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In-House Research - Whitepaper - Q1 2025

In Vitro Skin Irritation Assay: A Powerful Tool For Skin Irritation Of Chemical Compounds And Medical Device Extract.

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About Medistri

Medistri SA, a Swiss company established in 2006, plays a significant role in the medical devices and pharmaceutical industry. With a facility covering 13,193m² and a dedicated team of over 92 employees, Medistri offers specialized services including Sterilisation, Laboratory, Validation, Packaging, and Manufacturing.
With facilities in Domdidier, Fribourg, Switzerland, and Székesfehérvár, Hungary, Medistri operates 24/7 to support a range of clients, from startups to established enterprises.

Medistri is dedicated to enhancing healthcare product development and scalability. By providing crucial infrastructure and expertise, the company supports both new ventures and established organizations aiming for global expansion. Medistri's laboratory adheres to ISO 17025 standards and holds STS 504 accreditation, conducting a comprehensive range of tests for the Pharmaceutical, MedTech, and BioTech industries. This commitment ensures that products are developed and validated with the highest levels of accuracy and reliability.

To address common challenges in the Pharmaceutical and Medical Device industry, Medistri has prepared a Whitepaper focused on Skin Irritation, a frequent concern associated with Chemical Compounds and Medical Devices. This Whitepaper explores the underlying causes of skin irritation and offers practical strategies for prevention. It is intended to support companies in enhancing patient care and optimizing the performance of their Chemical Compounds and Medical Devices.

Medistri invites you to explore this Whitepaper as a resource for understanding and managing skin irritation in Chemical Compounds and Medical Devices. We hope it provides useful insights to assist in your efforts. For further information or to discuss how Medistri can support your projects, please feel free to contact us at contact@medistri.com.

— The Medistri Team

Medistri's Sterilization Chamber

In-House Medistri's Laboratory

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In-House Research

In Vitro Skin Irritation Assay: A Powerful Tool For Skin Irritation Of Chemical Compounds And Medical Device Extract

Skin irritation can manifest in various forms, including itchy, dry skin or a rash. The skin condition may be caused by medical pathology, but can also occur after prolonged or repeated contact of the skin to a chemical component. It is known as contact dermatitis. This whitepaper aims to provide a comprehensive overview of the skin structure and function, and the current methodology to evaluate skin irritation by chemicals. By understanding the underlying mechanisms of skin irritation and describing the most appropriate product evaluation techniques, this document provides valuable insights for healthcare professionals and individuals seeking to contribute to the development of safe medical devices.

Physiological Characteristics Of The Skin

Fundamentals Of The Skin

The skin is the body's largest and one of the most resistant organs, extending over 2m² and weighing up to 4 kg. It is composed of three main layers: the epidermis (the top layer), the dermis (the middle layer) and the hypodermis (the bottom layer), each of those layers having different functions.

The epidermis, which is directly in contact with external environment, acts as a protective barrier against bacteria and pathogens. This action is reinforced by the presence of Langerhans cells that are part of the immune system (macrophages) and help fight infections.

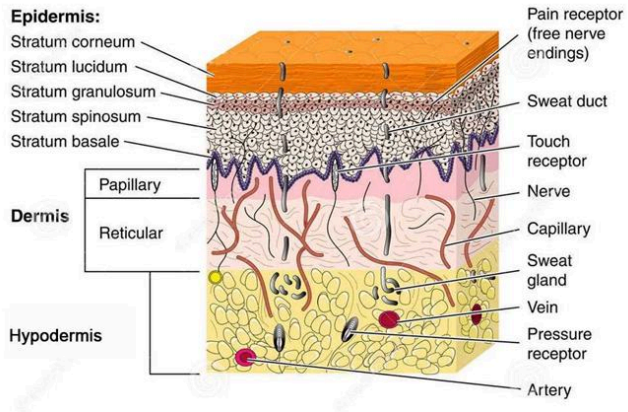

Figure 1 *- Schematic representation of the different skin layers. https://resolutionsforyou.com/epidermis-and-dermis-of-skin-diagram/*

The renewal of skin cells happens in the epidermis, more precisely in the basal layer. It takes up to 30 days for this layer to renew the entire skin of an individual. The cells present in the basal layer of the epidermis are also the ones responsible for the skin color, as they contain melanin.

