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Validation of Bioanalytical Methods; Investigation of Back-Conversion in Incurred Pharmacokinetic Samples

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Introduction: Lately growing attention has been dedicated to the occurrence of back-conversion, intended as the transformation of a drug metabolite to the parent compound during samples handling. Back-conversion brings to inaccurate quantitative determinations and EMA is imposing the validation of back-conversion in analytical methods for bioequivalence (Guideline on Bioequivalence 2010). While it is clear now that validation procedures shall check back-conversion, other methods than the use of biological samples spiked with metabolite standards, are unavailable. Unfortunately the metabolism of several well-known drugs is unclear and new molecules are coming: what to do? A validation approach based on incurred samples of subjects treated with studied drugs was developed; the results collected on 20 drugs will be presented.

Materials and methods: In all validations, HPLC-MS/MS and reversed phase or ion exchange columns separations were employed. These data compare the evaluation of back-conversion by classical procedures (spiked samples) with the findings gathered using incurred samples analyzed soon after sampling, then after different period/conditions of storage.

Results and conclusions: With one drug, only the incurred samples permitted to validate back-conversion and with another-one they allowed to perform a validation when metabolite standards were unavailable. In all other cases both approaches gave similar results; it never occurred that incurred samples results were contradictory with those based on spiked samples. In conclusion the incurred samples approach is very useful, if not the only one in some cases, to adequately validate analytical methods for back-conversion.