PHARMA
& MEDICAL
DEVICES

MEDICAL DEVICES

INNOVATIVE SOLUTION FOR THE HEALTHCARE

Because you care about consumers' health

MERIEUX NutriSciences

Because you care
about CONSUMERS' HEALTH

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**
- **ISO 13485:2016 - Quality management systems**
- **ISO 14971:2007 - Risk Management**
- **ISO 10993-1:2018 - Biocompatibility**
- **ISO 14155:2011 - Clinical studies**
- **MEDDEV 2.7/1 - Clinical evaluation dedicated ISO depending on the Medical Devices nature**

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

WITH QUALIFIED PARTNERS


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8

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

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

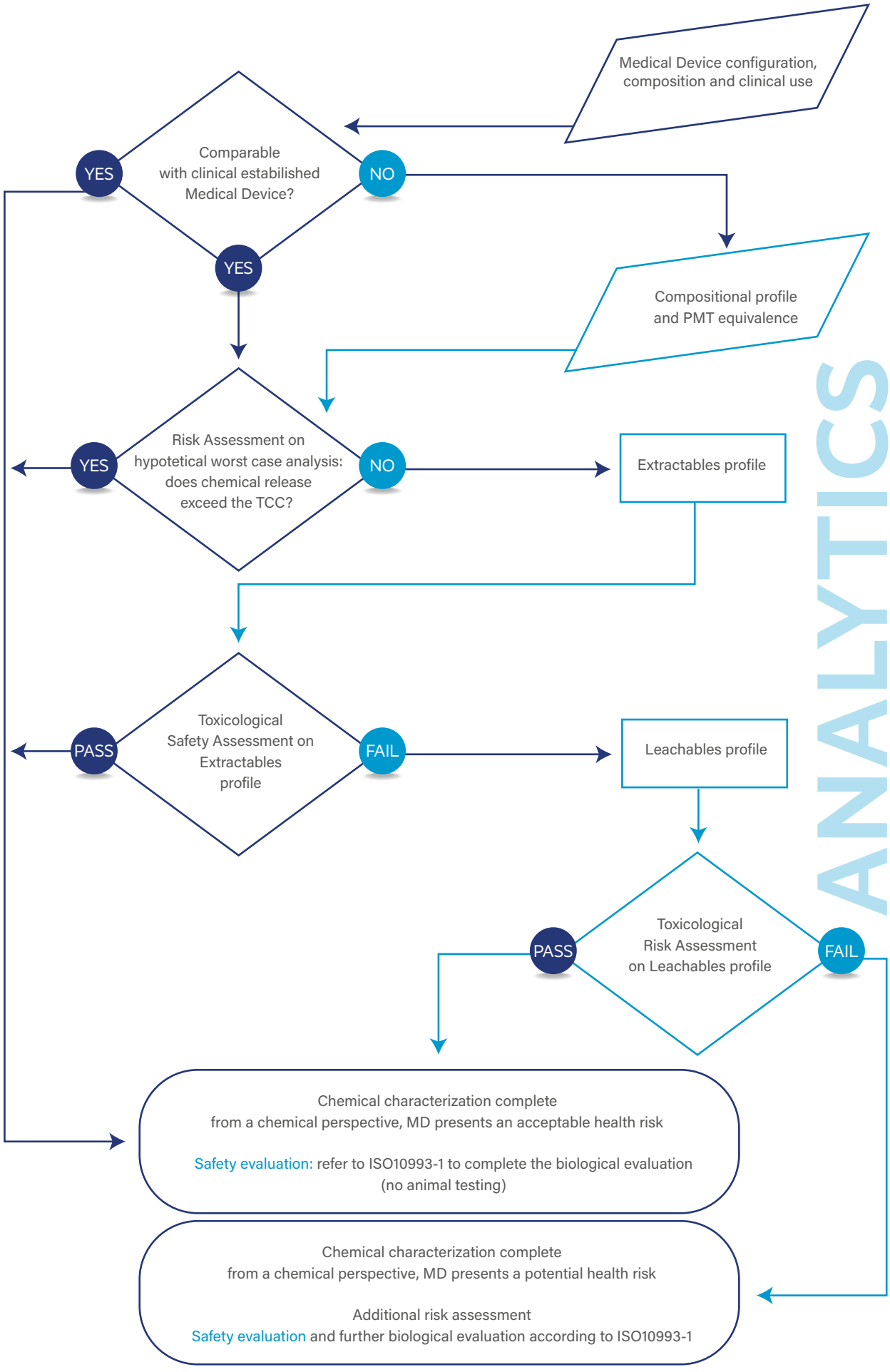
3. Estimate of the device's chemical release (worst-case scenario): perform extraction study and toxicological assessment of all reported extractables (ISO 10993-17)

