PHARMA SERVICE CATALOG

PHARMACEUTICAL LABORATORY SERVICES

Because you care about consumers' health

MERIEUX NutriSciences

MÉRIEUX NUTRISCIENCES

ASSETS

Scientific Excellence dedicated to chemical and microbiological tests on food, pharmaceutical products, biocides, medical devices and cosmetics

Top Level Quality Accreditations

GMP & GLP Authorization

A Unique Technological Platform

Global European Front Office ensures thorough local support to its customers thanks to optimal reactivity and high flexibility

PHARMACEUTICAL
SERVICES

- Analytical techniques
- Quality Controls
- Chemical Characterization
- Stability & Controlled Storage Conditions Studies
- Environmental Monitoring
- R&D and Validation Activities
- Identification of Foreign Particles
- Data Integrity and Computerized Systems Management
- Biopharmaceuticals and Validation Activities
- Medical Devices
- Acknowledgements & Authorizations

ANALYTICAL
TECHNIQUES

Amino Acid Analyzer
Atomic Absorption Spectroscopy (AA-FIAS)
Atomic Absorption Spectroscopy (AA-Flame)
Atomic Absorption Spectroscopy (AA-GF)
BET
Cell Culture Techniques

Differential Scanning Calorimetry (DSC)
Dissolution System for solid forms (Apps 1&2)
Dissolution System for Chewing-gums
Densimetry (including Tapped Density)
Disintegration System

Flow Cytofluorimetry

Granulometry (Analytical sieving) (micro)
Granulometry (Dynamic light scattering) (nano)
Granulometry (Laser light diffraction) (micro)
Granulometry (Dry Powder Laser Diffraction)
Gas Chromatography (GC-FID)
Gel Electrophoresis
Gravimetry

Head-Space Gas Chromatography (HS-GC)
HR Mass Spectrometry (LC-ESI/TOF)
HR Mass Spectrometry (LC-Q/Orbitrap)

ICP Atomic Emission Spectroscopy (ICP-AES)
ICP Mass Spectroscopy (ICP-MS)
Ionic Chromatography/ED
Ionic Chromatography/PAD
IR Spectroscopy (with ATR/μFT-IR)

Karl-Fisher (coulometric & semi-micro)

Liquid Chromatography (HPLC/ELSD)
Liquid Chromatography (HPLC/DAD)
Liquid Chromatography (HPLC/RID)

HR Mass Spectrometry (Q/Orbitrap)
Mass Spectrometry (GC-MS/MS)
Mass Spectrometry (LC-MS/MS)
Melting Point (metal block)

Nucleic Acid Sequencing

Optical Microscopy
Osmometry

pH-metry
Polarimetry

Rifractometry
Real Time PCR

Spectrofluorimetry
Spectrophotometry (UV-Vis)
Scanning Electron Microscopy (SEM/EDS)

Tensiometry
Thin Layer Chromatography (TLC)
Titrimetry (acid-base)
Titrimetry (colorimetric)
Titrimetry (complexometric)
Titrimetry (potenziometric)
Transmission Electron Microscopy (TEM)
TOC

Viscosimetry (capillary and rotational)

X-Ray Diffraction (XRD)
X-Ray Fluorimetry (XRF)

ANALYTICAL TECHNIQUES AVAILABLE
IN GxP FACILITIES

QUALITY
CONTROLS

CHEMICAL TESTING

- Chemical Characterization
- Related substances / Impurities
- Ninhydrin-positive substances
- Elemental impurities
- Nitrosamine impurities
- Residual analyses (solvents, pesticides, mycotoxins, genotoxic impurities, etc.)

PHYSICAL TESTING

- Dissolution and disintegration tests
- Particle size
- Spectral analyses
- Polymorphism (XRD)
- Visible and sub-visible particle counting

BIOPHARMACEUTICALS CHARACTERIZATION

- Amino acids composition
- Terminal amino acid sequence
- Peptide mapping
- Accurate mass

Mérieux NutriSciences offers a complete portfolio of GxP-compliant studies and laboratory analyses useful for the release of raw materials (API and excipients) and finished pharmaceutical products, as required as part of the drug development manufacturing and commercialization process.

