Safety Assessment of Human Metabolites in Drug Development: Current Perspective

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Disclaimer

- The views expressed in this presentation represent the opinions of the speaker
- This presentation is not intended to convey official US FDA policy
- There is no official support or endorsement by the US FDA

Presentation Objectives

- To identify relevant guidance documents related to safety assessment of human metabolites
- To define major, unique, and disproportionate metabolite(s)
- To understand when to characterize human metabolites in drug development
- To determine the type of studies needed to qualify human metabolites and the timing of submission to Regulatory Agencies
- To understand special considerations and potential exceptions to the standard nonclinical program to support safety of human metabolites
- To provide insight into the regulatory decision-making process regarding human metabolites

Outline

- Background
  - Regulatory Guidance Documents
    - ICH M3(R2), ICH M3(R2) Q&A document, FDA Metabolites Guidance, etc.
  - Definitions
    - Major, unique, and disproportionate metabolite(s)
  - When to characterize human metabolites
  - Type of nonclinical studies required and timing of submission
  - Special considerations and potential exceptions for safety assessment of human metabolites
- Case studies
- Summary and Perspectives
- References

Safety Assessment of Human Metabolites: Regulatory Guidance

- FDA Guidance for Industry, Safety Testing of Drug Metabolites, revised November 2016
- ICH Guidance M3(R2), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, January 2010
- ICH M3(R2) Q&A Document, Section II B, February 2012
- Other relevant guidance documents (indication-specific)
  - S9 Guidance "Nonclinical Evaluation for Anticancer Pharmaceuticals"
  - FDA Guidance for Industry "Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals"
  - FDA Guidance for Industry "Rare Diseases: Common Issues in Drug Development"

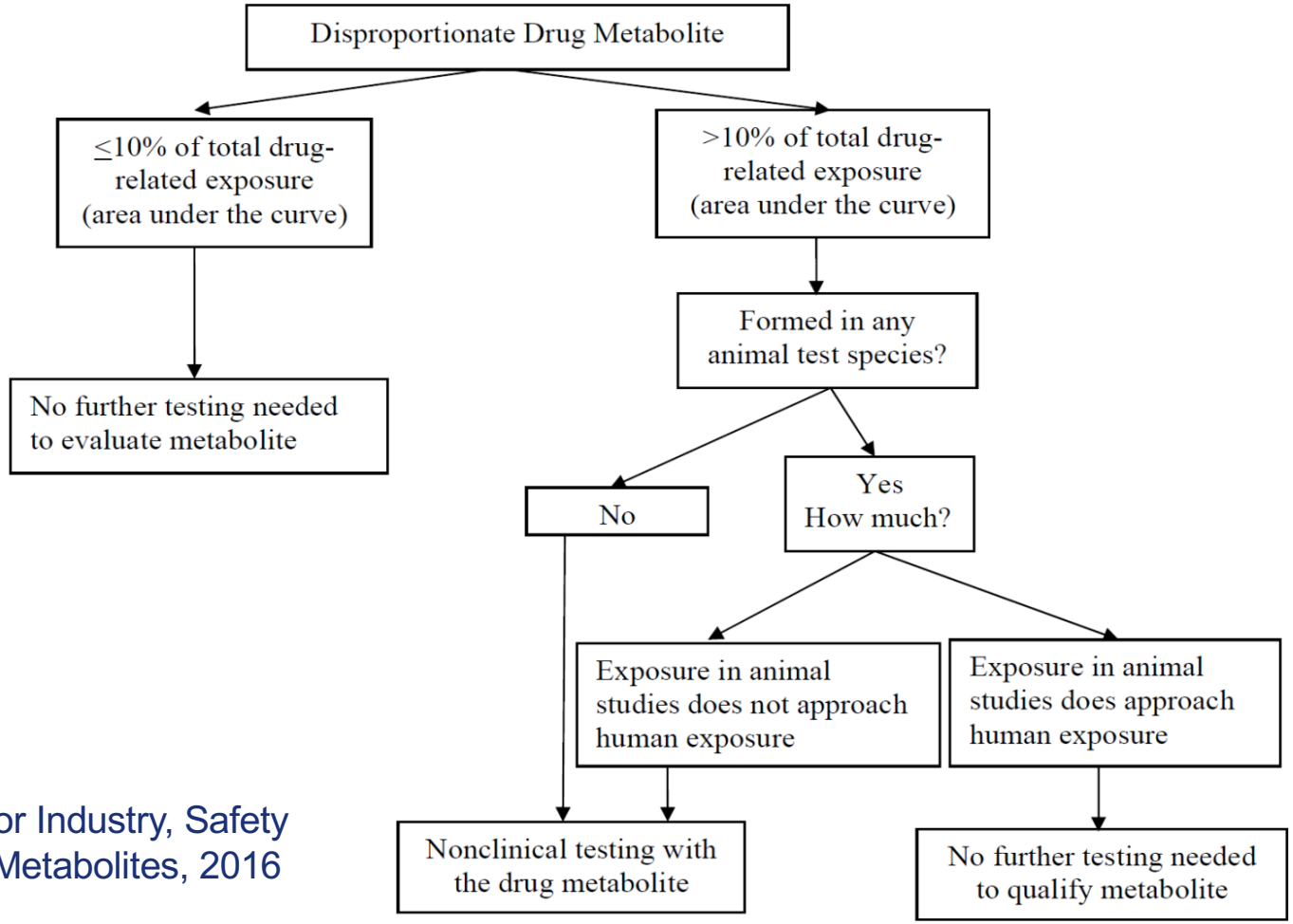
Safety Assessment of Human Metabolites: Definitions

