SCIEX

Pharma trends and solutions in drug discovery and development

September 2024

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The pharma industry: an infinite cycle of reinvention

Ferran Sanchez
Senior Market Development Manager - Pharma, SCIEX

During the last few years, the world as we know it has been shaken by events that have affected the economy and, consequently, the investment in different markets.

The pharmaceutical market is no exception, and we have identified and discussed different trends within our industry that can correlate with analytical needs to maintain the research and development of new drugs.

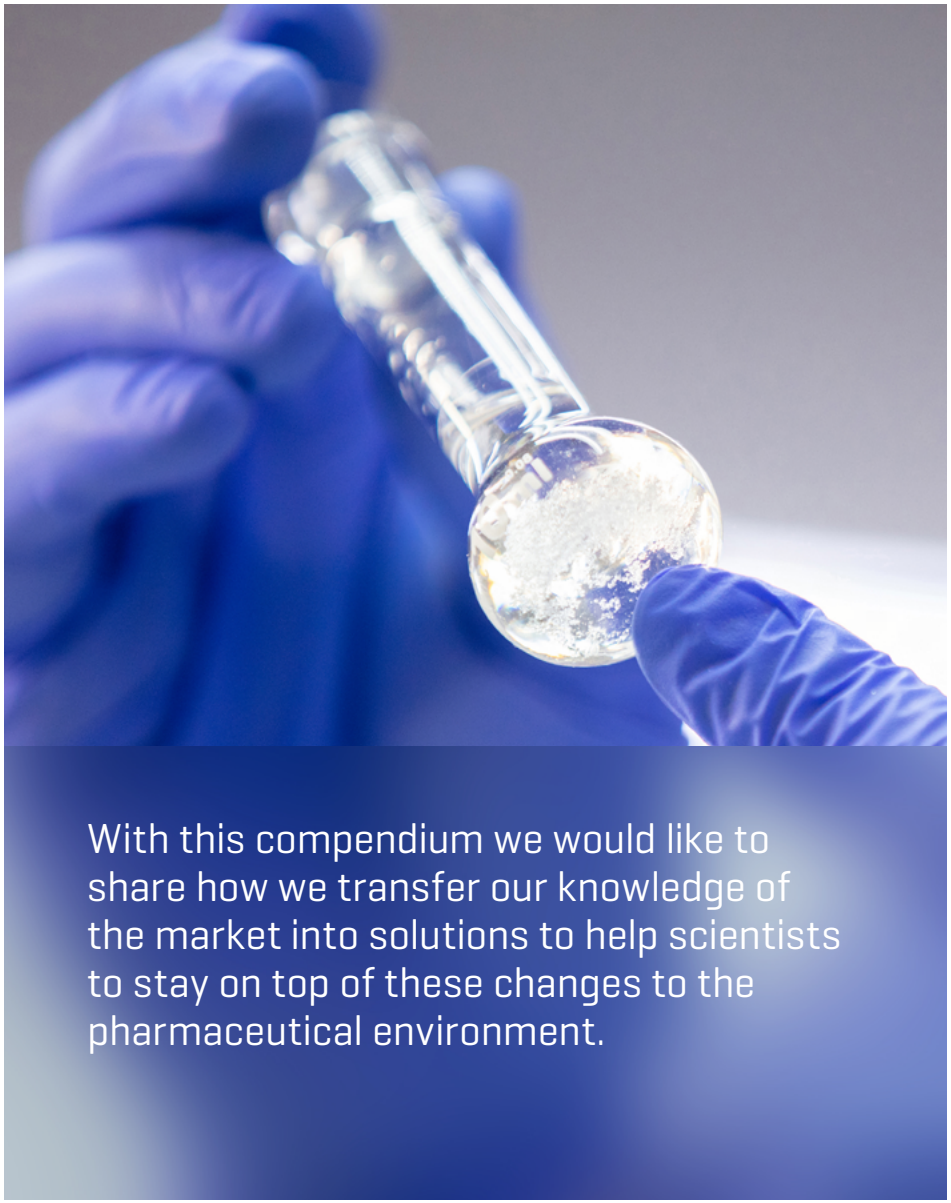
Despite the rise of the biopharmaceutical, most of the drugs in development and on the market in 2024 still fall into the category of chemically synthetized and / or small molecules; this includes targeted protein degraders, synthetic peptides and oligonucleotides. The speed of the process to discover the most effective molecule for the right target, at the lowest possible cost, is one of the key factors in the drug industry and must incorporate the ever-increasing costs of R&D, as well as the IP and regulatory revisions recently made by the EMA and the EU.

The balance between efficacy and speed must allow space for the study of the biotransformation of the drug, including the localization of modifications that occur during metabolism. Metabolite characterization is one of the main drivers of the drug discovery process to enable optimization of ADME properties. Having the right tools to accurately identify and localize sites of biotransformation, to allow investigation into drug safety, efficacy and kinetics, is a winning asset to accelerate the synthesis and development of new candidates.

