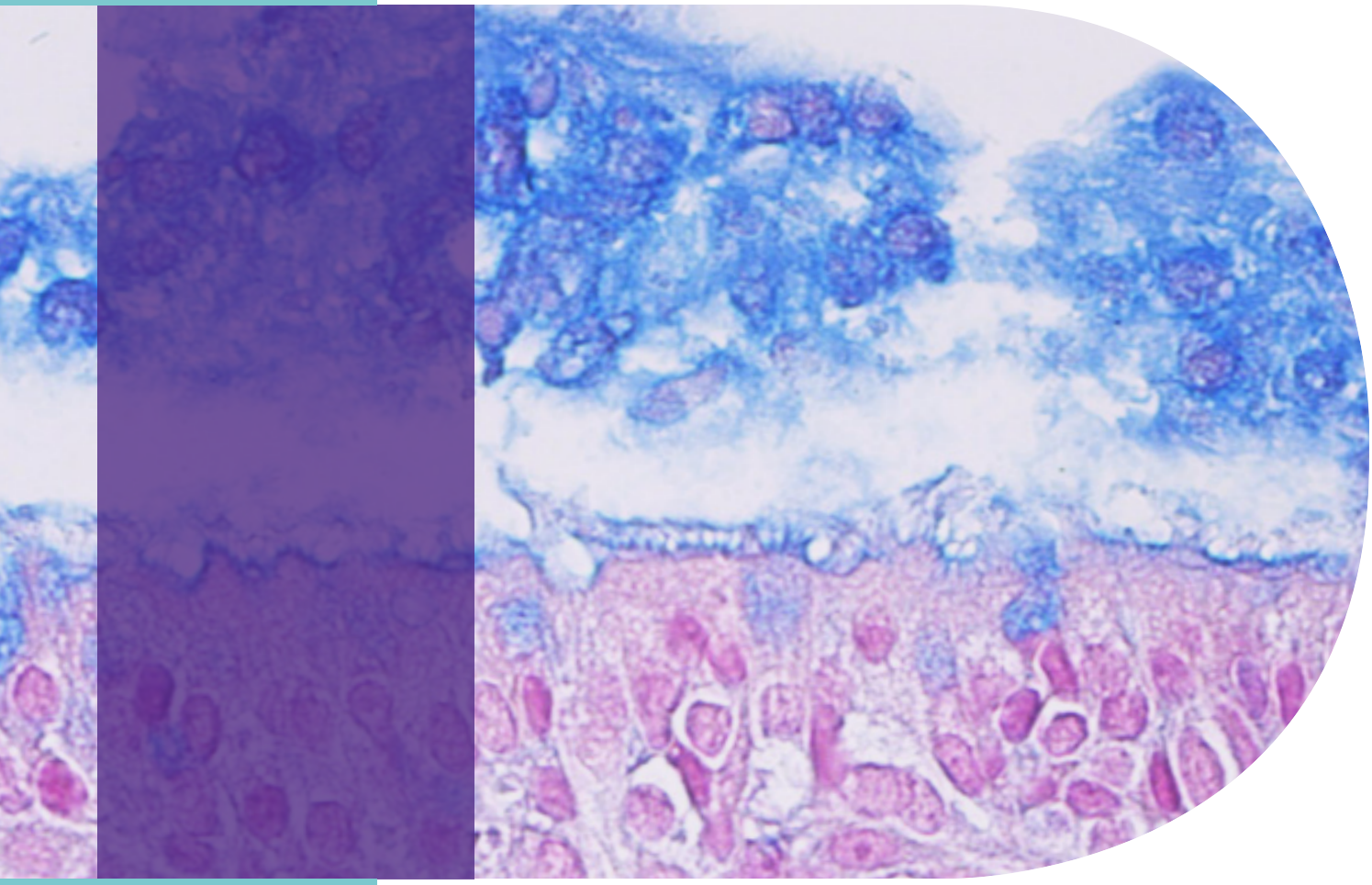
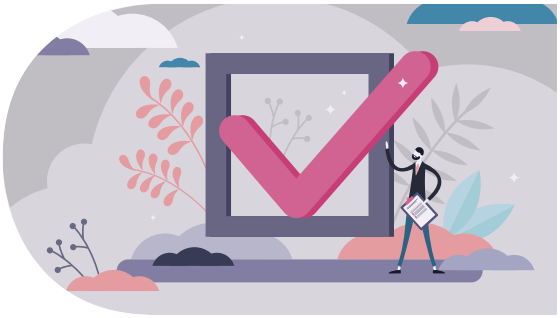
Medical Devices



Decongestant Efficacy on Nasal Epithelium

VitroScreen
Leading Innovation in Pre-Clinical Testing

VitroScreen's expertise to comply with MDR 2017/745



The new EU Medical Device Regulation 2017/745 (MDR) has defined more strict criteria for the quality and safety requirements of Medical Devices.

