

Dermatotoxicological and other Safety Testing Methods without Animals -
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Session 3: New challenges for toxicological safety testing

Embryotoxicity Testing with the High-Throughput EST

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At Roche, the Embryonic Stem Cell Test (EST) is routinely employed to detect potential teratogenic/ embryotoxic liabilities during lead optimization of early pharmaceutical drug candidates. Modifications to the assay design and prediction model considerably improved reproducibility of data and improved the prediction for pharmaceuticals. A recently updated retrospective analysis of all proprietary compounds tested in the EST showed a >90% concordance to rodent embryo-fetal development studies, whilst maintaining a low false positive rate. In our hands, the EST has now shown sufficient robustness and predictivity to allow for the assay to become a major decision-maker during lead optimization. As a consequence, the throughput and turnaround times of the EST needed to be adjusted to allow for parallel and regular testing of lead compounds on a weekly basis. This was achieved by developing a novel culturing tool, the Hanging Drop Culture Plate (HDCP) that allows for automated generation and differentiation of high quality embryonic bodies. With this bottleneck solved, a specially designed, fully automated platform combining compound handling, dose-response plates, cytotoxicity and differentiation test was developed. The updated historical EST analysis with case-studies will be presented as well as the results of the validation of the first fully automated HDCP-EST assay, and ongoing efforts to implement the next generation liquid handling platform for the EST.

