of numerous industrial, pharmaceutical, and food processes.

Anirban Roy Chowdhury
Amneal

They gained substantial attention in mid-2018 when NDMA, one such nitrosamine was detected in valsartan-containing drugs, prompting widespread recalls. Other medications, such as candesartan, irbesartan, olmesartan, pioglitazone, rifampin, rifapentine, and metformin also contained nitrosamine impurities like NMBA, NDIPA, NEIPA, NDEA etc. The Global Substance Registration System (GSRS) lists approximately 41% of APIs as potential nitrosamine precursors. According to the FDA database, over 1,400 product lots have been recalled due to nitrosamine contamination, indicating the severity of the issue.

41%

of APIs as potential nitrosamine precursors

Regulatory compliance requirements
Post 2018, regulatory agencies have implemented stringent compliance requirements to address nitrosamine contamination. The FDA had set an October 1, 2023, deadline for small nitrosamine impurities, requiring pharmaceutical companies to identify, evaluate, and control these impurities.

For Nitrosamine Drug Substance Related Impurities (NDSRIs), the compliance deadline is August 1, 2025. NDSRIs are nitrosated versions of the API or similar compounds. Key guidelines ICH M7, OECD 470 etc. establish standards for such type assessment and management. They are classified as Class 1 mutagenic carcinogens, under which a special category named "cohort of concern" impurities. Recent FDA and EMEA guidance introduced the Carcinogenic Potency Categorization Approach (CPCA) using structure-activity relationships to classify nitrosamines and set acceptable intake limits based on their carcinogenic potential. Also, the concept of enhanced Ames tests, a toxicity test for NDSRIs, is also propounded.

Testing and assessment
Since nitrosamines are very toxic, they are required to be quantified at often ppm and ppb level concentrations. Accurate detection and quantification of nitrosamines involve advanced techniques like high-resolution mass spectrometry (HRMS), or quadrupole and gas chromatography-tandem mass spectrometry (GC-MS/MS). These methods, though sensitive and specific, often face challenges such as false positives due to isobaric interferences, contamination, and in situ nitrosamine formation during analysis. Low molecular weight nitrosamines, with fragment masses as low as 43 amu, are particularly prone to external contamination. For NDSRIs, isobaric interferences from pseudo-nitrosamines like oximes and formyl impurities further complicate analysis.

Regulatory agencies have published few of the multiple methods required for the analysis of drug products, using LC-MS/MS and GC-MS/MS, to ensure accurate nitrosamine detection. The complexity of these analyses demands rigorous method development and challenging method validation to avoid false positive results. High-resolution mass spectrometry is sometimes required, to resolve close range mass interferences. To achieve sensitivity often high sample load is used multiplying the matrix effects, which sometimes result in ion suppression and ionisation challenges. Use of highly sophisticated instrumentation with high-caliber skillful analyst can circumvent the possible challenges.

Future challenges
Future challenges include the analytical quantification of trace-level nitrosamines and evaluating their toxicity potential. Balancing patient safety with the risk of drug shortages is becoming increasingly critical. The FDA has published NDSRI limits for over 250 products, typically up to 1500 ng/day. However, as an exception higher limits, such as 12000 ng/day for N-nitroso ciprofloxacin have been assigned. The criteria for such limit derivation is not very crystal clear to allow it to be applied to other projects. Cost-effective toxicity studies and approaches using less-than-lifetime exposure are still in development. As a part of risk mitigation reformulation or extensive toxicity studies may be required. However clear guidance for toxicity and supporting guidelines for bioequivalence study requirements for reformulated products are yet to be frozen. Collaborative efforts, regulatory oversight, and advanced quantification and toxicity evaluation methods are crucial to ensuring pharmaceutical safety and efficacy.

Accurate detection and quantification of nitrosamines involve advanced techniques like high-resolution mass spectrometry (HRMS), or quadrupole and gas chromatography-tandem mass spectrometry (GC-MS/MS).