The following areas have been recognized as the key fundamentals within the pre-clinical evaluation:

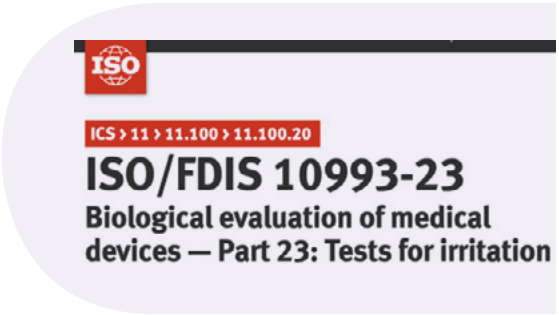
I. The choice of materials and substances used, particularly their toxicological profile.

II. The biocompatibility between the materials/substances used and biological tissues, cells, and body fluids taking into account the intended purpose of the device.

III. The need to demonstrate with sound experimental data the principal mechanism of action of the Device which cannot be pharmacological, immunological or metabolic.

IV. The MDR has made the point on the potential risks of medical devices composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body (*considerandum* 59 of MDR). It specifies when absorption, distribution, metabolism and excretion (ADME) have be to demonstrated (Annex 1 of MDR) and introduces how substance based MD have to be classified (Rule 21).

Biocompatibility according to ISO 10993-1 ISO 10993-23



VitroScreen carries out biocompatibility studies in compliance with GLP on 3D human tissue models for MD classes I, IIa, IIb and III.

To better address the MDR requirements and classification issues, VitroScreen has developed a robust approach for MD biological evaluation based on the endpoints identified in the ISO 10993-1:2018 and the new 10993-23 where, for the first time, an experimental protocol based on 3D human tissues has been validated. The approach on 3D tissues is applicable to all classes of MDs. It is more ethical and more predictive than other *in vitro/in vivo* methods.

Advantages:

- one single test covering both cytotoxicity and irritation potential
- the tissue model is selected on the basis of the intended use of the device and the part of the body involved
- it overcomes weaknesses and limitations of cell monolayer-based approaches and animal testing
- it is in compliance with Directive 2010/63/EU on animal experimentation

MD Biological Evaluation using *in vitro* approaches

	Endpoints	Biological models
Biocompatibility is performed with realistic in use doses and exposures	Cytotoxicity and irritation	3D reconstructed human epidermis, standard and injured (to address Class IIb requirements) Full thickness skin for long-term exposure (15 days)
		3D reconstructed human epithelia: Corneal, Vaginal, Oral, Oesophageal, Colorectal
		Intestinal models: Caco-2 mono layer and customized organoids
		Test methods
	Sensitization Potential	Validated OECD TGs: 442C, 442D, 442E EpiCS® IL-18 assay GARD®skin Medical Device: test applicable to MD developed for all therapeutic areas

Toxicological profile of ingredients: a new requisite

VitroScreen's Consultancy Unit, consistently with its mission of providing its Customers with high level *in vitro* Testing Strategies for Hazard and Risk Assessment, supports Medical Devices industries facing the new MDR and, in particular, provides:

- MD Raw Materials' toxicological characterization and safety assessment according to EN ISO 10993-1:2018 and following the process of an in-depth literature review as indicated in Annex C.
- Risk assessment on absorption, penetration and local distribution of devices composed of substances or of combinations of substances, that are intended to be introduced into the human body via a body's orifice or applied to the skin as required by Rule 21 of MDR.
- Toxicological expertise on the results of *in vitro* percutaneous absorption studies (OECD TG 428 and EFSA 2017 guidelines).
- Assessment of systemic exposure for the identified use and calculation of safety margins.

More on VitroScreen's Consultancy Unit

- Toxicological risk assessment of residual impurities from the manufacturing process (ISO 10993-18), products' degradation (ISO 10993-13/14/15) and substances extracted and/or released by the primary packaging in the MD (ISO 10993-17) including polymers (plastic/silicon), solvents, elemental and genotoxic impurities and definition of their safety limits.
- Biocompatibility Test Plan strategy development following 3R principles thus avoiding animal testing using Alternatives and *in silico* prediction.
- Biological Evaluation Plan and Design input within a risk management process in accordance with ISO 14971:2007 and Gap analysis to ISO standards.
- Interpretation of the results obtained in the biocompatibility and the overall biological safety in accordance with EN ISO 10993-1:2009 and the subsequent amendments.