The dermis is made up of elastic fibers, such as collagen and elastin, which give it the plasticity and flexibility it needs to maintain its structure. It is where the roots of the hair follicles, the blood vessels that bring nutrients to the epidermis by diffusion, and the nerves that conduct, among other roles, the information of pressure and touch, heat sensation and pain, are located. It produces oil to regulate water absorption and to keep the skin soft and smooth. It also releases sweat through skin pores to regulate the body temperature.

Finally, the hypodermis connects the skin to the underlying bones and muscles and supplies it with blood vessels and nerves. It consists of loose connective tissue, adipose tissue (fat) and elastin. Those tissues have different functions, such as energy reserve, thermal insulator (adipose tissue) as well as protection from shocks.

Skin Histology

The epidermis is a stratified, squamous, non-vascularized but innervated tissue (Fig. 1). It is made of four distinct layers[1]: the cornified layer (stratum corneum, outside layer), the granular layer (stratum granulosa), the spinous layer (stratum spinosum) and the basal layer (stratum germinativum, deepest layer).

The skin of palms and soles have a fifth layer, called the clear layer (stratum lucidum), located in between the stratum granulosa and the stratum corneum. The epidermis is composed of four different cell types: keratinocytes (80% of the cells) of ectoblastic origin, melanocytes form the neural crest, Langerhans cells from the hematopoietic marrow and Merkel cells derived from embryonic epidermal stem cells. The dermal-epidermal junction is particularly important to maintain dermal-epidermal adhesion. The basal cells of the epidermis connect to the dermis thanks to anchoring filaments and the superficial layer of the dermis connects to the epidermis thanks to anchoring fibrils.

The dermis has two zones: the papillary dermis (superficial layer), formed of loose connective tissue, and the reticular dermis (deeper layer), formed of dense connective tissue. These two areas are intensively vascularized and innervated (Fig. 1). Its connective character comes from its composition of protein-type macromolecules, mucopolysaccharides and various cells including fibroblasts and cells of the immune system (lymphocytes, mast cells, tissue macrophages). Collagen, elastin and fibronectin fibers give the skin suppleness, elasticity and tissue structure. The mucopolysaccharides form a gel containing macromolecules. This gel acts like a sponge, capturing water molecules from the dermis, and thus acts as a hydration reservoir.

The hypodermis is a subcutaneous tissue constituted of loose connective tissue, blood vessels and nerves and is a major site of fat storage in the body (Fig. 1). The adipocytes forming the subcutaneous fat are grouped together in lobules separated by connective tissue. The thickness of the hypodermis varies depending on its location on the body; the trunk (posterior and anterior), the buttocks and the legs are the body parts having the thicker layer of subcutaneous fat[2].

Skin Barrier

The skin forms an effective barrier between the body and the environment, preventing the invasion of pathogens, repelling chemical and physical aggression, and uncontrolled loss of water and solutes. The physical barrier is mainly located in the stratum corneum and consists of a continuous sheet of corneocyte cells enriched with cytoskeletal elements, desmosomes and lipid-enriched intercellular domains. The epidermis also contributes to the barrier through tight junctions, gap junctions and adhesion junctions, as well as desmosomes and cytoskeletal elements[4]. Lipids synthesized in keratinocytes are extruded into the extracellular domains, where they form lipid-enriched extracellular layers. The barrier function is largely influenced by human individual properties, anatomical sites and age, as sweating and hydration is naturally reduced in older individuals. Despite its incredible barrier abilities, some substances can penetrate the deeper layers of the skin and even be absorbed into the bloodstream.

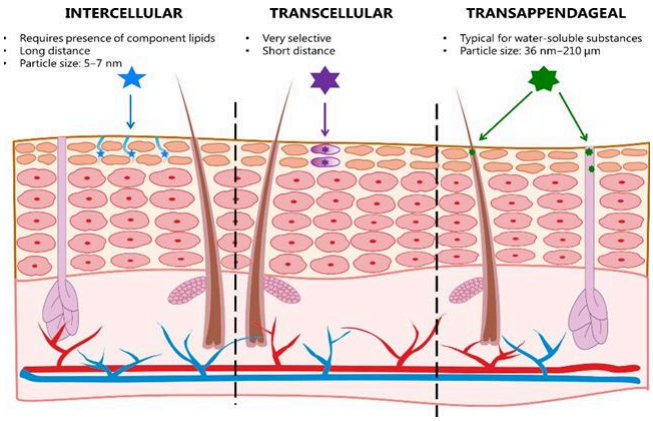

Figure 2 *- Schematic representation of skin penetration pathways[5]*

There are three main pathways that can be used by substances to penetrate the skin: 1) the intercellular (or paracellular) pathway, 2) the transcellular pathway and 3) the transappendageal pathway (Fig. 2). The intercellular pathway involves the transport of substances between the external epidermal layer cells (stratum corneum). The compounds penetrating the skin through this pathway have to be lipophilic and should not be bigger than 5-7 nm in order to stay intact during the diffusion through the skin[3]. The transcellular pathway involves keratinocytes in the transport of very selective substances through both the phospholipid membranes and the cytoplasm of the dead keratinocytes that constitute the stratum corneum. This pathway limits the penetration of compounds to short distances[5]. The transappendageal pathway involves various appendages, such as sweat and sebaceous

