Nelson Labs®
A Sotera Health company

Identifying Unexpected Impurities In Drug Products

NELSON LABS OFFERS

Complete confidence

Your test is done right every time. Our track record and reputation for quality and reliability sets us apart.

Industry-leading experts

We understand your business and the challenges you face. Thanks to our active monitoring of the regulatory landscape and working with industry groups we give a full perspective on critical topics and changes.

Exceptional Service

95% of all first-time customers partner with Nelson Labs for future testing. We serve our customers from a worldwide network of labs and facilities.

End-to-end solutions

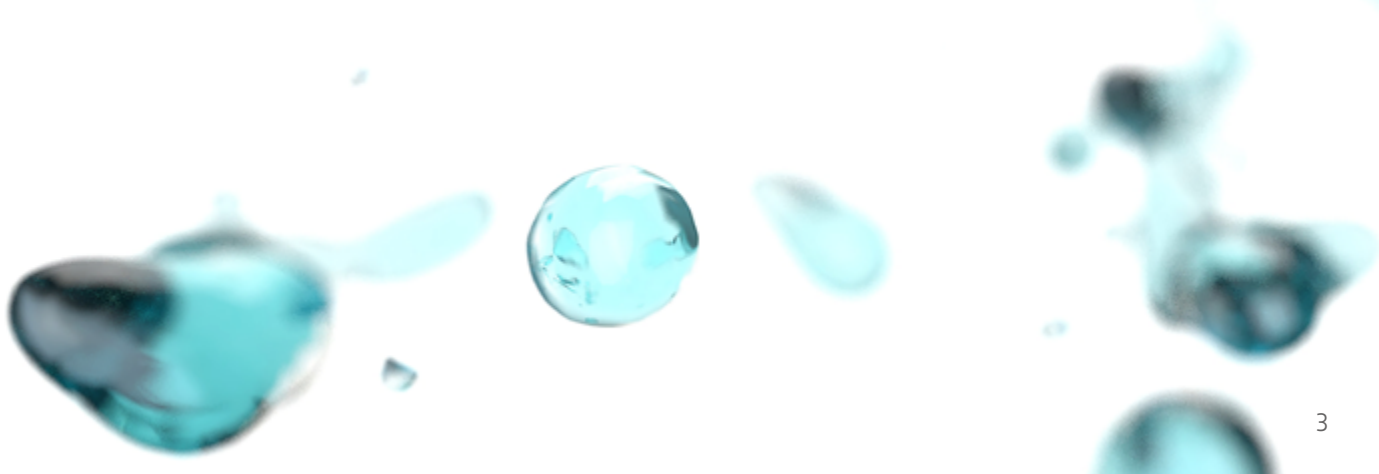
We are the only comprehensive provider of mission-critical services. Our experts can guide you along the entire product development life cycle.

We can identify.

We know impurities. We know all kinds of impurities. We know all kinds of impurities in drug products. These impurities could be related to the API or the composing ingredients of the drug product, they could be degradation products or they could be drug product adducts, being formed in the presence of other reactive impurities, such as reactive leachables (crosslinkers, accelerators, halogenated rubber oligomers,...)
However, a larger class of impurities is not related to the API or drug product ingredients. Typically, these are impurities which are introduced during production or during storage of the drug product in its final container closure system. These compounds could be polymer additives, anti-oxidants, processing aids, plasticizers and degradation compounds thereof. They could be monomers, oligomers, catalysts, curing agents, accelerators, colorants, processing and washing impurities, impurities coming from the secondary packaging or from the environment,...