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

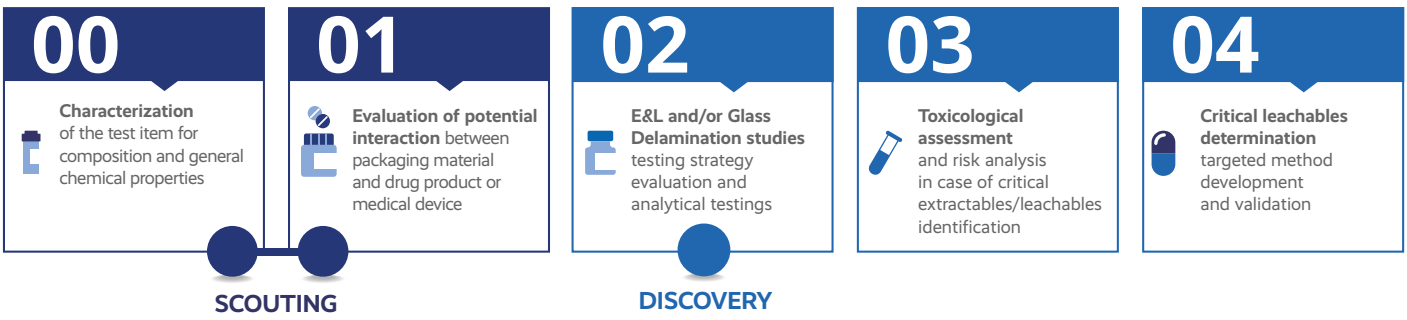
ANALYTICS



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.



TECHNOLOGIES

- 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

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 or 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
- Guinea pig maximisation test (GPMT) - ISO 10993-10
- Murine local lymph node assay (LLNA) - 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 device**s 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
- Nanoparticles released from implantable medical devices (including microplastics)
- Nanostructured formulations (as nanoemulsion, nanodispersions) characterization

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. Antioxidant activity (skin/tissue models)
4. Barrier action (skin/tissue models)
   - Permeability reduction
   - Anti-adhesive activity
5. Wound healing efficacy (skin models)
6. Reepithelialization activity
7. Chelating and detoxifying activity (skin/tissue models)
8. Mucoadesivity test (tissue models)
9. Protective effect
10. 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

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

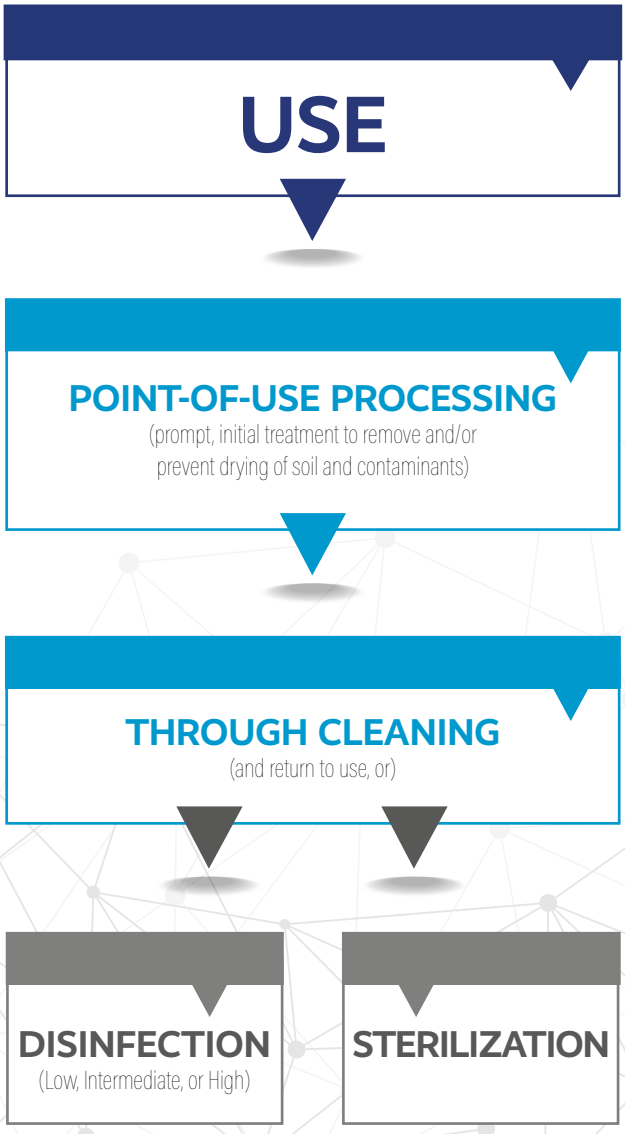
REPROCESSING VALIDATION

Validation of reprocessing 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.

