An FDA Perspective: Safety Testing of Drug Metabolites in Drug development

Z. Alex Xu, PhD, DABT
Pharmacology and Toxicology Reviewer
Division of Metabolism and Endocrinology Products (DMEP)
Office of New Drugs (OND), CDER, FDA

Disclaimer

The opinions expressed in this presentation are those of the speaker and do not necessarily reflect those of the FDA

Key points to consider

- Why metabolite safety testing is necessary ?
  - Toxicity profile may differ from the parent drug
  - Metabolites across species are often similar but not always
- Which metabolites may be of concern?
  - Human unique or disproportional metabolites
- When safety testing is needed?
  - Early (as feasible).
  - Discovery of unique or disproportionate metabolites in late development stage may cause development and marketing delays
- How to test the safety of metabolites?
  - Same strategy as parent compound or not?

Safety Testing of Metabolites Guidance Chronology

- Safety Testing of Drug Metabolites Draft Guidance, 2005
- Davis-Bruno KL and Atrakchi A., A regulatory perspective on issues and approaches in characterizing human metabolites, Chem Res Toxicolol, 2006
- Safety Testing of Drug Metabolites Guidance (final), 2008
- ICH M3(R2) step 4, 2009
- Robinson TW, Jacobs A, Metabolites in safety testing, Bioanalysis, 2009
- ICH M3(R2) Q&A, 2011
- Safety Testing of Drug Metabolites Guidance (revised to align with ICH M3(R2)), 2016

FDA practice on metabolites safety evaluation

- Pharmacology/Toxicology reviewers reference CDER metabolite guidance and ICH M3(R2) and ICH M3(R2) Q and A for metabolite safety evaluation in IND/NDA review
- Reviewer may consult with PK/TK subcommittee for additional input regarding unusual metabolite issues
- Regulatory decision is based on
  - Totality of PK and toxicity information
  - Case-by-case approach
- Ultimate goal is reduce the potential clinical risk without requiring unnecessary nonclinical studies

Timeline consideration for Metabolite Safety testing

- In vitro studies should be conducted before initiation of clinical trials
  - Note that in vitro metabolic profiles of drugs are not always the same (frequently different) as in vivo
- Early in vivo animal and human metabolism studies are encouraged in drug development
- FDA encourage the identification of differences in the drug metabolism between nonclinical species and humans as early as possible
- If safety testing of a drug metabolite is warranted, studies should be completed and study reports provided to the FDA before beginning large-scale clinical trials

- *Always a good idea to communicate with the Division early*

Identification of human metabolites with potential safety concern

- Human metabolites
  - ❑ >10% of total drug-related exposure at steady state can raise a safety concern: unique or disproportional
    - ❑ < 10%: case by case decision
  - ❑ For drugs of <10 mg daily administered dose, greater fractions of the drug related material might be more appropriate triggers safety concern.
    - Case-by-case decision
- Phase 1 metabolites more likely need safety assessment
  - ❑ Phase 2 metabolites are not of concern with exceptions (e.g. acylglucuronides)
- Pharmacologically inactive metabolites are not devoid of toxicity
- Unique animal metabolites is not of safety concern
  - ❑ Not human relevance

Safety evaluation: Avoid separate studies

- Coverage of a human metabolite from studies of parent compound in one animal species is considered to be sufficient
  - ≥ 50% of human AUC is considered adequate in general (ICH M3R2 Q&A)
  - < 50% human AUC
    - "Adequacy of exposure to drug metabolites that are present at disproportionately lower levels in animals used in nonclinical studies should be considered on a case-by-case basis" - CDER metabolite guidance.