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glands or hair follicles and is a typical route for the penetration of big (up to 210 µm) water-soluble substances[6]. It is considered as the least significant penetration passage, as the appendages cover only 0.1 % of the skin surface. Those weaknesses in the barrier properties of the skin can lead to inflammatory responses such as skin irritation and activate a myriad of downstream molecular pathways.

Main Skin Pathologies

The clinical signs of cutaneous irritation consist mainly of itching, pain, burning, erythema (redness), oedema and small papules (small red circles with a white center) on the skin (Fig. 3).

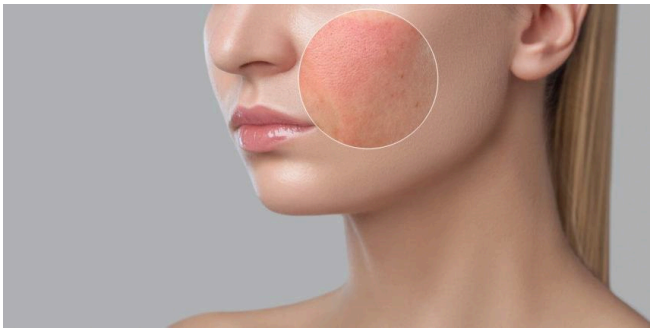

Figure 3 *- Example of Skin Irritation*
https://faceclinicslondon.com/blog/skin-inflammation-ultimate-guide-london/

Inflammation of the affected tissue is limited to the epidermis and the upper layer of the dermis. The skin irritation induced by the single or repeated application of a chemical substance to the same skin area, is usually a non-immunological local inflammatory reaction. It can possibly become an allergic reaction, mediated predominantly by T-cell response[7,8]. Chemicals or metal ions may exert direct irritant and toxic effects on the skin, or small reactive chemicals, called "contact allergens", may modify the proteins present in the skin and induce an immune response. Thousands of substances can cause an allergic response (more than 4000 contact allergens have been identified). The skin response to those "contact allergens" is clinically characterized by the term "contact dermatitis" (also called eczema). This contact dermatitis can have several origins, such as irritant contact dermatitis, allergic contact dermatitis and photodermatitis (pathology that is triggered by an interaction between the skin, a more or less harmful substance, and ultraviolet radiation). About 15% of the adult population is estimated to suffer from contact dermatitis once in their lifetime[9] and it accounts for 95% of occupational skin disorders[10].

Molecular Mechanisms In Contact Dermatitis Induced By Chemicals

When the skin is exposed to irritants, it activates a complex biological process involving immune signaling and cellular interactions. A key factor in this process is the cytokine interleukin-1α (IL-1α)[11], which plays a central role in initiating the skin's inflammatory response. The skin's reaction to irritants depends on the type and concentration of the irritant. Disruption of the epidermal barrier leads to the release of various immune mediators, including IL-1α, which contributes to the onset of skin inflammation and triggers repair mechanisms[12]. The repair process begins with the loss of water from the damaged epidermis, which results in a decrease in calcium levels in the stratum granulosum. This triggers a cascade of homeostatic processes that work to restore the skin's barrier. Lipid production and secretion of lamellar bodies are part of this recovery, helping to rebuild the skin's lipid barrier[13]. Nitric oxide (NO) also plays a critical role by regulating calcium levels, further aiding the repair process[14]. In allergic conditions such as contact dermatitis, the immune system response is more complex. Key proteins like IL-1β promote the activation and adhesion of immune cells, which contribute to inflammation. T cells, including both CD4+ and CD8+ subtypes, are crucial in recognizing allergens and regulating both inflammatory and anti-inflammatory responses[15]. In allergic conditions such as contact dermatitis, the immune system response is more complex. Key proteins like IL-1β promote the activation and adhesion of immune cells, which contribute to inflammation. T cells, including both CD4+ and CD8+ subtypes, are crucial in recognizing allergens and regulating both inflammatory and anti-inflammatory responses[16], while others help controlling the inflammation. Recent studies also suggest that natural killer (NK) cells play a role in skin responses to irritants and allergens. These immune cells can infiltrate inflamed skin and influence the skin's

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immune response, contributing to the overall inflammatory and repair processes[17]. While the mechanisms of skin irritation and allergies are becoming clearer, ongoing research is focused on identifying specific biomarkers to improve diagnosis and treatment[18].