Speed is important, but the efficacy and toxicity of the drug must be the first and foremost priority.

The earthquake created by the regulation of Nitrosamines since 2018 serves as a cautionary tale. The increased control and new regulations on this topic have obligated the pharmaceutical industry to evaluate their production processes, excipients, raw material suppliers and more. Consequently, the need for analytical methods for the identification, control and quantification of these impurities has been a factor of concern for most of the generic suppliers, but also for the originators, especially since NDSRIs are also important factors in the discussion.

The pharma industry: an infinite cycle of reinvention *continued.*



PK, PD, toxicity and bioanalysis play a crucial role in drug assessment. The diversity of the molecules analyzed has increased, from very small molecules to a range of new modalities including peptides, targeted protein degraders and oligonucleotides. These drive increased complexity in method development to enable the achievement of required LOQs and LODs. Versatility is a key need at this stage, especially for CROs working in this space, to allow the development of a broad range of methods, from sample preparation, to mass spectrometry optimization, to data collection and processing, all whilst working in a compliant environment.

Having modern software able to address all the customer questions and concerns around reporting in a safe environment must be one of the key responsibilities of the technology provider.

To summarize, the pharma industry stands on the precipice of a paradigm shift, with constant reinvention required to absorb the advancements in technology, regulatory shifts, acquisition of intellectual property and changes in market dynamics, underpinned by fluctuating investment and costs associated with research and development.

We at SCIEX are not independent of market dynamics. With this compendium we would like to share how we transfer our knowledge of the market into solutions to help scientists to stay on top of these changes to the pharmaceutical environment.

02

Drug discovery

Comprehensive hit finding in drug discovery: integrating HTS, FBS, and virtual screening for optimal preclinical candidates

Celine Legros, PhD
Drug Discovery Partnership Director, Target Validation, Hit Finding and Hit-to-Lead Business Line Leader, Eurofins

Dany Jeanne-Dit-Fouque, PhD
Mass Spectrometry Research Scientist, Eurofins

Drug discovery is critical to the generation of novel molecule candidates displaying the potential to treat acute and chronic diseases that improve human health. The primary goal is to swiftly discover the most promising hits and leads that combine excellent drug-like properties, deliver the desired in vitro pharmacological profile, and have a high probability of producing differentiated, patentable, and developable preclinical candidates to enter IND-enabling studies.

Hit Finding can be approached in multiple ways: Rational-based approaches employing Medicinal Chemistry and Computational Chemistry employing Virtual screening or literature starting points, as well as Fragment Based Screening (FBS) and conventional High Throughput Screening (HTS), for example.

These complementary methods can be performed either individually or in parallel and rely on quality assays and robust screening cascades to assess hit quality and tractability. Whether it is a novel approach to a well-validated target, or an entirely new target, HTS and FBS are proven methods for the identification of novel structural chemotypes which can successfully deliver leads and preclinical candidates.

Despite the rapid expansion and the high-quality of virtual screening capabilities, at Eurofins Discovery, we believe that conventional HTS (screening hundreds of thousands of compounds) and FBS still play an important role in hit finding programs. Virtual screening success is enhanced for structurally enabled targets, with multiple known ligands and solved protein structures which is not often publicly available for more novel biology. In such cases, a HTS screen serves as the first step in identifying novel chemical matter that can be augmented by subsequent virtual screening.

HTS technology continues to evolve, bringing with it shifts in screening cascades paradigms. The expansion of label-free technology, led by high throughput mass spectrometry, particularly the SCIEX Echo® MS system, as well as the recent acceleration of the throughput of the biophysics assays in combination with the growing expertise in production of purified membrane proteins, enables the identification of more biologically relevant hits, and binders, with limited technological bias.

At Eurofins Discovery, we believe that there no "standard" approach for HTS, and we strongly encourage the consideration of a multi-modal approach for our clients' projects. We do our utmost to offer comprehensive hit finding solutions, including the use of Compound Libraries, small molecules and fragments, as well as innovative technologies, supported by a team of scientific experts and project managers.

Revolutionizing high-throughput screening: The Echo® MS Plus system for label-free, rapid, and versatile analysis

Jacob, McCabe
Sr. Scientist, SCIEX

The speed and quality of fluorescence-based High-Throughput Screening (HTS) methods have become key problems in the drug discovery process, yet remain common due to their sensitivity, ease of use and adaptability to HTS formats. Labeled compounds, as well as increasing the cost per sample, can be affected by fluorescent quenchers, colored compounds, and form aggregates. These Pan-Assay Interference Compounds (PAINs) effects are problematic as they produce false-positive results but are difficult to predict.

Alternative approaches to fluorescence assays for high throughput sample analysis are being implemented as a result, such as mass spectrometry, which utilizes label-free detection of the analyte via the mass-to-charge ratio. However, traditional LC-MS analysis of 384 samples takes hours to analyze versus seconds using a plate reader.

