

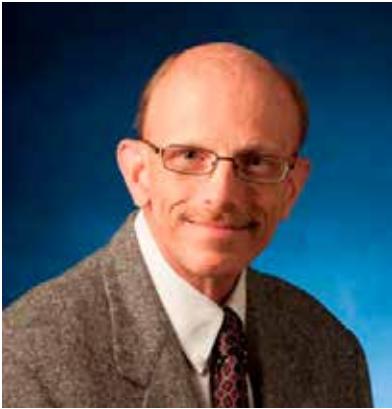


FORMERLY TOXIKON EUROPE



Extractables & Leachables
Benefit from our Unmatched Experience!

INTRODUCTION



It is good to be sure.
It is good to be
confident. Knowing
that your products
are tested by
Nelson Labs Europe.

Pharmaceuticals provide therapeutic outcomes that save, sustain and enhance lives. However, impurities present in pharmaceuticals decrease their therapeutic impact and thus need to be rigorously identified, monitored and controlled.

Leachables are those foreign impurities, present in pharmaceuticals, due to their unavoidable interaction with their manufacturing, packaging and administration systems. The adverse effect that leachables can have on a pharmaceutical's suitability for use is well documented and it is reasonable to expect that the pharmaceuticals of the future will be even more susceptible to leachables-induced adverse effects.

These circumstances have led to a greater regulatory emphasis on, and tighter regulatory requirements for, chemical suitability for use assessments, supported by leachables and extractables studies.

As a global leader in extractables and leachables assessment, Nelson Labs Europe partners with its clients to:

- Design leachables and extractables studies that are efficient, effective and compliant
- Implement well-designed testing protocols using powerful, appropriate and state-of-the-art methodologies which have been developed, optimized and qualified to meet the most exacting regulatory expectations
- Interpret and correlate high quality test data to definitively establish that a pharmaceutical is suited for its intended use, particularly with respect to foreign impurities such as leachables.

Dennis R. Jenke
*Principal Consultant,
Nelson Labs Europe*



CUSTOMIZED STUDY DESIGNS

Both **USP <1663>** on extractables testing and the **USP <1664>** on leachable testing, as well as the recommendations of **PQRI** on inhalation applications (**OINDP**), parenteral applications (**PDP**) and ophthalmics (**ODP**) offer a general framework for the design of both extractable & leachable studies. As these USP monographs and the PQRI documents are **either informal or recommendations, it is the responsibility of the holder of the NDA to provide sufficient justifications for the scientific approach** that is taken in these projects.

A series of variables can be taken into account in order to optimize these study protocols, such as:

- Materials and their compatibility with extraction solvents
- Type of container
- Type of contact between the container and the medicinal product
- Storage conditions
- Specific administration or reconstitution procedures
- Type of medicinal product
- Route of administration
- Dosing regimen and associated threshold requirements

Nelson Labs Europe can assist you in developing tailored protocols, specifically designed for your requirements or needs.





INHALATION DEVICES

Metered dose inhalers (MDI), dry powder inhalers (DPI), inhalation solutions and nasal sprays all belong to the group of orally inhaled and nasal drug products (OINDPs). OINDPs represent the highest risk drug products due to their route of administration. Additionally, the likelihood to introduce impurities via container-closure contact is also considered high (or medium in case of DPIs). Moreover, their container-closure systems are often composed of different parts (e.g. canisters, valves, actuators, gaskets...), and thus a

variety of different materials (PE, PP, PBT, POM, etc.) are used in its construct. Therefore, it is imperative to have an excellent material knowledge and understanding of the mechanism of polymer leaching in order to set-up appropriate E&L studies.

Nelson Labs Europe is a leader in qualifying container-closure systems for all inhalation applications, starting from typical compendial EP/USP testing up to a very detailed level of extractable and leachable studies.

LARGE VOLUME PARENTERALS

Large volume parenteral applications are characterized by high volume doses of a drug product, which are administered intravenously. Flexible bag systems, which are the typical container-closure systems for LVP's, often contain a combination of different components and materials, all potentially contributing to the leachables profile of the contained drug product.