NDSRIs – analytical challenges

N-Nitrosamines are potentially mutagenic impurities that may pose a risk of cancer to humans when exposed over a prolonged period. Since 2018, global regulatory bodies have required pharmaceutical manufacturers to control and strive to mitigate the presence of nitrosamines in their products to protect patient safety and avoid regulatory recalls in the future.

Dr. BM Rao
QDOT associates

The current major focus in N-Nitrosamines testing, and cause of many of the most recent drug recalls, is the formation of 'Nitrosamine Drug Substance Related Impurities' (NDSRIs). NDSRIs are formed when nitrosating agents interact directly with the active pharmaceutical ingredient (API) during manufacturing or in storage. Control of NDSRIs, through analytical testing, has presented unprecedented challenges due to their relatively high potential for formation and often very low level regulatory acceptable intake thresholds.

According to the recent guidance published by both the FDA and EMA, nitrosamines and NDSRIs must be monitored at the low ng/mL using highly sensitive analytical methodologies such as LC-MS/MS. The choice of test method depends on the specific nitrosamine compound being tested for, the type of drug product being tested, and the sensitivity required for the analysis. This assessment of methodology used should be part of the risk assessment performed per product. Accurate determination and quantitation of nitrosamine impurities and NDSRIs in drug substances and products using LC-MS/MS based analytical strategies that can readily be adopted. Matrix effects were shown to be critical considerations and should be effectively mitigated in trace-level quantification of nitrosamine impurities in pharmaceuticals by LC-MS/MS. Specific challenges also arise, such as minimizing low mass interference for small N-nitrosamines or managing structural similarities to the API and isomeric separation for NDSRIs. Minimizing contamination and N-nitrosamine formation during sample preparation is always critical.

Quantification of an NDSRI at levels down

10-30 ppb

To prove the absence of an NDSRI, analytical methods are required to have an LOQ at 10% of the content limit derived from the NDSRI's acceptable intake and the API's maximum daily dose. Quantification of an NDSRI has been estimated to be routinely achievable at levels down to 10-30 ppb (ng/g drug product) on **SCIEX 5500 plus system**. However, in the case of NDSRIs for which control in categories 1-3 is required by the CPCA, this may not be sufficient, as the low acceptable intakes in combination with even moderate allowed daily API doses - may result in LOQ requirements beyond technical feasibility. The analytical challenge may be exacerbated if the NDSRI co-elutes with the API due to high physicochemical similarity, or by the lack of robust reference standards. A good source of information and tools can be found in the United States Pharmacopeia (USP) Nitrosamine Exchange (an open platform). The Exchange includes a database of analytical methods for detecting nitrosamine impurities in drug products, as well as a forum for discussing regulatory updates and industry trends.

Future of nitrosamine analysis

Nitrosamines, which feature a nitroso group (NO+) bonded to a deprotonated amine, were classified by International Agency for Research on Cancer way back in May 1978 as probable human carcinogens based on the reported animal studies.

Dr. Saranjit Singh
Ex-Professor at NIPER, SAS Nagar and Independent Industry Consultant/Trainer

The agency issued monographs on evaluation of carcinogenicity risk of almost 18 nitrosamines, which were found to be present in food, beer and multiple other manufactured and natural consumer goods. It was much later in July 2018 that the US FDA found the presence of high level of N-nitrosodimethylamine (NDMA) in a lot of an angiotensin II receptor blocker (ARB). Owing to desperate call attention by EMA and USFDA on nitrosamines, there were a series of marketed product recalls, leading even to critical drug supply shortages.

These regulatory authorities responded to this sudden challenge by proposing GC-MS and LC-MS methods for trace nitrosamine determination in drug actives and their products, considering their essentiality for risk evaluation and routine quality control. Later, lots of application notes were developed by instrument companies and research laboratories in private sector and academia addressing issues of method sensitivity, specificity, and reliability. The compendial agencies were not to be left behind, and they also rose to the emergent situation by issuing general chapters, production sections in select monographs, and through supply of reference standards of simple nitrosamines as well as complex nitrosamine drug substance related impurities (NDSRIs). The present day

trend is towards developing methods that i) are able to detect and quantify this new category of carcinogens well below their Acceptable Intakes, ii) can help quantify multiple of them in a single run, and iii) are applicable to quantitatively analyse specific nitrosamines in biological fluids. Also in focus are the use of novel techniques, including sensors, for the purpose. There is active discussion going on to set limits of reactive impurities, e.g., nitrite, in excipients and water. Determining such trace reactive impurities in the said matrices is a forthcoming challenge.

