Lead Optimization Strategies and Integrated Assessment of *In Vitro* and *In Vivo* Toxicology Studies for the Rapid Identification of Clinical Candidates

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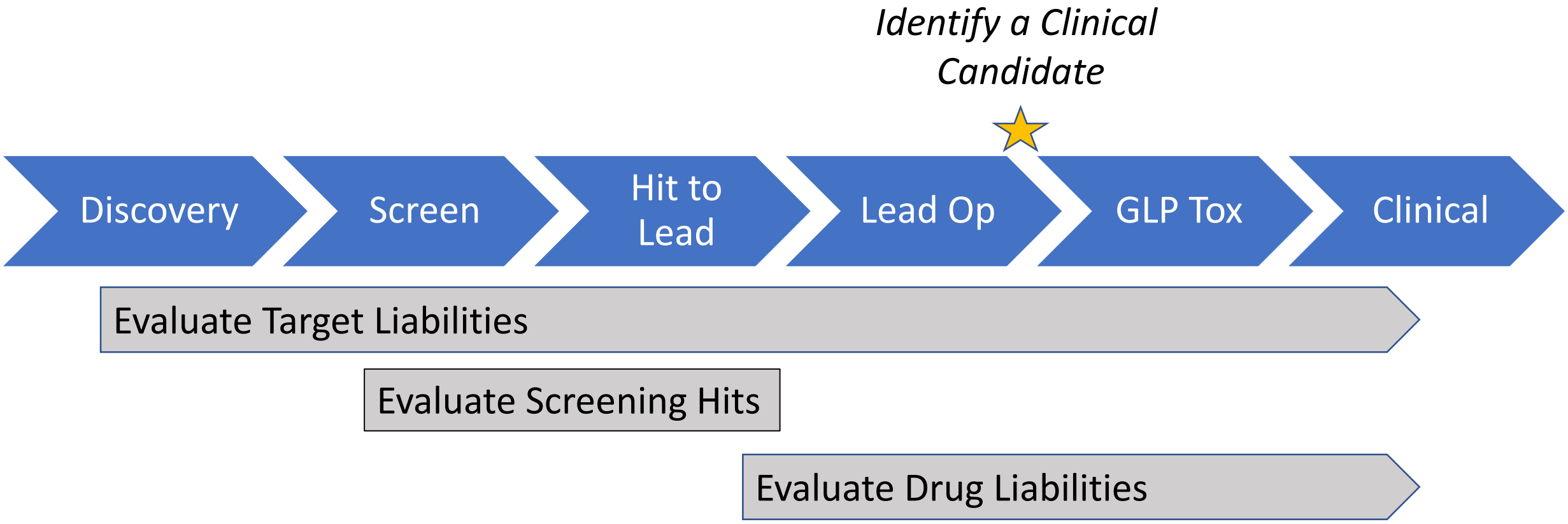
Conflict of Interest Statement

Neither myself nor any of my coauthors, including members of our immediate families, have any financial interest or affiliation of the type described above with a commercial organization that has a direct or indirect interest in the subject matter of my presentation.