Considerable amounts of leachables can be expected in these presentations, especially when the drug solution is terminally sterilized in the packaging system. In addition, if the contained drug product has a high organic content (such as lipid solutions, nutrition solutions, emulsions...)

the interaction with the container-closure system is even enhanced. The high daily administered doses, combined with the conservative analytical thresholds, as recommended by the PQRI PDP working group, will often result in analytically challenging E&L studies.

In recent years, Nelson Labs Europe has developed and invested in methodologies and analytical techniques to deal with the pitfalls of E&L assessments for large volumes parenterals. These developments allow identification and quantification of extractables and leachables at extremely low trace levels.





SMALL VOLUME PARENTERALS

Small volume parenterals (SVP) are amongst the drug products with highest risk for introduction of E&L impurities, due to both the high degree of interaction with the container-closure (CC) system, the materials of construct used in the manufacture of SVP-container-closures (eg rubbers) and to their direct introduction into the patient's general circulation. This has led to strengthening by the regulatory authorities of safety guidelines associated with such products.

Container-closure systems for Injectables include materials as diverse as rubbers, glass, labels and a broad range of polymers, all of them with different extractables profiles and the associated potential to contaminate the drug product.

Nelson Labs Europe is specialized in qualifying container-closure systems for a wide range of parenteral applications, such as pre-filled syringes, cartridges, vials, polymer syringes, lyo-vials, etc....

Nelson Labs Europe has developed a vast expertise in setting up the most adequate study design for the characterization of container-closure systems as diverse and challenging as those of Injectable drug products.

Nelson Labs Europe has established partnerships with the following companies:



BLOW-FILL-SEAL APPLICATIONS

Blow-Fill-Seal (BFS) is a rapidly growing production process used for a variety of sterile applications such as ophthalmic, inhalation and parenteral products.

This technique reduces the risk for microbial contamination by formation, filling and sealing of the primary container in a continuous process by one machine in a very cost effective way. The materials used for the formation of the

primary container are often polyolefin based and therefore typically semi-permeable. This makes these presentations potentially more prone to introduction of leachables originating from the secondary and tertiary packaging items, such as labels, printing inks, aluminium foils, but also leaflets and carton boxes. A thorough evaluation of the complete packaging system is thus required for BFS applications.

For Blow-Fill-Seal applications, Nelson Labs Europe has established a partnership with:





OPHTHALMIC APPLICATIONS

Ophthalmic drug products are administered directly to the eye. Therefore local topical effects play a high role in this type of applications. The direct exposure of the leachables to the eye, shifts the focus on leachable substances which might cause irritation or sensitization. Semi-permeable, squeezable primary containers are typically used for storage of ophthalmic

solutions. Due to the semi-permeable character of the primary container material, compounds of the secondary packaging materials can also easily migrate into the ophthalmic drug. The impact of these secondary packaging leachables is even higher in the case of single-dose units where the ratio of contact surface area of the packaging materials versus the filling volume is high.

TOPICAL APPLICATIONS

Topical, dermal or transdermal drug products represent a variety of different dosage forms, such as creams, emulsions, lotions, aerosols, gels, ointments, pastes, solutions, suspensions, ... Most of these dosage forms are generally intended for a localized action (not systemic) on one or more layers of the skin or oral mucosal surface. Because these drug products are presented in a liquid phase, there is a significant potential for leaching of compounds from the packaging component into the dosage form.

Since most topical drug products are mostly non-aqueous based and often quite complex in their composition, this class of applications present numerous analytical challenges to perform a toxicological risk assessment on leachables at sub ppm levels, as is often required.

Nelson Labs Europe developed a broad expertise in qualifying container-closure systems for all topical applications, starting from the typical compendial USP and EP testing up to a detailed level of E&L studies.