To help industry in meeting the stringent regulatory expectation of controlling the afore-mentioned cohorts of concern, multiple specialized and well-equipped private testing laboratories have originated globally. An interesting report has been published recently, according to which 'the global nitrosamines testing market size was valued at USD 119.32 million in 2022 and is expected to expand at a CAGR of 9.85% during the forecast period, reaching USD 209.64 million by 2028'. With ever increasing number of NDSRIs/active substance-derived nitrosamines in regulatory lists, the testing is certainly going to get expanded in future. It may be the case even of countries and regions, where nitrosamine testing is not yet a formal requirement.

Phenomenex solutions for nitrosamine

James Turner
Phenomenex

Nitrosamines in pharmaceutical drugs can be formed during chemical synthesis and formulation; they are of particular concern as they are known to be carcinogenic. This has led to pharmaceutical regulators setting strict limits on the presence of nitrosamines and NDSRI (nitrosamine drug substance-related impurities) in drug substances (API) and drug products.

Due to the extremely low levels these compounds are required to be analyzed at (pg/g) combined with their lack of a chromophore it is necessary to use LC-MS/MS to achieve the desired levels of sensitivity. Even when using a highly sensitive mass spectrometer, it is still necessary to load a significant amount of drug substance or drug product onto the analytical HPLC column. This poses challenges as the amount of API entering the mass spectrometer will cause overloading, which is likely to lead to contamination and hysteresis effects. A further challenge is that nitrosamines are small and polar, making them challenging to retain and separate in a reversed phase HPLC system.

As reversed phase HPLC interfaces well with MS/MS systems, the use of a polar stationary phase which is suitable for reversed phase use, with the ability to retain nitrosamines can be beneficial when analysing nitrosamines in pharmaceutical drug products. Kinetex Biphenyl offers high efficiency due to the core-shell morphology of the packing material. The combination of the particle morphology with the pi-pi and dipole-dipole interactions for the biphenyl phase the column is able to retain and resolve nitrosamines from interfering sample matrix components, producing narrow peaks which assist in analyte quantitation. This column choice is also effective in the analysis of NDRSIs which can pose significant challenges for pharmaceutical manufacturers given the structural similarities with the parent drug compounds.

02

SCIEX solutions for nitrosamine

Regulatory requirements of nitrosamines

Sr. No.	Impurity Name	Abbreviation	FDA	USP	EMA	Ph. Eur
1	N-Nitrosodimethyl amine	NDMA	✓	✓	✓	✓
2	N-Nitrosomorpholine	NMO			✓	
3	N-Nitroso-Nmethyl-4-aminobutyric acid	NMBA	✓	✓	✓	✓
4	N-Nitrosodiethylamine	NDEA	✓	✓	✓	✓
5	N-Ethyl-N-nitroso-2-propanamine	NEIPA	✓	✓	✓	✓
6	N-Nitrosodi-n-propylamine	NDIPA	✓	✓	✓	✓
7	N-Nitroso-di-n-propylamine	NDPA				✓
8	N-Nitroso-methyl phenylamine	NMPA			✓	
9	N-Nitrosodibutylamine	NDBA	✓	✓	✓	✓
10	N-Nitroso methyl ethyl amine	NMEA			✓	
11	N-Nitrosopyrrolidine	NPY				
12	N-Nitrosopiperidine	NPP				

