Medical Devices

Innovative Solution for the Healthcare

Mérieux NutriSciences

Innovative Solution for the Healthcare

MEDICAL DEVICES CLASSIFICATION

The **Regulation 745/2017** defined as Medical Device any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state
- providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products are also considered Medical Devices:

- devices for the control or support of conception
- products specifically intended for the cleaning, disinfection or sterilisation of devices

Thanks to the continuous research and innovation of a department dedicated to medical devices, Mérieux NutriSciences aims to promote all the possible options to *in vivo* testing in favour of a solid *in vitro* approach.

The 3R principle

The purpose of this approach is to reduce or replace animal testing wherever possible:

- **REPLEACEMENT** of the animal model with in vitro models
- **REDUCTION** in the number of animals used in trials while maintaining the same level of information, where it is not possible to replace the animal model
- **REFINEMENT** of the suffering level imposed by actively improving the quality of life of the animal during the experimental procedures

Medical Devices Classification

For a correct classification of Medical Devices, it is advisable to check the intended use and the mechanism of action.

Medical Devices are classified into risk classes according to duration, mode and type of interaction with the body:

- **CLASS I** (including Is & Im): all non-invasive devices with some exceptions for surgical instruments and for invasive devices related to body orifices - lower risk
- **CLASS II** (including IIa and IIb): invasive devices related to body orifices and invasive surgical nature, and devices based on substances
- **CLASS III**: invasive surgical devices and devices based on substances

Regulatory Reference

- New Medical Device regulation (EU) 2017/745
- Quality management systems - ISO 13485:2016
- Risk Management - ISO 14971:2007
- Biological evaluation of medical devices
- ISO 10993-1 Part 1: Evaluation and testing within a risk management process
- ISO 10993-18:2020 Part 18: Chemical characterization of medical device materials within a risk management process
- ISO 10993-23 Part 23: Tests for irritation
- Clinical studies - ISO 14155:2011

REGULATORY SUPPORT & RISK ASSESSMENT

A qualified support on medical devices:

- full assistance in planning the best path for the certification of any medical device
- support the technical and pre-clinical data collection for regulatory purposes
- development of sound regulatory approaches to getting clearance in many different countries: Russia, US, China, India and many more

CE marking

- Audit & Consulting
- Technical File Preparation
- Administrative Procedures Management - Submission & follow up

OBL (Own Brand Labelling) procedures

- Audit & Consulting
- Administrative Procedures Management
- OBL submission & follow up

ISO 13485 certifications

- Audit & consulting
- Quality System Documentation Preparation - Support during inspections

Clinical evaluation

Drafting of Clinical Evaluation Plans (CEP) and Clinical Evaluation Reports (CER) for medical devices of any class. The service is designed to assist the manufacturer at all stages of the process of the clinical evaluation:

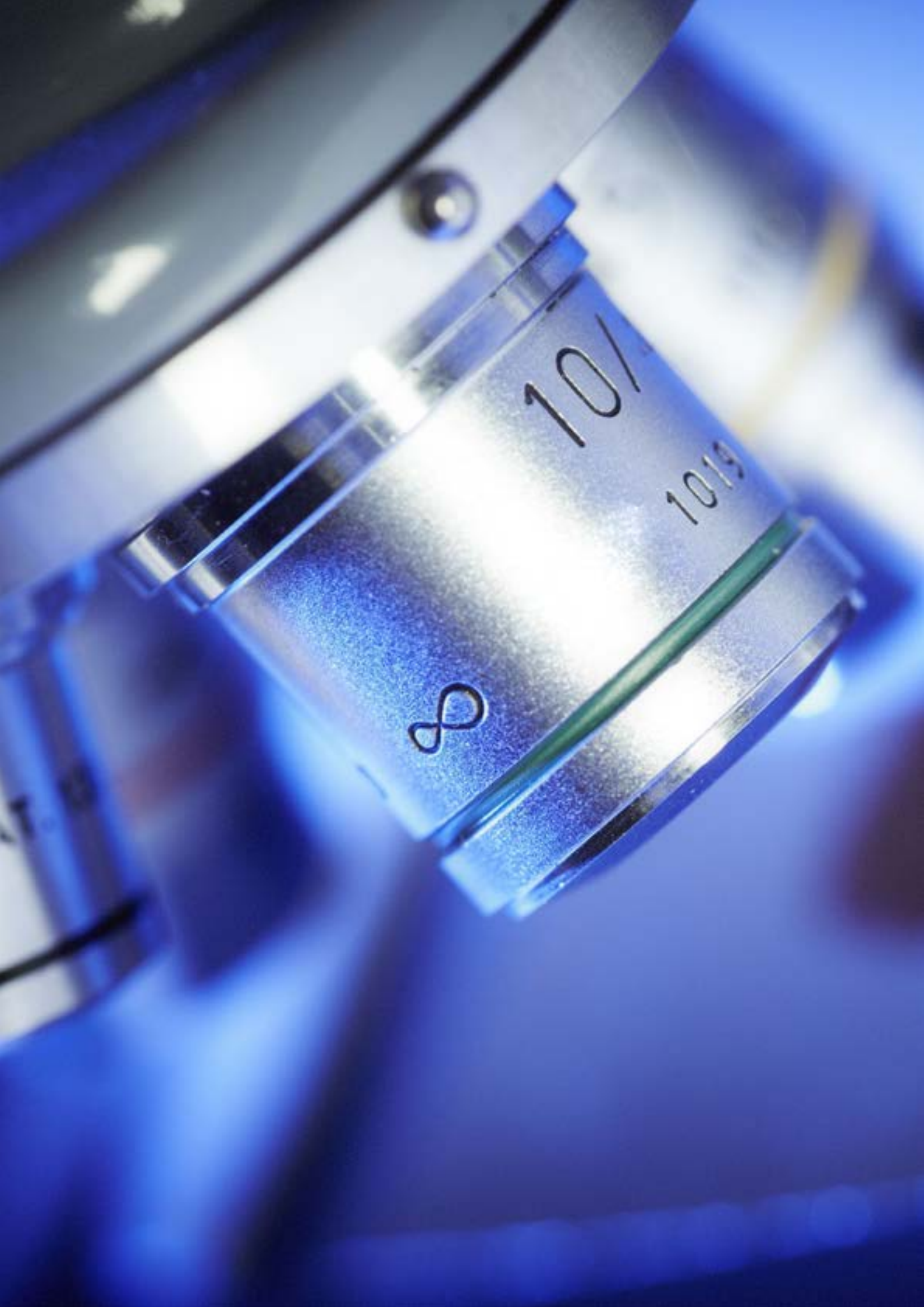
- Planning the device specific clinical evaluation according to the requirements of MEDDEV 2.7/1 revision 4
- Identifying pertinent clinical data searching the relevant sources
- Appraising the identified clinical data from clinical investigations as well as scientific literature and other sources
- Analysing the relevant data sets and build the body of evidence based on sufficient clinical data
- Compiling the clinical evaluation report, summarizing the results of clinical evaluation in support of evidence of the general safety and performance requirements