Reconstructed Human Skin Model, An Alternative

Skin Irritation Testing

Skin damage can be caused by different chemical agents (alkaline and acidic solutions, organic solvents, surfactants), or physical agents (UV radiation, heat, cold and mechanical factors). Medical devices developed by MedTech may be manufactured from new materials or from raw materials that have been tested but whose construction phases have involved chemical agents of proven toxicity. For this reason, regulatory bodies require extensive testing before products are placed on the market. The norms ISO 10993-10 and 10993-23 give guidance for skin irritation testing. To respect animal welfare, it is now recommended not to use animal models when in vitro models can be tested.

Alternative methods to animal experimentation have been developed in vitro for toxicology research and cosmetic industry. Companies have developed reconstructed human skin models and both EPISKINTM and EpiDermTM models reliably identify irritating chemicals[19]. They both meet the standards set by the Organization for Economic Co-operation and Development (OECD) adopted in 2010, test guideline[20] number 439, and are further recommended by ISO 10993. The European Centre for the Validation of Alternative Methods (ECVAM) has validated MatTek's Reconstructed Human Epidermis (RHE) method[21] as a complete alternative to the Draize test for skin irritation. The principle of the in vitro irritation test in a reconstructed skin model assumes that irritant chemicals can penetrate the stratum corneum by simple diffusion and are cytotoxic to the cells in the underlying layers. The assay directly covers the initial stage of the inflammatory cascade and mechanism of action (cellular and tissue damage causing localized trauma) occurring during irritation in vivo. Assay corresponds to endpoint measurement of cell viability by colorimetry. Moreover, the determination of the production of the inflammatory mediator Il-1a by the epidermis may increase the sensibility of the test and the confirmation of a negative response.

EpiDermTM Model (MatTek)

MatTek is an American (also based in Europe) provider of in vitro solutions for safety and efficacy assessments and a world leader in 3D reconstructed human tissue (RHE). In November 2008, ESAC (ECVAM Scientific Advisory Committee) concluded that the Modified EpiDerm™ SIT had sufficient specificity (77.4 % and 77.1 % for EU DSD and UN GHS / EU CLP, respectively), sufficient sensitivity (83.3% and 94.1 % for EU DSD and UN GHS / EU CLP, respectively) and sufficient accuracy (80 % and 78.2 % for EU DSD and UN GHS / EU CLP, respectively)[22]. MatTek RHE (Fig. 4) is an in vitro reconstructed human epidermis model, consists of normal human keratinocytes cultured in chemically defined medium, until epidermis maturity (functional barrier function), on an inert polycarbonate filter at the air-liquid interface[23].

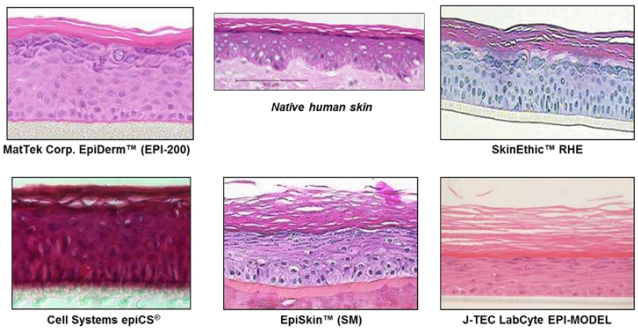

Figure 4 *- In Vitro reconstructed human epidermis (RHE) Models validated for regulatory purposes Skin Irritation Test (SIT, OECD 439)[20]*