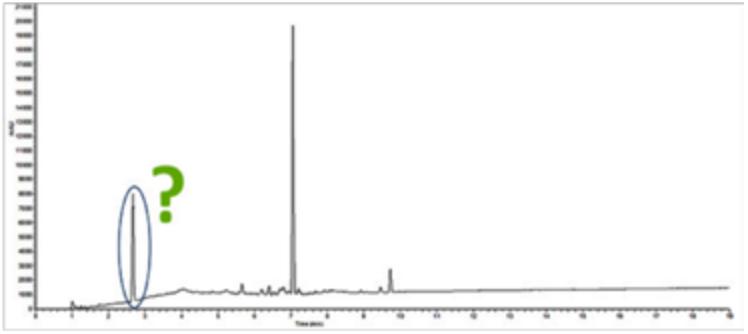
Based upon the extensive scientific analytical work we have been performing in the last 15 years in this field, Nelson Labs Europe has developed optimized scientific procedures, centralized databases (e.g. Nelson Labs Compounds Screener Database, based on over 5.000 authentic standards; an internal data management database), tailored and customized protocols, smooth state-of-the-art analytical testing (e.g. through a.o. our accurate mass analytical platforms), and comprehensive reporting, in line with the global regulatory requirements.

Indeed, we know organic impurities and we know how to identify them. But most of all, we understand the needs of our customers!



INTRODUCTION

Unexpected impurities may create significant stress and anxiety within a pharmaceutical company. These unexpected impurities are not always identified at first, since they often are initially detected with non-specific detectors. At Nelson Labs Europe, specific methods are in place to investigate and identify organic impurities.



chromatography screening

THE NELSON LABS EUROPE SOLUTION

In order to make the identification process a little bit smoother, The **"Structure Elucidation Team"** of Nelson Labs Europe has developed a 6 step approach to enhance the efficiency of the overall process.

STEP 1: UNDERSTANDING WHAT IS KNOWN ALREADY

STEP 2: IMPURITIES PROFILING OF THE DRUG PRODUCT USING THE UNIQUE COMPOUNDS SCREENER DATABASE

STEP 3: CHALLENGING THE RESULTS OF THE IMPURITIES PROFILING STUDY AGAINST CUSTOMER CHROMATOGRAPHY

STEP 4: LINKING THE IMPURITIES TO THEIR SOURCE

STEP 5: CONFIRMATION OF THE IDENTITY OF THE IMPURITY AND ITS QUANTIFICATION VIA GENERIC HPLC-UV METHOD – SYNTHESIS OF COMPOUND

STEP 6: PERFORMING A TOXICOLOGICAL ASSESSMENT

STEP 1: UNDERSTANDING WHAT IS KNOWN ALREADY

Although an isolated view of an HPLC-UV chromatogram may not allow giving any further specifics about the compound and its identity, the context where this impurity was detected may include some clear indications in which direction to look and how to optimize the identification strategy.

- Is the compound already present in previous QC-chromatograms of the drug product?
- Did the peak show up after a change in the process?
- Is there any indication that the compound could be related to the API?
- Could the compound be related to the packaging, can it be a leachable?
- Is there a relationship observed between the ageing period and the concentration of the compound?
- Based upon the specifics of the HPLC-UV method, is it possible to draw any conclusion on the polarity, volatility or expected molecular weight range of the compound?
- What is the estimated concentration of the compound?
- Is the HPLC-UV method, in which the impurity was detected, transferable to an LC/MS system?

STEP 2:
IMPURITIES PROFILING OF THE DRUG PRODUCT USING THE NELSON LABS COMPOUNDS SCREENER DATABASE

An impurities profiling study, as described by the ICH Q3A and Q3B Guidelines, tries to map all drug product impurities in a very broad way, this even at trace levels, using generic screening methods.

For organic compounds, typically an orthogonal analytical approach will be used combining three different complementary techniques:

1. Headspace GC/MS allows determination and identification of volatile, low molecular weight organic compounds (VOC)
2. GC/MS, GC/Q-ToF or derivatization GC/MS allows the determination of the semi-volatile organic compounds (S-VOC)
3. (U)HPLC - High Resolution Accurate Mass (HRAM) Spectrometry enables the determination of non-volatile organic compounds (N-VOC)

Nelson Labs Europe has developed a Compounds Screener Database based on authentic standards and containing over 5.000 volatile, semi-volatile and non-volatile organic compounds. This allows performing a high level of first pass identification in impurities profiling studies.