PRODUCTION & PROCESSING EQUIPMENT

Leachables in pharmaceutical products could also originate from manufacturing items (filters, bioreactors,...) used in the production process. With the increasing use of disposable process technology in the pharma industry, the concern in E&L has also developed considerably in this area. Biopharma industry groups (**BPSA, BPOG**) have published recommendations when and how to perform E&L studies for these materials. Moreover, the **USP <665>** monograph addresses considerations for Extractable & Leachable assessment for production materials in the (bio)pharmaceutical industry.

Nelson Labs Europe has the broad practical expertise in performing the challenging type of study set-ups that comes with disposable technology. Furthermore, in-house testing procedures were developed and optimized to offer compliant USP <665> testing. Combined with the state-of-the-art analytical techniques, this will assist both disposable component manufacturers, as well as pharmaceutical companies in qualifying their materials.

MEDICAL DEVICES – CHEMICAL CHARACTERIZATION

Recently, updated guidances, standards and regulations for medical devices have driven the device industry to take a more **risk based approach** in the safety evaluation of their products.

ISO10993 - Part 1 now considers **chemical characterization** of the materials of construction as a crucial first step in the biological evaluation process of a medical device, where possible. The extent of chemical characterization may depend on different variables, such as the nature and duration of body contact, any existing material safety

or toxicological data, etc... However, a characterization study should – at a minimum – be able to identify the chemical constituents potentially released from a device, as well as to quantify the potential exposure to the patient.

ISO 10993 – Part 18 provides a detailed generic framework on how a chemical characterization could be performed.

ISO 10993 – Part 12 describes in more detail how the test articles should be prepared prior to analytical testing.

DEVELOPMENT AND OPTIMIZING STUDY PROTOCOLS

Over the last 15 years, Nelson Labs Europe has been working on chemical characterization according to the FDA, EMA and ISO guidelines for:

- Medical devices
- Combination products
- Colorants





E&L COMPOUNDS SCREENER DATABASE

Nelson Labs Europe has developed an extensive and detailed database - which contains over 5000 extractable compounds, built from authentic standards, for **a fast and unique compound identification** across three different chromatographic platforms:

- Headspace GC/MS
- GC/MS
- LC/MS (High Resolution Accurate Mass (HRAM technology; (Q-)Exactive Orbitrap)

This identification process is based upon a **double identity confirmation** via a **retention time match** and high quality **mass spectrum fit**.

As a consequence, an extremely broad diversity of compounds can be readily identified during “first pass” testing in a standard extractables (or leachables) protocol.

All analytical standards, used in the development of the database, were either purchased from qualified vendors or synthesized through the in-house synthesis services. The documentation and use of the database is fully GMP-compliant.

SECOND PASS: IDENTIFICATION OF UNKNOWNNS

In order to perform an adequate risk and safety evaluation of a container-closure system based upon either extractable or leachable data, it is of the utmost importance to broadly identify all organic compounds detected in the **combined chromatographic methods**.

Although it is evident that Nelson Labs' unique Compounds Screener Database will assist tremendously in compound identification, still some compounds may remain unidentified.

"Second Pass Testing" is then the ideal way of addressing the safety assessment of these unknowns: using the high-end state-of-the-art analytical techniques like GC-Q-ToF or UPLC-HRAM (Q-Exactive) will assist in elucidating their structure which further allows an in depth risk assessment.

The analytical expert team at Nelson Labs Europe is renowned for their ability to elucidate the structure of unidentified compounds in a broad set of materials via the above mentioned accurate mass platforms.