Risk assessment

In accordance with **ISO 14971:2007, the biological assessment of any medical material or device intended for use in humans shall be part of a structured biological assessment plan as part of a risk management process**. This risk management process involves the identification of biological hazards, the estimation of the associated biological hazards and the determination of their acceptability:

- Human health risk assessment and estimation of safe threshold
- Toxicological assessment of extractables and leachables and degradation products
- Risk assessment following quality issues
- Reviews of published literature of toxicological data and evaluation of toxicological profiles
- *In silico* predictions and TTC (Threshold of Toxicological Concern)
- Biological evaluation of medical devices performed according to ISO 10993-1 guidance

perfomed with qualified partners



QUALITY CONTROLS & STABILITY

Physico-chemical controls

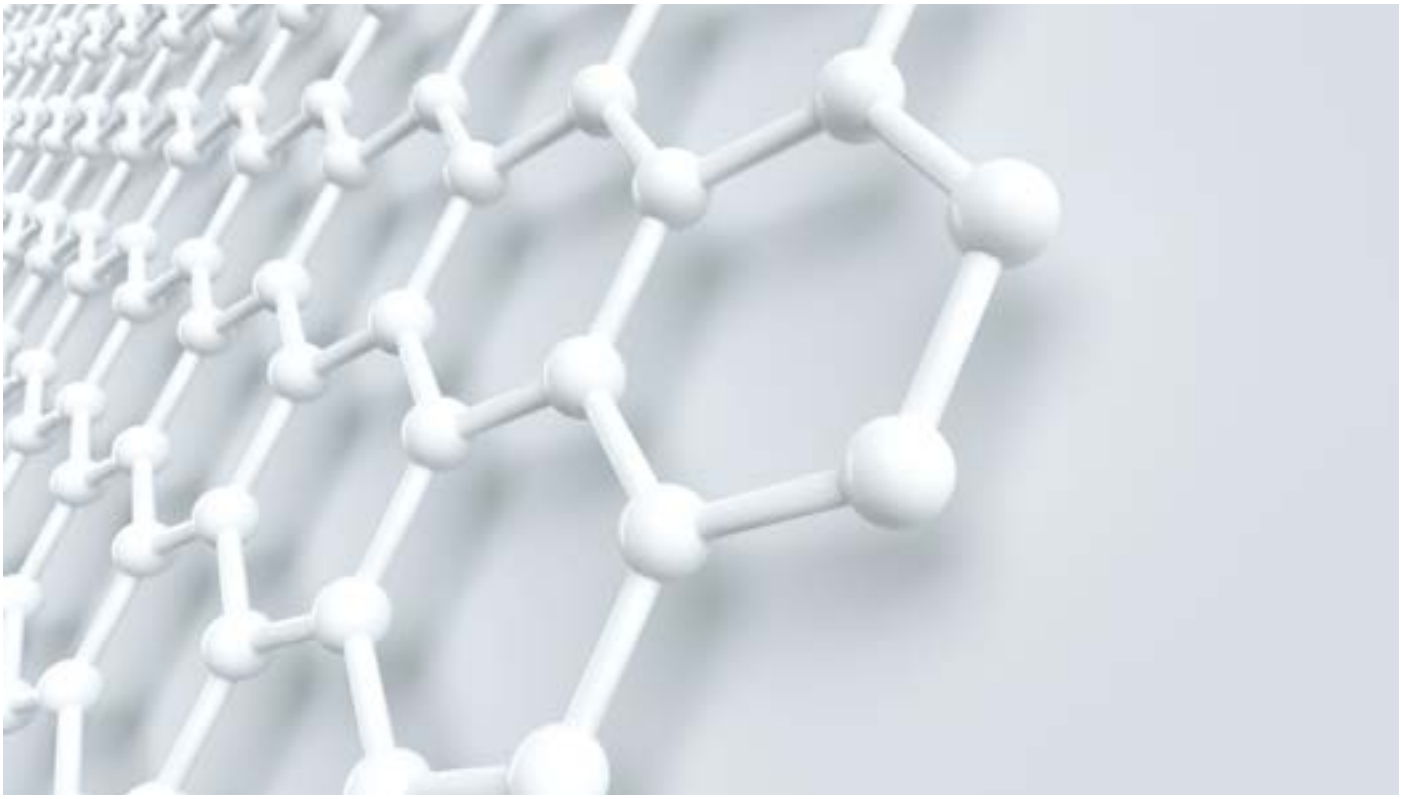
- Morphological characterization of materials
- Assays and residual tests
- Degradation products
- Ethylene oxide and related degradation products

