A Fistful of Dollars and For a Little Bit More…? The Good, Bad, and Ugly of Supporting Human ADME Studies

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Why ADME? – *What the body does to the drug*

Non-Clinical Development	Clinical Development	NDA Filing
▪ Understanding differences in tox signals between species ▪ Justifying choice of species for chronic tox studies (MIST guidances)	▪ Understanding inter-subject variation in drug response (good or bad) ▪ Predicting drug-drug interactions ▪ Part of predicting ethnic/racial differences (global drug development)	▪ Full description required for major markets

Strategic Question for Drug Developers:

What to know when?

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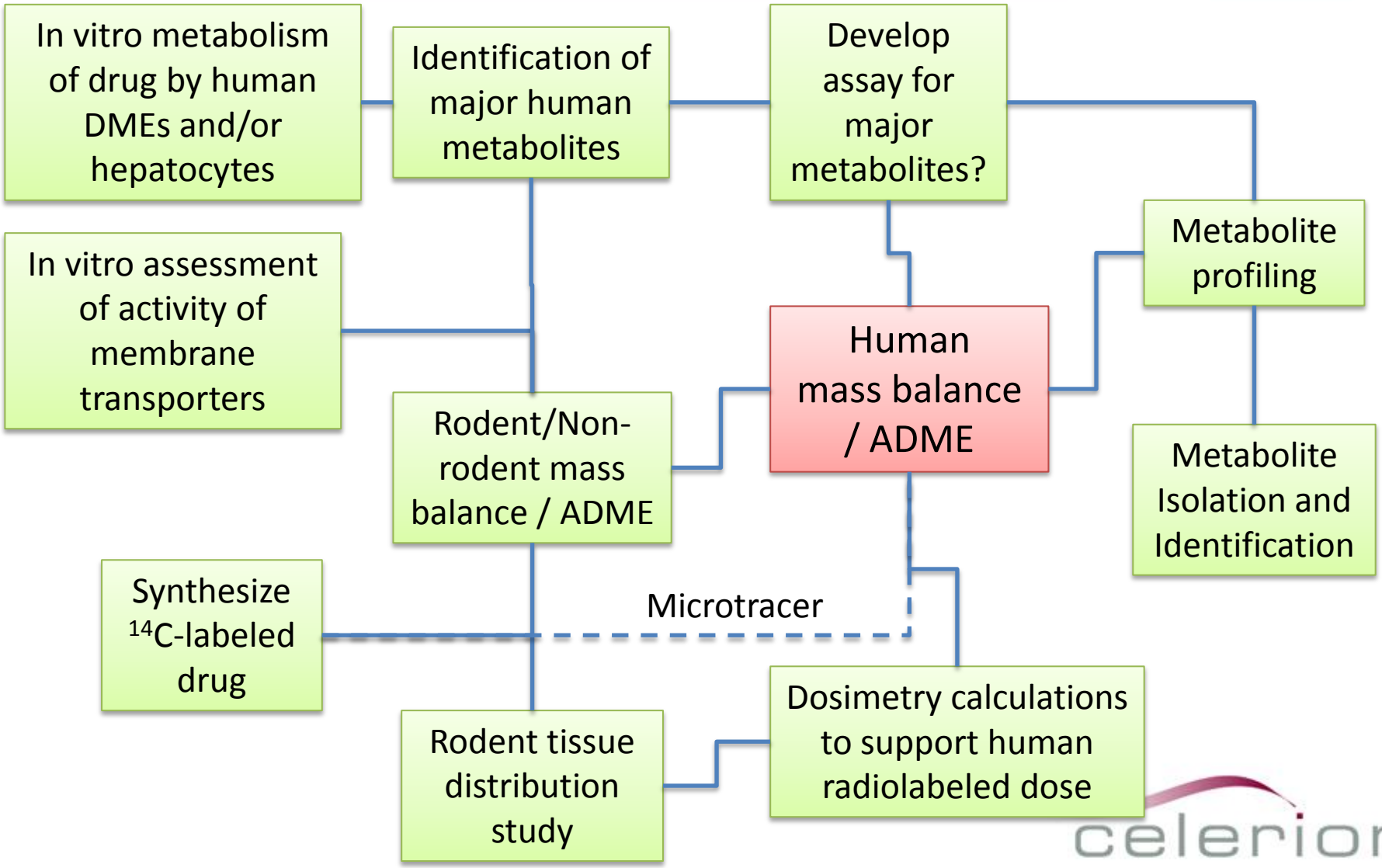
ADME Flowchart



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The Art in The Science

Macrotracer or Microtracer?

