INTRODUCTION The safety and efficacy of the topically administered drugs depend on the cutaneous absorption influencing systemic exposure. The systemic exposure can be either desired if the systemic effect is expected or undesirable if the drug is expected to be active only locally. The drug presence in the general circulation can also lead to the interactions with other, concomitantly taken drugs, regardless of their dosing route. As the topical drug application, apart from the local toxic effects, is generally considered safe, such potential effect is not studied although can be clinically important as suggest the safety drugs alerts reporting serious adverse drug reactions [1-4]. Aim of the work was to assess the usability of the in vitro - in vivo extrapolation approach at the population level for the skin and systemic disposition after topical and oral drugs administration for the safety assessment.

MATERIALS AND METHODS The simulated studies included combination of the topically and orally administered drugs with metabolic drug-drug interactions. The predicted values were compared against the clinical results when possible. All simulations were run on the Simcyp platform (V12R2) [5,6].

STUDY 1 – topical erythromycin (+ oral simvastatin)

A. Administration of a single 0.4 mg of erythromycin (topical - 2 cm² area of the forearm) with 40 mg of simvastatin (oral) was used as a model scenario to validate the model and compound. Topical erythromycin anticipated exposure mimicking the corresponding clinical study [7]. Drug related model parameters were predicted with use of the Simcyp built-in QSAR models and lotion formulation was simulated by modification of the permeability constants (k50 for the stratum corneum (SC) and viable epidermis (VE)). Fraction unbound in SC was 0.31 and fraction non-ionised on the skin surface was assumed to be 1. Amount of erythromycin collected from the skin surface and fraction of the dose recovered from the SC were compared against the clinical observations (6 healthy volunteers).

B. Second leg of the study included simulation of the theoretical clinical situation where realistic doses of oral simvastatin (40 mg QD, 7 days) and topical erythromycin (40 cm² area of the forearm, 40 mg per dose, BID, 3 days from day 4) were used. Simulation study included 10 groups of 6 individuals.

STUDY 2 – topical ketoconazole (+ oral simvastatin)

Administration of a single dose with 0.4 mg of ketoconazole (topical – forearm, various areas) with 40 mg of simvastatin (oral) were used as the model scenarios. Drug related model parameters were predicted with use of the Simcyp built-in QSAR models and various formulations/occlusion were simulated by modification of the permeability constants (x2 and x3 for the stratum corneum (SC) and viable epidermis (VE)). As the adverse drug reaction report did not contain type of application details, small (100 cm²) and large (400 cm²) application areas were tested separately to apply for various possible scenarios. Fraction unbound in SC and fraction non-ionised on the skin surface was assumed to be 1. All simulations were run in 10 replicates (10 trials) for 10 healthy individuals in each trial (proportion of females - 0.5).

RESULTS The simulated output were compared against the endpoints measured in the clinical study.

STUDY 1 – topical erythromycin (+ oral simvastatin)

A. 0.4 mg of erythromycin (topical - 2 cm² area of the forearm) clinical trials data reported as the amount of drug collected from the skin surface and fraction recovered from the stratum corneum

B. oral simvastatin (40 mg QD, 7 days) and topical erythromycin (40 cm² area of the forearm, 40 mg per dose, BID, 3 days from day 4) simulated results are presented as the population average AUCₜₚ/AUC and Cmaxₜₚ/Cmax ratios

STUDY 2 – topical ketoconazole (+ oral simvastatin)

single dose with 0.4 mg of ketoconazole (topical – forearm, various areas) with 40 mg of simvastatin (oral) simulated results are presented as the population average AUCₜₚ/AUC and Cmaxₜₚ/Cmax ratios, maximal values derived for individuals are reported separately for various scenarios

CONCLUSIONS Topical drugs application is generally considered safe although there are reports of the clinically observed major side effects resulting from the drugs interactions. Netherlands Pharmacovigilance Center reported in 2009 few cases of the topical ketoconazole/oral simvastatin interaction resulted in myalgia [8]. The simulation results stay in agreement with the clinical observations suggesting lack of the clinically important DDIs but pointing for the potentially sensitive individuals (AUCₜₚ/AUC > 1.5 and Cmaxₜₚ/Cmax > 1.3).