MICROBIOLOGICAL TESTING

- TAMC and TYMC
- Sterility Test
- Bioburden Test
- Challenge Test
- Microbial Assays for Antibiotics
- Bacterial endotoxins detection (LAL Test) - PHEUR 2.6.14 and USP<161>
- Monocyte Activation Test (MAT) *in vitro* test for pyrogen detection - EP 2.6.30

MICROORGANISMS IDENTIFICATION (BACTERIA, YEASTS AND MOLDS)

Microorganism identification by **Matrix Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF)** represents a highly accurate, robust and fast proteotypic approach based on an identification software: microorganisms express many different proteins. **Differences in the pattern of proteins expressed and in the levels of expression generate the "diversity"**. The MALDI-TOF technique **exploits this unique characteristic to distinguish between microorganisms from their own spectrum**. By comparing with former single-instrument identification, this approach is faster and increases the possibilities of successful identification, by reducing the need of sequencing.

MALDI-TOF systems available:

- BrukerDaltonics-BiotyperSoftware
- Vitek-MS (Biomérieux)-MYLASoftware

If identification by MALDI-TOF is not reliable, **we apply identification by 16S rDNA for bacteria and D2LSU for yeast and molds**.

CONTROL
OF IMPURITIES

Mérieux NutriSciences GxP Facilities could develop and validate suitable and high sensitive methods to detect, identify and quantify organic and inorganic impurities at trace levels. Impurities are identified and quantified by means of state-of-the-art analytical equipment's (LC-MS/MS, LC-HRMS, GC/MS, GC-MS/MS, GC-HRMS, ICP/MS, ICP/OES, XRD, MALDI-TOF/TOF, IC, AAA, etc.).

Organic impurities

- Control of starting materials, by-products, intermediates (including chiral impurities) in compliance with pharmacopoeia requirement or Sponsor specifications.
- Degradation products characterization by means of forced degradation studies (stress test) under acidic, basic, oxidative, and various heat and light-exposure conditions.

Genotoxic impurities

Polymorphic impurities

Residual Solvents according to pharmacopoeia and ICH Q3C specifications

Elemental Impurities according to ICH Q3D specifications

Mérieux NutriSciences applies enjoys state-of-the-art technologies and more than 20 years' expertise in elemental analyses and quantitative determination of elemental impurities thanks to dedicated tools:

- ICP/MS
- ICP/OES
- AA with graphite furnace and hydride system

Nitrosamines impurities

The GMP facility of Mérieux NutriSciences is equipped with all the most suitable and sensitive analytical techniques available for nitrosamine impurities in APIs and DP (i.e. LC-MS/MS, LC-HRMS, GC-MS/MS, GC-HRMS).

Integrated Services for Elemental and Nitrosamine impurities

- risk assessment
- testing strategy definition
- screening/multiresidual tests
- methods development and validation
- quality controls & analytical batch release

Identification of Unknown Impurities

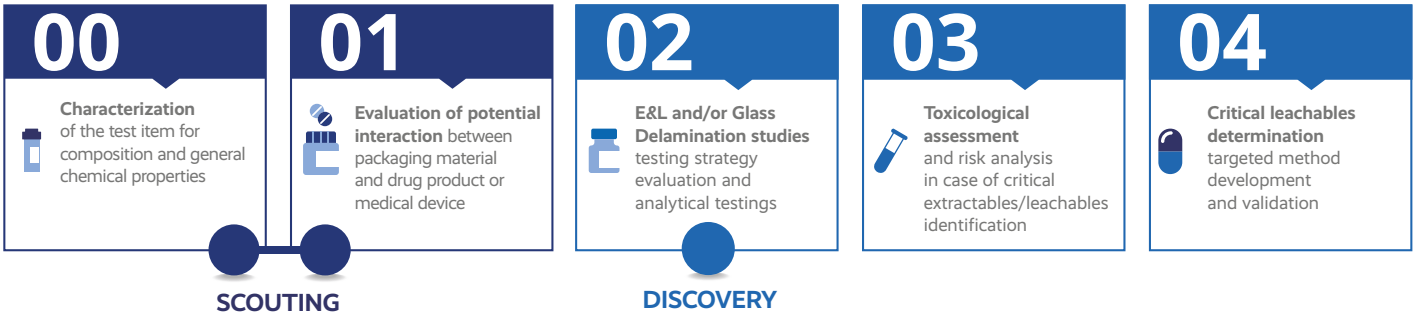
Mérieux NutriSciences proposes strategies for the identification of pharmaceutical impurities using various approaches and instruments, including:

- LC- HRMS
- GC-HRMS
- 1H /13C - NMR

EXTRACTABLES & LEACHABLES

The interaction between primary and secondary containers and the medical device, or between the device and biological fluids/tissues, may affect the composition of the device itself, thus adversely affecting its ability to produce the expected clinical outcome, or its safeness. Extractables and Leachables studies provide a full-integrated testing strategy together with toxicological assessment and risk analysis, in six main steps:

1. Profiling of extractables: generation of the extract.
2. Characterization of **extractables**:
   a. **Screening research** of VOC, SVOC and NVOC using different techniques (e.g. TOC, HS-GC/MS, GC-MS, GC-HRMS, HPLC UV/DAD, LC-MS/MS, LC-HRMS)
   b. **Targeted analysis of elemental impurities** and **anions** using different techniques (e.g. AAS, ICP-MS, IC)
   c. **Targeted analysis** for specific compounds of toxicological concern, using dedicated methods that focus on monomers, additives and extractables typical of the material considered (more than 150 targeted methods available)
   d. **Extractable nanoparticles and microplastics identification**
3. Primary and secondary **leachables profile**.
4. **Unknown** extractables/leachables tentative identification by HRMS techniques (if needed).
5. Toxicological evaluation and risk assessment.
6. **Development and validation of targeted methods** suitable for the quantification of critical leachables.



GLASS DELAMINATION

Testing strategy according to USP <660> "*Containers –Glass*" and USP <1660> "*Evaluation of the inner surface durability of glass containers*":

1. Determination of visible and subvisible glass particles
2. Determination of extracted elements
3. Characterization of glass inner surface by SEM/EDS

STABILITY & CONTROLLED

STORAGE CONDITIONS STUDIES

MÉRIEUX NUTRISCIENCES PROVIDES COMPREHENSIVE ICH-COMPLIANT, CLIMATE CONTROLLED STORAGE FACILITIES, INCLUDING:

- 58 m^3 walk-in room (n. 2)
- 44 m^3 walk-in rooms (n. 2, one equipped for low humidity conditions)
- 22 m^3 walk-in rooms (n. 7)
- 1,5 m^3 cabinets (n. 5, one equipped for photostability testing)
- Various dimensioned cabinets for customized storage conditions
- Complete range of ICH climatic conditions

THE FOLLOWING STABILITY CONDITIONS ARE AVAILABLE FOR PHARMACEUTICAL STABILITY STORAGE:

- 25°C ± 2°C / 60% RH ± 5% RH
- 30°C ± 2°C / 65% RH ± 5% RH
- 30°C ± 2°C / 75% RH ± 5% RH
- 40°C ± 2°C / 75% RH ± 5% RH
- Photostability (according to ICH Q1B, option 1 and 2)
- Transport Stability (freeze and thaw, cycle test)
- In-Use Stability
- Customer specific conditions available

All conditions are **continually monitored and recorded with Labguard® environmental monitoring system ensuring a totally secure and controlled environment**. Access, alarms and changes are under audit trail and electronic signature according to the Annex 11 of the EU GMP and the Part 11 of 21 CFR.

STABILITY STUDIES

Formal stability studies (long term, accelerated and intermediate) are undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of an API or the shelf life of a finished product.

ENVIRONMENTAL
MONITORING

CLEANING VALIDATION

Validation of cleaning method **gives documented evidence that an approved cleaning procedure will provide clean equipment**, suitable for its intended use.

The service includes:

- Selection of appropriate sampling and analytical strategies for determining chemical residues or biological contamination
- Selection of appropriate detection methods
- Development of specific methods for the research of contaminants
- Analytical cleaning Method Validation

VALIDATION OF DISINFECTION PROCEDURES & EFFECTIVENESS AGAINST TARGET ORGANISMS

Mérieux NutriSciences performs studies to **assess the efficacy of disinfectant products in compliance with ISO 17025 or GLP**.