Available methodologies from SCIEX

	NDMA	NMO	NMBA	NDEA	NEIPA	NDIPA	NDPA	NMPA	NDBA
Valsartan	✓	✓	✓	✓	✓	✓	✓		✓
Telmisartan	✓	✓	✓	✓	✓	✓	✓	✓	✓
Olmesartan	✓	✓	✓	✓	✓	✓	✓		✓
Irbesartan	✓	✓	✓	✓	✓	✓	✓		✓
Losartan	✓	✓	✓	✓	✓	✓	✓		✓
Candesartan	✓	✓	✓	✓	✓	✓	✓		✓
Ranitidine	✓								
Metformin	✓	✓	✓	✓	✓	✓	✓	✓	✓
Metformin-FDC	✓	✓	✓	✓	✓	✓	✓	✓	✓
Zileuton	✓	✓	✓	✓	✓	✓	✓	✓	✓
Oseltamivir	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sacubitril & Valsartan	✓	✓	✓	✓	✓	✓	✓	✓	✓
Nitisinone	✓	✓	✓	✓	✓	✓	✓	✓	✓
Esomeprazole	✓	✓	✓	✓	✓	✓	✓	✓	✓

SCIEX solutions

There, where it counts. Time and time again. Providing the precision detection and quantitation of molecules needed for scientists to make discoveries that change the world.

QTRAP 4500 system

Known as the LC-MS/MS workhorse, this is the intelligently re-engineered design of the 4000 QTRAP platform, and sets a new benchmark for robust quantitation and library searching.

SCIEX 5500+ system

The best just got better. The **SCIEX Triple Quad 5500+ system** is equipped to conquer your laboratory's most complex workflows and opportunities. With this LC-MS/MS system, you have the sensitivity and performance to meet analytical and regulatory demands for low-level trace detection with ease.

SCIEX 6500+ system

The **Triple Quad 6500+ system** features multi-component IonDrive technology including the IonDrive High Energy Detector+ that pushes the boundaries of LC-MS/MS quantification farther than ever before.

SCIEX X500R

For the modern researcher who needs flexible and scalable workflows that deliver reliable, high-quality, accurate mass results with confidence, the **X500R** will quickly become your workhorse.

SCIEX OS software

Streamline and simplify your workflows, delivering more and faster with software engineered for all your SCIEX mass spectrometry systems.

Metformin

Metformin, a biguanide developed from galegine, is an oral antihyperglycemic agent most widely used in the treatment of type 2 diabetes. Chemically, it is a hydrophilic base which exists at physiological pH as the cationic species (>99.9%). It is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4, with the pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The tablets are available under various brand names for oral administration containing 500 mg, 750 mg or 1000 mg of metformin hydrochloride.

Technical notes

Analysis of nitrosamine impurities in a metformin drug substance and drug product Using the SCIEX X500 QTOF System

Metformin, a biguanide developed from galegine, is an oral antihyperglycemic agent most widely used in the treatment of type 2 diabetes.

Read technical note

Enhanced sensitivity for nitrosamine analysis in a metformin active pharmaceutical ingredient (API)

In this technical note, sensitive analysis of 13 nitrosamines in a metformin API was performed using the **SCIEX 7500 system** with limit of quantitation (LOQ) values as low as 0.01 ng/mL in solution.

Read technical note

SCIEX 5500+ system

Combining patented mass spec technologies with sophisticated yet intuitive software, the **SCIEX 5500+ System** delivers a high level of sensitivity, robustness and productivity for the most demanding quantitative analyses.

This LC-MS/MS system will help you respond to low-level trace detection and quantification challenges with ease while meeting regulatory requirements. **SCIEX 5500+ system** comes with an upgrade path to QTRAP functionality. Upon quick license activation, the QTRAP Ready functionality will boost your quantification workflows with additional scan types for more data and information out of the same injection.

Turbo V ion source

Extraordinary robustness and superior performance across a wide range of compounds.

HED detector and high capacity CEM

Increased productivity with fast polarity switching of 5 msec enabling up to 6 orders of magnitude of linear dynamic range.

Scheduled MRM Pro algorithm

With Analyst software, maximize the number of MRM transitions to analyze more compounds in a single run without sacrificing precision.

