Flushing Out Translational Excretion Data: How Well Do Nonclinical ADME Results Predict Clinical Findings?

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BACKGROUND

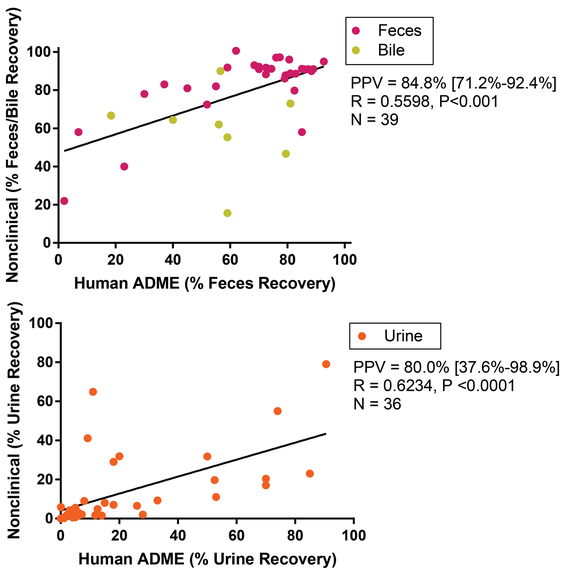
- A mass balance study uses a radiolabeled drug to obtain quantitative information on the absorption, distribution, metabolism and excretion (ADME) of an investigational drug.
- Nonclinical mass balance studies help inform the clinical ADME study design. However, there are several metabolic and technical inter-species factors that may impact the translation of nonclinical to clinical ADME results.
- How well do nonclinical excretion results translate to human findings, and what accounts for possible differences?

METHODS

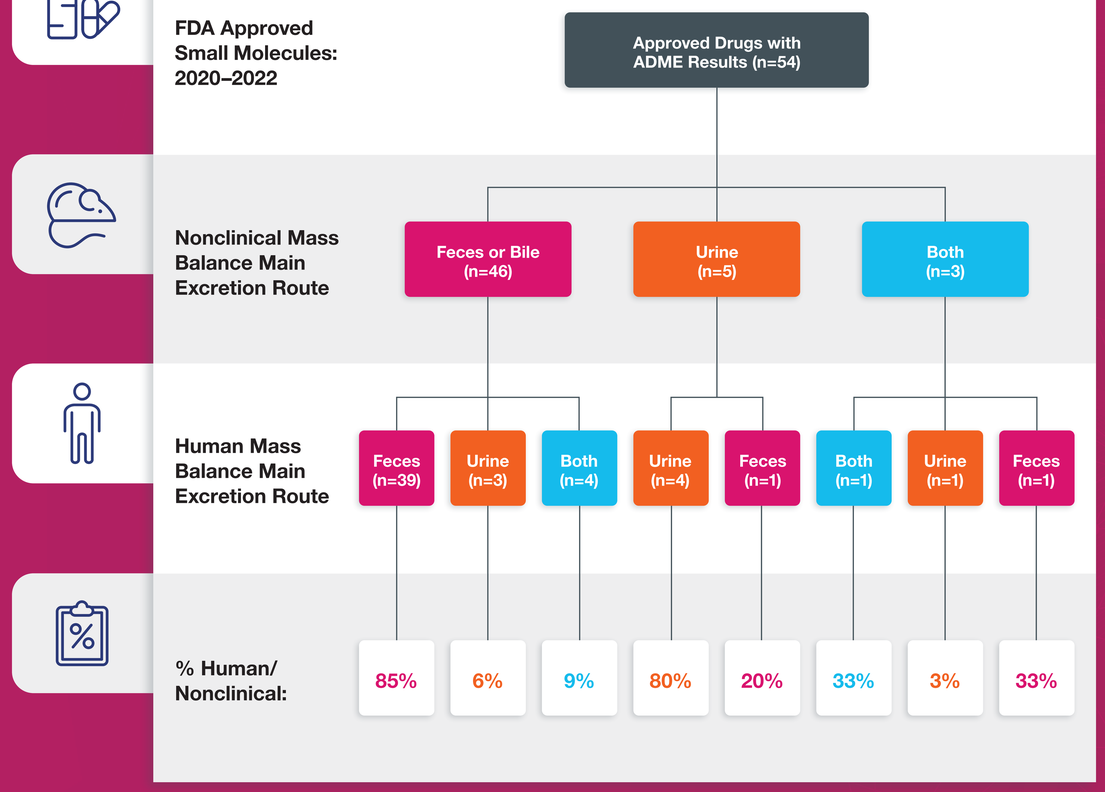
- Recent radioactivity recovery excretion data were extracted for 54 approved small molecules from FDA clinical pharmacology reviews from Drugs@FDA.
- Nonclinical-clinical performance was assessed by positive predictive value (PPV) (%, [95% CI]) and Pearson correlation (R, p-value).

RESULTS

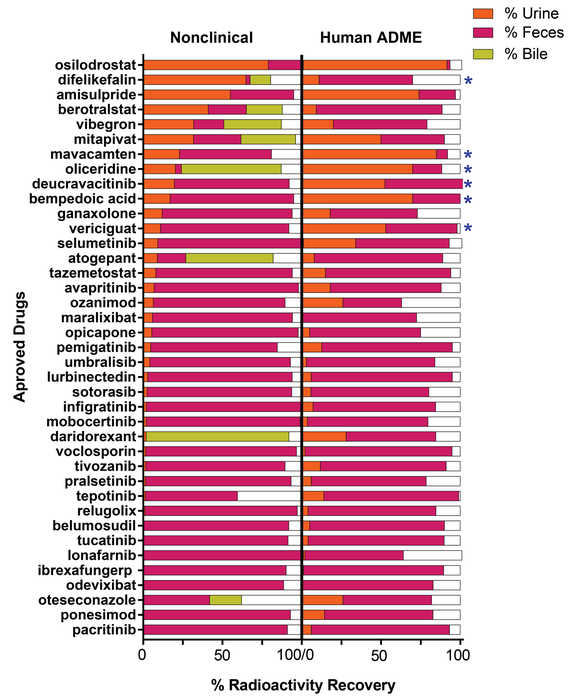
Feces, Bile & Urine Radioactivity Recovery



Despite technical and metabolic differences between nonclinical and human ADME studies, the animal data strongly predicts and correlates with human findings.



Nonclinical — Clinical Excreta Recovery



* Discrepant nonclinical/clinical recovery rates

- Excreta profiles reveal similar nonclinical and clinical recovery rates with feces as main route of elimination for both species.
- Interestingly, only 15% of drugs demonstrate profile discordance between nonclinical-clinical recovery.

Understanding Discordant Results

- Difelikefalin: hADME in hemodialysis patients; 20% radioactivity removed in dialysate
- Mavacamten: Extensive CYP2C19 metabolism. CYP2C19 activity >10-fold lower in rats
- Oliceridine, Deucravacitinib & Vericiguat: Glucuronide metabolites readily excreted in urine in humans vs rats
- Bempedoic acid: Rat is not a sensitive model; in monkey 86% cleared by kidneys

CONCLUSION

- Overall there was strong agreement between nonclinical and clinical mass balance excretion data.
- Only a few cases had large discrepancies, which were associated with CYP2C19 and glucuronidation drug metabolism.
- In these cases, metabolite profiling could help elucidate the drug excretion data in humans, as they might be quite different from rat models.

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