



Meeting Report

VitroScreen Seminar – Substance-Based Medical Device Qualification and Classification: Pre-clinical Approaches to Mechanism of Action

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Open discussion with Notified Bodies and MD authorities during VitroScreen Seminar

On February 9, 2023, in Milan, VitroScreen, a research laboratory committed to the application of *in vitro* preclinical testing methods and new approach methodologies (NAMs) in different regulatory contexts, organized a hybrid scientific seminar to open a discussion on the qualification and classification issues for substance-based medical devices (SBMDs).

According to the Medical Device Regulation (EU) 2017/745 (MDR), manufacturers are requested to report in the technical file the rationale for the qualification of their products as devices and to justify by state-of-the-art scientific data the principal mode of action (MoA) of such devices. In particular, the demonstration of the principal MoA is crucial for devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin or epithelia and that are absorbed by or locally dispersed in the human body. For product qualification and classification of SBMDs, clear information supporting the principal MoA should be provided through different options: i) literature research, ii) pharmacotoxicological expertise on functional substances, iii) experimental studies, iv) clinical data. All this evidence can be used separately or in a complementary way to support product qualification and to apply correct classification.

The seminar's aim was to stimulate a discussion with stakeholders of the medical device (MD) industry (health authorities, notified bodies, academia, industry, and International Organization for Standardization representatives) on the MDCG 2022-5 guidance on borderline products analyzing the available state-of-the-art

scientific approaches to provide evidence on the principal MoA of SBMDs and through such evidence respond to MDR requirements.

Dr **Marisa Meloni**, VitroScreen's founder and CEO, welcomed the participants to the seminar and highlighted the critical moment the medical device industry is facing: In order to respond to the MDR requirements, efforts are required not only by manufacturers but also by notified bodies and competent authorities. The seminar's goal was to have a transparent, open, and constructive discussion among the various actors, to share experiences and critical issues, and to seek answers from different perspectives. Dr Meloni emphasized VitroScreen's commitment to develop and validate experimental protocols adapted to the MD sector to ensure safety and efficacy for patients.

Dr **Giulia Magri**, Quality and Regulatory Affairs manager, Confindustria Dispositivi Medici, Italy, gave a lecture entitled "Introduction to MDCG 2022-5 and industry perspectives". This guideline, which revises the previous MEDDEV 2.1/3 REV.3 on the border between MDs and medicinal products, addresses some strategic topics for the sector of SBMDs and, if maintained in the current state, will pose significant issues for companies (510 in Italy) manufacturing SBMDs. The first concern regards the definition of the pharmacological MoA proposed in the MDCG 2022-05, which broadens its concept, risking to affect the qualification of products that are currently considered MDs, potentially leading to an unintended exclusion of many devices from the scope of the MDR without an alternative market assessment route. The second critical aspect regards the concept of "*a substance which, if used separate-*



ly, would/may/can be considered a medicinal product” and “that has an action ancillary to that of the device”. Without an appropriate interpretation, there is the risk that application of rule 14 of MDR is extended to consider any device containing a substance that can be used as a medicinal product as class III, without considering, for example, the amount of such substance contained in the device. The third aspect regards the classification criteria proposed in the MDCG 2022-5 for products containing medicinal plants that would make it impossible to use complex natural substances for the development of SBMDs or use them in therapy unless resorting to so-called traditional use. Indeed, as they are complex substances, their MoA cannot be traced back to a single constituent and, therefore, to a pharmacological mechanism, which occurs when a well-defined (purified) molecule interacts in a targeted way with a single cellular constituent. The result would be the loss of new therapeutic opportunities and a block of any form of research and innovation. Dr Magri concluded that a collaboration between all relevant stakeholders is fundamental to overcome the discrepancies introduced by the MDCG 2022-5 and prevent a non-legally binding document (as a guideline) from distorting the intentions of the European legislator who, since 2017, has widely recognized the value of SBMDs, providing specific requirements and a dedicated classification rule.