Since the launch of SCIEX's first Echo® MS product in 2019 high throughput screening of small molecules has been a key driving force industry as an alternative to traditional fluorescence base experiments as we're getting QQQ quality data at the speed of plate readers without having to label the target analyte. With the launch of the Echo® MS +system increased analyte modalities can be analyzed with the coupling to the ZenoTOF 7600 system.

The new versatility of having both a triple quad and a high-resolution time of flight system allows for a large variety of compounds such as single amino acids to intact antibodies to be analyzed in a high throughput environment. The speed of analysis and the low sampling volume allows for rapid turnaround of data where the HTS has expanded from the screening of millions of compounds to the goal of rapid turnaround time of key samples to make informed decisions quicker.

The Echo® MS+ system, with its integration of the ZenoTOF 7600 system, delivers rapid, label-free, and versatile analysis of a wide range of compounds, revolutionizing high-throughput screening by offering QQQ quality data at the speed of plate readers.

Read more →

03

Bioanalysis

Adapting to the Evolving Landscape of High Throughput ADME-Tox and Bioanalysis

Simon Wood
Head of Analytical Sciences at Cyprotex

At Cyprotex we support High Throughput ADME-Tox applications and Bioanalysis of Discovery PK studies. The majority of these have LC-MS or LC-MS/MS detection and quantitation end points.

With a comprehensive range of nominal and high resolution mass spectrometry at our disposal we have the ability and capacity to handle most things that come our way.

We have also noted an increase in the number of requests to quantify very small molecules (usually as exploratory biomarkers). Whilst these are ionisable they are often too small to obtain good MS/MS data. Here we always turn to High Resolution mass Spectrometry to provide sensitive and selective data without fragmentation. Additionally HILIC chromatography is often required for chromatographic retention of these molecules

Increasingly diverse molecular modalities are also a more recent trend. Specifically Peptides, PROTACS and Oligonucleotides all have their analytical challenges and bespoke LC-MS solutions are required to meet these.

Finally, the request for efficient workflows with added value from richer data sets. A good example of this is additional softspot Metabolite Identification data from in vitro Metabolic stability samples and early PK in vivo samples whilst quantify the fate of the dosed parent molecule. For this we turn to fast scanning and reliable High Resolution Mass Spectrometry.

In recent years, we're faced new challenges due to the increasing diversity of molecules we are asked to analyse, as well as the evolving complexity of the solution workflows required.

Current trends and challenges in bioanalysis

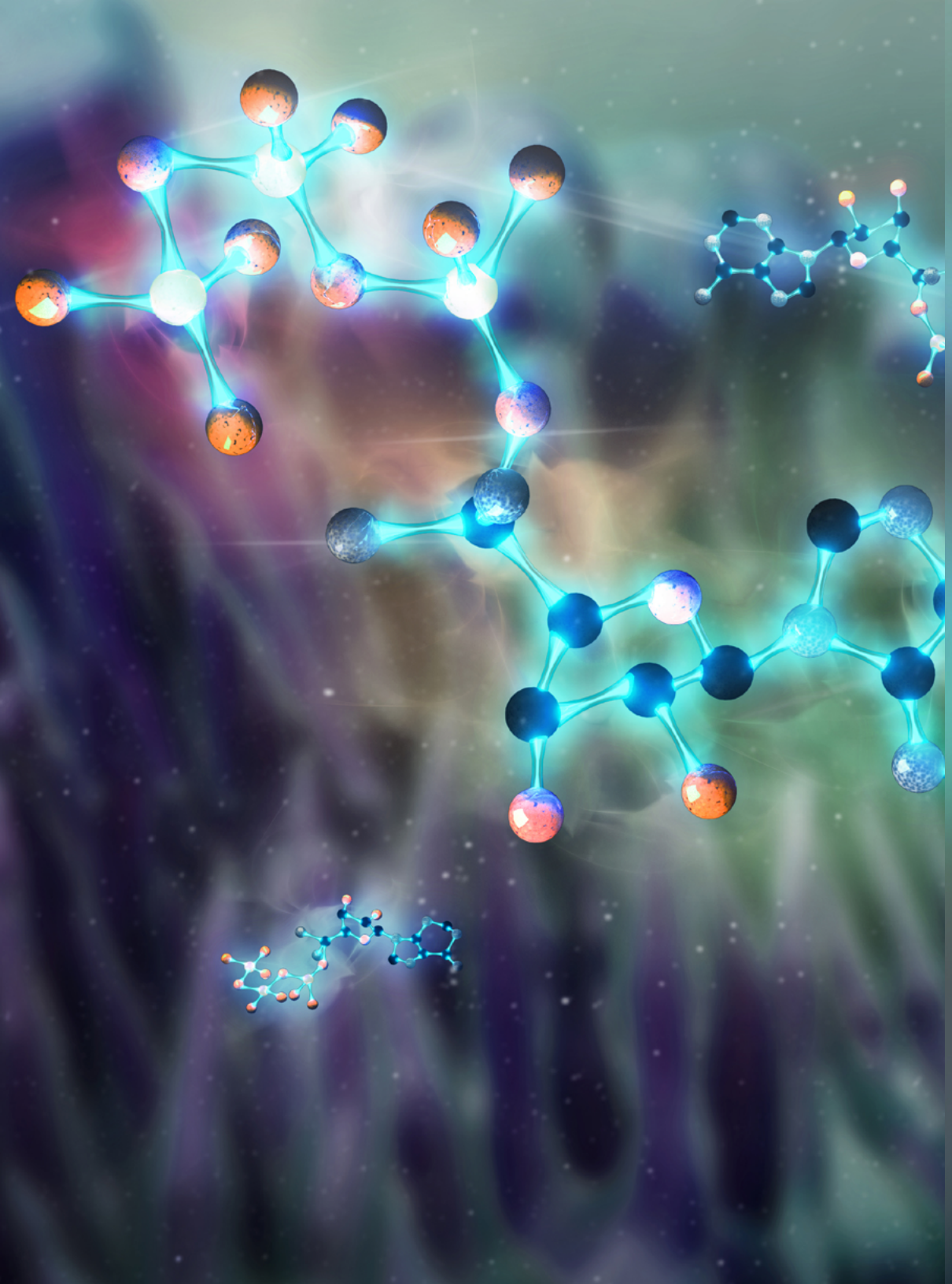
Cathy Lane
Application Lead, Pharma
& Peptide Quant, SCIEX

Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) has for many years been the workhorse of accurate and high-quality bioanalysis, which is critical for successful drug development. However, market trends and new applications leave Bioanalysts facing demands for high-confidence detection and quantitative performance at ever-enhanced levels of sensitivity. This is driven in part by development programs focusing on more efficacious, lower dosage compounds, but also by the emergence of challenging new modalities such as targeted protein degraders, peptides and oligonucleotide therapeutics.

The triple-quadrupole mass spectrometer is the gold standard for bioanalytical LC-MS/MS. The SCIEX 7500 system provides enhanced sensitivity in both positive and negative polarity through key hardware features that maximize the generation, capture and transmission of ions. Fast polarity switching (5 ms) and up to 6 orders of magnitude linear dynamic range (LDR) make the SCIEX 7500 system the triple-quad of choice for bioanalysis. High resolution mass spectrometers (HRMS) such as quadrupole-time-of-flight (QTOF) instruments are being increasingly adopted for quantitative bioanalysis due to their greater selectivity, improved mass resolution, and the flexibility of TOF MS/MS data analysis. Historically, the quantitative performance of QTOF platforms has been limited by duty-cycle issues (typical duty cycle for classical QTOF systems < 30%). The ZenoTOF 7600 system features a Zeno trap, which improves the duty cycle to ≥90%. This enhancement in sampling efficiency is highly advantageous for quantitative workflows that require high sensitivity and helps maintain accurate quantitative performance across a LDR spanning 5 orders of magnitude.

Both the SCIEX 7500+ and ZenoTOF 7600 systems allow streamlined data management using SCIEX OS software: an easy to learn, easy to use, fully 21 CFR Part 11 compliant, platform for data acquisition and processing. Use of the rugged, reliable and highly efficient OptiFlow and Turbo V ion sources, coupled with the ability to schedule ionization, enable sustained performance and maintain system robustness, making the SCIEX 7500+ and ZenoTOF 7600 systems ideally suited for the demands of bioanalysis in 2024 and beyond.

Read more →



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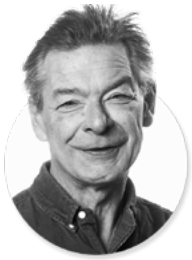
04

Metabolite Identification

Advanced techniques in early human AME studies: the future of Metabolite Identification



