Predictive Value of Nonclinical ADME Findings for Clinical Excretion Routes

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BACKGROUND

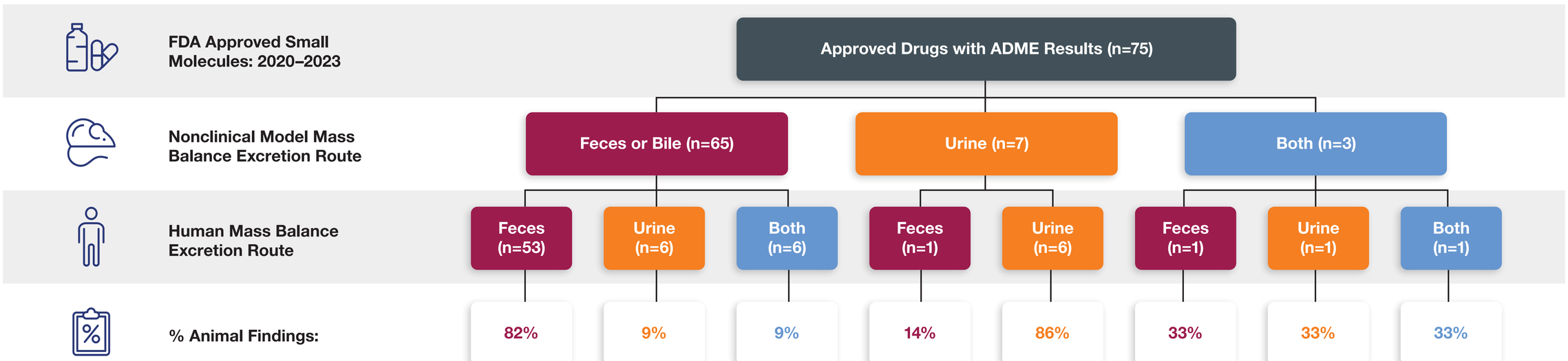
- A mass balance study uses a radiolabeled drug to obtain quantitative information on the absorption, distribution, metabolism and excretion (ADME) of an investigational drug.
- Nonclinical mass balance studies help inform the clinical ADME study design. However, there are several metabolic and technical 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?

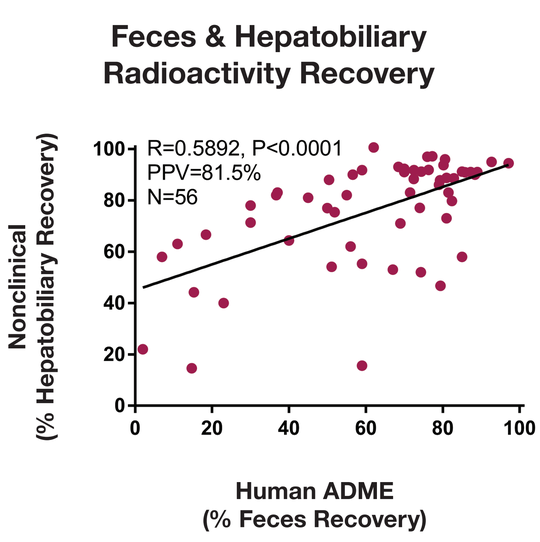
METHODS

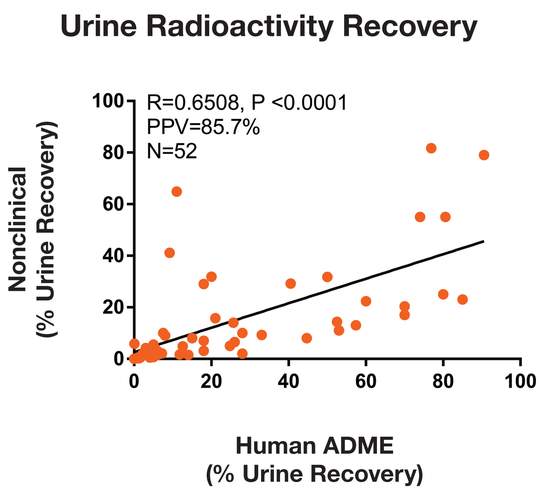
- Recent radioactivity recovery excretion data were extracted for 54 approved small molecules from FDA clinical pharmacology reviews from Drugs@FDA.
- Nonclinical-clinical performance was assessed by positive predictive value (PPV) (%, [95% CI]) and Pearson correlation (R, p-value).