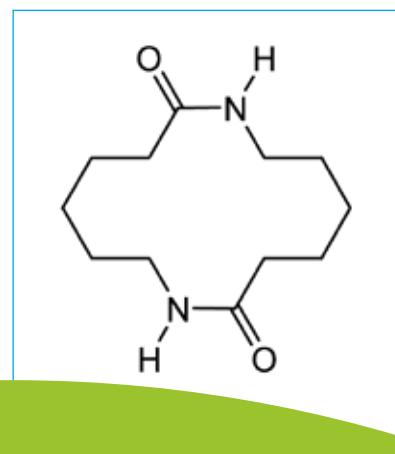
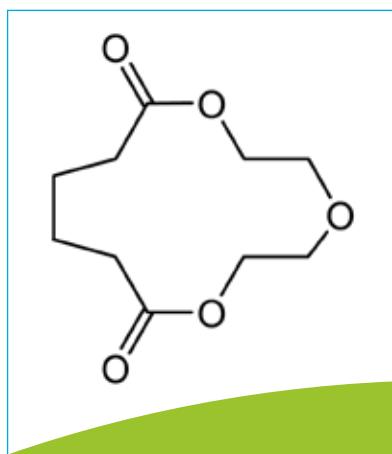
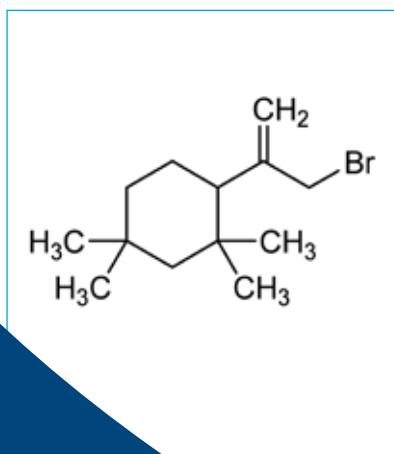


EVALUATIONS

Extractable studies on packaging components often result in long lists of compounds which are identified either after first pass testing (using the compounds screener database) or after second pass testing (using high-end analytical instrumentation).

A toxicological assessment may be very cumbersome, even for experienced toxicologists, because of the lack of accurate toxicological information on the reported compounds.

With our approach, every single extractable that is reported and identified in an extraction study, is evaluated based upon a Structure Activity Relationship (SAR) Assessment (combined Cramer Classification and Derek Nexus Assessment). As a result, **extractable compounds of concern will be picked-up immediately**. This will allow selecting the right target compounds for the subsequent leachable study from the start of the leachable study design onwards.

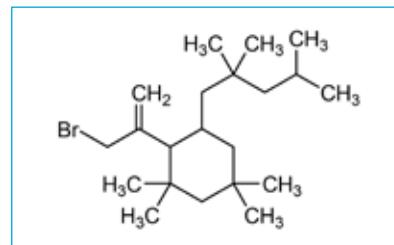
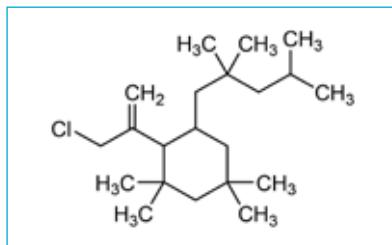
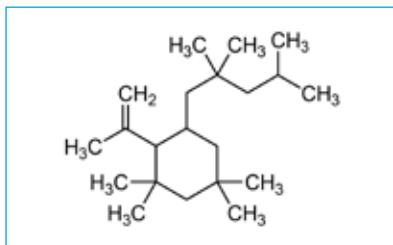
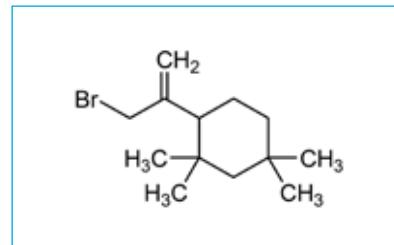
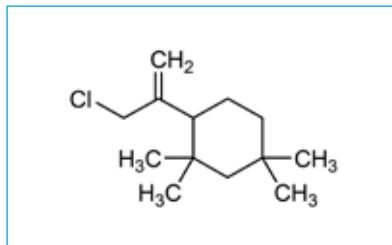
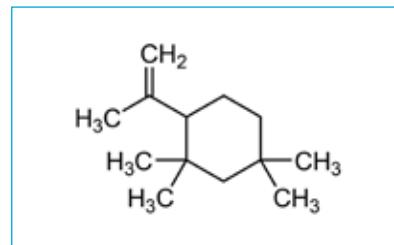


RUBBER OLIGOMERS

For a wide range of small volume parenteral (SVP) applications (such as syringes, vials, cartridges...), halobutyl rubbers are used as a closure to guarantee the integrity of the drug product. It is widely known that these materials contain substantial amounts of **halogenated oligomers** that are **potentially carcinogenic** (according to a SAR assessment) and are shown to be very **reactive compounds**, as they can be considered as alkylating agents.