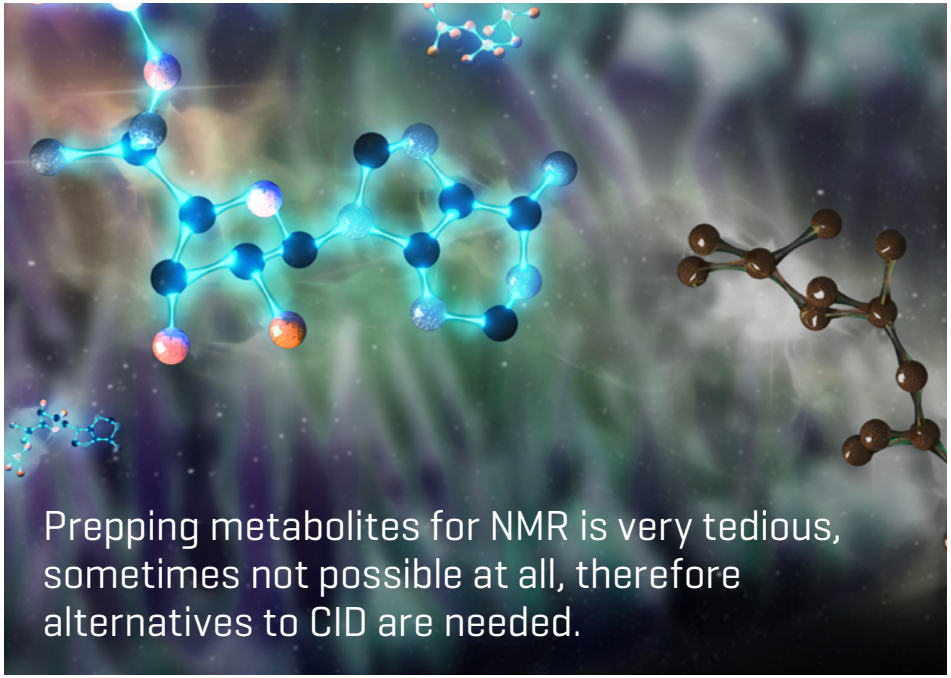
Elwin Werheij
Principal Scientist, Peregrion

The availability of early human data on the absorption, metabolism, and excretion (AME) during drug development is significantly beneficial. FIH studies can provide this information even before (microdose) or during Phase I (microtrace). A very small amount of radiolabeled (often 14C) drug is administered to a human volunteer solely or on top of the intended therapeutic dose.

The labeled drug and its metabolites can be analyzed in blood, plasma, urine, and feces using extremely sensitive accelerator mass spectrometry (AMS) to provide excretion, PK, and MetID data. This approach is not only applicable for adult humans, but is also successfully applied in pediatrics, including neonates as the ultra-low 14C dose is not considered to be a health risk. For metabolite identification the samples (extracts) are fractionated by UPLC using a post-column split for AMS analysis of the fractions and, in parallel, high resolution mass spectrometry (hrMS).

Fragmentation is mandatory for MetID, however, for isomeric metabolites, i.e. oxidation, glucuronidation, CID often doesn't provide enough information to answer 'at what site did the modification occur?

The AMS 14C profile provides the retention time of all metabolites and their relative abundance (AMS doesn't suffer from variable response factors due to chemical differences between compounds). Knowing where to look in the LC-MS data, combined with MetID software is extremely valuable, at first just accurate mass and isotope pattern. Fragmentation is mandatory for MetID, however, for isomeric metabolites, i.e. oxidation, glucuronidation, CID often doesn't provide enough information to answer, 'at what site did the modification occur?'. Prepping metabolites for NMR is very tedious, sometimes not possible at all, therefore alternatives to CID are needed. The introduction and development of alternatives to CID fragmentation, EAD (electron activation dissociation) and IRMPD (infra-red multi-photon dissociation), will aid the arduous MetID process. All of these, combined with high resolution ion mobility mass spectrometry, in the same instrument, with powerful MetID software (AI?), would be dream come true.



Enhancing metabolite identification with ZenoTOF and new insights in Drug Development