Dr **Laura Ceriotti**, regulatory specialist, VitroScreen, spoke on “Pre-clinical efficacy on 3D reconstructed tissue models: case studies” (Tab. 1). The potential application of VitroScreen’s 3D fit-for-purpose models to provide evidence on the principal MoA of SBMDs on the relevant tissue on which they are intended to act was shown based on case studies. As a relevant example of mechanical means, the protocol to quantify the film-forming properties of SBMDs was presented on reconstructed human epidermis (Casiraghi et al., 2017) and on esophageal epithelium (Ceriotti et al., 2022; Meloni et al., 2021). A newly developed model on 3D colon epithelium applied to assess a glycerin-based and a macrogol-based product was presented, suggesting that morphological evaluation can be used to support the difference in the MoA of the two products due to the physicochemical properties of their constituents. To address ancillary action, an inflammatory model developed by optimizing the exposure of a reconstructed human epidermis model to sodium dodecyl sulfate (SDS) was presented: the presence or absence of ancillary action is important for the correct classification of the medical device.

Dr **Laura Brambilla**, microbiology specialist, VitroScreen, introduced the Microbiome Research Unit committed to the development of colonized tissue models to investigate short- and long-term host-bacterium interaction. She highlighted the interest to investigate and demonstrate by scanning electron microscopy analysis the prevention of *E. coli* adhesion and biofilm formation in the absence of antimicrobial activity on reconstructed human epidermis and bladder epithelium for MDs intended for the prevention of recurrent cystitis. A new approach using a millifluidic system applied to 3D tissues (MIVO, React4Life) was introduced to perform bacterial colonization in dynamic conditions, simulating the fluid dynamic context occurring *in vivo*.

Dr **Francesco Carriero**, histology specialist, VitroScreen, presented a successful application of the VitroScreen histomorpholo-

gy platform: a wound healing model on full-thickness skin models infected with methicillin-resistant *S. aureus* developed within the international project EuroStars E! 113238 Lyse-EFEKT.

Dr **Maria Grazia Leone**, pharmacologist, Directorate General of Medical Devices and Pharmaceutical Services, Italian Ministry of Health, delivered a presentation entitled “MDCG 2022-5: the qualification process” focused on the definition of pharmacological means for which, according to both MEDDEV 2.1/3 rev.3 and MDCG 2022-5, two sequential steps are foreseen: the interaction between the substance and a constituent of the human body, and ensuing signal transduction. This means that within the pharmacological MoA, the interaction by itself is not sufficient to determine the therapeutic effect, which is mediated by the subsequent signal transduction pathway (specific interaction). On the contrary, the MD’s MoA is based on a simple interaction sufficient to determine a therapeutic effect without triggering signal transduction (generic interaction) (Leone, 2022). However, in practice, the demarcation between pharmacological and physical/mechanical MoA is not always clear, for example in the case of laxative products, e.g., macrogol, for which a discussion is ongoing at European level. There are cases at the European Court of Justice on product qualification which are still open: Should the primacy of the regime governing medicinal products in accordance with Art 2.2 of Directive 2001/83/EC be applied to these cases? New *in vitro* but also *in silico* models are welcome to assess the MoA of SBMDs. This is particularly relevant for herbal products, for which, being multicomponent mixtures, it is difficult to identify all the different components and the active component responsible for the principal MoA. Furthermore, there could be synergies between different substances, some even at very low concentrations, that need to be taken into consideration and for which the product as a whole should be tested. Dr Leone suggested to make scientific data available to the European authorities and to all the actors involved in the MD sector as a basis for sound scientific regulatory decisions and to foster innovation.

Dr **Alessia Frabetti**, biologist, Director Medical Device Division Kiwa Cermet, introduced two fundamental topics for SBMDs according to the MDR: 1) product qualification with the demonstration of the principal MoA not achieved by pharmacological, immunological or metabolic (Ph.I.M.) means and 2) safety and quality requirements for which preclinical data (kinetic aspects, toxicology, and interaction with other substances, drugs, MD) are requested. Specifically, due to the heterogeneity of SBMDs and the fact that there could be a close correlation with products belonging to different sectors (e.g., pharma, cosmetics, food supplements), MD qualification is fundamental during the R&D phase to describe the principal MoA with scientific and objective evidence justifying their non-Ph.I.M. means. Manufacturers should seek this evidence based on the knowledge of the MD components and the state-of-the-art of the production process and discuss critically such evidence, on a case-by-case basis together with experts (biologists, pharmacologists, toxicologists, chemists). According to Dr Frabetti, the first hurdle during product qualification is the correct interpretation and distinction between the therapeutic effect of the product and its MoA, which often are confused. The MoA relates to where (site of action) and how the product (its constituents) in-