Depending upon the composition of the drug product, those halobutyl oligomers may leach into the drug product to an extent that they may become either a risk to the patient or could compromise the quality of the drug product.

Nelson Labs Europe has all 6 major butyl and halobutyl oligomers available as authentic analytical standards in support of their extractable and leachable programs. This allows us to develop analytical strategies to qualify and quantify these potentially toxic and reactive compounds, even at very low accumulation levels.



STATE-OF-THE-ART EQUIPMENT

Nelson Labs Europe uses state-of-the-art analytical equipment to study either the impurities, present in polymers, plastics and rubbers (extractables studies), or the leachables, introduced from the primary packaging into the medicinal product during its shelf life.

All instruments are fully qualified (IQ/OQ/PQ).

Typical techniques, used at Nelson Labs Europe:

- Static and Dynamic Headspace GC/MS (*Volatile Organic Compounds*)
- GC/MS & GC-QQQ (*Semi-Volatile Organic Compounds*)
- GC/Q-ToF
- HRAM LC/MS Exactive Orbitrap, Q-Exactive Orbitrap (*Non-Volatile Organic Compounds*)
- LC/QQQ (*Non-Volatile Organic Compounds*)
- ICP-OES & ICP-MS (*Element / Metals Analysis*)
- Ion Chromatography (*Volatile Organic Compounds*)
- Total Organic Carbon
- FTIR





METHOD DEVELOPMENT & VALIDATION

Prior to any quantitative leachable assessment in the medicinal product, specific analytical methods need to be developed and validated. Although deviations (*e.g. reduced validation levels for certain applications*) are possible, the basis for the method development & validation for organic compounds is the ICH Q2(R1) guideline on method validations.

These validations may include the following parameters:

- Specificity
- Linearity
- Method Range
- Accuracy
- Precision
- LOD/LOQ
- Robustness





STABILITY SERVICES - LEACHABLES

Leachables studies (e.g. according to USP <1664>) want to follow the migration behavior of any material impurity being introduced into the drug product as a result of the interaction with the materials of construct **during the intended use**. The conditions of “intended use” for leachable studies often refer to the storage conditions, selected for the stability studies for the API.

Nelson Labs Europe has a large capacity for storing leachable samples under temperature and humidity controlled conditions in climatic chambers. All chambers are fully qualified (IQ/OQ/PQ) and are temperature mapped. The climatic chambers are monitored online.

Nelson Labs Europe can offer a broad variety of storage conditions, ranging from -20°C up to 40°C across different climatic zones.

In addition, our stability services can also be offered for API's and finished product testing using pre-defined protocols. These services include storage, analyses and reporting under full compliance with cGMP and ICH guidelines.

PHARMACOPOEIAL TESTING

US (CMC) and European (CTD) submissions often need to contain Certificates of Analysis (CoA) to prove compliance of the materials to the current US and European pharmacopoeias, respectively. Nelson Labs Europe offers a wide range of physicochemical, in-vitro and in-vivo pharmacopoeial testing:

USP - PHARMACOPOEIA TESTING

- <87> In-Vitro Biological Reactivity – Cytotoxicity Testing
- <88> In-Vivo Biological Reactivity – Class I–VI Testing
- <381> Elastomers
- <661> & <661.1> Materials of Construction
- <661.2> Plastic Systems

E.P. - PHARMACOPOEIA TESTING

- 3.1 Series; Materials used in the Manufacture of Pharmaceutical Containers
- 3.2 Series; Containers

J.P. - PHARMACOPOEIA TESTING



BIOCOMPATIBILITY TESTING

For “combination products”, some container-closure systems may either be considered as a pharmaceutical container or as a medical device. For medical devices, appropriate biocompatibility testing according to the ISO 10993 Standard series should be performed. Nelson Labs Europe has a 40 year long history and a vast experience in biocompatibility testing for the medical device industry.