STEP 3:
CHALLENGING THE RESULTS OF THE IMPURITIES PROFILING STUDY AGAINST CUSTOMER CHROMATOGRAPHY

When performed, the mapping of the impurities in the drug product against the compounds screener database can significantly narrow down the number of candidates for the unexpected compound of interest. These results, however, must be challenged against the customer's chromatography to discriminate the targeted impurities from the other possibilities.

To unequivocally identify impurities during this phase, Nelson Labs Europe currently chooses to transfer and hyphenate the customer's chromatography to (U)HPLC with hybrid high resolution accurate mass spectrometry using the combined quadrupole – Orbitrap Technology (**Q-Exactive**) of **ThermoFisher Scientific** and if necessary complementary analyses with **GC-QToF can be performed.**

Coupling the customer chromatography to this high-end instrumentation capacitates the acquisition of useful data on the impurities, even if they slipped through the net during the profiling study.

STEP 4: LINKING THE IMPURITIES TO THEIR SOURCE

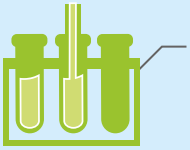
When the impurity is a degradation product of the active ingredient, the situation is quite clear. Impurities can then be linked to degradation, synthesis, formulation, dosage form, method, ageing and environment.

All these processes are integrated in in-house software and database, containing over more than 5.000 potential impurities and able to generate potential pathways for both API and excipients.

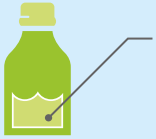
When the unexpected impurity is not API-related, there is a relatively high probability that the impurity has been introduced into the drug product as a result of a contact between a material and the drug product.

These compounds can be:

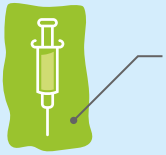
Chemical compounds, introduced into the drug product as a result of an interaction between the primary packaging and the drug product (Leachables).



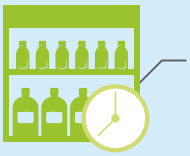
Chemical compounds, introduced in the drug product as a result of the contact between processing materials and the product stream.



Secondary leachables, being formed as a result of a chemical reaction between the leachable and drug product components.



Leachables coming from the secondary packaging.



Impurities introduced into the API during intermediate storage.

STEP 5:
IDENTITY CONFIRMATION OF THE IMPURITY AND QUANTIFICATION VIA GENERIC HPLC-UV METHOD

The ultimate identity confirmation of the identity and the determination of the concentration of the unexpected impurity should be considered at 3 levels:

1. By injection of an analytical "authentic" standard of the impurity into the (U)HPLC-HRAM method, developed on the Q-Exactive Orbitrap LC/MS of ThermoFisher.
2. A final analysis should be performed by the pharmaceutical company, to confirm the retention time match between the drug product impurity and the analytical standard, using the generic HPLC-UV chromatography.
3. The generic HPLC-UV method should be validated for the impurity (ICH Q2R1), which would allow a subsequent determination of concentration in the drug product. The accurate concentration of the impurity in the drug product is primordial in order to perform a toxicological assessment (STEP 6).

If no analytical authentic standard of the impurity is available, Nelson Labs Europe can offer different possibilities:

- Preparative LC to isolate the unknown compound of interest from the drug product. This allows using additional techniques – such as NMR – to further elucidate its structure. NMR can be offered in an R&D environment.

STEP 6:
PERFORMING A TOXICO-LOGICAL ASSESSMENT

Nelson Labs Europe can assist its customers in the toxicological assessment of the identified impurity at different levels:

1. At Nelson Labs Europe, there is a direct link to the DEREK NEXUS software, where a **Structure Activity Relationship (SAR) assessment** report can be generated.
2. The result of a DEREK NEXUS SAR-assessment can then be taken up in **a full toxicological evaluation report**, in which the broader toxicological literature of the compound (or related compounds) is reviewed. Subsequently, a risk assessment is performed, based upon the "worst case" administration regimen of the drug product. This should allow verifying the amounts, found for the impurity in the drug product, against the (expected) Permitted Daily Exposure for the compound.
3. In case no toxicological data are available for the identified impurity, Nelson Labs Europe can fully assist you with a broad array of **in-vitro and in-vivo** toxicological testing.