Tab. 1: Experimental models on 3D reconstructed human tissues to provide evidence on physico-chemical-mechanical MoA of SBMDs

Means by which the MD acts	Experimental model	Test system
Mechanical	Film-forming and persistency properties	Reconstructed human epidermis, esophageal, oral, gingival, corneal, nasal, vaginal, bladder epithelium, intestinal models
	Protection from acid damage	Esophageal epithelium
	Antibacterial adhesion	Reconstructed human epidermis, oral, gingival, corneal, nasal, vaginal, bladder epithelium
Chemical	Decongestant activity	Oral, corneal, nasal epithelium
	Moisturizing efficacy	Reconstructed human epidermis, vaginal, corneal epithelium
	Laxative function	Colon epithelium
Physico-chemical	Control of bacterial growth	Microdilution on agar plate

teracts with the body (its components). The therapeutic effect is the result produced by/after product interaction. For herbals and complex formulations (chemical with herbal/biotechnology constituents), a high number of molecules acting in synergy, often generating more than one mechanism of action, can be involved, and their mechanisms should be assessed on the entire product and not on its constituents. For these formulations, literature data may not be sufficient, and tests are needed (chemical characterization, ADME, etc.), also to demonstrate quality and safety. The involvement of experts is essential for both product qualification and toxicological assessment.

Dr **Chiara Novi**, project manager and product assessor, TÜV Rheinland Italia, mentioned the difficulties encountered by manufacturers in providing evidence on the MoA from the notified body's perspectives: i) The action and role of a specific ingredient in the whole are not clearly identified; ii) the actual working principle underlying the MoA is not well known; iii) the claims stated are not really proven and demonstrable; iv) equivalence evidence with MDs that are already on the market is absent. To overcome these issues, the manufacturer is requested to use scientifically published data, data present on other technical and scientific regulations/legislation such as the *European Pharmacopoeia*, EMA, and others, opinions from experts in the field (e.g., clinicians, pharmacologists), information on similar formulations, but most importantly data on one's own formulations (both single ingredients and, also, the overall formulation). The data collection must be conducted in a critical way and according to the documented procedure that the manufacturer has implemented in their quality system. She concluded that, in case of testing, the complete formulation must be considered, the tests must be designed by experienced personnel, and the conditions of clinical use, mode of intake, and target anatomical site should be taken into consideration. Moreover, the test results must be taken in charge by the manufacturer in collaboration with sector experts (i.e., toxicologist, pharmacologist, chemical analyst) able to explain the data obtained and the relative considerations.

Dr **Alessandra Sepe**, coordinator of the Medical Devices Operating Unit, Istituto Superiore di Sanità, focused on Rule 14, with reference to the ancillary action as presented in MDCG

2022-5. According to this guideline, the ancillary action of a substance must be based on scientific evidence, regardless of the purpose for which the manufacturer has added it to the device. In the evaluation of the ancillary activity, it should be considered whether a device would perform its function even in the absence of the substance or if this function is performed only thanks to the presence of the ancillary substance. The amount of substance available to the human body must be taken into consideration when assessing the ancillary activity of the substance, and its bioavailability should be demonstrated. If the ancillary action is not demonstrated, Rule 14 is not applied, and no benefits brought by the substance itself can be claimed (Art. 7, MDR). In case of a consultancy procedure for "legacy devices", manufacturers must provide non-clinical and clinical documentation on quality and safety of the substance. Regarding herbal products, according to the MDCG 2022-5, if it is demonstrated by the manufacturer that a substance of plant origin achieves its intended main action by means other than Ph.I.M., the product could be qualified as a MD. In particular, if the action of the herbal constituent is ancillary, and if the principal intended action is achieved by physical or mechanical means, the product may also be qualified as MD. In all cases, the principal MoA of the product and any ancillary activity must be investigated for proper product qualification.

