

Novamass Ltd - Discovering Success

We provide the "M" in ADME

FDA Guidance for Industry, Feb 2008

Safety Testing of Drug Metabolites

Message:

Metabolism studies earlier
Focus on human metabolism
Species comparison earlier

**Avoid delays in
 development and marketing**

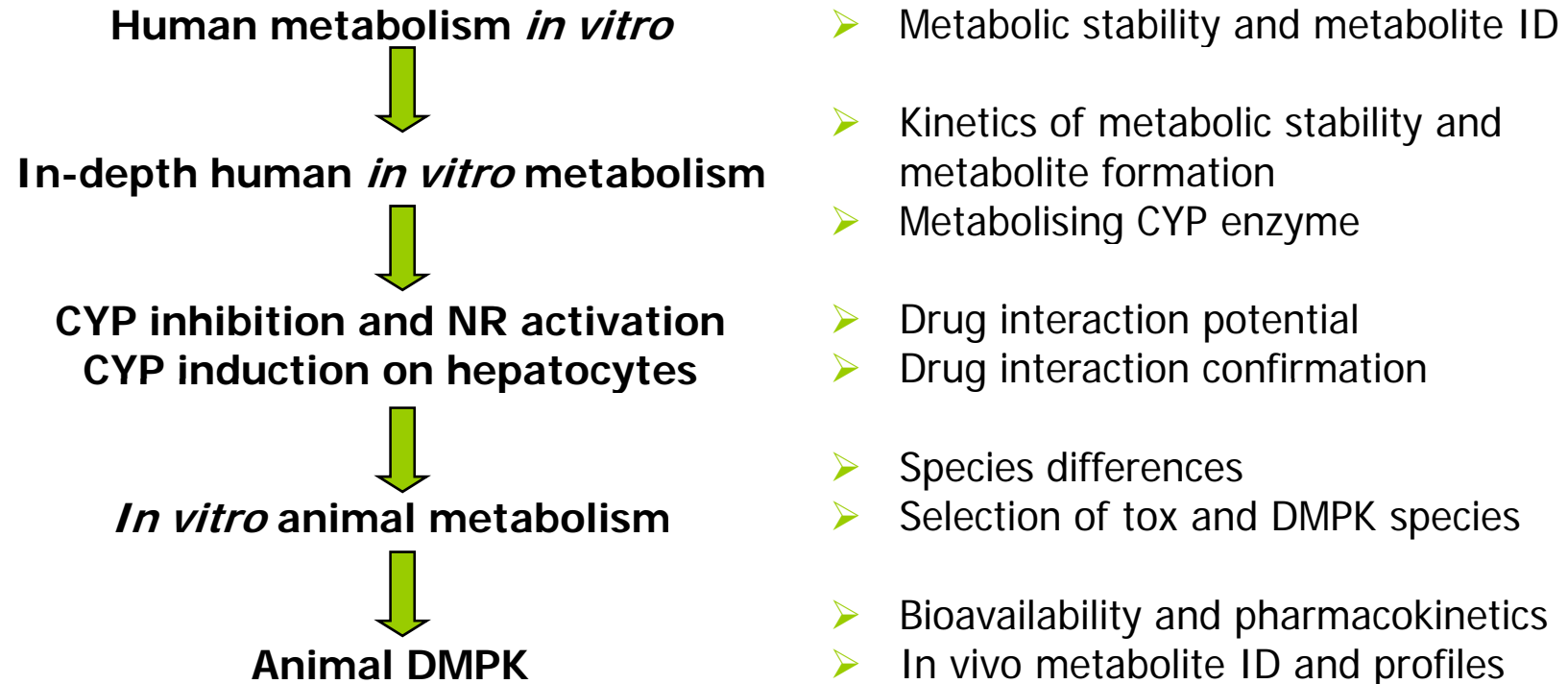
- Generally, metabolites identified **only in human** plasma or metabolites present at **disproportionately higher levels in humans** than in any of the animal test species should be considered for safety assessment.
- We encourage the identification of differences in drug metabolism between animals used in nonclinical safety assessments and humans **as early as possible** during the drug development process. The discovery of disproportionate drug metabolites late in drug development can potentially cause **development and marketing delays**.
- In vivo metabolism study results in nonclinical test species generally should be available **early in drug development**, and their results will either confirm the results obtained from the in vitro studies or reveal quantitative and/or qualitative differences in metabolism across species.
- Human in vivo metabolism studies usually have been performed relatively later in drug development, but we **strongly recommend** in vivo metabolic evaluation in humans be performed **as early as feasible**.
- Metabolite concentrations cannot be inferred by measurement of parent drug concentrations. The metabolic profile of the drug **should be identified** during the drug development process.
- **Technological advances** during the past decade have greatly improved the analytical capabilities to **detect, identify, and characterize metabolites** and allow for better understanding of the role metabolites play in drug safety assessment.
- In this approach, **analytical methods** that are capable of identifying and measuring the metabolite in nonclinical toxicity studies **should be developed**.
- We encourage contacting the FDA **early in drug development** to discuss these issues.
- **Early identification** of disproportionate drug metabolites can provide clear justification for nonclinical testing in animals, assist in interpreting and planning clinical studies, and **prevent delays in drug development**. If toxicity studies of a drug metabolite are warranted, studies should be completed and study reports provided to the FDA **before beginning large-scale clinical trials**.



Novamass' expertise in metabolite identification

- 1. Metabolic stability / pharmacokinetics**
 - Analysis of *in vitro* or *in vivo* DMPK samples by UPLC/TOF-MS
 - Samples from toxicokinetic and phase I studies reanalyzed
 - Prediction/calculation of parent pharmacokinetics
- 2. Biotransformation screening**
 - MetaboLynx of blank and metabolised samples
 - Accurate mass data to ID biotransformations and form metabolite profiles
- 3. Metabolite identification**
 - In-source fragmentation analysis with accurate mass data to predict metabolite structure
- 4. Additional structural analysis**
 - H/D exchange studies: number of exchangeable protons
 - LC/MS/MS studies to ID metabolite structure
- 5. Structural elucidation**
 - Metabolite extraction and isolation from *in vitro* or *in vivo* DMPK samples, if feasible
 - Structural elucidation with multidimensional NMR and LC/NMR
- 6. Quantification of the metabolite**
 - Pharmacokinetic profile on the metabolite and safety evaluation

Novamass cascade for metabolism studies



Novamass: not just data, but strategic analysis

- Unique *in vitro* and *in vivo* DMPK service provider that delivers comprehensive data with qualitative assessments that help you decide early which molecules and projects to keep developing and which to kill
- Core competence is in drug metabolism; metabolite identification as spearhead expertise
- Even customers using other CROs bring their data to Novamass for interpretation
- Full service capabilities: one stop DMPK shop
- Novamass has capacity to deliver service at the time you need

Intelligence – Capacity – Full service

Intelligence – Capacity – Full service

Please turn to us for price, turnout time
and in-depth study information.

Medipolis Center
Kiviharjuntie 11
FI-90220 Oulu
Finland

Tel +358 207 639 666
Fax +358 207 639 660
info@novamass.net
www.novamass.net