Storage and stability studies

- GMP managed stability climatic and thermostatic chambers
- Coverage of all ICH climatic condition
- Controlled temperature shipping service

Microbiological controls

- Microbiological tests (Bioburden, TAMC, TYMC, Pathogens)
- Sterility test
- Challenge test
- Environmental monitoring
- Microorganism identification: MALDI-TOF and DNA sequencing
- 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
- Sterility tests - EN ISO 11737-2, EP 7th edition <2.6.1> and USP 34 – NF 29 <71>



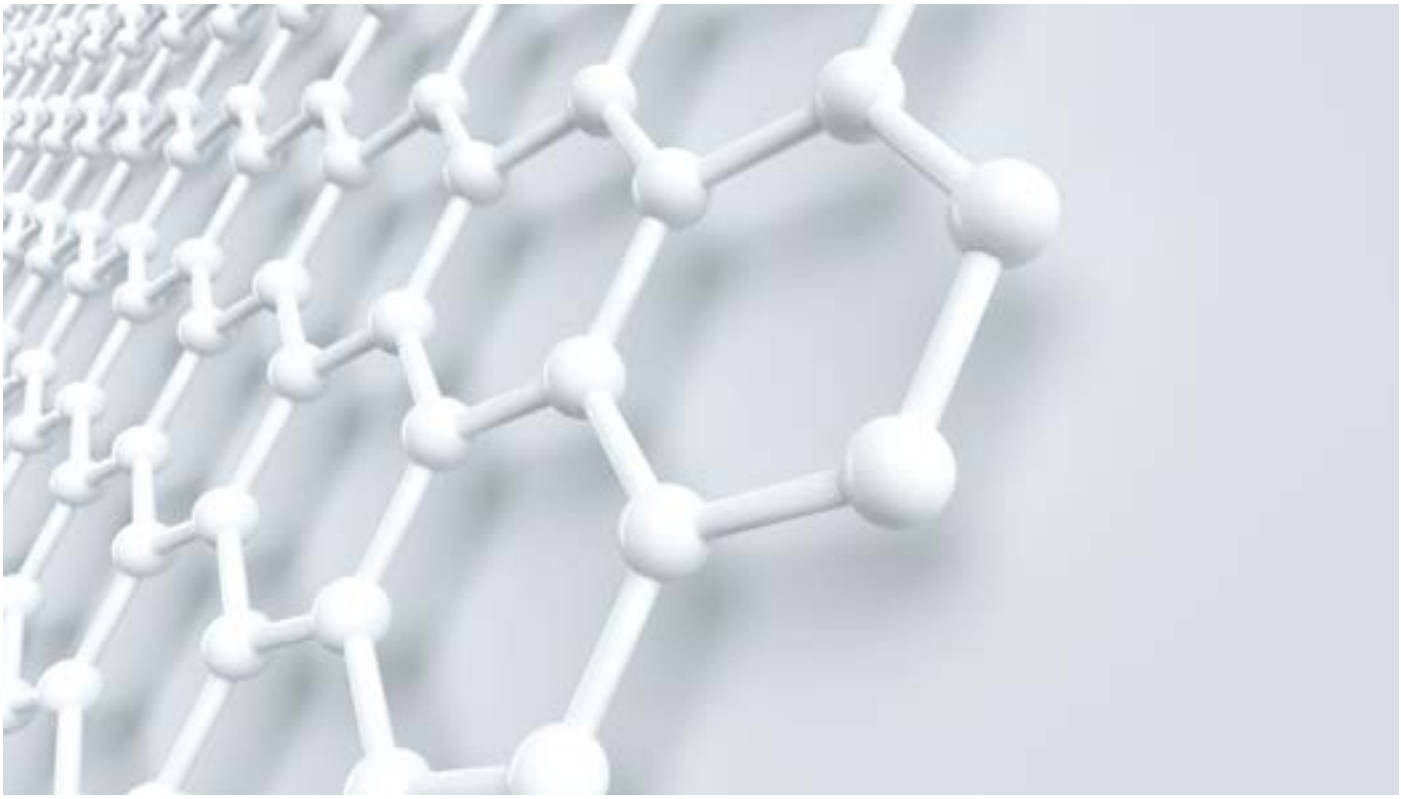
BIOLOGICAL SAFETY ASSESSMENT

Chemical characterization of materials (ISO 10993 series)

Medical devices are often composed of several materials and components with different physico-chemical characteristics. Material selection and risk analysis are integral parts of the design process for medical devices.