Safety evaluation of metabolites: avoid separate studies

- Some factors to consider for case-by case analysis of disproportional or unique human metabolites:
  - Extent of human exposure compared to that of animals
  - Any known toxicity risk
  - Potential for genotoxicity
  - Accumulation with repeated dosing
  - Any new adverse clinical signal
  - Knowledge of the metabolism pathway
  - Background knowledge of the drug class
  - Difficulty in synthesis of the metabolites
  - Alternate animal model

Safety evaluation of metabolites: separate metabolite studies

- "Characterization of metabolite toxicity would generally be considered adequate when animal exposure is at least 50% the exposure seen in humans" - ICH M3(R2) Q&A
  - But not always
- Metabolite may be added to the parent drug groups in animal studies

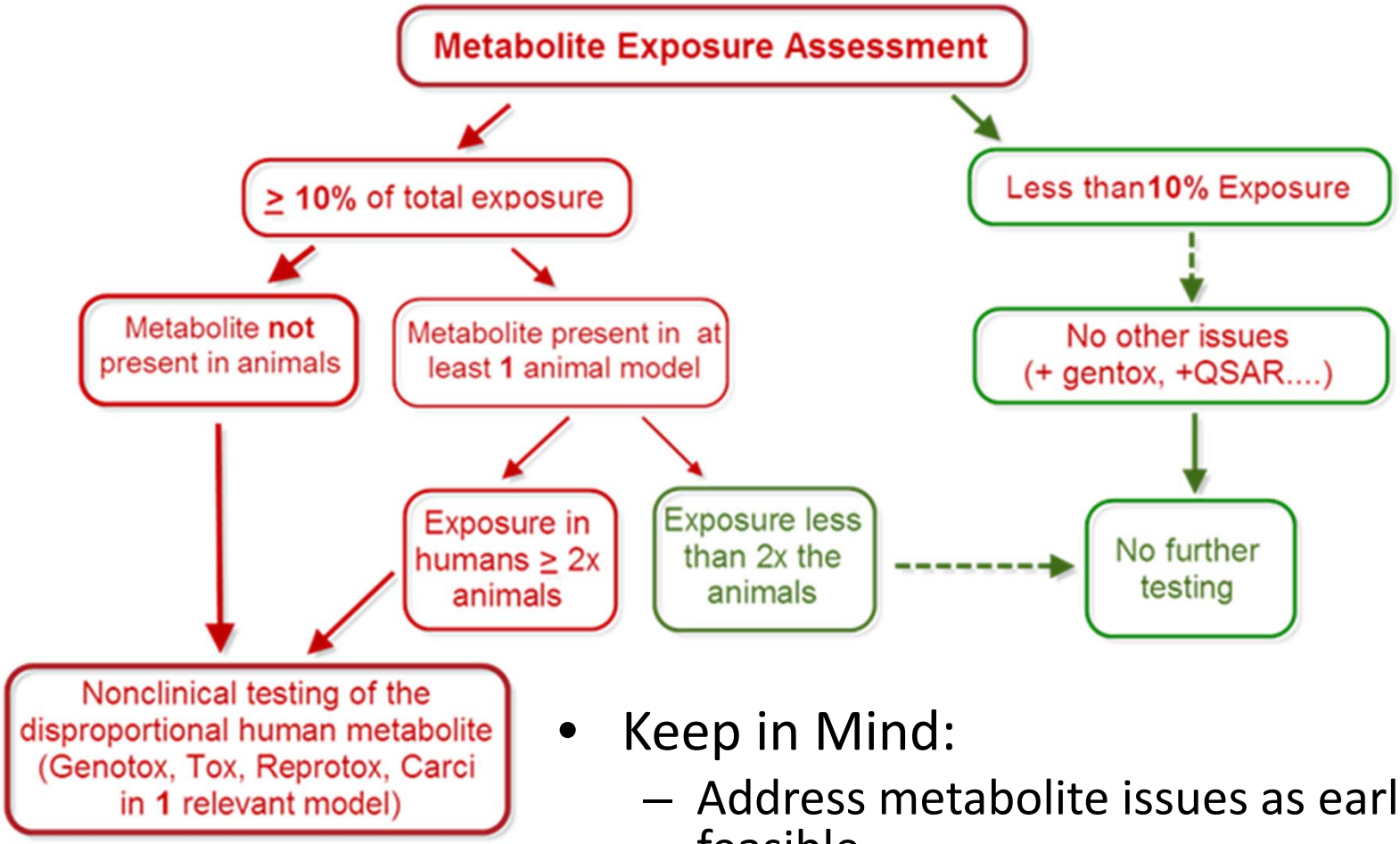
Safety evaluation of metabolites: separate metabolite studies