- Metabolite: a compound derived from the parent drug through Phase I and/or Phase II metabolic pathways
- Major human metabolite: metabolite(s) observed at exposures greater than 10 percent of total drug-related exposure in humans
- Unique human metabolite: metabolite(s) observed only in humans and not in animals
- Disproportionate human metabolite: metabolite(s) with exposures substantially higher (≥2x) in humans vs. animals

Safety Assessment of Human Metabolites: When to Characterize Human Metabolites

- Metabolite exposure greater than 10% of total drug exposure will need further consideration
  - From FDA Guidance (Nov 2016): “metabolic profiles can vary across species both quantitatively and qualitatively, and there are cases when clinically relevant metabolites have not been identified or adequately evaluated during nonclinical safety studies. This situation can occur if the metabolite is formed only in humans and is absent in the animal test species or if the metabolite is present at disproportionately higher levels in humans than in the animal species used in the standard toxicity testing with the parent drug.”

APPENDIX A:
DECISION TREE FLOW DIAGRAM



FDA Guidance for Industry, Safety Testing of Drug Metabolites, 2016

Safety Assessment of Human Metabolites: Type of Nonclinical Studies

- Genotoxicity
  - *In vitro* battery (point mutation and chromosomal aberration)
  - *In vivo* study may be required if positive or equivocal in the above studies
  - Follow S2(R1) Guidance
- General Toxicology in single relevant species
  - Duration of the study should follow M3(R2) Guidance
  - Use parent drug's intended route of administration, if possible
  - Include TK analysis to ensure adequate metabolite exposure
    - At least 0.5x AUC margin required
- Embryo-fetal development in single relevant species
  - Other reproductive studies may be required on a case-by-case basis
  - Follow S5(R2) Guidance
- Carcinogenicity in single relevant species

Safety Assessment of Human Metabolites: Timing of Submission

- *In vitro* profiling – before first-in-human study
  - Preliminary information obtained
    - e.g., protein binding, *in vitro* metabolism
  - Compare *in vitro* metabolite profiles across species
    - Useful for nonclinical species selection (rodent and non-rodent)
  - May not correlate with *in vivo* data
    - IMPORTANT: Need to confirm with in vivo assessment

Safety Assessment of Human Metabolites: Timing of Submission

- *In vivo* characterization– prior to large scale clinical trials
  - The earlier, the better
    - If there is a need for nonclinical studies with the metabolite, they should be submitted for review prior to large scale clinical trials
  - ADME information
  - Compare *in vivo* metabolite profiles across species
  - Determine whether there are any unique or disproportionate metabolites that need further safety assessment
  - Flexibilities for oncology and severely debilitating or life-threatening (SDLT) indications - Refer to appropriate Guidance document and Contact Review Division
    - S9 Guidance “Nonclinical Evaluation for Anticancer Pharmaceuticals”
    - FDA Guidance for Industry “Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals”
    - FDA Guidance for Industry “Rare Diseases: Common Issues in Drug Development”