Heather Chassaing
Accurate Mass Workflow Specialist, SCIEX

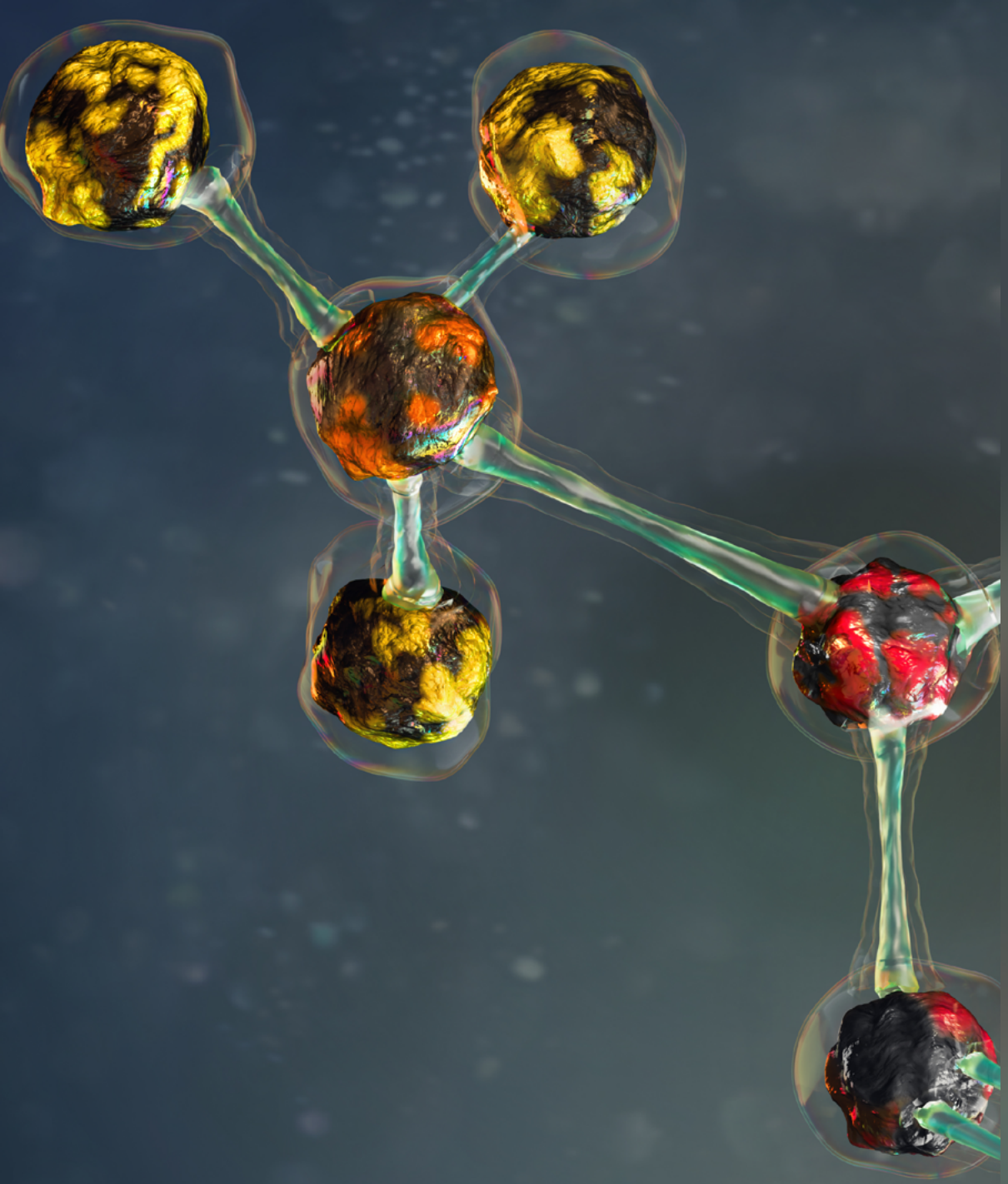
Metabolite identification is an integral part of the drug discovery and development process, underpinning both drug design and toxicology studies. The earlier MetID information is available the easier it is to make timely and effective decisions for drug candidate progression. The ZenoTOF 7600 system fits perfectly in this type of analytical environment, it combines the speed, sensitivity, and dynamic range of a high-end triple quad, with high resolution and two fragmentation techniques. This provides essential data for the identification, relative quantitationand structural assignment of potentially toxic metabolites.

Mass Spectrometry is the principal choice for MetID studies, it is fast, and gives structural and semi quantitative data with minimal sample preparation of complex biological matrices. However, CID fragmentation is often limiting, giving few diagnostic ions, and causing the neutral loss of labile functionalities, such as glucuronide conjugates. To identify the position of these labile moieties, further sample preparation is often needed for NMR analysis or chemical derivatization. This takes time and can be complicated by a lack of sample. The alternative fragmentation cell that is present in the ZenoTOF 7600 system, EAD (Electron Activated Dissociation), can provide much needed additional fragmentation information. It fragments high energy bonds, such as those found in aliphatic chains and ring structures, whilst conserving glucuronides in place so that their position can be confirmed.

The EAD cell is positioned before the CID cell, either cells can be used alone or together to create new fragmentation patterns that can help towards the characterization of metabolites. In addition, the Zeno boosting that increases duty cycle at the level of MS2 assures that the quality of the spectra is maintained, despite the creation of many more diagnostic ions.

Metabolite identification is pivotal in drug development, and with the ZenoTOF7600 systems innovative EAD cell, we're able to provide enhanced fragmentation information, accelerating the characterization of potentially toxic metabolites and facilitating timely decision-making for drug candidate progression.