Prof. **Alessandra Semenzato**, professor at the Department of Pharmaceutical Sciences, University of Padova, gave a presentation entitled "Looking for a common perspective" on the importance a formulator has in the MD sector. The knowledge about the physiopathology of the human skin and mucosae is continuously evolving; therefore, formulators need to bring together possible novel curative approaches with regulatory requirements. Topical products for the skin and mucosae that can be used as drug adjuvants are formulated as MDs or as cosmetic products, according to the respective regulation, but they are often not perceived as different products by most patients and physicians. To respond to the new MD regulatory context, all the players involved (R&D formulators, notified bodies, testing facilities) must look at the specificity of MDs, taking into account the complex scenario of healthcare products (topical drugs, cosmetics, food supplement). MDs provide a complementary, not equal, action to medicinal



products. For example, barrier cream MDs are considered a fundamental baseline treatment for atopic skin because if used continuously they improve the patient's quality of life and reduce the need for pharmacological (e.g., anti-inflammatory) treatment. Furthermore, barrier creams can guarantee safety on injured skin during repeated and long-term use. A topical medical device for skin and mucosae requires a very different formulation approach from that of topical drugs, where the active pharmaceutical ingredient is the heart of the formulation and the excipients are selected to promote its bioavailability. The effectiveness of an MD is generated by the combination of all functional ingredients (including excipients and emulsifiers, which also contribute to the efficacy) and in particular by those which, due to their film-forming properties, protect skin and mucosae, stimulating and improving their physiological barrier properties; this approach is closer to the formulative cosmetic approach than to the pharmaceutical approach.

Dr **Christian Pellevoisin**, PhD, ERT, Scientific Director MatTek Corporation, Convenior ISO/TC-WG8, Chairman AFNOR S92J, delivered a lecture entitled "Updates on ISO activities", presenting the ongoing activities in the ISO technical committee 194 (ISO TC194) to update ISO standards on the biological (ISO 10993) and clinical (ISO 14155 and 18969) evaluation of medical devices. He highlighted the ISO/TC Working Group 8 activities for integration of non-animal methods: Tests for irritation (ISO 10993-23:2021), tests for skin sensitization (ISO 10993-23:2021), and ISO/DTS 11796. Such activities allowed to validate *in vitro* methods for irritation of medical device extracts using reconstructed human epithelium (RhE) by adapting methods previously validated in the cosmetics and chemical sector (OECD TG 439). The ISO 10993-23:2021 standard is now also implemented in countries outside the EU, including Japan and China, but not yet by US FDA, who, however, recently committed to exploring and evaluating alternative methods to replace laboratory animals in developing new drugs and products (FDA Modernization Act 2.0). While ISO 10993-23 has replaced rabbit irritation tests with *in vitro* methods, it still recommends *in vivo* irritation tests to assess the irritation potential of MDs in contact with mucosal membranes (e.g., eyes, penis, oral, rectal and vaginal mucosa). Some publications are available on the use of 3D models on these mucosal tissues to evaluate *in vitro* ocular (Meloni et al., 2019; Yun et al., 2016), vaginal (Ayehuni et al., 2018; Sica et al., 2022), and oral (Yang et al., 2021; Aizawa et al., 2023) irritation of MDs; together with methods validated for eye irritation potential of chemicals (OECD TG 492, 492B), these could represent potential *in vitro* methods for MD assessment. In the case of skin sensitization, ISO TS 11796 has recently been approved and will soon be published to drive qualification for MD assessment of OECD methods already validated with and for neat chemicals (as described in Annex C of ISO 10993-10:21). According to Dr Pellevoisin, the definition of the requirements for interlaboratory studies to demonstrate the applicability of validated methods to MDs should accelerate their qualification and their regulatory acceptance, reducing the MD sector's dependence on animals.

The seminar was attended by 87 participants from Italy, Sweden, Spain, Switzerland, UK, France, Lithuania, and the Netherlands.

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