Source: Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling - March 17, 2015
https://www.fda.gov/media/80265/download



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.

SHIPPING VALIDATION

According with **Annex I** of **MDR 2017/745**, shipping validation is an important step for ensuring the packaging integrity and safety of all medical devices (not exhaustive list):

- Drops (manual handling) - ASTM D5276
- Peel or stripping strength test of adhesive bonds - ASTM D903-98
- Surface and bulk homogeneity - UNI EN ISO 11979-3
- Climatic stressing - ASTM F2825-18
- Vertical impact test by dropping - ISO 2248:1985
- Antimicrobial barrier test - ASTM F2638
- Seal leaks by dye penetration - ASTM F1929-98
- Seal strength of flexible barrier materials - ASTM F88/F88M-15
- Accelerated ageing - ASTM F1980

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

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 (Laser dry dispersion)
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 (MALDI-TOF/TOF)
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)

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

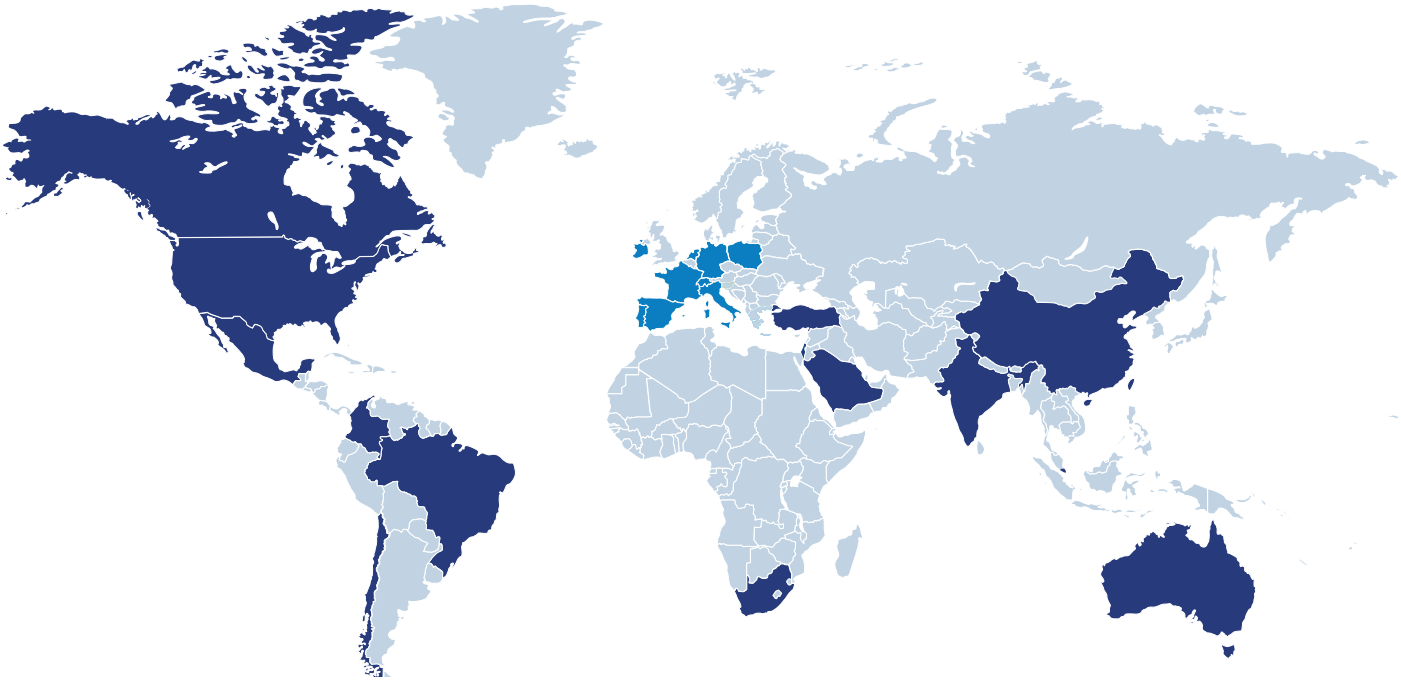
GLOBAL EUROPEAN FRONT OFFICE ENSURES THOROUGH LOCAL SUPPORT TO ITS CUSTOMERS THANKS TO OPTIMAL REACTIVITY AND HIGH FLEXIBILITY

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)

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.

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

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