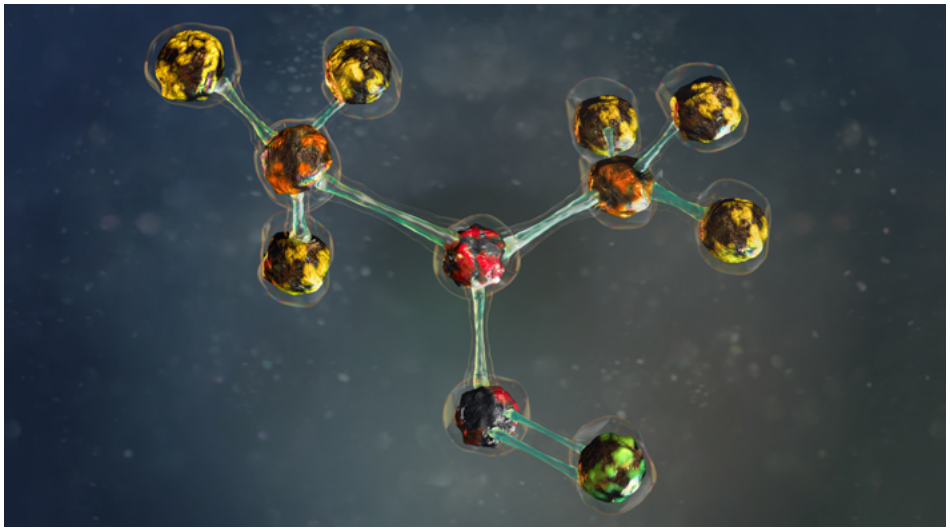
This is not without it's challenges however, and due to the vast number of drug products involved the need for optimization is often needed in both sample preparation and chromatography. In addition, the number of compounds implicated and discovered within drug products continues to grow, highlighting the need to continue development and to increase the scope of LC-MS methods.



05 Nitrosamines

Expanding horizons: comprehensive nitrosamine analysis across diverse sectors

Emiliano de Dominics
Chemistry Research Director, Mérieux NutriSciences



Here at Mérieux NutriSciences, we've had the opportunity to analyze and study nitrosamine molecules since 2009 (beginning with tobacco matrices and extending to food, water, and cosmetic products), for various purposes and in relation to different toxicological and regulatory situations.

In the following years, 2019-2021, in line with regulatory developments, we strategically positioned ourselves within the pharmaceutical sector by developing, validating, and analyzing "small nitrosamines" following the initial alerts regarding the detection of NDMA (N-nitroso dimethylamine) in ranitidine and sartans (APIs and finished products).

Subsequently, 2022-2024, we shifted our focus to the greater risk posed to the pharmaceutical world by "complex NDSRIs" (Nitrosamine Drug Substance-Related Impurities), investing in laboratories, personnel, technology, and achieving validation of over 70 Confirmatory GMP Methods, applied as GMP Quality Control for APIs and Finished Products.

Today, we observe a growing awareness that the Nitrosamines extends beyond pharmaceutical domain to include cosmetic, food and packaging sectors.

Consequently, we have developed analytical methods and techniques capable of operating at various levels: ranging from different Nitrosation Assay Procedures (NAP), to highly specific and selective methods targeting specific Nitrosamines using mass spectrometry. Moreover, we offer suspect screening and/or non-targeted screening, with or without retrospective capabilities, tailored to the sponsor's objectives taking into consideration toxicological, regulatory, and economic aspects.

The targeted services developed and available across various business sectors are validated and accredited according to the respective quality assurance system.

The suspect-non targeted services go 'BEYOND' because they aim to anticipate future needs through research and development activities and investments that align with forthcoming trends.

If Nitrosamines are present in pharmaceutical products, why wouldn't they also be found in food, novel food, packaging, water, and also environment?

Nitrosamines are indeed present; the attention has simply not yet been focused on this aspect. However, we believe that this focus will soon shift, and therefore, we are preparing accordingly.

Nitrosamine concerns in pharmaceuticals: addressing analytical challenges with advanced LC-MS solutions from SCIEX

Ferran Sanchez
Senior Market Development Manager - Pharma, SCIEX

Since 2018, nitrosamines have been a topic of concern across the pharmaceutical market, with numerous recalls issued and testing needed across numerous drug products and active pharmaceutical ingredients (APIs). After the initial nitrosamine interest, a number of drug products were also implicated as having a possible nitrosamine drug substance related impurity (NDSRI). These compounds, instead of being part of the 'generic' group of nitrosamines (NDMA, NDEA etc) are more closely related to the structure of the API.

