



DRUG DEVELOPMENT

- Safety
- Efficacy
- Pharmacokinetics of parent drug
- Elimination via Metabolism and excretion
 - Safety of metabolites
 - (Efficacy of metabolites)
 - > PK of metabolites
 - > Elimination of metabolites



SAFETY ASSESSMENT PRINCIPLES

- Exposure
 Toxicity
 Risk
- > First: Parent drug toxicological assessment in animals
- But what about metabolites? FDA guidance on Safety testing of drug metabolites:
 - The safety of drug metabolites may need to be determined in nonclinical studies because these metabolites are either identified only in humans or are present at disproportionately higher levels in humans than in any of the animal species used during standard nonclinical toxicology testing.
 - '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 percent of total drug-related exposure at steady state.'



DRUG DEVELOPMENT PIPELINE

Preclinical

Clinical Phase 1 Clinical Phase 2

Clinical Phase 3

Animal safety

Human and Animal Safety

Animal metabolism

Human unique metabolite

Dosimetry

Human metabolism



HUMAN METABOLISM DATA

- Generally generated late Phase 2, or Phase 3
 - High 14C dose administration not ethical in early phase

- Lower the 14C dose significantly (e.g. 1000 fold)
 - No ethical concern even if compound is killed
 - No QWBA



FASTER HUMAN DATA

Preclinical

Clinical Phase 1 Clinical Phase 2 Clinical Phase 3

Basic animal safety

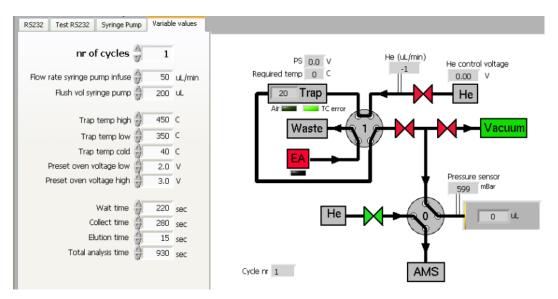
Human and Animal Safety

Human metabolism

Animal metabolism



AMS@TNO: HIGH VOLTAGE ENGINEERING EUROPE 1MV TANDETRON WITH GAS SOURCE

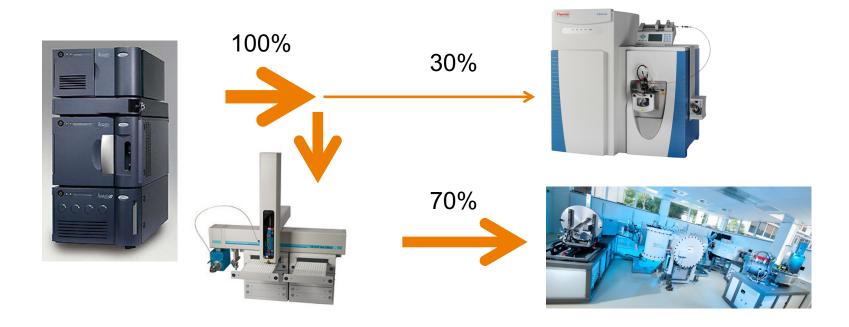


Elemental analyzer (EA) combusts sample. Gaseous CO₂ is used instead of graphite



MIST STUDY SAMPLE ANALYSIS

> Combine UPLC, fraction collection, and AMS with high resolution MS/MS-identification





TYPICAL EARLY MIST STUDY DESIGN

- No dosimetry data needed
- No separate clinical trial needed (ICRP class 1 study)
- Include in early clinical trials
- Close to intended therapeutic dose
- Include 100 nanoCi to 1 microCi of ¹⁴C labelled drug
- Sampling blood, urine, faeces
- Profile samples with chromatography
- Count fractions (AMS) and identify with LC-hrMS/MS

Often combined with mass balance study (discharge from clinic based on AMS data)



WHAT ABOUT CHILDREN?

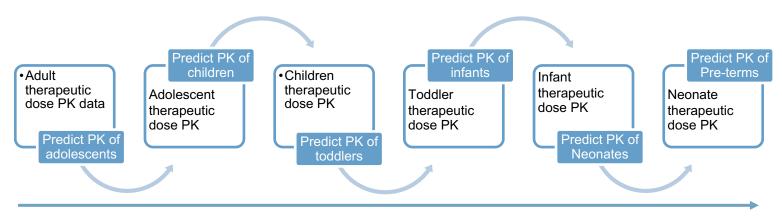
Back to the FDA guidance?

- The safety of drug metabolites may need to be determined in nonclinical studies because these metabolites are either identified only in children or are present at disproportionately higher levels in children than in any of the animal species used during standard nonclinical toxicology testing.
- Generally, metabolites identified only in children's plasma or metabolites present at disproportionately higher levels in children than in any of the animal test species should be considered for safety assessment. Children's metabolites that can raise a safety concern are those formed at greater than 10 percent of total drug-related exposure at steady state.'
- High radioactive dose (100 microCi) studies?
- Microtracer studies?