- 100 microCi dose justified by dosimetry based on rodent tissue distribution
- <500 nanoCi (microtracer) dose measured using AMS but does not require dosimetry (in Nebraska)

Preparing the Human Dose

- Solutions of GMP-manufactured radiolabel added to cold dose solutions at study site
- Use a certified pharmacy clean room to prepare compounded dose forms for immediate use under USP regulations

Metabolite Isolation and Identification

- Requires creative use of chromatography to separate metabolites
- Need access to instrumentation (LC/MS/MS, MaldiTOF, NMR) to identify structure and measure amounts

To Label or Not to Label?

Good	Challenging (Bad?)	Ugly
^{14}C-radiolabeled drug easily synthesized	Complex ^{14}C-labeled synthesis	Cannot label with 14C
Radiolabel located in metabolically stable part of the molecule	Radioactivity makes drug molecule chemically less stable	Drug breaks into two or more large pieces that need to be tracked to define metabolic profile
Drug has low volume of distribution	Drug/metabolites have high volume of distribution (plasma/blood sensitivity issues)	Complex formulation makes it difficult to know how much radioactivity was given to each subject
Drug not metabolized or has simple metabolic profile	Complex metabolic profile	

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Outsourcing Human ADME

Good	Challenging (Bad?)	Ugly
Sponsor can fund a proper study	Multiple vendors – complicated logistics for shipment of radioactive drug and samples	Radioactive contamination at site (especially for microtracer studies)
1 or 2 vendors can handle everything from radiosynthesis to metabolite I&I	Shipments across international borders	Inadequate facilities for preparing, handling or storing radiolabeled drug formulation
Study conduct site has appropriate clinic for housing subjects excreting radioactivity and staff experienced in handling radioactive samples	IRB inexperienced with reviewing studies involving radiolabeled drug	Inadequate facilities or processes to ensure complete collection of excreta
Experienced subjects	Tissue distribution done with different batch of radiolabeled drug	

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Conduct of Human ADME Study

Good	Challenging (Bad?)	Ugly
Dosimetry allows for 100 microCurie single dose	Radiolabeled drug needs to be repurified before human use	Radiolabeled drug cannot be solubilized
Drug and metabolites have half-lives less than 24h	Drug has long half-life requiring prolonged confinement	Rodent tissue distribution did not include pigmented animals
Greater than 90% of radioactive dose recovered in excreta	Some radiolabel excreted as $^{14}CO_2$ in expired air	Less than 80% of radioactive dose recovered in excreta
Metabolite I&I work occurs shortly after completion of study conduct	Drug can only be given to patients (e.g. oncology)	Radioactivity lost during sample shipment

Analysis of Human ADME Study

Good	Challenging (Bad?)	Ugly
Concentrations of radioactivity in plasma/blood sufficient to accurately quantify major circulating metabolites	Polymorphic poor metabolizers in study lead to inter-subject variation in metabolite profiles	Concentrations of radioactivity in samples are insufficient to produce quantifiable metabolic profiles
Metabolic profile consistent with animal tox species	Unique human metabolite identified compared to animal tox species	Unstable metabolites
Unknown metabolites account for less than 10% of total radioactive dose	Drug or metabolite might be further metabolized by gut bacteria	Radioactivity lost during shipment or storage of samples

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Summary

- Cost and effort to define ADME dependent on the molecule

- ADME studies require talents of several scientific experts (radiochemists, radiopharmacists, radiotoxicologists for dosimetry, experienced investigator and clinical staff, bioanalysts, pharmacokineticists, metabolite isolation and identification scientists)

  - often leads to multi-vendor outsourcing → complicated sample shipment

- MIST guidances are forcing Human ADME to be done earlier in development

- Microtracer approaches offers a good solution to getting information on human metabolic profile early in clinical development