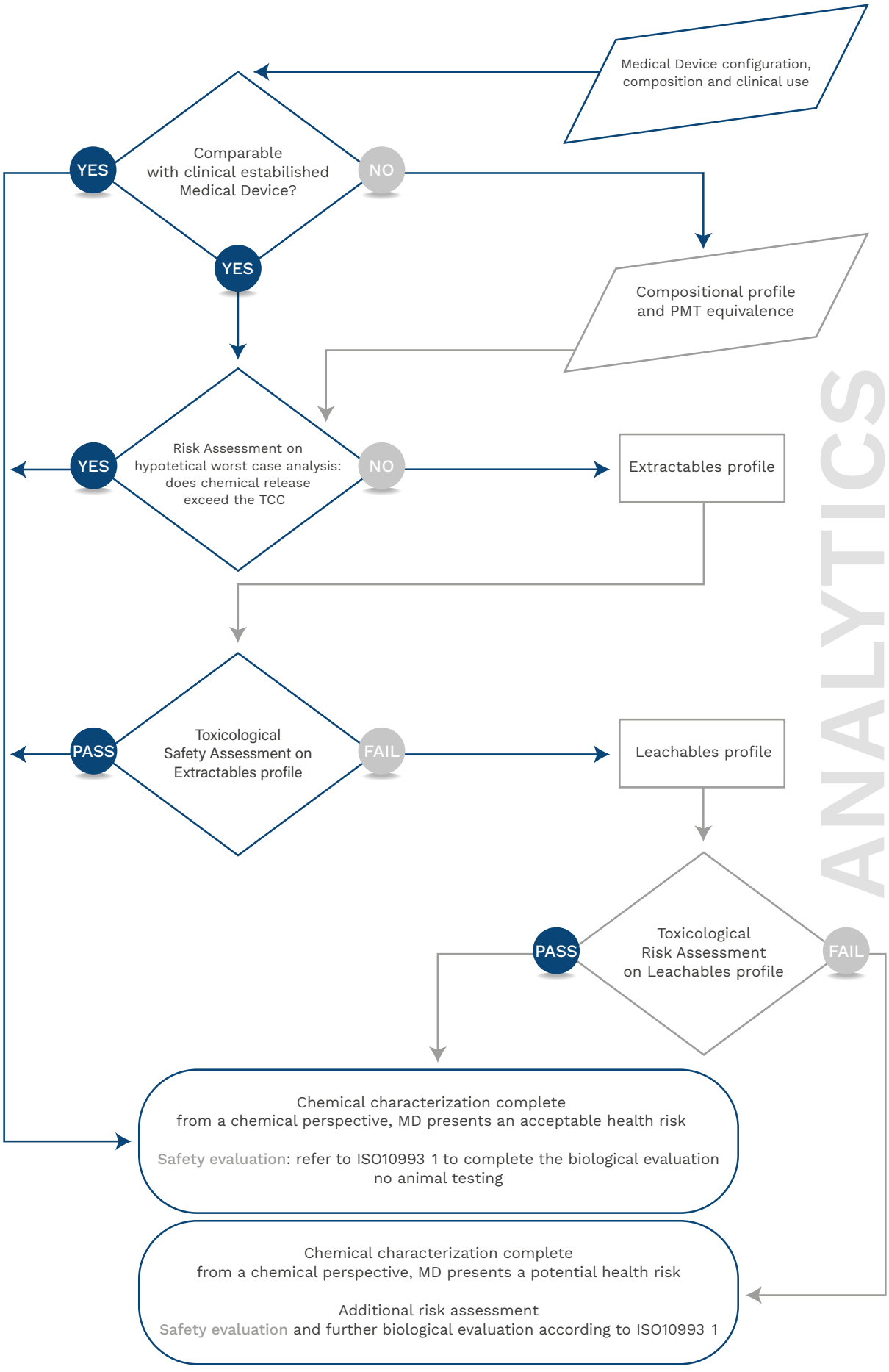
The description of the chemical components of direct and indirect contact medical devices and the consideration of material characterization, including chemical characterization, must precede any biological test (ISO 10993-18) and provides the necessary input into the device's biological evaluation and toxicological risk assessment (ISO 10993-1 and ISO 10993-17).

1. Information gathering on the medical device: establish the type of contact and configuration, identify materials (including residues and chemical components)
2. Material equivalence for Risk assessment: demonstrate the equivalence of configuration, composition, and clinical use, to a clinically established device deemed safe for use
3. Estimate of the device's chemical release (worst-case scenario): perform extraction study and toxicological assessment of all reported extractables (ISO 10993-17)
4. Actual chemical release of the device: perform leachables study
5. Toxicological risk assessment: estimate clinical exposure for all reported leachables (ISO 10993-17)



CONSULTANCY

ANALYTICS



Extractables & Leachables

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.