Safety Assessment of Human Metabolites: Special Considerations

- Phase II metabolites
  - May not need separate studies
- Consider structural similarity of metabolite(s) and parent
- Metabolite present in rodent vs. non-rodent
  - Impact reproductive and developmental toxicity studies and carcinogenicity assessment
- Unique vs. disproportionate metabolite
  - Safety assessment approach may be different
- Pharmacology active vs. inactive metabolite
- Structural alert for genotoxicity
  - Positive vs. negative for genotoxicity
- Flexibility in nonclinical assessment of metabolites might be considered for oncology and SDLT indications

Metabolite Case Studies

Safety Assessment of Human Metabolites: Case Study #1

- Background
  - Disproportionate human metabolite
    - Higher exposure in humans *vs.* nonclinical species
  - Accounted for 1/3 of total drug-related exposure (AUC)
  - Phase 2 product
  - Present in mouse
    - Metabolite coverage was demonstrated in repeat-dose mouse toxicity studies

Action

Division requested monitoring of systemic exposure in future nonclinical studies with parent

Genetic toxicity

In silico evaluation for mutagenicity

Found no structural alerts for mutagenicity

Ames assay not requested

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Safety Assessment of Human Metabolites: Case Study #2

- Background
  - Metabolite 10-15X parent in humans
    - Considered a major metabolite
  - Nonclinical species generate metabolite at much lower levels
    - Disproportionate metabolite
  - Pharmacologically active
  - Longer $t_{1/2}$ compared to parent
  - Genetox: Ames and MLA negative

Action

Sponsor conducted a complete safety assessment with metabolite

General toxicity studies in two species (parent + 2 doses of metabolite)

Fertility and EFD assessment (parent + 2 doses of metabolite)

Carcinogenicity in two rodent species (parent + 2 doses of metabolite)

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Safety Assessment of Human Metabolites: Case Study #3

- Background
  - *In vitro* studies: found similar profiles across human and nonclinical species
  - *In vivo* studies: found 1 disproportionate human metabolite with minimal or no exposure in animals
  - 25% of parent
  - Metabolite is a glucuronide

Action

O-glucuronides are rapidly filtered by kidneys

No further nonclinical assessment necessary

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Safety Assessment of Human Metabolites: Case Study #4

- Background
  - *In vitro*: found 4 metabs across species (human, monkey, dog, rat, mouse)
  - *In vivo* characterization: found 1 metabolite with no exposure in rodents. Monkey metabolite exposure was 1/3 of parent.
  - New toxicity signal in monkeys (60% of human exposure)
    - Disproportionate metabolite
  - Human exposure 4X of parent
  - Pharmacologically inactive
  - *In vitro* genetox – genotoxic

Action

Full safety assessment needed - General toxicity, reprotox, carcinogenicity

Safety Assessment of Human Metabolites: Case Study #4

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  - *In vitro*: found 4 metabs across species (human, monkey, dog, rat, mouse)
  - *In vivo* characterization: found 1 metabolite with no exposure in rodents. Monkey metabolite exposure was 1/3 of parent.
  - New toxicity signal in monkeys (60% of human exposure)
    - Disproportionate metabolite
  - Human exposure 4X of parent
  - Pharmacologically inactive
  - *In vitro* genetox – genotoxic
- Action
  - Full safety assessment needed - General toxicity, reprotox, carcinogenicity

Safety Assessment of Human Metabolites: Case Study #5

- Background
  - Metabolite 13% of total radioactivity in humans (major metabolite)
  - Only trace amount in rats (not in other species)
    - Unique human metabolite
  - Metabolite orally bioavailable in rats

Action

Sponsor proposed full safety assessment

In vitro genetox (Ames and Chromosomal aberration)