Nelson Labs Europe offers a broad range of biocompatibility tests, such as:

- ISO 10993 – Part 3: Tests for Genotoxicity, Carcinogenicity, Reproductive Toxicity
- ISO 10993 – Part 4: Selection of Tests for Interactions with Blood
- ISO 10993 – Part 5: Tests for In-Vitro Cytotoxicity
- ISO 10993 – Part 6: Tests for local Effects after Implantation
- ISO 10993 – Part 10: Tests for Irritation and delayed-type Hypersensitivity
- ISO 10993 – Part 11: Tests for Systemic Toxicity
- OECD 471: AMES testing (Mutagenicity)





FULL TOXICOLOGICAL ASSESSMENTS

For a full toxicological assessment on the final outcome of a leachable study, a two phase approach is considered.

First, as described within the ICH M7 guideline, Structure Activity Relationships are investigated by using QSAR software packages in order to predict its mutagenic potential amongst other toxicological endpoints.

In a second stage, an in-depth literature review is performed by a registered toxicologist to determine the human Permitted Daily Exposure (PDE). Based on the clinical dosing regimen, the final toxicological safety Assessment report would conclude with a safety margin, attesting whether or not the impurity poses a risk to patient safety and product quality.

Nelson Labs Europe has successfully supported our clients with over 250 product safety assessments enabling them to obtain approval by international receiving authorities. We can provide the most used and widely accepted commercial QSAR systems such as **Derek, Multicase, Leadscope, ...**

Nelson Labs Europe has applied its safety assessment strategy to extractables & leachables, to API related degradation products as well as for the assessment of medical device material characterization studies.



CONSULTANCY VIA TRIAD SCIENTIFIC SOLUTIONS

Triad Scientific Solutions LLC, an independent consulting organization, founded by Dennis Jenke, provides the pharmaceutical industry with integrated, science-based, and practical solutions to suitability for use challenges for packaging, manufacturing components and systems, and administration devices.

As a **“Principal Consultant” to Nelson Labs Europe**, Dr. Jenke is available to Nelson Labs Europe clients to discuss general principles, practices, policies, expectations, concepts, tactics and/or strategies related to the chemical characterization and qualification of materials, components and systems used in these industries.

As a well-recognized expert in the science and practice of chemical assessment, Dr. Jenke can provide Nelson Labs Europe clients with expert insights into the design, justification, implementation, interpretation and reporting of chemical assessment studies and programs, insuring that such studies and programs effectively and efficiently address the current, and anticipate the future, global regulatory requirements.





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 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 and has been successfully audited by the FDA for their GMP programs.





FORMERLY TOXIKON EUROPE

Safeguarding Global Health™

CONTACT US

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About Nelson Labs Europe (formerly Toxikon Europe NV)

Nelson Labs Europe, formerly Toxikon Europe, is an independent contract research organization, specializing in and fully dedicated to providing premium Extractables & Leachables services to the pharmaceutical industry.

Based in Belgium, Nelson Labs Europe supports pharmaceutical companies – across the globe in developing worldwide compliance testing strategies to qualify Container/Closure Applications and Pharmaceutical Production Equipment from an Extractables & Leachables perspective. Over the last 15 years, Nelson Labs Europe supported over 200 submissions to the FDA and to the EMA.

From a quality perspective, Nelson Labs Europe is ISO 17025 accredited and GLP-certified. Nelson Labs Europe has received a GMP accreditation from the European Authorities. Nelson Labs Europe is FDA registered. In 2017, Nelson Labs Europe was successfully audited by the FDA.

Nelson Labs Europe is part of Nelson Labs, the leading global microbiological and analytical lab testing platform. Nelson Labs, along with sister companies Sterigenics and Nordion, are part of Sotera Health, the world's leading, fully-integrated protector of global health.

www.nelsonlabs.be