

GUIDANCE FOR INDUSTRY

SAFETY TESTING OF DRUG METABOLITES

Organon wishes to comment on the guidance document as follows:

1. The definition of “major metabolite” as proposed in the draft guidance can be questioned because it is expressed in relative (> 10% of the dose or systemic exposure) rather than absolute terms. This approach does not take the actual dose or AUC into account. This could lead to the odd situation where the exposure to a metabolite of a low dose product (e.g. 50 µg per day) would require preclinical testing of that metabolite, while no testing would be needed for a metabolite at a far higher level of exposure from a high dose product (e.g. 1 g per day) because it did not reach the 10% limit.
2. Qualitative species differences in terms of concentrations of metabolites exist. It is not uncommon that a major human metabolite is sufficiently present in one species but only at very low levels in the second species. The question is then if the toxicity of the metabolite has been adequately investigated. The answer to that question would very much depend on the suitability of the species with the high metabolite exposure. The guidance document does not address this issue.
3. Among the four recommended studies for safety testing of metabolites safety pharmacology studies are missing. The role of pharmacology studies is only briefly mentioned in line 152. There may be cases where suitable pharmacology studies contribute more to the safety assessment than toxicity studies. This would depend on the nature of the adverse effect.
4. It is welcomed that the guidance document does not give a figure for an acceptable ratio between human and animal exposure of a major human metabolite. The case by case approach and consultation of the agency are suitable avenues.
5. It is recommended that the high-dose for a general toxicity study, if necessary with the metabolite, be the MTD or maximum feasible dose of 2 g per kg per day. A more scientific approach to safety assessment of the metabolite would be selecting the high-dose to give a multiple (e.g. 25x) of the systemic human exposure.