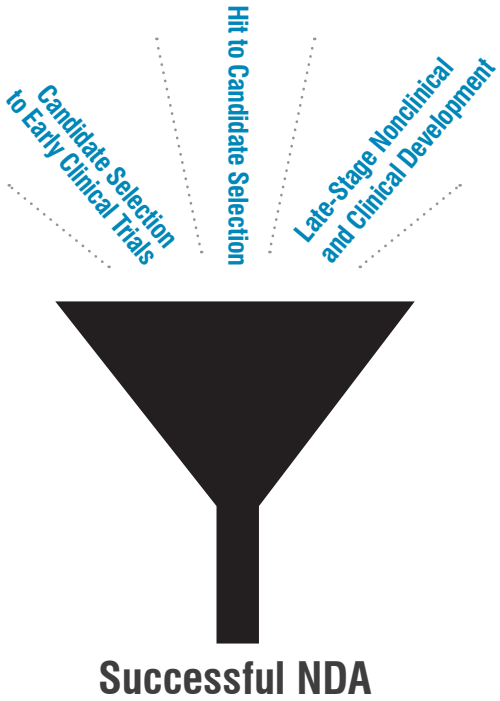

DMPK
Program Considerations
charles river


1
Support From Discovery to Registration


Candidate Selection to Early Clinical Trials
Hit to Candidate Selection
Late-Stage Nonclinical and Clinical Development
Successful NDA

2

Summary of DMPK at Charles River

In Vitro Services

- Metabolic stability
  - Whole cells and subcellular fractions
  - Human and preclinical species
- Metabolite profiling
  - Accurate mass MS and nuclear magnetic resonance (NMR)*
- Drug absorption
  - Intestinal and dermal
- Drug-drug interactions
  - Induction and inhibition
- Plasma protein binding
- Assessment of reactive metabolite formation

In Vivo Services

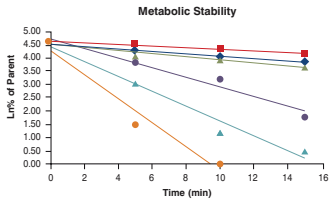
- PK assessment
  - Naïve and non-naïve animals
  - Rodents and large animals
  - HPV cannulated models
- Mass balance
  - Intact and bile duct
- Tissue distribution
  - QWBA, microautoradiography, and dissect and burn
  - Mass spectrometry imaging
- Metabolite profiling
  - Accurate mass MS and NMR*
- Milk and placental transfer

**In partnership with a local university.*

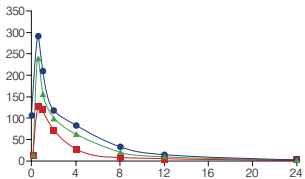
3

Program Considerations

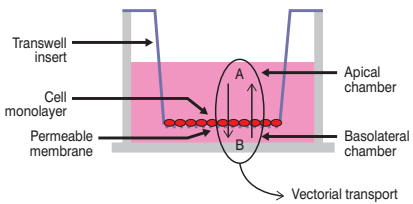
What DMPK Activities Would You Recommend During Screening to Aid Candidate Selection?



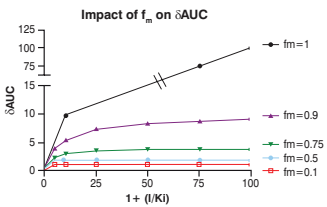
***In vitro* metabolic stability**
(microsomes and/or hepatocytes)



PK/formulation assessment
(rodent and nonrodent)



Intestinal absorption
(Caco-2 cell monolayers)



CYP inhibition
(CYP3A4)

Are Any ADME Studies Required Prior to FTIM?

ICH M3 R2 Guidelines states, “plasma protein binding data for animals and humans… in the species used for repeated-dose toxicity studies generally should be evaluated before initiating human clinical trials.”

We can assess plasma protein binding by:

- Equilibrium dialysis
- Ultrafiltration
- Ultracentrifugation
- In humans and preclinical toxicology species

Any Other ADME Studies Recommended Prior to FTIM?

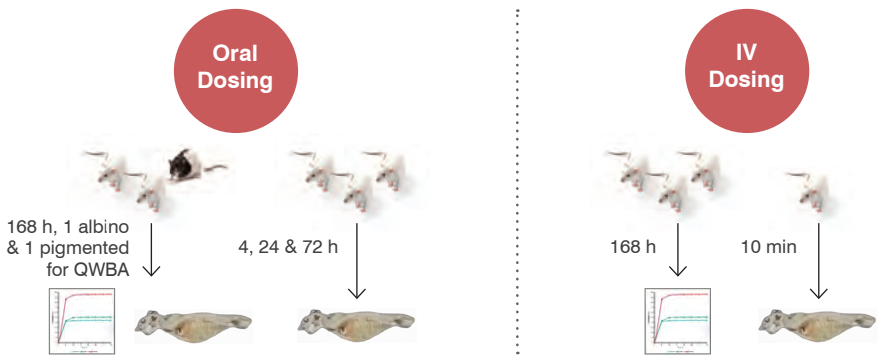
ICH Guideline M3 (R2) additionally recommends that *in vitro* metabolic data from humans and intended repeat dose toxicity species should be available prior to first in man studies.

