NON-ANIMAL TEST METHODS FOR MEDICAL DEVICES

WAIVERS

Devices may be demonstrated to be substantially equivalent to a predicate device and qualify for limited additional testing using the 510(k) submission process.

In a pre–market approval application for the U.S. Food and Drug Administration (FDA), data from existing approvals or clearances or the published literature may support the omission of some toxicity tests. For example, no-observed-adverse-effect-level (NOAEL) and low-observed-adverse-effect-level (LOAEL) data could be used to justify waiving acute, subchronic, or chronic systemic toxicity assessments. See US FDA guidance documents "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process'" (2020) and "Benefit-risk factors to consider when determining substantial equivalence in premarket notifications [510(k)] with different technological characteristics" (2018).

If limited or no data on extractables and leachables are available, then the threshold of toxicological concern (TTC) concept can be used to establish exposure levels that pose negligible risk. Substances that present below the TTC may require no additional testing.[1]

IN SILICO APPROACHES

Computational modelling and simulation studies can be used to help evaluate the safety and effectiveness of medical devices.[2] For example, QSAR, structural alerts, and read-across approaches can be used in a weight-of-evidence approach. See FDA guidance on reporting of computational modelling studies in medical device submissions.

FDA DISCUSSIONS

The FDA encourages device sponsors to discuss testing options, including alternatives, with the Center for Devices and Radiological Health (CDRH) well in advance of planning or conducting any testing. See FDA's guidance on its Pre-Submission Program and Meetings and FDA CDRH guidance on the use of International Standard 10993 (2020).

Companies may also discuss alternatives with the agency through its Experiential Learning Program and its Medical Device Development Tools (MDDT) programme.

SELECT ENDPOINTS

PYROGENICITY

The monocyte activation test (MAT) is a replacement for the rabbit pyrogen test (RPT) and the bacterial endotoxins test (BET)/limulus amoebocyte lysate (LAL) test, including for medical devices. The MAT measures cytokine release from monocytes when human blood is exposed to a test substance. Cytokines released in the activation process are quantified by the enzyme-linked immunosorbent assay (ELISA). No preparation of an eluate is necessary, and medical devices themselves can be directly exposed to human blood. See ThePSCI.eu/our-work/pyrogenicity. The FDA CDRH guidance on the use of International Standard 10993 (2016 to 2020) states that the CDRH accepts validated methods equivalent to the RPT and gives preference to *in vitro* models when they yield equally relevant information. The MAT is undergoing review through the FDA's MDDT programme to qualify as a standalone release test to satisfy biocompatibility and sterility testing requirements.

ACUTE SYSTEMIC TOXICITY

In vitro tests including high-throughput assays and more complex microfluidic organs-on-chips can be used to evaluate the acute systemic toxicity of test substances. Organs-on-chips emulate tissue and organ physiology and can be systematically organised to mimic the arrangement of human organs. See ThePSCI.eu/Chips.

VAGINAL IRRITATION

MatTek's EpiVaginal™ has a human-like three-dimensional organotypic tissue structure that can be used to assess vaginal irritation. Tissue viability can be assessed by MTT reduction; barrier disruption can be measured by transepithelial electrical resistance and sodium fluorescein leakage; inflammatory cytokine release patterns for IL-1α, IL-1β, IL-6, and IL-8 can be examined; and a histological assessment can be performed.[3]

An EpiVaginal™ qualification study is ongoing through the FDA's MDDT programme. See ThePSCI.eu/Our-work/Personal-lubricant.

A modified human repeat insult patch test (HRIPT) can identify many irritants using skin applications on volunteers.

SKIN IRRITATION

Three-dimensional reconstructed human skin models (e.g. EpiDerm™ by MatTek Corp and SkinEthic by L'Oréal) can be used to determine irritation potential of medical device extracts.[4] Following exposure to a test extract and a post-exposure incubation period, tissue viability is assessed by MTT reduction and the pro-inflammatory response is assessed by IL-1α release.[5] The ISO 10993-23 standard on skin irritation testing gives preference to *in vitro* methods.

See ThePSCI.eu/skin-irritation.

A modified HRIPT can identify many irritants using skin applications on volunteers.