Efficacy Tests on disinfectants **used in the medical, veterinary, industrial or domestic area according to national and international standards** (e.g. EN 13704, EN 13697 and USP<1072>) are performed against the following organisms (not exaustive list):

- Bacteria (Gram-negative and Gram-positive) (e.g.: *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Enterococcus hirae, Salmonella typhimurium, Listeria monocytogenes, Enterococcus faecium, Legionella pneumophila, Proteus vulgaris,* MRSA, MRSE, VRE, *Enterobacter cloacae*)
- Yeasts and Molds (e.g.: *Candida albicans, Saccharomyces cerevisiae Aspergillus brasiliensis*)
- Spores (e.g.: spores of *Bacillus subtilis*, spores of *Bacillus cereus*)
- Mycobacteria (e.g.: *Mycobacterium tuberculosis* and *Mycobacterium terrae*)
- Bacteriophages (e.g.: *Bacteriophage* P001 and P008)
- Viruses (e.g.: *Poliovirus* type 1, *Adenovirus* type 5, *Murine Norovirus, Murine Parvovirus, Vacciniavirus, Aujeszky's, Bovine Viral Diarrhea, Porcine and Bovine Enterovirus, Hepatitis A virus, Human Respiratory Syncytial Virus, Human coronavirus, Bovine Parainfl uenza, Cardiovirus,* PRRSV, *Pseudorabies*)
- Isolated strains

SAFETY TEST - TOXICOLOGICAL *IN VITRO* AND *IN VIVO* TEST

Sensitization

- Skin sensitization with 3D models
- Human-cell line activation - hCLAT (OECD 442E)
- Human-cell line activation - U-SENS (OECD 442E)
- Local Lymph Node Assay - LLNA (OECD 429)
- Guinea Pig Maximization Test - GPMT (ISO 10993 - 10)

Irritation - UNI EN ISO 10993-10

- epiCS® skin irritation test (SIT)
- Skin irritation test on 3D Recostructed Human Epidermidis (RHE) model - OECD 439
- Skin corrosion test on 3D Recostructed Human Epidermidis (RHE) model - OECD 431
- Dermal irritation Kit DB - ALM 157 OECD Accepted
- Bovine corneal opacity and permeability (BCOP) test method - OECD 437
- Acute eye irritation/corrosion test - OECD 405
- Ocular irritation test - OECD 491-492
- Intracutaneous reactivity test - UNI EN ISO 10993-10
- Patch test carried out by qualified technicians under the supervision of dermatologists
- Irritation test – internal methods*

** on demand on rectal, vaginal, bronchial mucosa – not exhaustive list*

Cytotoxicity

- Cytotoxicity test - UNI EN ISO 10993-5

Toxicity

- Acute systemic toxicity test - UNI EN ISO 10993-11
- Subchronic toxicity and implantation test - UNI EN ISO 10993-6
- Acute Oral toxicity: Acute Toxic Class Method - OECD 423
- Acute Oral Toxicity: Up-and-Down - OECD 425

Absorption Studies

Absorption evaluation properties of compounds and their metabolites

Haemocompatibility

Haemocompatibility test - UNI EN ISO 10993-4

Genotoxicity

- Bacterial reverse mutation test (Ames test) - OECD 471
- Mammalian cell micronucleus test - OECD 487
- Mammalian cell gene mutation test using thymidine kinase gene - OECD 490
- Mammalian erythrocyte micronucleus test - OECD 474