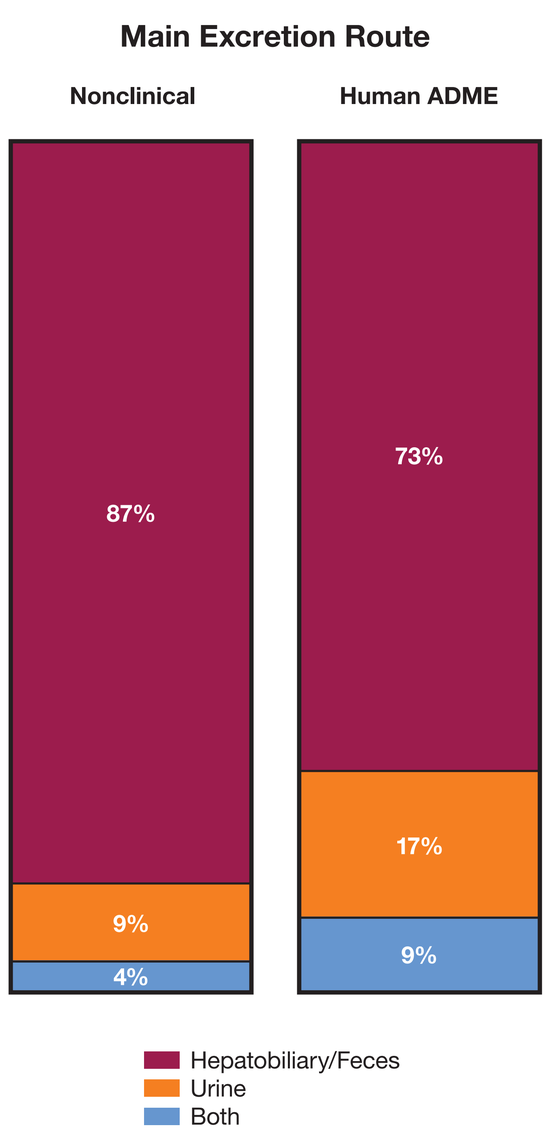
RESULTS

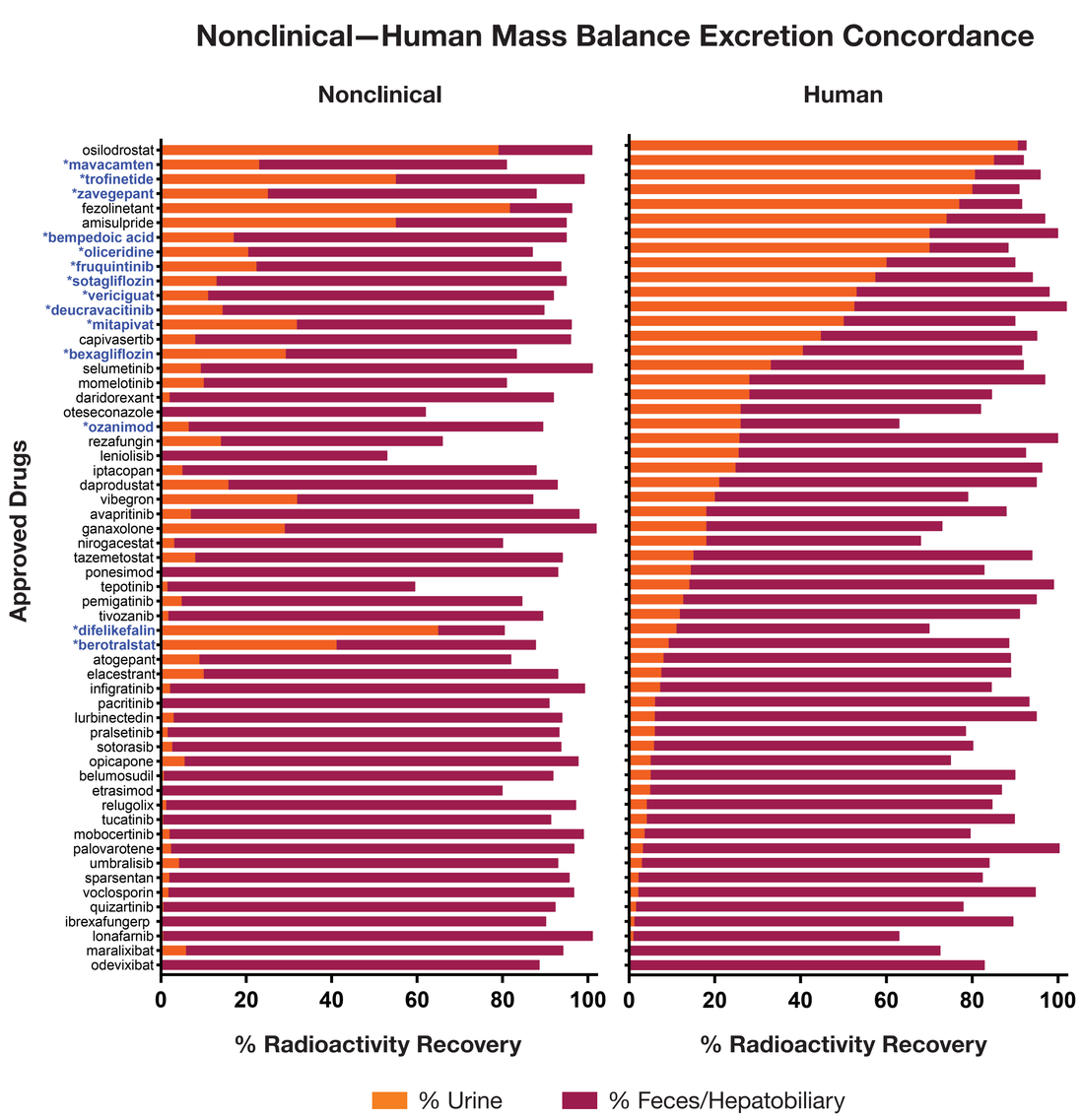
Animal ADME Data Strongly Predict and Correlate with Human Findings











**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 20% of drugs demonstrate profile discordance between nonclinical-clinical recovery.
- Understanding discordant results
  - hADME conducted in hemodialysis patients: radioactivity removed in dialysate; e.g. difelikefalin.
  - Lower CYP activity in rats than in humans: e.g. mavacamten; extensive CYP2C19 metabolism in humans and >10-fold lower CYP2C19 activity in rats.
  - Glucuronide metabolites readily excreted in urine in humans, not in rats: e.g. oliceridine, deucravacitinib & vericiguat.
  - Rat is not a sensitive model: e.g. bempedoic acid; 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 human-animal differences in CYP activity and drug glucuronidation.
- 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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