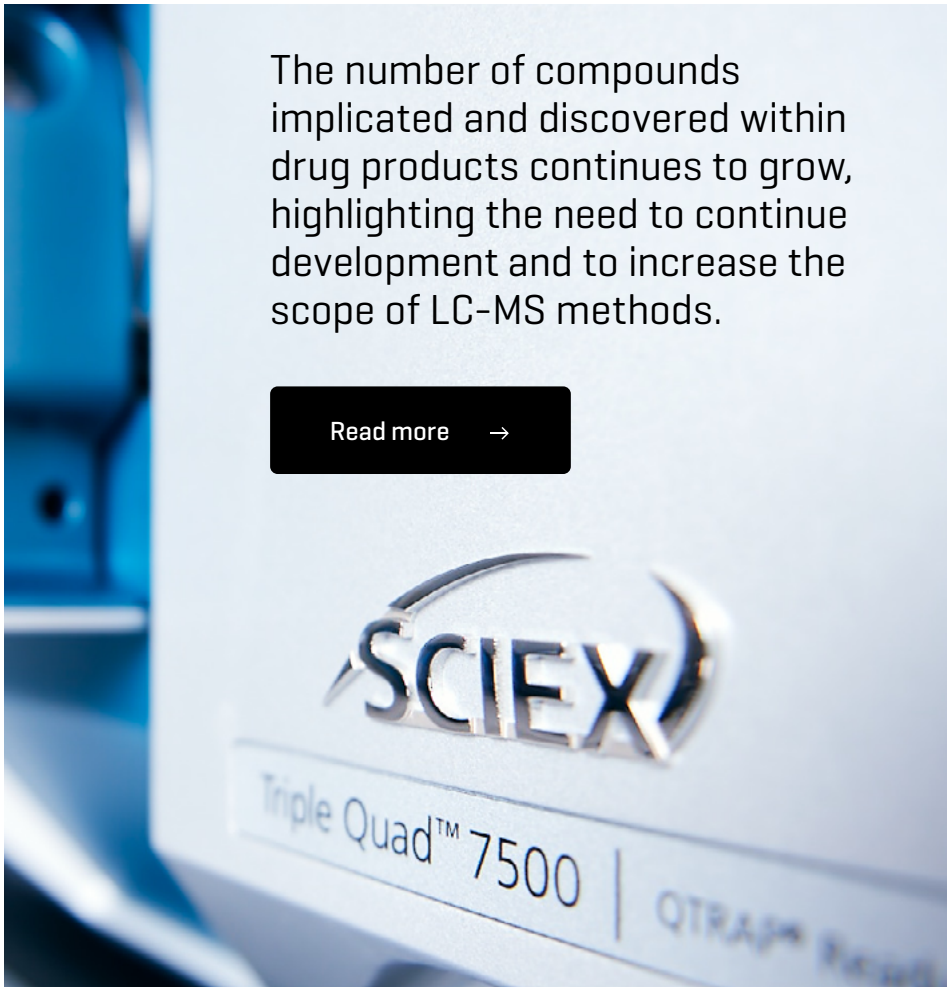
Subsequent to the initial nitrosamine interest, a number of drug products were also implicated as having a possible nitrosamine drug substance related impurity (NDSRI).

Concerns for human well-being have then arisen for both the generic and drug substance related nitrosamines due to the genotoxicity of some nitrosamine compounds demonstrated in animal studies.

To alleviate these concerns, nitrosamine levels must be regulated and controlled through analytical methods such as LC-MS.

This is not without it's challenges however, and due to the vast number of drug products involved the need for optimization is often needed in both sample preparation and chromatography. In addition, the number of compounds implicated and discovered within drug products continues to grow, highlighting the need to continue development and to increase the scope of LC-MS methods.

At SCIEX, we have solutions optimized around both nominal (triple quadrupole) and accurate mass spectrometry (QTOF) to cover the typical compounds requested (NDMA, NDEA etc.) but also NDSRIs such as N-nitroso propranolol and many more.



06 Software

The transition made easy: Why does updating your software even matter?

Jessica Smith
Sr. Market Development Specialist

The truth is that it can be tedious, costly, and inconvenient. Most of us have been guilty of ignoring those notifications you get on your phone for a software update until it is necessary (including myself) or until our hands are forced. The disruption and inconvenience of losing time with your device doesn't seem worth it, right? Maybe the update will alter a feature you love.

So, you wait it out. Then suddenly, your device starts to slow down, your apps crash, and you wonder , if you'd just spent that time updating your software in the first place, maybe you would have already adapted to those new features. Maybe this change wasn't as big as you first thought, and if you had just done it in the first place, you probably would have saved time overall.

When implementing a new workflow in a compliant environment there are many aspects that need to be considered, from validation, data integrity, method transfer between laboratories and training of personnel to be able to execute the analysis. Each part needs to be considered when implementing a new workflow and proposing software solutions. Any analytical method that is new to a lab requires adequate training, that is why user friendliness and usability of both hardware and software is fundamental to enhance robustness of data acquisition and simplify data processing. When at SCIEX we talk about making the transition from Analyst software to SCIEX OS software, it isn't a switch of software; it is an upgrade to something better. Something we believe will make your working day a little bit easier. Imagine that instead of spending all morning processing your data, the software could do this for you automatically, and you could complete another task instead, or better yet, grab a coffee! Or suddenly you don't have to validate those Excel spreadsheets anymore, and we could build your calculations into the software itself. No more exporting data, calculating, and validating those spreadsheets. It is features like this that make software upgrades worthwhile.

In this challenging market, we know budgets are constricted and time spent validating new software can be inconvenient. At SCIEX, we recognize this, but we also want you to get the best out of your purchase and ensure your analysis is as smooth as possible. We have a full migration assistance program with SCIEX OS experts to make sure, whether you are switching from Analyst to SCIEX OS software or are new to SCIEX OS software, that it fits into your workflow, and we address all your needs. Alongside this, we have a full Change Control Support Plan where we can support your software updates and validation needs.

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