To comply with Rule 21

VitroScreen's expertise and quality system assure a robust and comprehensive approach to ADME requirements as requested by the MDR and Rule 21 on substance-based MDs from the very beginning of the MDs' biological evaluation.

- A decision tree is established in agreement with the sponsor based on MD type, formulation, ingredients toxicological profile, mechanism of action and analytical method sensitivity and specificity allowing to define a science and risk based "testing" or "non testing" decision.
- **Absorption and penetration studies** are performed on human skin explants, 3D reconstructed human epidermis, full thickness skin, 3D human epithelia (oral, gingival, vaginal, ocular, bladder, nasal, bronchial, rectal and oesophageal mucosa) and intestinal models.
- The principles and quality requirements of the OECD TG 428 recognized as relevant "EU common, harmonized and scientifically valid standard method" are applied.
- Customized protocols are established according to MD Class, exposure, mode of use in order to quantify absorption, penetration and local distribution of the ingredient on intact and injured tissues.

READ MORE - www.vitroscreen.com/WEBVS/adme-studies

MECHANISM OF ACTION

The demonstration of the MD mechanism of action needs to be addressed in the technical file and before conducting clinical trials as a fundamental requirement within the MDR.

- VitroScreen's protocols on 3D reconstructed human tissue models allow to provide experimental evidences to **exclude pharmacological, immunological, metabolic (Ph.I.M.)** mechanism of action.
- These protocols are optimized for each specific therapeutic area.
- The protocols are ranked in 4 levels according to the complexity of the mechanisms to be demonstrated/excluded.

The main therapeutic areas where VitroScreen proposes standard and customized experimental protocols on 3D human tissues suitable to demonstrate the primary MoA and non-Ph.I.M. mechanisms are:

- **Dermatology**
- **Gastroenterology**
- **Gynecology**
- **Ophthalmology**
- **Oral Care**
- **Urology**
- **Respiratory tract**

4 LEVELS PROTOCOLS TO DEMONSTRATE THE MECHANISM OF ACTION

LEVEL 1: PHYSICAL, MECHANICAL, CHEMICAL MEANS	FILM FORMING on skin and epithelia (specific pH and exposures) and PERSISTENCY (long lasting)
	BOOSTING and PROTECTING EPITHELIAL BARRIERS
	MUCO-ADHESION
	ANTI-BACTERIAL ADHESION
	ANTI-VIRUCIDAL ADHESION (research in progress)
	PROTECTION AGAINST BACTERIA INDUCED DAMAGES
	ANTI-BIOFILM PROPERTIES and EFFICACY IN BIOFILM DISRUPTION
	PROTECTION FROM PHYSICAL STRESS: Ultraviolet A and B, IR and Blue Light
	PROTECTION FROM ENVIRONMENTAL POLLUTANTS, POLLEN, ALLERGENS
	PROTECTION FROM INDOOR POLLUTANTS
	CILIA BEATING, MUCOCILIARY CLEARANCE (partnered), PHAGOCYTOSIS (airway epithelia)
LEVEL 2: SUPERFICIAL ACTION NOT INTERFERING WITH TISSUES HOMEOSTASIS	MOISTURIZING EFFICACY: skin, mucosae, Dry Eye Disease
	ANTIMICOTIC EFFICACY on skin and nails
	RE-EPITHELIZATION and WOUND HEALING
	SOOTHING and DECONGESTANT EFFICACY (reconstructed human oral mucosa, reconstructed human nasal epithelium, oesophageal model)
	APTHOUS LESION on oral epithelium
	ANTI-FERMENTATIVE ACTIVITY, ANTI-CAVITY and ANTI-BIOFILM FORMATION on gingival mucosa
LEVEL 3: TO EXCLUDE Ph.I.M. MECHANISMS	Customized protocols to demonstrate the non-Ph.I.M. mechanism of action taking into-account: doses, kinetics, exposure and persistency on the site of action. Experimental designs are based on gene and protein's expression and include reference molecules.
LEVEL 4: TO SUPPORT MECHANISMS RELATED TO IMPLANTABLE AND INVASIVE DEVICES AT TARGET ORGAN LEVEL	VitroScreen ORA models: ENDOMETRIUM, CARTILAGE, PROSTATE, DERMIS, CORNEAL STROMA, HAIR FOLLICLE, ADIPE

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