OUR ACCREDITATIONS

Our experience on validation studies for drug products, and our high laboratory standards - in compliance with GMP, GLP, and ISO 17025 - allow us to perform extractables and leachables studies that have recognized value by international regulatory authorities such as the FDA:

- Mérieux NutriSciences E&L laboratories employ methods compliant with **ISO 17025:2005 standard**, and **certified by Accredia**, the Italian accreditation body;
- accreditation and validation of **migration test methods on specific FCM compounds** (depending on compound).

Analytical techniques

- HPLC-ELSD, HPLC-MS/MS, HPLC UV/DAD, IC
- LC-MS/MS, LC-HRMS Q/Orbitrap
- HS-GC, HS-GC/MS, GC/FID, GC-MS, GC-HRMS Q/Orbitrap
- ICP-OES, ICP-MS, AAS
- MALDI-TOF
- TOC
- SEM/EDS, TEM/EDS

In vitro and *in vivo* biocompatibility

A wide range of laboratory tests to ensure the **quality and safety of medical devices**, in compliance with applicable harmonized standards. Our team of experts can also **develop and validate methods** for specific requirements.

Sensitization

- Human-cell line activation (hCLAT) - OECD 442E
- Human-cell line activation (U-SENS) - OECD 442E
- Skin sensitisation with 3D models

Irritation - UNI EN ISO 10993-10

- epiCS® Skin irritation test (SIT)
- Skin irritation test on 3D Recostructed Human Epidermidis (RHE) model - OECD 439
- Dermal irritation Kit DB - ALM 157 OECD Accepted
- Ocular irritation test - OECD 491-492
- 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 - UNI EN ISO 10993-5

- Cytotoxicity test

Absorption studies

Absorption evaluation properties of compounds and their metabolites

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

(not exhaustive list, please refer to MxNS dedicated customer care)

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.

Our capabilities

Our dedicated virology labs control the viral safety of your product by **assessing the capacity of the production processes to clear infectious viruses**.

The objective of viral clearance studies is to **evaluate the ability of the manufacturing process to inactivate/remove known or even unknown viral contaminants**, and to estimate process robustness by characterizing its ability to clear different model viruses.

Nanomaterials and nanoparticles identification and characterization

- Identification and characterization of non-intentionally released nanoparticles
- Nanoparticles released from implantable medical devices (including microplastics)
- Nanostructured formulations (as nanoemulsion, nanodispersions) characterization

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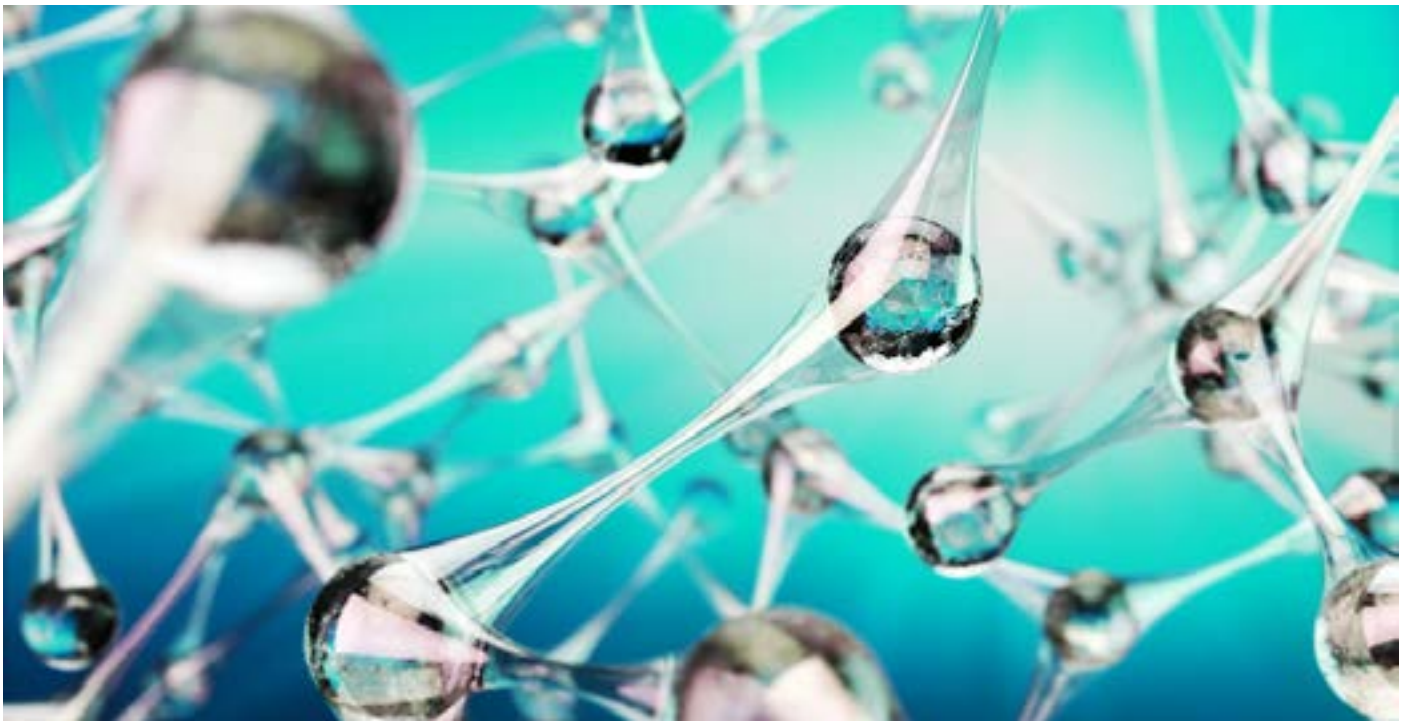