OptiFlow Turbo V ion source

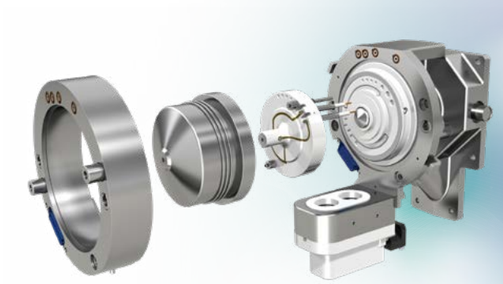
Upgrade to the OptiFlow source for low-flow analysis. It is robust and simple to operate, with a flow-rate range of 1 -200 µL/min.

QTRAP ready

Activating your license through a quick and easy process opens up your **SCIEX Triple Quad** to a world of possibilities with MS/MS confirmation, enhanced selectivity with MRM3, and other valuable scan types.

Extra selectivity to overcome challenging ion separations

SelexION technology delivers highly-selective, robust and reproducible ion separation that significantly enhances your quantitative and qualitative performance. Designed to install between the ionization source and the vacuum interface of your mass spectrometer, SelexION Technology simply installs and de-installs within 2 minutes without breaking vacuum.



SCIEX Triple Quad 6500+ system

Detect and identify analytes across a wide range of chemistries simultaneously, regardless of mass or polarity. The **SCIEX 6500+ Series**, equipped with IonDrive™ system technology, significantly enhances performance across various key applications.

IonDrive™ technology—pushing the sensitivity barrier

IonDrive technology with the enhanced high energy detector and **SelexION®+** technology built into the **6500+ Series** LC-MS/MS systems pushes the boundary even further.

IonDrive technology simultaneously targets 3 critical areas of enhancements in the **6500+ Series**, ruggedly driving best-in-class performance improvements and unrivaled sensitivity in 3 key components of the system:

- The production of more ions with the optimally designed IonDrive™ Turbo V Ion Source
- The capture and transmission of more ions with the unique IonDrive QJet Ion Guide
- The detection of more ions with the enhanced IonDrive High Energy Detector+

Enhance your methods with QTRAP® systems

See the full MS/MS picture for every MRM
When combined with the QTRAP technology, the **6500+ Series** delivers the MRM sensitivity you need for quantification, with added 100X increase in full-scan sensitivity over basic triple quads. The combined triple quadrupole and linear ion trap scan functions provide unrivaled confidence by complementing sensitive MRM detection with enhanced product ion and complete MS/MS profiles for unequivocal identification.

MRM3 —a generation of quantification without interferences
When high background or challenging co-eluting interferences make standard MRM quantification difficult, enhanced quantitative selectivity is a mouse click away with MRM3. The **QTRAP 6500+ system** enables MRM3 scans that are twice as fast as previous generations of QTRAP technology, enabling faster chromatography.