VIRAL CLEARANCE

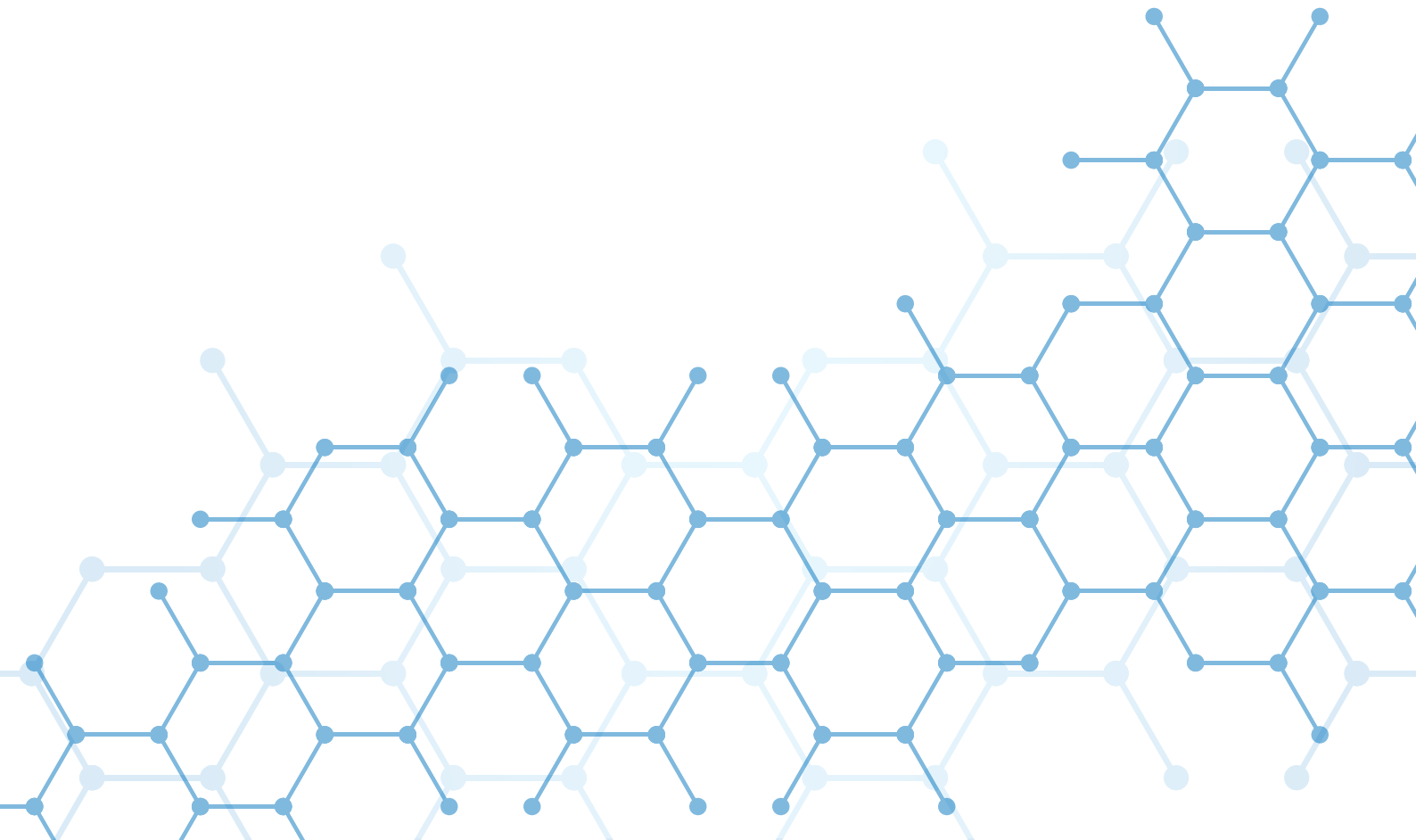
Viral clearance studies are required to **assess the safety of biopharmaceuticals**, such as blood products, monoclonal antibodies, recombinant proteins, tissue derived products, **and medical devices** prior to entering clinical trials and ahead of commercial launch.

The control of biopharmaceuticals and medical devices must take place at three levels:

1. **selecting and testing the raw material**, i.e. cell lines, tissues, organs, media components, for the absence of undesirable viruses which may be infectious and/or pathogenic for humans;
2. assessing the **capacity of the production processes to clear infectious viruses**;
3. **testing the product** at appropriate steps of production for the absence of contaminating infectious viruses.

NANOMATERIALS AND NANOPARTICLES IDENTIFICATION AND CHARACTERIZATION

- Identification and characterization of non-intentionally released nanoparticles
- Nanostructured formulations (as nanoemulsion, nanodispersions) characterization



R&D
AND VALIDATION ACTIVITIES

Quality is always an **imperative prerequisite** when we consider any product and it becomes prime when it relates to life saving products like pharmaceuticals. **The concept of Validation is the overall expression for a sequence of activities in order to demonstrate and document that a specific product can be reliably manufactured by the designed processes** (**so it is closely related to the substance quality**).

