XenoGesis

Metabolites in Safety Testing (MIST) Guidelines

Understanding whether a research compound or new Investigational Medicinal Product (IMP) forms metabolites that are uniquely produced in humans is highly recommended by the regulatory bodies. The safety assessment of the total drug exposure will not have been tested in regulatory toxicity studies if a unique metabolite is formed in significant amounts.

XenoGesis offers a screening tool and stepwise approach to analyse this risk based upon the revised FDA guidance (Safety testing of Drug Metabolites 2016[i]), which was updated to align with the ICH M3 (R2) guidelines[ii].

This service is relevant to the research phase and all parts of the development stage. If conducted early enough in the research phase, design input to medicinal chemistry removes this liability, resulting in significant cost and time savings during the development stage.

The XenoGesis approach does not rely on metabolite identification software packages as they can miss the more unusual metabolites and generate many that, when interrogated, are not parent compound related. The team at XenoGesis uses its skill and experience to process data manually on a scan by scan basis which provides the client with more accurate results.

Description of full metabolite identification services

Mid to late discovery

Risk assessment with option to influence and change chemistry

1 ***in vitro***
Cryo-preserved hepatocytes - pooled human, and the relevant toxicological species

Summary table of identified metabolites (pseudo-quantified by UV or MS signal), indicating unique human metabolites

2 ***in vivo***
Rat - single low dose, all metabolites identified in plasma, urine, bile and/or faeces

Summary table of identified metabolites (pseudo-quantified by UV or MS signal)

Cross-reference to *in vitro* data (1) to assess circulating metabolites not identified in hepatocytes

Clinical development

More detailed risk assessment

3 ***in vivo***
Pre-clinical toxicology species - high steady-state dose, all metabolites identified in plasma using the Hamilton pooling approach[iii]

Summary table of identified metabolites (pseudo-quantified by UV or MS signal)

Cross-reference to *in vitro* (1) and *in vivo* (2) data to assess circulating metabolites not previously identified

4 **Clinical**
Phase 1, 2 or 3 clinical trials - medium/high steady-state dose, all metabolites identified in plasma using the Hamilton pooling approach[iii]

Summary table of identified metabolites (pseudo-quantified by UV or MS signal), presented as percentage of total IMP-related material

Cross-reference to *in vitro* (1) and *in vivo* (2, 3) data to assess circulating metabolites not previously identified - ultimate outcome to report unique circulating human metabolites at steady-state versus the equivalent regulatory high dose toxicity studies

Follow-up quantification relative to the parent IMP if authentic standards for identified metabolites are synthesised

Full Word/PDF report deliverables

To find out more, contact a member of the XenoGesis team.
Telephone: +44 (0)115 837 0626
Email: info@xenogesis.com

[i] https://www.fda.gov/media/72279/download

[ii] https://www.ema.europa.eu/en/ich-m3-r2-non-clinical-safety-studies-conduct-human-clinical-trials-pharmaceuticals

[iii] Hamilton RA, Garnett WR, Kline BJ. Determination of mean valproic acid serum level by assay of a single pooled sample. Clinical Pharmacology and Therapeutics. 1981;29:408-413

XenoGesis Ltd is an independent laboratory-based contract research organisation specialising in pre-clinical drug metabolism & pharmacokinetics (DMPK), quantitative bioanalysis, pharmacology and expert interpretation.

XenoGesis has state-of-the-art *in vitro*, *in vivo* and bioanalytical capabilities. With its expert pharmacokinetic/pharmacodynamic (PK/PD) interpretation and consultancy services, XenoGesis provides bespoke, iterative, data-driven feedback to clients with next step recommendations.