100x
increase in full-scan sensitivity over basic triple quads

Key features of the SCIEX QTRAP® 6500+ System for nitrosamine analysis

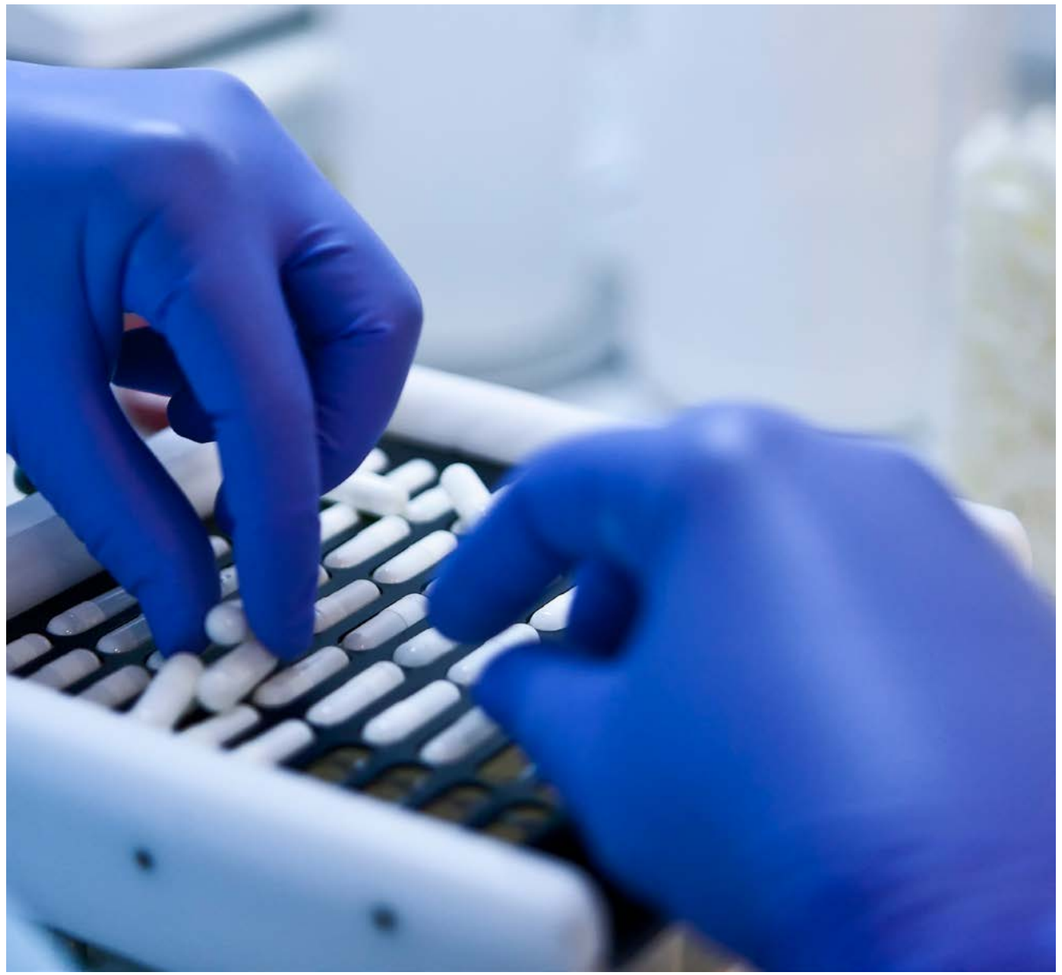
Mass range
Triple quadrupole: 5 – 2,000 Da

Detector type
IonDrive High Energy Detector+

Flexible ionization options
Options include OptiFlow Turbo V Electrospray ionization (ESI) and heated nebulizer ionization probes

Polarity switching
5 msec in MRM and Scheduled MRM modes

Selective, robust and powerful ion separation
Optional SelexION+ differential mobility spectrometry



Sartans

Sartan drugs, also known as angiotensin II receptor blockers (ARBs), are medications used to treat high blood pressure and heart failure. Some examples of sartans include valsartan, irbesartan, candesartan, losartan, and Olmesartan. These drugs work by blocking the activation of AT1 receptors found in the heart, blood vessels, and kidneys. Angiotensin II is a hormone that tightens blood vessel muscles, leading to an increase in blood pressure. By blocking these receptors, sartans help reduce blood vessel tightening and lower blood pressure.

Highly selective and sensitive method for quantification of nitrosamines in valsartan drug substances

Recently, certain Valsartan drugs have been recalled due to contamination with N-nitrosodimethylamine (NDMA), which is a potential human carcinogen.

Read technical note

Analysis of nitrosamine compounds in multiple sartan APIs: a review and optimization of the Ph. Eur. monograph

Nitrosamine analysis has recently become one of the largest areas of interest in the pharmaceutical industry after their production in numerous active pharmaceutical ingredients (APIs) and drug products was found to be possible.

Read technical note

Technical notes

Analysis of genotoxic nitrosamines in losartan using the SCIEX 7500 system

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) continue to closely monitor nitrosamine levels in pharmaceutical products since the initial discovery of N-nitrosodimethylamine (NDMA) in valsartan in 2018 prompted recalls of the drug.

Read technical note

Analysis of genotoxic nitrosamines in losartan and ranitidine active pharmaceutical ingredients

In recent years, there have been several high profile drug recalls of angiotensin II receptor blocking saratan class drug (valsartan, losartan, irbesartan), due to contamination of the final drug products with potentially genotoxic nitrosamine compounds, including n-nitrosodimethylamine (NDMA).