EFFICACY EVALUATION

In vitro test methods, which are **appropriately validated, reasonably and practically available, reliable and reproducible**, shall be considered for use in preference of in vivo tests - ISO 10993-2, 2009:

1. Regenerating action (skin/tissue models)
2. Soothing action (skin models)
3. Barrier action (skin/tissue models)
   - Permeability reduction
   - Anti-adhesive activity
4. Wound healing efficacy (skin models)
5. Re-epithelialization activity
6. Mucoadesivity test (tissue models)
7. Protective effect
8. Absorption efficacy evaluation (tissue models)

Efficacy test of **disinfectants used in medical area** are performed according to EN and ISO standards:

1. Bactericide
2. Virucide
3. Fungicide
4. Antiseptics

Medical area:

hospitals, nursing homes, kitchens that cook food for patients

- EN 13727
- EN 13624
- EN 14561
- EN 14562
- EN 14563
- EN 14348
- EN 16615
- EN 17126
- EN 12791
- EN 17387
- EN 1499
- EN 1500
- EN 14476
- EN 16777
- EN 17111

PROCESS VALIDATION

Sterilization validation

Sterilization dose determination - ISO 11137

Determining the sterilizing dose using microbial load information (Bioburden):

- select the sterility assurance level: it's important to select samples that must be representative of routinely sterilized products;
- determine the average microbial load of the batches - method based on ISO 11737-1;
- obtain the verification dose - referring to ISO11137-2;
- conduct verification dose experiments on irradiated pieces - method based on ISO 11737- 2;
- interpret the results;
- establish the sterilisation dose based on the results.

Sterilization site validation - β e γ rays

Verification of the ability of the site to sterilize the packaging of medical devices:

1. spiking: inoculation of relevant strains with a known title on the packaging;
2. sending the packaging to the site for the sterilization procedure execution;
3. verification of the effective ability of the sterilization procedure by our laboratories.

Sterilization site validation - Ethylene dioxide

One of the most popular methods of sterilization of medical devices is through exposure to Ethylene Oxide gas (EtO/EO).

1. Preconditioning and/or Conditioning of device through temperature & humidity variations;
2. Gas Dwell Phase/Sterilizing Cycle where the device is exposed to the EtO gas;
3. Aeration of exposed device for removal of gas from the product.

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:

1. Selection of appropriate sampling and analytical strategies for determining chemical residues or biological contamination
2. Selection of appropriate detection methods
3. Development of specific methods for the research of contaminants
4. Analytical cleaning method validation

ISO 19227:2018 Implants for surgery - Cleanliness of orthopedicimplants - General requirements

Disinfection validation

Validation of disinfection methods are performed differently depending on the level of disinfection required, high level disinfection, intermediate level disinfection or low level disinfection.
The level of disinfection is determined by the Spaulding Category of the device, critical, semi-critical or non-critical.

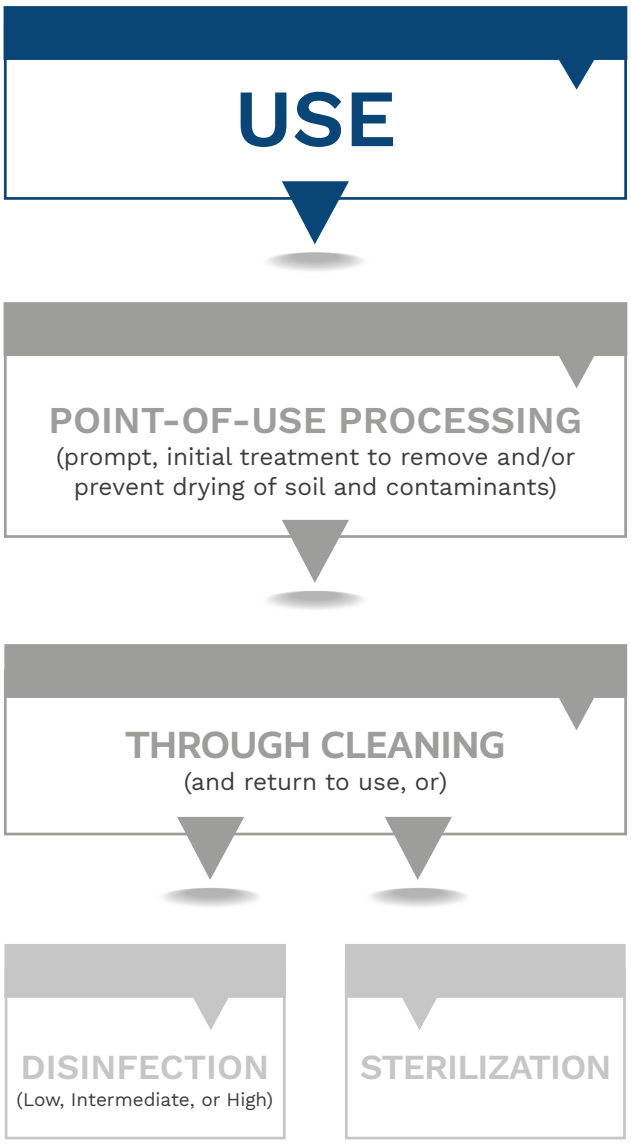
1. The device is inoculated with bacteria and then exposed to the disinfectant
2. Any remaining bacteria is extracted from the device and grown on plates in a manner similar to a bioburden test

Reprocessing Validation

Validation of eprocessing instructions of single-use/reusable medical device.