28-day toxicity study with metabolite alone

Sub-chronic and chronic toxicity studies in one species with parent + spiked metabolite

Segment I and III studies with parent + spiked metabolite

Segment II studies in two species with metabolite alone

Carcinogenicity study (one rodent species) with parent + spiked metabolite

Safety Assessment of Human Metabolites: Case Study #5

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  - Metabolite 13% of total radioactivity in humans (major metabolite)
  - Only trace amount in rats (not in other species)
    - Unique human metabolite
  - Metabolite orally bioavailable in rats
- Action
  - Sponsor proposed full safety assessment
    - *In vitro* genetox (Ames and Chromosomal aberration)
    - 28-day toxicity study with metabolite alone
    - Sub-chronic and chronic toxicity studies in one species with parent + spiked metabolite
    - Segment I and III studies with parent + spiked metabolite
    - Segment II studies in two species with metabolite alone
    - Carcinogenicity study (one rodent species) with parent + spiked metabolite

Safety Assessment of Human Metabolites: Case Study #6

- Background
  - Four major metabolites identified (MET1, MET2, MET3, MET4)
    - MET1 – acyl glucuronide present at 18.9% (human, monkey, mice)
    - MET2 – acyl glucuronide present at 14.5% (human, monkey, mice, rat; but **disproportionate**)
    - MET3 – O-glucuronide present at 14% - will not be discussed further
    - MET4 – acyl glucuronide present at 9.87% (**not detectable in animals**)
  - No complete information on pharmacological activity
  - No structural alerts for mutagenicity based on QSAR
  - Sponsor claimed MET4 was not a major metabolite (< 10%) – no need to qualify

Action

Division considered MET4 is a major metabolite and should be qualified for safety

Sponsor proposed total system burden approach to qualify AGs– questionable by Division

Division requested proposal to evaluate Reprotox and Carcinogenicity

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  - Four major metabolites identified (MET1, MET2, MET3, MET4)
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- Action
  - Division considered MET4 is a major metabolite and should be qualified for safety
    - Sponsor proposed total system burden approach to qualify AGs – questionable by Division
  - Division requested proposal to evaluate Reprotox and Carcinogenicity

Safety Assessment of Human Metabolites: Case Study #7

- Background
  - Drug for SDLT indication (oral)
  - Three metabolites identified (MET1, MET2, MET3)
    - MET1 – active similar to parent, levels covered by toxicology studies
    - MET2 – active, but less potent vs. parent, disproportionate, low oral bioavailability in animals
      - SC studies in rats/dogs - severe injection site reactions - terminated after <1 week of dosing (no other tissues affected)
      - Negative in Ames and Chromab, EFD in rabbits
    - MET3 – inactive, only single-dose data in animals and humans (covered with margin of ~7), sponsor didn't plan further assessment

Action

Although data are not ideal for MET2 and MET3, totality of data for each metabolite acceptable

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    - MET3 – inactive, only single-dose data in animals and humans (covered with margin of ~7), sponsor didn't plan further assessment
- Action
  - Although data are not ideal for MET2 and MET3, totality of data for each metabolite acceptable

Summary and Perspectives

Safety Assessment of Human Metabolites: Summary and Perspectives

- Important to identify metabolites early in development
  - Faster resolution of metabolite safety issues
  - Avoid potential delays in development
- A case-by-case approach is necessary for safety evaluation of metabolites
- Decision making is based on the totality of the information
- Discuss your proposal with the FDA early in development
  - Consider starting discussions at the Pre-IND stage if *in vitro* data are available
  - Number and type of studies needed may be modified for serious disease conditions

Safety Assessment of Human Metabolites: References (1 of 2)

- ICH Guidance for Industry M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, January 2010
- FDA Guidance for Industry: Safety Testing of Drug Metabolites, February 2008
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Safety Assessment of Human Metabolites: References (2 of 2)

- Obach, R.S. (2013). Pharmacologically Active Drug Metabolites: Impact on Drug Discovery and Pharmacotherapy. *Pharmacological Reviews*, 65, 578-640.
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- S9 Guidance "Nonclinical Evaluation for Anticancer Pharmaceuticals"
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Thank you!

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