Read technical note

Quantification of genotoxic nitrosamines in a telmisartan drug product

Telmisartan is a drug substance that is susceptible to the presence of nitrosamine impurities. Based on results from animal testing, nitrosamines are classified as a probable carcinogen by the World Health Organization/ International Agency for Research on Cancer.

Read technical note

5-[4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-tetrazole (AZBT) quantification in a sartan drug substance and drug product

In April 2021, AZBT, which is a known impurity in some sartan medications, tested positive on 2 independent Ames tests, suggesting that this compound might be a mutagenic impurity.

Read technical note

03

Other molecules

Technical notes

Quantification of N-nitrosodimethylamine (NDMA) in azithromycin drug products Using the QTRAP 4500 system

NDMA is a genotoxic compound that belongs to a group of compounds deemed the "cohort of concern" by the European Medicines Agency (EMA) due to its possible impact on human health.

Read technical note

Precise and accurate quantification of nitrosamine impurities in an esomeprazole API

Esomeprazole is a proton pump inhibitor that is used to mitigate the symptoms of gastroesophageal reflux disease (GERD) and other conditions which occur due to excess gastric acid by inhibiting acid production in the stomach.

Read technical note

Low-level quantification of 10 mutagenic nitrosamine impurities in acyclovir

This technical note demonstrates a highly selective and sensitive method for quantifying 10 nitrosamines in acyclovir.

Read technical note

Sensitive and reproducible quantification of N-nitroso propranolol in a propranolol drug substance and product

This technical note describes the quantification of the N-nitroso propranolol impurity in a propranolol drug substance and product using the **QTRAP 6500+ system**.

Read technical note

Low-level quantification of 10 mutagenic nitrosamine impurities in Pioglitazone hydrochloride using accurate mass spectrometry using X500R QTOF system

This technical note presents an accurate mass spectrometry method for quantifying 10 mutagenic nitrosamines in Pioglitazone hydrochloride, including NDMA.

Read technical note

SCIEX Triple Quad 4500 system

When your lab is faced with lots of samples and impending deadlines, you can't afford an unreliable mass spec system that could put your lab or your reputation at risk.

Some mass spec solutions can crack when faced with pressure:

- Data quality erodes during long runs
- Data processing is time consuming and becomes a bottleneck
- Getting immediate answers to solve problems as they arise is impossible

These challenges can be detrimental to your lab's productivity. The **4500 system** is designed to conquer them.

The Turbo V™ ion source provides high-sensitivity analysis over a wide range of flow rates with quick-change APCI and TurboIonSpray® probes. From 50 µL/min to 3 mL/min, the Turbo V source is the perfect match for narrow bore, standard bore and UHPLC flow rates, delivering unprecedented desolvation and stability for even the toughest high-flow applications.

The patented QJet® ion guide improves ion containment and operates at high pressure, providing better collisional focusing to enhance ion transmission for ultimate sensitivity. The proven design also reduces the gas load, allowing the turbopump to run cooler in its ideal operating range. It all adds up to our most reliable system – and with tool-free maintenance, clean-up is simple and straightforward.

Flexible ionization options

Options include Electrospray (ESI) ionization and heated nebulizer ionization probes.

Mass range

5 – 2000 Da.

Polarity switching

50 msec in MRM and Scheduled MRM modes.

Detector type

AcQuRate Pulse Counting CEM.

The power of precision

SCIEX Now support network

SCIEX Now

- Manage your instruments.
- Submit and manage support cases, track status and view history.
- Access online training courses and articles.
- Manage software licenses linked to your registered instruments.
- View and report critical instrument statistics when connected to StatusScope remote monitoring service.
- Be a part of the SCIEX community by submitting questions and comments.
- Receive notifications from SCIEX with content based on your preferences.

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SCIEX Now learning hub

- SCIEX Now learning hub success programs provide LC-MS and CE training customized to meet your exact needs.
- With a selection of training methods and certifications available, you can build a mass spectrometry program that is most suited to your lab and users.
- Starting with a clear understanding of your desired learning outcomes, we aim to help you improve lab productivity and consistency by designing and delivering a program that is focused on knowledge advancement and retention.

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