- Genotoxicity: full battery is not required
  - In vitro assays for point mutations and chromosomal aberrations are required
    - Using human S9 fractions are acceptable in in vitro genotoxicity assays
  - In vivo studies are needed if equivocal and/or positive from one or both in vitro assay
- General toxicity studies in single animal species
  - A 13-week metabolite study is sufficient for chronic indication
  - Alternative route of administration may be acceptable with justification

Safety evaluation of metabolites: separate metabolite studies

- Embryo-Fetal Development Toxicity Studies
  - One animal species is considered to be sufficient with justification
  - Study may not be needed if the parent drug is teratogenic
- Carcinogenicity study
  - A single 2-year study in mouse or rat
  - 6-month transgenic animal model may be acceptable
  - *Recommended to discuss with Exec CAC early*

Summary



- Keep in Mind:
  - Address metabolite issues as early as feasible
  - Case-by-case analysis
  - Communicate with the Division

Case Example 1

- Metabolite studies in two INDs (both during phase 1 development)
  - Sponsor tend to address potential metabolite issues early

Pharmacokinetics Study Reports (IND1)
Identification and characterization of the metabolites of drug X – Final Report (revised version)
Metabolite profiling of Drug x in human plasma after a single oral dose of $X \cdot H_2O$ (Phase 1 Clinical Study of drug X –Single Dose Study– (xx-13-001)) – (revised version)

Pharmacokinetics Study Reports (IND2)
Identification of the of drug Y Metabolites in Rat, Dog and Human Liver Microsomes
In vivo metabolism of compound drug Y in rat bile, plasma and urine
Comparison of Metabolites of drug Y in Systemic Circulation in Rat, Dog & Human plasma

No unique or disproportional human metabolites identified

	RT	Species		
		Rat	Dog	Human
M1a	7.28	0.0%	0.0%	1.5%
M4	7.92	1.4%	0.0%	1.1%
M8	9.11	4.8%	3.1%	9.8%
M18	11.88	29.1%	22.1%	25.2%
Parent	13.92	36.4%	31.6%	17.2%

Case Example 2

Drug OXO is indicated for chronic indication with human experience outside of US. Preliminary comparison indicated at least 13 peaks found in human plasma samples but not in rat, dog, and monkeys; not known in mouse. A 14-day Phase 1 study was proposed with a strategy for metabolite safety evaluation.

Question 1: Mouse carcinogenicity was planned. Is it OK to conduct in vivo mouse micronucleus studies instead of in vitro genotoxicity studies, for human and mouse specific disproportionate metabolites?

FDA Response:

- No. A single in vivo MNT study is not appropriate. Qualification must include the two in vitro assays though an in vivo mouse micronucleus study may be appropriate if either of the in vitro studies is positive. You don't need to characterize mouse-specific metabolites

Case example 2

Question 4: The GI absorption of some metabolites is very low, and difficult to synthesize. Is it OK to conduct a 4-wk SC or IV rat study rather a 13-wk oral study?

FDA response:

- Alternative route of administration might be acceptable. 13-week is required unless a persuasive scientific justification is provided.

Question 6: the parent compound indicated teratogenic. no plan to conduct additional animal developmental toxicity studies with metabolites. Is it acceptable?

FDA response:

- We agree

Case example 2

Question 7: If downstream metabolites are produced after incubation of a primary metabolite in rat liver S9, would negative Ames and chromosomal aberration studies using the primary metabolite be a sufficient for the downstream metabolite?

FDA response:

- No need to characterize rat-specific metabolites in genetic tox studies. For a human downstream metabolite, we recommended you conduct the in vitro genotoxicity studies using human S9 mix to replace rat S9 mix if the same metabolite is not observed in rats with comparable plasma levels as compared to human.

Case Example 3

- **Case-by-Case analysis: additional studies may be needed for phase II metabolite**

  - A drug was submitted for a chronic indication. Phase II metabolite was not detected in animal species, but high concentration of phase II metabolite with long half-life (non acyl glucuronide)
  - FDA response
    - The Sponsor was asked to provide justification for not assessing the safety of this phase 2 metabolite

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Questions?


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