Thanks to highly qualified experts and state-of-the-art instruments, Mérieux NutriSciences offers services as:

- Method development and validation on pharmaceuticals products.
- Forced degradation studies (tests made under acidic, basic, oxidative, and various heat and light conditions to identify potential degradants of the API and to validate the stability indicating properties of the analytical procedures).

IDENTIFICATION
OF FOREIGN PARTICLES

The presence of Foreign Particles (FP) in sterile pharmaceutical products can affect their efficacy and safety. FP may originate from both organic and inorganic sources, as corroded or damaged equipment parts, cross contamination during the process or from biological sources. **Thanks to a sophisticated instrumentations combined with a pool of experts in different fields, Mérieux NutriSciences can offer various strategies and approaches for the identification of FP**:

Microscopic examination for visible and sub-visible particles
The technique allows a first evaluation of sample and the information acquisition order to decide eventual further microbiologic analyses. In some cases, it permits the identification FP.

SEM-EDS and TEM-EDS
The association between SEM (Scanning Electron Microscopy) or TEM (Transmission Electron Microscopy) and EDS (Energy Dispersive Spectrometry) allows to carry out morphological and elemental microanalyses on very small organic and inorganic particles, including nanoparticles of 10-100nm dimension (TEM).

FT-IR microscopy and imaging/µFT-IR spectrometry
It allows to carry out FT-IR microanalysis on very small particles (10-1000 µm dimension) and guarantee good performance on several organic and inorganic matrices identification.

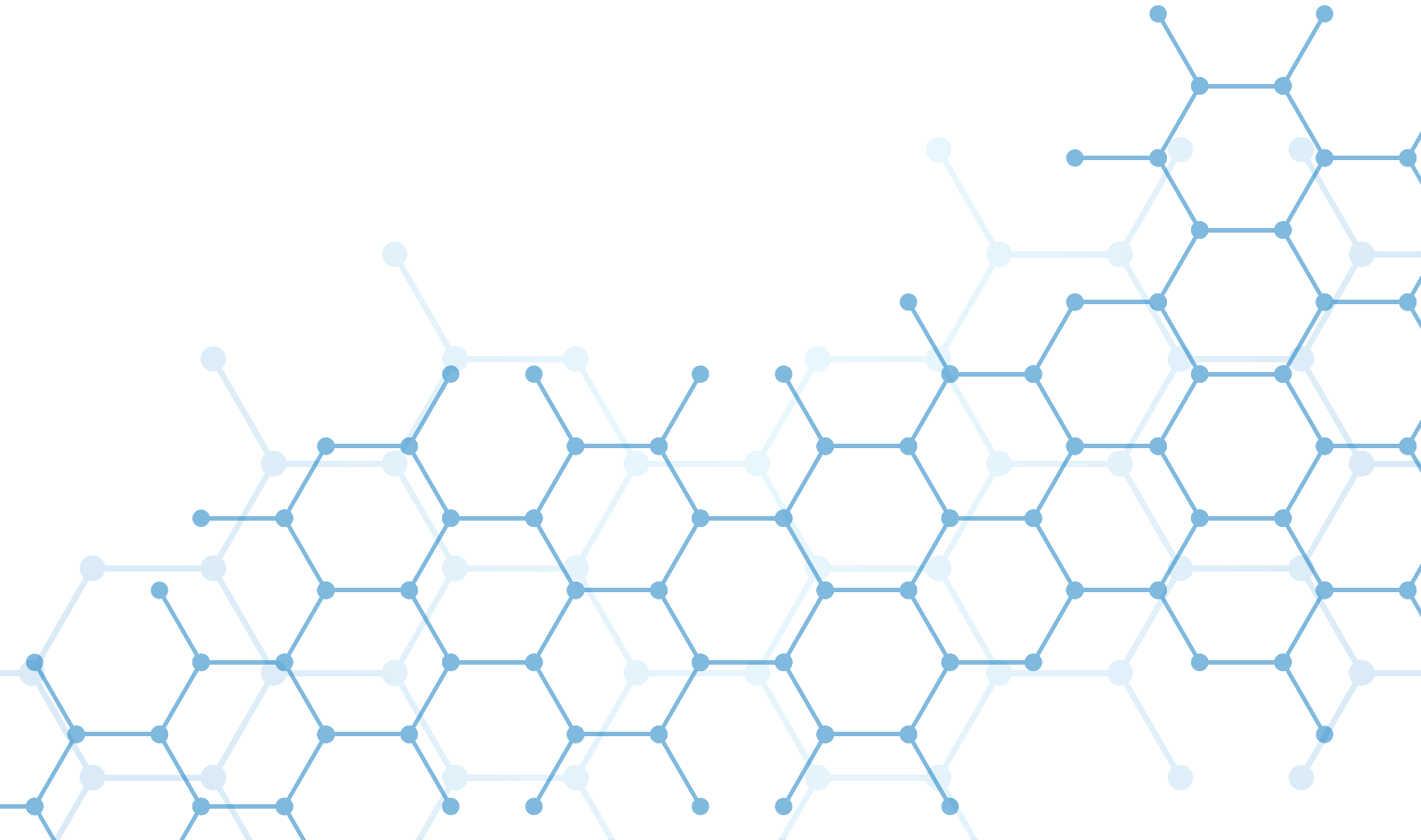
DATA INTEGRITY
& COMPUTERIZED SYSTEMS MANAGEMENT