CLASSICAL PAEDIATRIC DEVELOPMENT

Asses PK differences with adult PK as starting point; single dose if dose-linear in adults (ICH E11)



Time



MICRODOSING-BASED PAEDIATRIC DEVELOPMENT

Dose linear PK adults from microdose to therapeutic dose Microdosing in adolescents Microdosing in children Microdosing in toddlers Microdosing in infants Microdosing in neonates

Asses PK differences with adult PK as starting point; single dose if dose-linear in adults ICH E11):

- With rapid PK: Individual child could benefits from knowing its' individual PK to personalize dosing for the specific child
- Investigate potential ontogenic differences



Time



PROOF OF CONCEPT - STUDY DESIGN I

- > First pediatric [14C]microtracer study to generate metabolite profiles
- Midazolam is a widely used marker for CYP3A4/5 activity, with lower activity in neonates than in adults
- 12 critically ill children included in this substudy (96 patients were eligible, 46 consented)
 - Inclusion criteria:
 - Postmenstrual age >36 weeks
 - Bodyweight > 2.5 kg
 - Clinical need for iv midazolam
 - Indwelling arterial line in place for blood sampling
 - Exclusion criteria
 - Anticipated death in 28 hrs
 - Circular/kidney/liver failure
 - Comedication known to interact with midazolam
 - Gastrointestinal disorders

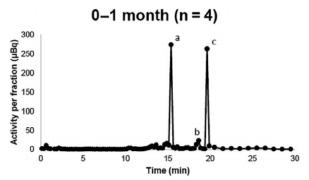


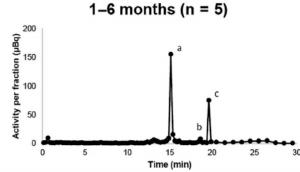
PROOF OF CONCEPT -STUDY DESIGN II

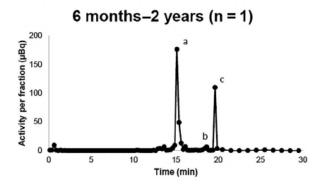
- > First pediatric [14C]microtracer study to generate metabolite profiles
- Oral ¹⁴C-midazolam microtrace 60 Bq/kg, intravenous therapeutic dose of midazolam (0.05-0.3 mg/kg/hr continuous infusion)
- Blood sampling up to 24hr after dosing
- Hamilton plasma pool 0-24h per age group
 - > 0-1 month (4 patients)
 - > 1-6 months (5 patients)
 - > 0.5-2 years (1 patient)
 - > 2-6 years (2 patients)
- Urine and fecal collection up to 72 hrs after dosing

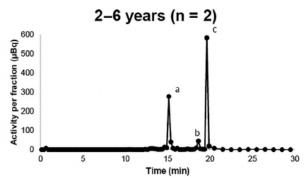


METABOLITE PROFILES









- 10H-MDZ-GLU most abundant, followed by unchanged MDZ and 10H-MDZ
- Unspecified metabolites < 10% of total drug related material
- MDZ-GLU and 4-OH-MDZ

^a1-OHMG ^b1-OHM ^cMidazolam



METABOLITE PROFILES

Table 4 Mass balance results after administration of an oral [14C]midazolam microtracer

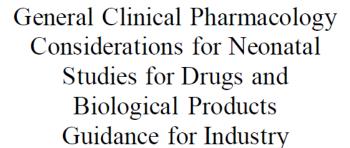
Subject	Sampling time (hour)	Urine		Feces		
		Total recovery (Bq)	Fraction of administered dose	Total recovery (Bq)	Fraction of administered dose	Total fraction of the administered dose recovered in urine and feces
1	20	155	0.74	6.21	0.03	0.77
2	48	124	0.74	31.5	0.19	0.93
3	48	81	0.49	64.1	0.39	0.88
4	71	330	0.92	7.12	0.02	0.94

- Longer sampling time for subject 1 may have resulted in a higher recovery
- Adults: 90% urinary recovery after oral dosing



TAKE HOME MESSAGE

- The sample size of this pilot is too small however:
- Microtracers and detection with AMS enable safe dosing to children of ¹⁴C labelled drugs
- Avoid delay in drug registration for this vulnerable population
- Radioactivity studies that are being conducted in adults may also be conducted in children:
 - Microdosing can aid in establishing better first therapeutic dosing in children
 - Microtracers combined with cold therapeutic dosing enable
 - Derive absolute bioavailability in children
 - Derive routes of excretion and mass balance
 - Derive metabolite profiles



DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within ______ days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm 1061, Rockville, MD 20852. All comments should be identified with the docket mumber listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact CDER at CDER OCP GPT@fda.hhs.gov and CBER, Office of Communications, Outreach, and Development at (240) 402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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230 231 232	(3.) (Metabolism)				
233 234 235 236 237 238	Drug metabolism commonly occurs in the liver, but may also occur in the blood, gastrointesting tract, kidney, lung, and skin. Information on the metabolism of specific drugs in neonates is generally limited. Each metabolic pathway has unique ontogenic characteristics that should be considered when designing clinical pharmacology studies in neonates. In addition, some metabolizing enzymes may have higher expression and activity in neonates compared to older populations (e.g., CYP3A7 and CYP3A4), respectively. 9,10				
239 240 241	Before conducting a clinical pharmacology study in neonates, consider the following:				
	Contains Nonbinding Recommendations				
	Draft — Not for Implementation				
242 243 244 245	 To plan neonatal pharmacokinetic studies, a thorough review of the scientific literature should be conducted to obtain information about the metabolic pathways for the specific drug. 				
246 247 248	 As the postnatal ontogeny of many of these metabolic pathways has not been fully elucidated, it may be necessary to perform additional in vitro or preclinical studies. 				
249 250 251 252	• When appropriate, microdosing studies in neonates may be conducted to assess for potential ontogenic differences in the metabolic pathway compared to older populations. 11,12				