The cultures have a stratified epidermis with a functional stratum corneum above the basal, spinous and granular layers, mimicking the architecture of normal human skin and allowing direct topical application of products. It is histologically like the human epidermis in vivo. The MatTek model contains the main structures of human skin. By electron microscopy, structures such as hemidesmosomes with plaques were identified as well

as components of the lamina densa (referred previously as the basal lamina) and anchoring filaments. The general lipid composition of the MatTek model is quite similar to normal human epidermis. Some variations are nevertheless present in the model; free fatty acids and cholesterol esters are present in lower amounts in the model, and glucosylceramides are present in higher quantities. The ceramide profile of the model is comparable to human epidermis with the presence of ceramide 2, 5 and 6, ceramide 7 is the only one absent in the model[23]. A lipid composition as close as possible to that of the native tissue is desirable because it determines its permeability, flexibility, and other aspects of skin biology. Biochemical markers, called "differentiation markers" are expressed in the reconstructed epidermis and are specific of the different layers that constitute the tissue. For example, Involucrin, a protein precursor of the cornified envelope, as well as transglutaminase and keratin 1, 10 and 6 are especially expressed in granular cell layers. Loricrin, skin-derived antileukoproteinase (SKALP) and Small Proline Rich Protein 2 and 3 (SPRR2 and 3) are found in upper granular layers[23].

In summary, the general structure of the epidermis in this in vitro model is very similar to that of the human epidermis. Moreover, a seven laboratory Round Robin study to evaluate reconstructed human epidermis models for an in vitro skin irritation test showed the robustness and transferability, due to its simplicity of the test for detecting irritant activity on medical device extracts[24].

Procedure For Reconstructed Skin Assay: Skin Irritation Test (SIT)[25] And Skin Irritation From Medical Device Extract (MDE)[26]

MTT Assay Principle (SIT And MDE) And Experimental Procedure

Once the EpiDerm™ tissues reach full maturity (Fig. 5A), they can be exposed to either the chemical compounds (STI) or the medical device extract (MDE) intended for testing. After the designated exposure period—24 hours for STI and 18 hours for MDE—the tissues are thoroughly rinsed, and the MTT assay is performed. If the compound is strongly pigmented or interferes with the MTT assay, appropriate corrections can be applied to the data. The detailed procedures are described in the OECD test guideline[20] number 439, and ISO 10993.

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) reduction assay was originally proposed by Mosman in 1983[27] and has since been widely adopted to evaluate cells and tissue viability. The MTT salt is a yellow compound that is converted by metabolically active cells to a blue or purplish compound with a maximum absorbance at 570 nm (Fig. 5B). The exact cellular mechanism that catalyzes the reduction of MTT to formazan has been extensively studied, and several cellular enzymes are thought to be involved in the reaction. Formazan formation occurs mainly in the cytoplasm, in the mitochondria and at the cell membrane[28]. Formazan accumulates in the cell close to the cell surface and in the culture medium as insoluble crystals. They are solubilized with acidified isopropanol (0.04 N HCl in 70% isopropanol), DMSO or dimethylformamide and the absorbance is quantified at 570 nm wavelength with a spectrophotometer or a microplate reader.

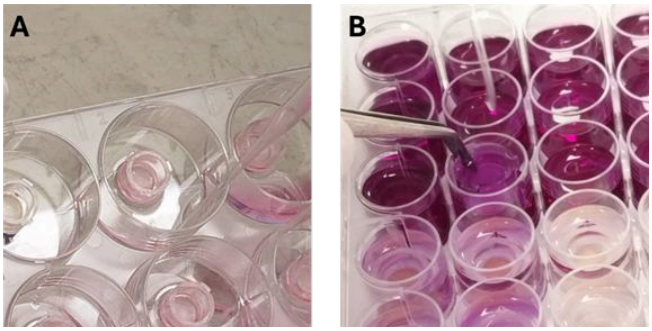

Figure 5 *- A) RHE tissues in culture medium; B) MTT assay, the purple color comes from the reduction of the MTT to Formazan. As only living cells are able to do this reduction, a darker color suggests that the compound (or MDE) is NOT irritant, whereas a lighter color indicates an irritation reaction.*

If the cell viability is quantified ≤ 50%, then the test substance is classified as irritant (Category 1 or 2). To further classify the irritant into subcategories (1A, 1B, 2A, 2B), a skin corrosion test may be conducted. Skin corrosion refers to the irreversible damage or destruction of skin tissue caused by exposure to a corrosive substance. While the assay principle is similar to that of STI and MDE, the contact time is shorter for the skin corrosion test, as the substance is already known to be irritating.

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Other models and assays are available, allowing the testing of specific human tissues, such as cornea, intestinal tissue, kidney tissue, nasal tissue, and many more.

Medistri aims to integrate, as a starting point, the Skin Corrosion Test using the EpiDerm™ model into our laboratory's testing capabilities, reinforcing our commitment to ensuring the safety and integrity of our clients' products.