Reprocessing is defined as **validated processes used to render a medical device, which has been previously used or contaminated, fit for a subsequent single use**.

These processes are designed to remove soil and contaminants by cleaning and to inactivate microorganisms by disinfection or sterilization.



Resources for developing reprocessing instructions:

- Labeling recommendations (FDA)
  - AAMI TIR12
  - AAMI TIR30
  - AAMI/ANSI ST81
- List of FDA-recognized test methods
- Clinical practice guidelines (e.g. from the Centers for Disease Control, CDC)

Packaging validation

Performance (physical-chemical) analysis

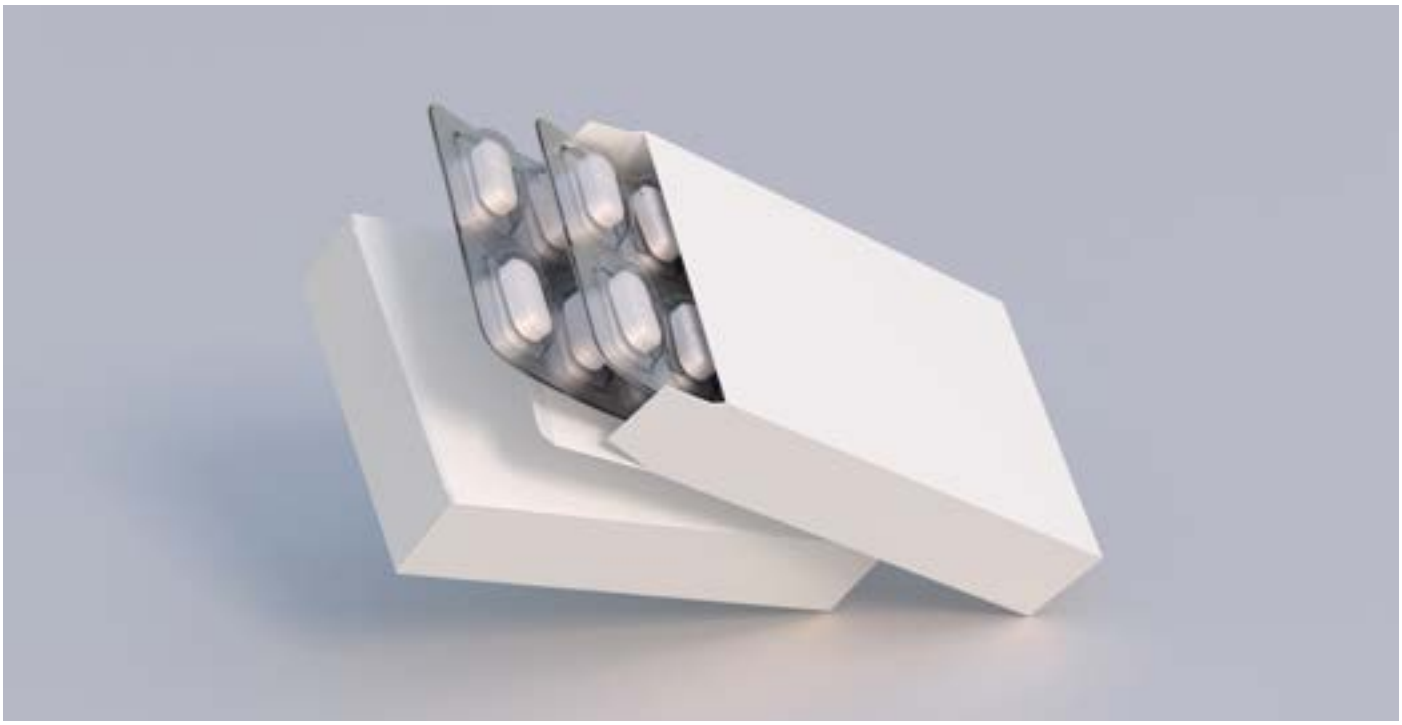
- **Seal strength test - ASTM F88/F88M-15**
- Standard test method for the determination of maximum force needed for opening the packaging, the package integrity as well it measures the ability of the process to produce consistent seals.
- **Peel or stripping strength test of adhesive bonds - ASTM D903-98**
- Standard test method for the determination of maximum and mean force needed for peeling it.

Microbiological barrier

- **Sterility test - <71> STERILITY USP 41-NF36**
- Standard test method for verifying the medical device sterility.
- **Microbial barrier test - DIN 58953-6:2010**
- Standard test method for verifying the resistance to the microbial passage through the material used for the medical device packaging, in wet and dry conditions.

