MIST:

Insight from the DVDMDG May 24, 2011 Rozman Symposium

By

Christopher J. Kemper, Ph.D.

Pharma Navigators, LLC

"MIST" = Metabolites in Safety Testing

From Tom Baillie (2011):

Central Question:

"Are human *metabolites* of a drug candidate, as well as the parent compound, adequately evaluated for safety during preclinical toxicology studies?"

Issue:

Historically, lack of consistency in approach to the issue (from both industry and regulators)

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Some History

- Sterling Winthrop and Wyeth were early Drug Metabolism departments in pharma
  - Ruelius/Janssen 1-O-Acyl Glucuronide work in the ’70/80s
- Baillie et al. 2002; MIST paper
- Hastings et al., 2003; FDA commentary on the MIST
- Baillie et al., 2003; Reply to FDA
- FDA *Draft* Guidance on Safety Testing of Drug Metabolites, 2005
- Guidance *Finalized* 2008

and a Small Part by the DVDMDG

- Lew Klunk, 2002
- Martin Green, FDA, June 2005
- Aisar Atrakchi, FDA, September 26, 2008
- Rozman May 24, 2011

“MIST” – An Opportunity for Poetic License

D. A. Smith and R. S. Obach, “Seeing through the MIST…..”
Drug Metab. Dispos., **33**, 1409-1417 (2005)

D. A. Smith *et al.,* “Clearing the MIST of time…..”
Chemico-Biol. Interact., **179**, 60-67 (2009)

L. Leclercq *et al.,* “Which human metabolites have we MIST?.....”
Chem. Res. Toxicol., **22**, 280-293 (2009)

D. A. Smith and R. S. Obach, “Metabolites: have we MIST out the importance of structure and physicochemistry?”
Bioanalysis, **2**, 1223-1233 (2010)

A. N. R. Nedderman and P. Wright, “Looking back through the MIST…..”
Bioanalysis, **2**, 1235-1248 (2010)

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So What's the Big Deal?

- "…..(the MIST Guidance), if interpreted *verbatim,* creates the potential for a resource burden during early development and through Phase II that could increase the scrutiny of metabolites that have a negligible chance of contributing to pharmacology or toxicology"
- **Key concerns for industry:**

(1) **Resource and time implications for drug development**

(2) **Scientific merit of extensive studies on metabolites**

FDA Guidance on “Safety Testing of Drug Metabolites”

- Applies only to small molecule non-biologic drug products
- Excludes:
  - Anti-cancer agents
  - Drug conjugates (other than acylglucuronides)
  - Reactive intermediates
- Focuses on:
  - Stable metabolites circulating in human plasma
  - Unique or “disproportionate” metabolites in humans
- Key Recommendations:
  - Metabolites whose AUC_p at steady-state is <10% that of parent need no further study
    - If AUC_p is >10% of parent, require “coverage” (exposure margin $\geq$1) in at least 1 tox species
  - Otherwise, human metabolite is “disproportionate” and may require testing
- Types of Toxicology Studies that may be Required:
  - General tox (3 months), genotoxicity, embryo-fetal development tox, carcinogenicity

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079266.pdf

ICH Topic M3 (R2)
Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Key recommendations:

- - Only those human metabolites observed at levels ≥10% of *total drug-related exposure* require nonclinical characterization, if they circulate at "significantly greater" levels in humans than the maximum exposure in animal toxicology studies

- - For drugs dosed at <10mg / day, a larger % of the total drug-related material might be appropriate before safety testing is needed

- Some metabolites do not warrant testing (eg "most GSH conjugates")

- "Unique human metabolites" should be considered on a case-by-case basis

- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/M3_R2/Step4/M3_R2__Guideline.pdf

Practical Issues with MIST Guidances

FDA Guidance

- How to assess those metabolites in human plasma that circulate at ≥10% AUC of parent drug under steady-state dosing conditions?
  - Multiple ascending dose (safety/tolerability) study with "cold" drug and LC-MS/MS?
  - Availability of validated assay for metabolite(s)?
  - Projections from single dose PK data?

ICH Guidance

- How to assess "total drug-related exposure" in plasma?
  - Radioactive dose (with required GMP synthesis, dosimetry, etc)?

As of January, 2010, where the FDA and ICH Guidances differ, the ICH Guidance supersedes the FDA guidance

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf

T. W. Robinson and A. Jacobs, *Bioanalysis,* **1**: 1193-1200 (2009)

Where are We Today with MIST?

- Recognition of the importance of obtaining information on the identities and circulating levels of drug metabolites in humans *as early as practically possible,* and relating these data to animal studies
- Widespread adoption of *new methodologies* (eg NMR, HRMS, *in vitro/in vivo* modeling) to accomplish these objectives in the absence of radiolabeled tracers
- Broader appreciation of the complexity of drug metabolism issues, and the need for a *case-by-case approach* to MIST that is based on sound scientific principles (and common sense)
- Improved understanding of *acyl glucuronides* (*vis-à-vis FDA* classification as "toxic compounds")
- Increased awareness of *species differences* in drug metabolism (eg through reactions catalyzed by aldehyde oxidase)

Conclusions

- After over 40 years, the technology has allowed us to obtain copious amounts of biotransformation data
- There is no “check box” process to deal with metabolite safety issues
- The concept of a “case by case basis” is still fundamental

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