- Radiolabelled and nonradiolabelled test items can be incubated with isolated enzymes, subcellular fractions or hepatocytes.
- Metabolite profiling and identification is conducted by accurate mass MS (Waters Q-Tof, Shimadzu IT-Tof, Waters Synapt G2-S) with radiodetection.

When Should We Consider Conducting *In Vivo* ADME Studies?

ICH Guideline M3 (R2) recommends that ADME data are available in preclinical toxicology species before widespread exposure of human subjects to the drug (i.e., generally before Phase III clinical trials).

- An abbreviated study design (in rodents) can be used to provide an early understanding of rates and routes of metabolism and excretion and the potential for tissue accumulation.
- Full mass balance studies in both rodents and large animals can be undertaken to support later stage clinical trials.



When Is It Appropriate to Address Metabolite Profiling?

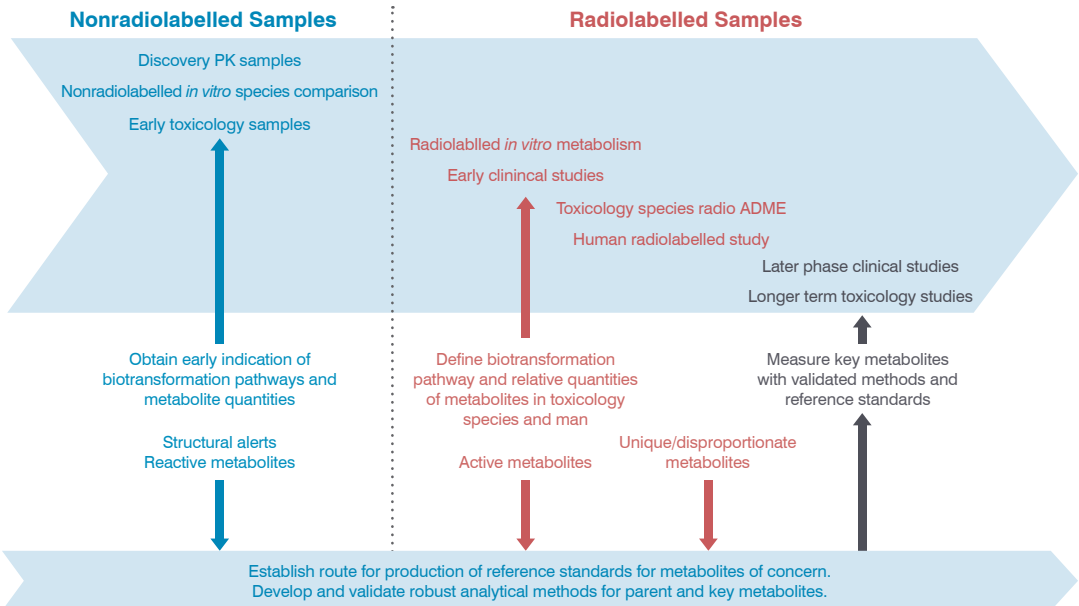
ICH Guideline M3 (R2)

- Nonclinical characterization of a human metabolite(s) is only warranted when that metabolite(s) is observed at exposures greater than 10% of total drug-related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies.

FDA Guidance: Safety Testing of Drug Metabolites

- 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.
- Human metabolites that can raise a safety concern are those formed at greater than 10% of parent drug systemic exposure at steady state.

Metabolites in Safety Testing Strategy



What Useful Information Would I Gain from a Tissue Distribution Study?

- Tissue half-life
- Target organ penetration (e.g., brain)
- Dosimetry calculation for clinical mass balance study
- Understanding of toxicology findings

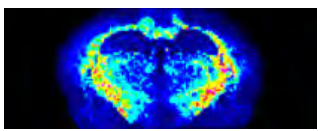
Dissect and Quantify

- Analysis by LC-MS/MS or radioquantification

Quantitative Whole Body Autoradiography (QWBA)

Microautoradiography (MARG)

- Both require radiolabelled materials



Mass Spectrometry Imaging (MSI)

- Can be conducted label free (in collaboration with Imabiotech)

Additional Studies Required When Considering Women of Childbearing Age

To support/validate pre- and postnatal toxicity studies:

- Placental transfer
  - Conducted by QWBA or dissect and analyze
- Milk transfer
  - Assess milk: plasma ratio of total radioactivity, prediction of exposure in suckling young to drug-related material

Assessment of Drug-Drug Interactions

FDA (Draft Guidance 2012)

- Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing and Labelling Recommendations

EMEA (2013)

- Guideline on the Investigation of Drug Interactions

Inhibition Assays

- Phase I and Phase II metabolism
- Direct and time dependent inhibition (TDI)
- Transporters
- MDR1 and BCRP

Induction Assays

- Activity and mRNA endpoints

Additional Program Considerations

In support of toxicology or for mechanistic investigations:

- *Ex vivo* enzyme induction studies
- *In vitro* and *in vivo* investigation of reactive metabolite formation
- Bile duct and hepatic portal vein (HPV) cannulation studies in small and large animals

DMPK at Charles River

Reno, Nevada
Discovery PK (biologics)

Wilmington, Massachusetts
Discovery PK (small molecule)

Edinburgh, Scotland
Development DMPK (small molecule & biologics)
Discovery DMPK (small molecule & biologics)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