Integrity analysis

- **Dye penetration test - ASTM F1929**
- Standard test method for assessing resistance and detecting the presence of fractures, channels or abnormalities of the packaging containing the medical device by dye penetration assay (Toluidine Blue).
- **Visual inspection test - ASTM F1886 / F1886M-09**
- Standard test method for determining integrity of seals for flexible packaging by visual inspection.



HUMAN FACTOR SERVICES

Usability

Medical device usability is defined by the **standards IEC 62366 (IEC 62366-1:2015 and IEC 62366-2:2016)** as "the characteristics or features of the user interface that facilitate use and thereby effectiveness, efficiency and user satisfaction in the intended environment of use". **Usability services** performed with **professional** or **consumer users; only Late Formative and/or Summative Evaluation** steps of the user's interface usability evaluation are available:

- Expert reviews
- One-to-one interviews
- PCA
- Simulations
- Survey
- Task analysis
- Usability tests

Labelling

Our experts can evaluate **if the labels on both the device and the packaging** (such as single unit packaging and/or sales packaging) comply with the additional labelling requirements as per **Annex I - 23.1a of the MDR 2017/745**, as:

- in the language accepted in the Member States where the device will be sold
- indelible
- easily legible
- readily understood by the intended end-user

Consumer test and market research

Our Sensory Services

Discriminating methods

- "A", "non-A" tests
- Triangle test
- Ranking test

Descriptive methods

- Time intensity
- CATA | RATA
- QDA
- Deviation from reference profile
- Projective mapping
- Consensus profile
- TDS – Temporal Dominance of Sensations

Our Market Research Services

Exploring
the qualitative approach

- Trend map – semiotics
- Consumer profile
- Concept writing & screening

Measuring
the quantitative approach

- Product test (blind & as marketed)
- Claim test
- Usability test
- Usage & attitudes

ANALYTICAL TECHNIQUES

Amino Acid Analyzer
Atomic Absorption Spectroscopy (AA-FIAS)
Atomic Absorption Spectroscopy (AA-Flame)
Atomic Absorption Spectroscopy (AA-GF)

BET (Brunauer–Emmett–Teller)

Cell Culture Techniques

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

Electrophoresis (capillary & gel)

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)
Gas Chromatography (GC-TCD)
Gravimetry
Head-Space Gas Chromatography (HS-GC)

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)
MALDI-TOF
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

SDS-PAGE
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)

Western blot

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

MÉRIEUX NUTRISCIENCES ASSETS

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

Top Level Quality Accreditations

A Unique Technological Platform, offering best-in-class CRO services in Brazil

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

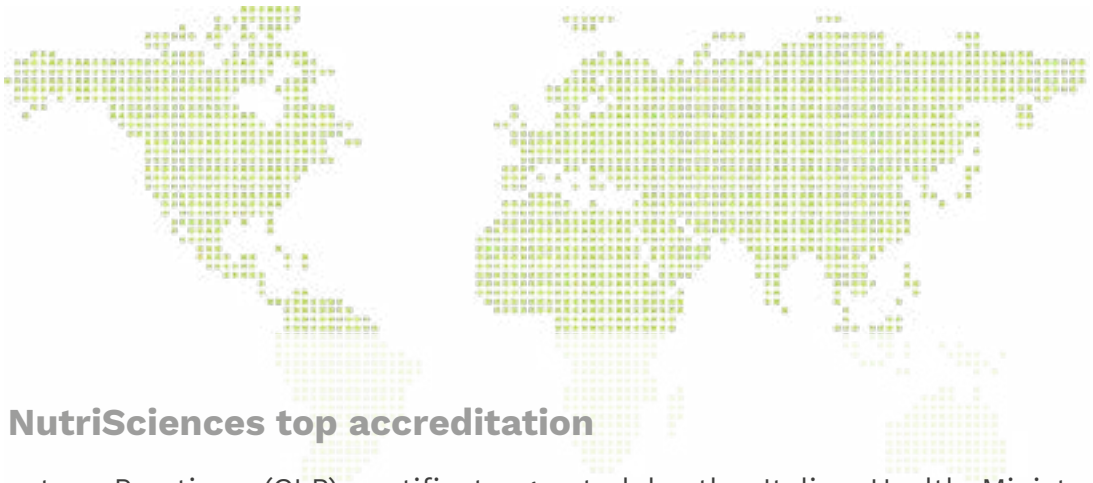
Regulatory and Scientific Assistance includes EU legislation requirements (REACH, Cosmetics, Biocides and Pesticides Regulations)

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)
EcoVadis sustainability rating (2021)

Mérieux NutriSciences

A STRONG PRESENCE IN EUROPE AND WORLDWIDE



Mérieux NutriSciences top accreditation

Good Laboratory Practices (GLP) certificate granted by the Italian Health Ministry for Good Manufactory Practices (GMP) granted by AIFA (Italian Medicines Agency) ISO 9001: 2008 – if the referred market is the USA it is necessary to perform the testing in GMP - US FDA registration as Testing Facility in compliance with cGMP requirements - ISO/IEC 17025:2005 accreditation granted by Accredia (Italian Accreditation Body) - ISO 9001:2008 certificate granted by Certiquality Srl - ISO 14001:2004 certificate granted by Certiquality Srl

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

Mérieux NutriSciences

Better Food. Better Health. Better World.

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