In Mérieux NutriSciences' GxP Laboratories each test is set-up in a fully validated Laboratory Information Management System (LIMS) compliant to CFR 21 Part 11 and Eudralex Annex 11, in order to:

- Enable fully automated analysis eliminating as much as possible the manual input of data
- Allow the supervision of laboratory operations, performance, and productivity
- Deliver the right information to the right people at the right time
- Fill out an online e-form for testing requests
- Deliver a greater data integrity ensured by instruments interface with our LIMS
- Manage the stability study directly by LIMS
- Manage standard laboratory activity using an integrated Electronic Laboratory Notebook (ELN)

Regarding lab equipments:

- Chromatographic instruments are managed by Empower 3
- New instrument requirements are in compliance with CRF 21 Part 11 and Eudralex Annex 11



BIOPHARMACEUTICALS
AND VALIDATION ACTIVITIES

Purity
- Impurities (host cell proteins, host cell DNA, inducers, antibiotics, or media components)
- Contaminants (chemical and biochemical materials, and/or microbial species)

Physico-chemical Properties
- Molecular weight or size
- Isoform pattern
- Extinction coefficient
- Electrophoretic patterns
- Liquid chromatographic patterns
- Spectroscopic profiles

Biosafety Testing Services
- Viral clearance studies to demonstrate the removal and/or inactivation of viruses
- Cell banking system, characterisation, and testing to demonstrate the absence of bacteria, fungi, mycoplasma, viruses and other potential contaminants (Residual DNA)

MEDICAL
DEVICES

Regulatory support & Risk assessment

Quality controls & Stability

Biological Safety assessment
- Chemical characterization of materials
  - Extractables & Leachables
  - Glass Delamination
- *In vitro* and *in vivo* biocompatibility
  - Sensitization
  - Irritation
  - Intracutaneous
  - Cytotoxicity
  - Toxicity
  - Absorbition studies
  - Genotoxicity
  - Haemocompatibility
- Viral Clearance
- Nanomaterials and nanoparticles identification and characterization

Efficacy

Process Validation
- Sterilization & Cleaning validation
  - Sterilization of health care products Radiation - ISO 11137
  - Sterilization site validation - β e γ rays
  - Cleaning validation
- Reprocessing validation
- Packaging validation
  - Physical-chemical analysis
  - Microbiological analysis
  - Mechanical analysis
  - Shipping validation

