MIST:
Insight from the DVDMGDG May 24, 2011 Rozman Symposium

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“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)
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 DVDMGD

- 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…..”

L. Leclercq *et al.*, “Which human metabolites have we MIST?…..”

D. A. Smith and R. S. Obach, “Metabolites: have we MIST out the importance of structure and physicochemistry?”

A. N. R. Nedderman and P. Wright, “Looking back through the MIST…..”
“…..(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 $\text{AUC}_p$ at steady-state is $<10\%$ that of parent need no further study
    - If $\text{AUC}_p$ 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

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 \( \geq 10\% \) 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.

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


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 (e.g., 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 (e.g., 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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