

High-throughput manufacturing of human epidermal models

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Human epidermal models are routinely used in an increasing number of skin irritation and toxicity testing following OECD guidelines. However, only a fraction of the current demand can be met by producing these models manually. The high-throughput manufacturing of such tissue models requires a standardized and automated production infrastructure. Thus the objective of the »Tissue Factory« project was to build a prototype machine for the production of in vitro test models. The aim was to reduce the production costs, standardize the manufacturing methods, and allow the production to run nonstop year round.

The first model that was generated with the »Tissue Factory« was the Open Source Reconstructed Epidermis (OS-REp) model, an epidermal model originally developed by Henkel AG & Co. KGaA. For the transfer of this manual protocol into automated production individual process adaptations had to be implemented. To be able to deliver a standardized and homogenous product, the cultivation process requires a contactless and stress-free handling of the tissue models, implemented by a tissue culture plate redesign. The automation of this process was focused on those requirements as well as on the scaled-up processing of biological materials under sterile conditions.

The successful establishment of an automated production protocol for the OS-REp model was confirmed by performing quality control including histological analyses, viability testing and barrier function determination. The morphology of the OS-REp model was evaluated histologically by H&E staining. The tissue architecture of the OS-REp models revealed layers similar to those found in healthy human skin: a structured basal layer consisting of keratinocytes in a palisade-like pattern followed by spinous and granular layers and covered by several layers of cornified keratinocytes. No differences in the structure of OS-REp models produced either manually or automatically were observed.

Additionally, a barrier function test, the determination of the ET50 after a Triton X-100 treatment, was carried out in order to verify that the epidermal models were a suitable test system for skin irritation. In all production lots epidermal models with an ET50 value of at least 2 hours were produced, a barrier function which matched the quality criteria for OS-REp.

Skin irritation tests were performed with automatically produced OS-REp tissue equivalents at day 19 at the air-liquid interface culture. A set of 10 reference chemicals, consisting of 5 skin-irritating and 5 non-irritating substances, as defined in the EURL-ECVAM performance standards, was topically applied onto the epidermal models. The automatically produced OS-REp showed reproducible and specific results in this skin irritation test set-up according to international test guidelines.

The »Tissue Factory« is designed for a maximum of 30 x 24-well plates a week, which equate to 720 epidermal models. During steady state, 37,440 epidermal models can be produced a year. Future work includes cultivation of other tissues types, e.g. full thickness skin or cornea, and strategies to deal with increasing demand for automated laboratory processes.

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