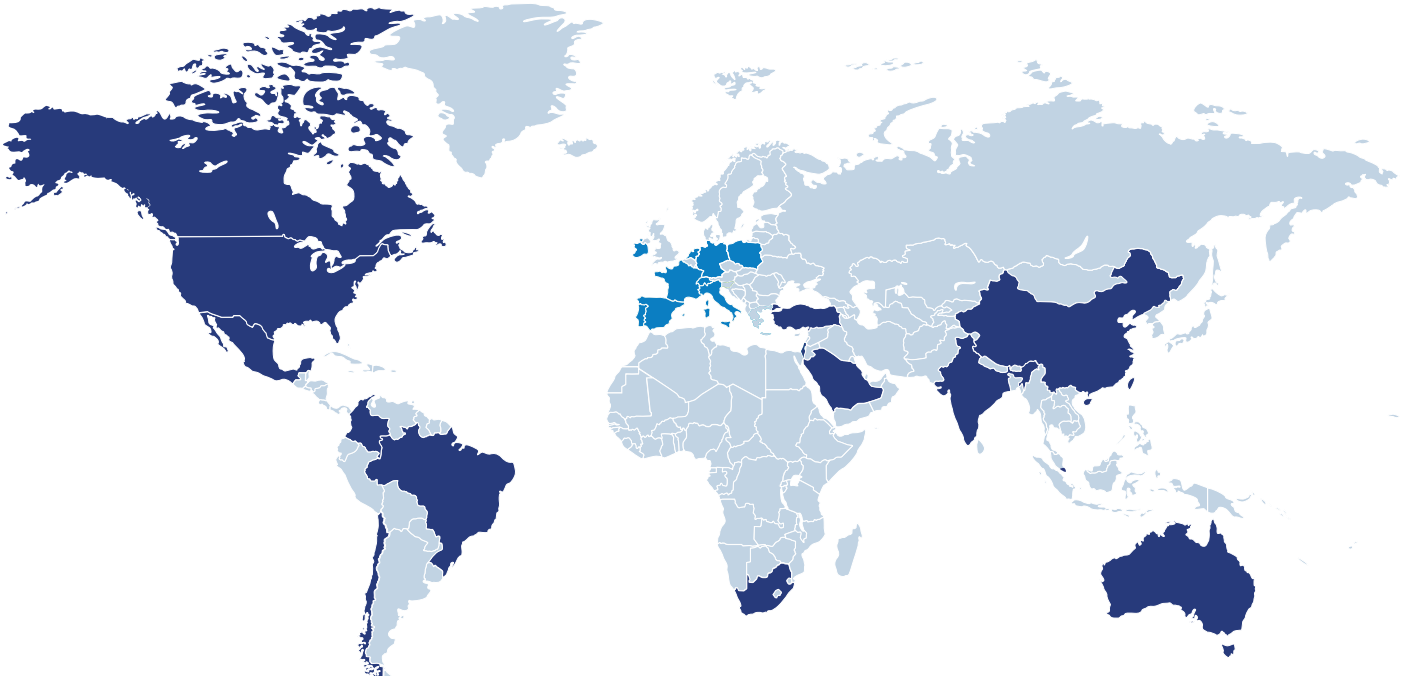
Human factor services
- Usability
- Labelling
- Consumer test and market research

ACKNOWLEDGEMENTS
& AUTHORIZATIONS

QC LABORATORY AUTHORIZATION FOR HUMAN MEDICINAL PRODUCTS (AIFA)
QC LABORATORY AUTHORIZATION FOR MEDICINAL PRODUCTS FOR VETERINARY USE
FDA ESTABLISHMENT INSPECTION REPORT
GLP CERTIFICATE
GMP CERTIFICATE FOR HUMAN MEDICINAL PRODUCTS (AIFA)
GMP CERTIFICATE - HEALTH MINISTRY (VET MEDICINAL PRODUCTS)
ISO 9001:2015 CERTIFICATION
AUTHORIZATION FOR USE OF INTERNATIONALLY CONTROLLED SUBSTANCES
LICENSE FOR DRUG PRECURSORS
APPROVED ORGANISATION CARRING OUT R&D ACTIVITIES FOR THE RECOGNITION OF THE FRENCH CREDIT D'IMPOT RECHERCHE (CIR)
ACCREDIA ACCREDITATION FOR EFFICACY STUDIES ON BIOCIDE PRODUCTS AND VIRUSES DETECTION
AUTHORIZATION TO ANALYTICAL CONTROLS ON PRESIDI MEDICO CHIRURGICI (PMC)

Mérieux NutriSciences

A STRONG PRESENCE IN EUROPE AND WORLDWIDE



MÉRIEUX NUTRISCIENCES OFFERS ITS SCIENTIFIC EXCELLENCE IN PHARMACEUTICAL, CHEMICAL, BIOCIDE, COSMETIC AND FOOD PRODUCTS TESTING AND CONSULTING TO ENSURE SUPPORT, OPTIMAL REACTIVITY AND FLEXIBILITY TO ITS CUSTOMERS ALL OVER THE WORLD.

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