SKIN SENSITISATION

Three-dimensional reconstructed human skin models (e.g. EpiDerm™ by MatTek Corp and SkinEthic by L'Oréal) can be used to determine sensitisation.[6] For example, the SenCeeTox® assay has been demonstrated to be predictive for chemicals or extracts from medical devices.[7] Other promising models that test devices are the SENS-IS assay and GARD™skin assay (Senzagen) (ImmunoSearch).[8,9] Planning for a multi-laboratory round-robin study within ISO Technical Committee 194 is underway.

See ThePSCI.eu/skin-sensitisation.

The HRIPT is a clinical method that can identify many skin sensitisers using repeated skin applications on volunteers.

HAEMOCOMPATIBILITY

For thrombogenicity testing, non-animal test methods include clinical ELISA assays (e.g. vacuum test tube, saline heparin–filled test tube, and closed loop) and the Chandler-loop model, among others. The tests expose human blood or plasma to devices and analyse the blood for coagulation and inflammatory activation markers.[10-14]

Generally, methods must be validated and incorporated into International Standard 10993 before they are likely to be accepted for regulatory use. However, companies should discuss with regulators the use of non-standard methods, and when these are not accepted for regulatory use, companies can conduct parallel non-animal testing to become familiar with them. Additionally, these methods can be used currently for internal/non-regulatory testing.

ADDITIONAL TEST METHODS

Medical device extracts may be suitable for testing using some OECD-approved methods. Read more at ThePSCI.eu/alternatives.

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References

[1] Partosch F, *et al.* Internal threshold of toxicological concern values: enabling route-to-route extrapolation. *Arch. Toxicol.* 2015;*89*(6):941–948.

[2] Viceconti M, *et al. In silico* assessment of biomedical products: The conundrum of rare but not so rare events in two case studies. *Proc Inst Mech Eng H.* 2017;*231*(5):455–466.

[3] Ayehunie S, *et al.* Development of an *in vitro* alternative assay method for vaginal irritation. *Toxicology.* 2011;*279*(1–3):130–138.

[4] De Jong WH, et al. Round robin study to evaluate the reconstructed human epidermis (RhE) model as an *in vitro* skin irritation test for detection of irritant activity in medical device extracts. *Toxicol In Vitro.* 2018;*50*:439–449.

[5] Casas JW, *et al. In vitro* human skin irritation test for evaluation of medical device extracts. (2013). *Toxicol In Vitro.* 2013;*27*(8):2175–2183.

[6] McKim JM, *et al.* An *in vitro* method for detecting chemical sensitization using human reconstructed skin models and its applicability to cosmetic, pharmaceutical, and medical device safety testing. *Cutan. Ocul. Toxicol.* 2012;*31*(4):292–305.

[7] Coleman KP, *et al.* Evaluation of an *in vitro* human dermal sensitization test for use with medical device extracts. *Appl. Vitr. Toxicol.* 2015;*1*(2):118–130.

[8] Cottrez F, *et al.* SENS-IS, a 3D reconstituted epidermis based model for quantifying chemical sensitization potency: Reproducibility and predictivity results from an inter-laboratory study. *Toxicol In Vitro.* 2016;*32*:248–260.

[9] Johansson H, *et al.* Validation of the GARD™skin assay for assessment of chemical skin sensitizers: Ring trial results of predictive performance and reproducibility. *Toxicol. Sci.* 2019;*170*(2):374–381.

[10] Sinn S, *et al.* A novel *in vitro* model for preclinical testing of the hemocompatibility of intravascular stents according to ISO 10993-4. *J. Mater. Sci. Mater. Med.* 2011;*22*(6):1521–1528.

[11] Girdhar G, *et al. In-vitro* thrombogenicity assessment of flow diversion and aneurysm bridging devices. *J Thromb Thrombolysis.* 2015;*40*(4):437–443.

[12] Girdhar G, *et al.* Thrombogenicity assessment of Pipeline Flex, Pipeline Shield, and FRED flow diverters in an *in vitro* human blood physiological flow loop model. *J Biomed Mater Res A.* 2018;*106*(12):3195–3202.

[13] Girdhar G, *et al.* Thrombogenicity assessment of Pipeline, Pipeline Shield, Derivo and P64 flow diverters in an *in vitro* pulsatile flow human blood loop model. *eNeurologicalSci.* 2019;*14*:77–84.

[14] Wolf MF, *et al. In vitro* methodology for medical device material thrombogenicity assessments: A use condition and bioanalytical proof-of-concept approach. *J Biomed Mater Res B Appl Biomater.* 2021;*109*(3):358–376.

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