Session 3: Characterization of active pharmaceutical ingredients

Toxicological characterization of new active pharmaceutical ingredients for dermatics

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When designing the preclinical toxicological program for the development of dermatologically active drugs, the specific characteristics and the particular requirements of dermatologically active substances have to be taken into consideration. Usually dermatics are designed to act locally and to avoid systemic exposure. Depending to their application they are potentially exposed to environmental factors, especially to the sun, and may first and/or only be metabolized in the skin. Therefore the toxicological characterization may include the investigation of local toxic effects and systemic toxicity caused by absorption of the pharmaceutical ingredient or its metabolites into the organism. The toxicological profile gained by the multiple toxicological tests has to be combined with the therapeutic profile to get an adequate risk-benefit assessment for the application of the drug to humans.

First, introductory experiments should address the potential phototoxicity, including the photoallergenicity and photogenotoxicity of the substance as well as the systemic exposure. As systemic exposure may highly depend on the formulation, it has to be considered as an important component of the compound to be tested in the toxicological program. If it can be demonstrated that the active ingredient in the formulation used is not systemically available the toxicological program might be limited to the evaluation of the local tolerance which includes potential sensitization reactions and eye irritation but also potential genotoxic activities.

In the case that the systemic availability has to be considered, the complete safety testing program for systemically effective substances has to be applied. This includes for programs leading into phase I clinical trials single dose and repeated dose toxicity studies in two adequate species (one of them rodent, one of them non-rodent) and the safety pharmacology core battery. For later stages, studies about reproduction toxicity and carcinogenicity also have to be considered. The application routes to be tested have to be decided on a case by case basis. Depending on the pharmacological, metabolic and kinetic properties of the substance, a test program using only one dermal application route might be sufficient. In other cases, a combination of the dermal application route with the intravenous or subcutaneous application route might be appropriate or the dermal application route might be replaced by a combination of subcutaneous testing of systemic toxicity and dermal local tolerance testing. Metabolism of the active ingredient and resorption of the drug must be taken also into consideration when choosing the appropriate non-

rodent species for the preclinical testing.

Local and international authorities support all aspects of preclinical testing of dermatics by appropriate guidelines which are published on their web sites.