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Conclusion

Introducing new products to the market, such as medical devices, must comply with specific standards defined by the notified bodies of the different countries. Medical devices are governed by the ISO 10993 standard and devices in contact with the skin are regulated by chapters 10 and 23 that cover irritation tests. Traditionally, animal models have long been used to assess the toxicological effects of new chemical molecules or new materials. However, these models have shown their limitations (they reflect poorly the effect on human physiology) and alternative methods to animal experimentation are gradually being introduced. The development of cell-based products of human origin eliminates the need to extrapolate from animal studies to humans, as it is possible to use adult human cells to create 3D cell models. This is the case with the reconstructed skin model from human adult keratinocytes. The EpiDerm™ model has been validated to replace the Draize test for skin irritation and is now implemented at Medistri. This in vitro model allows for better turnaround time compared to the in vivo analyses (about a week time for the assay), as well as greater scalability. By using this approach, we are committed to applying the 3Rs principles (Replace, Reduce, Refine) and limiting in vivo analyses as much as possible, in order to respect animal welfare. By continually expanding its laboratory capacity and testing offering, Medistri aims to provide a wide range of analyses to more fully meet the needs of its customers.

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About the Author

With over eight years of experience in Biology, Dr. Jordan joined Medistri in 2023 as a Biology Technical Expert Assistant. In her role, she supports the development of laboratory protocols and reports, oversees the implementation of new analytical methods, and plays a key role in ensuring the scientific accuracy and regulatory compliance of testing procedures.

At Medistri, she regularly works with the different endpoints of ISO 10993-1, providing guidance to pharmaceutical and medical industries. Driven by a passion for scientific integrity and patient safety, Dr. Jordan brings a pragmatic and research-based approach to Medistri's laboratory operations.

The Medistri Lab team's expertise spans across biocompatibility testing, microbiology, chemical characterization, and method validation, ensuring compliance with international standards such as ISO 10993 and ISO 17025. Medistri Lab and its team of experts support manufacturers and regulatory professionals in navigating the evolving landscape of biocompatibility assessments with confidence, clarity and regulatory compliance.

The team's commitment to precision, reliability, and continuous improvement reflects Medistri's broader mission to deliver integrated solutions that meet the highest standards of safety and quality in pharmaceutical and medical device testing.

Dr. Aurore Jordan
Biology Technical Expert Assistant, Medistri

Dr. Jordan holds a PhD in Biology from the University of Fribourg (CH), where her research focused on the Neurogenetic and Behavioral aspects of pain perception. Before joining Medistri, she worked in Academia, contributing to research in both behavioral and cellular responses. Her background combines a deep understanding of biological systems with practical experience in laboratory environments, making her a valuable contributor to the advancement of Medistri's testing capabilities.

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About Medistri

Founded in 2006, Medistri has been focused on building infrastructure for the healthcare industry. Companies of every size, from startups & university projects to Fortune 500 companies use our services to save time, scale and focus on what they do best. Medistri combines all its technical infrastructure together and places quality at the heart of our day-to-day operations. Allowing you to simplify your supply chain management and focus on growth.

Laboratory Infrastructure

- Chemistry
- Biocompatibility & Toxicology
- Sterility Assurance
- Extractables & Leachables

Manufacturing Infrastructure

- Product Assembly
- Custom Packaging Solutions
- Quality Control & CE Marking
- Labelling & Distribution

Sterilisation Infrastructure

- Steam Sterilisation
- EO Sterilisation

Validation Infrastructure

- Sterilisation Validation
- Cleaning Validation
- Process Validation
- Disinfection Validation

Packaging Validation

- Transport Simulation
- Sterile Barrier Integrity Testing

At Medistri, we've built the infrastructure that tomorrow's healthcare companies need today. By combining sterilisation, laboratory, validation, and manufacturing services under one roof, we help you move faster, simplify complexity, and bring your products to life — all while maintaining the highest standards of precision and quality.

Contact us at customerservice@medistri.com to explore how Medistri can help accelerate your next development.

Medistri is continually innovating its **in-house** range of services. We're expanding our infrastructure to offer a completely integrated stack of services for healthcare companies. Organisations of every size — from startups to large enterprises use our suit of services to start, grow & optimise their business.

Within our site located at the heart of Switzerland, Medistri **combines all its technical infrastructure together** and places quality at the heart of its day-to-day operations. Allowing you to simplify your supply chain management, focus on growth & maintain excellence.

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