NELSON LABS COMPOUNDS SCREENER DATABASE

Nelson Labs has developed a unique compounds screener database.

Gradually built over decades of Extractables & Leachables testing for the pharmaceutical industry, this database contains more than 5000 authentic standards. This not only allows a broad compound identification based upon double identity confirmation, it also greatly minimizes the risk of missing or misidentifying compounds.
All analytical standards were either purchased from qualified vendors or synthesized in house. The use of this database is fully GMP-compliant.

- API and API-degradants
- Drug Product Ingredients (e.g. excipients) and their degradants
- Polymer residues (e.g. monomers)
- Glue / adhesive residues
- Polymer oligomers & degradation compounds
- Polymer additives & degradation compounds
- Impurities in polymer additives
- Filter residues rubber ingredients and impurities
- Plasticizers tubing residues
- Colorants
- Impurities from secondary packaging
- Known API-impurity adducts

STATE-OF-THE-ART-EQUIPMENT

Nelson Labs Europe uses state-of-the-art analytical equipment to study the impurities. All instruments are fully qualified (IQ/OQ/PQ). Typical standard routine techniques, available at Nelson Labs Europe:

- Headspace GC/MS
- GC/MS (Q, QQQ and HRAM)
- LC/MS (QQQ and HRAM)
- ICP/OES/MS
- Ion chromatography
- LC/UV (analytical & semi-preparative)

In addition, Nelson Labs Europe has invested in hyphenated chromatography – accurate mass spectrometry platforms (GC Q ToF MS, (U)HPLC Orbitrap MS) which allow identifying compounds at an elemental composition level:

- GC-QToF MS
- (U)HPLC Orbitrap MS

GC-QToF equipped with EI and CI ionization and capable of performing online derivatization. Typically, full scan CI measurements allow determining the molecular formula of the impurity, while full scan EI and targeted CI MS/MS contribute to structural elucidation. The presence of polar chemical groups such as alcohols or acids is assessed by derivatization.

Q-Exactive Orbitrap (U)HPLC/MS equipped with ESI and APCI ionization sources with the possibility of two dimensional LC configurations provide the necessary tools to investigate unknown peaks observed in LC runs. The instrumentations capabilities of combined targeted and untargeted measurement modes clear the path to the determination of compound specific data at an elemental composition scale and specific further structural elucidation experiments.

QUALITY

Nelson Labs Europe obtained the **ISO 17025** (BELAC) accreditation in 2003. In order to offer the highest level of quality data, Nelson Labs Europe has also received the **GLP** certification (2010) and the **GMP** accreditation (FaGG/aFmPs, Federal agency for medicinal and Health Products) for the release of medicinal products.

Nelson Labs Europe is **FDA registered.**

All results from impurity elucidation studies can be presented as a formal report suitable for regulatory submission.

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with every test we complete

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About Nelson Labs

Nelson Labs, A Sotera Health company, is the leading, global provider of lab testing and expert consulting services. We perform microbiological and analytical laboratory tests across the medical device, pharmaceutical, and tissue industries. The company is regarded as a best-in-class partner with a strong track record of collaborating with customers to solve complex problems. We have over 700 scientists, technicians, and service specialists who diligently perform more than 700 rigorous tests in 13 global laboratory locations.

Based in Belgium, Nelson Labs Europe specializes in providing premium Extractables & Leachables testing services to the pharmaceutical and medical device industries. We also support pharmaceutical companies across the globle in developing worldwide compliance testing strategies to qualify container/closure applications and pharmaceutical production equipment from an Extractables & Leachables perspective.

With decades of expertise, we stand behind the quality of our results and the strength or our customer partnerships. Along with sister companies Sterigenics and Nordion, we are part of Sotera Health, the world's leading, fully-integrated protector of global health.

www.nelsonlabs.com