Presentation Outline

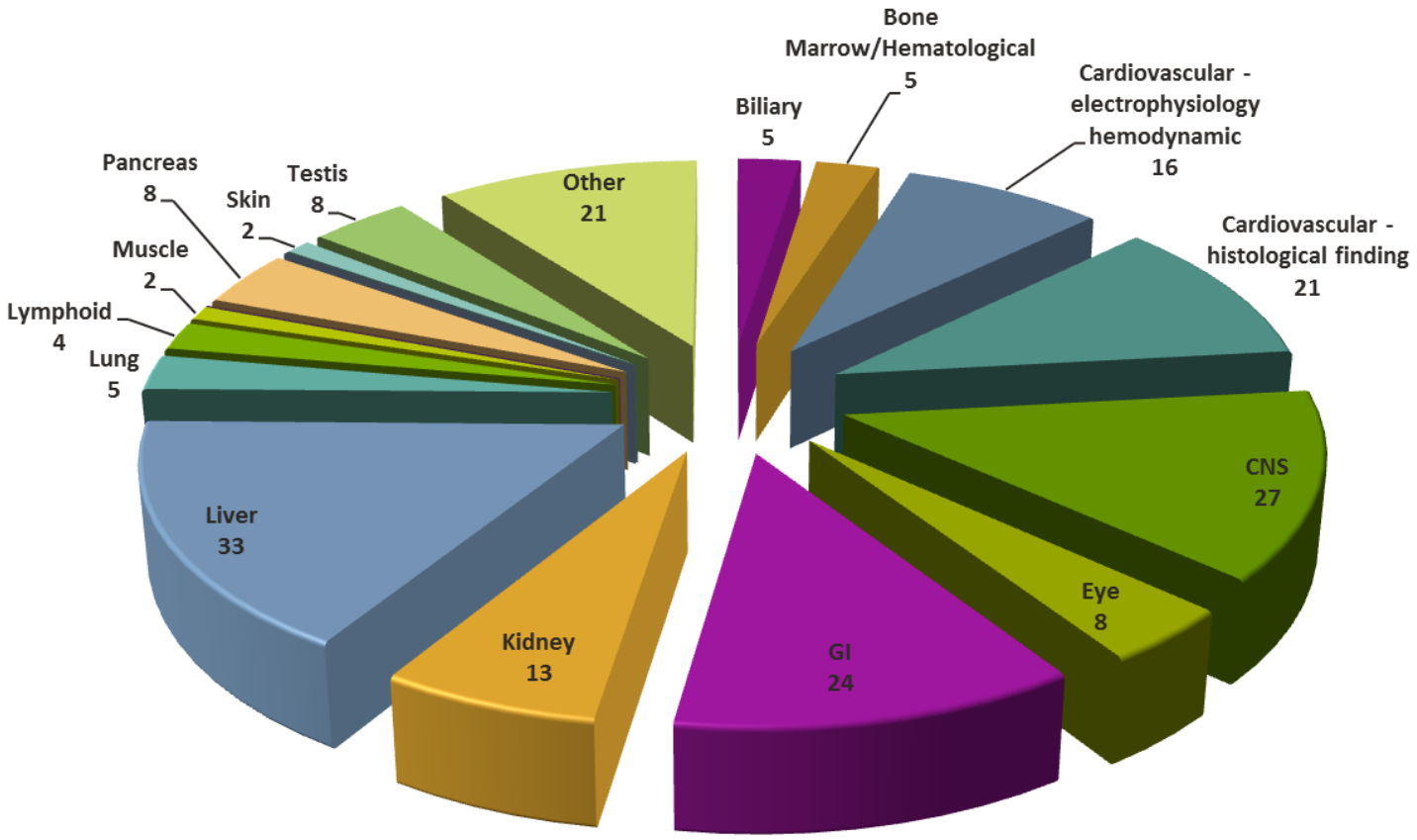
- Goals of lead optimization
- The LO flow scheme: putting it all together
- Case Study 1: common issue
- Case Study 2: unanticipated issue
- How to expedite candidate selection

Getting to the Lead Optimization Stage



Proactive staged approach to understand target and drug liabilities in order to inform project progression and clinical candidate selection, and reduce late stage attrition

Anticipated Challenges



- Primary toxicity was associated with the following target organs:
  - Cardiovascular (18%), Liver (16%), GI (12%), and CNS (13%)
- Cardiovascular was most prominent reason for termination
  - Electrophysiology/hemodynamic and histological findings

Sherry Ralston. IQ DruSafe Attrition of Pharmaceuticals during Preclinical Development. SOT 2017.

Safety Goals for Lead Optimization

- Establish safety profile of clinical candidate to support candidate selection and progression into the clinic
  - Identify maximum tolerated dose
  - Identify target organs of toxicity (and MOA if possible)
  - Preliminary estimate of safety margins
  - Inform design of FIH-enabling GLP tox studies

What do I Need from Other Functions?

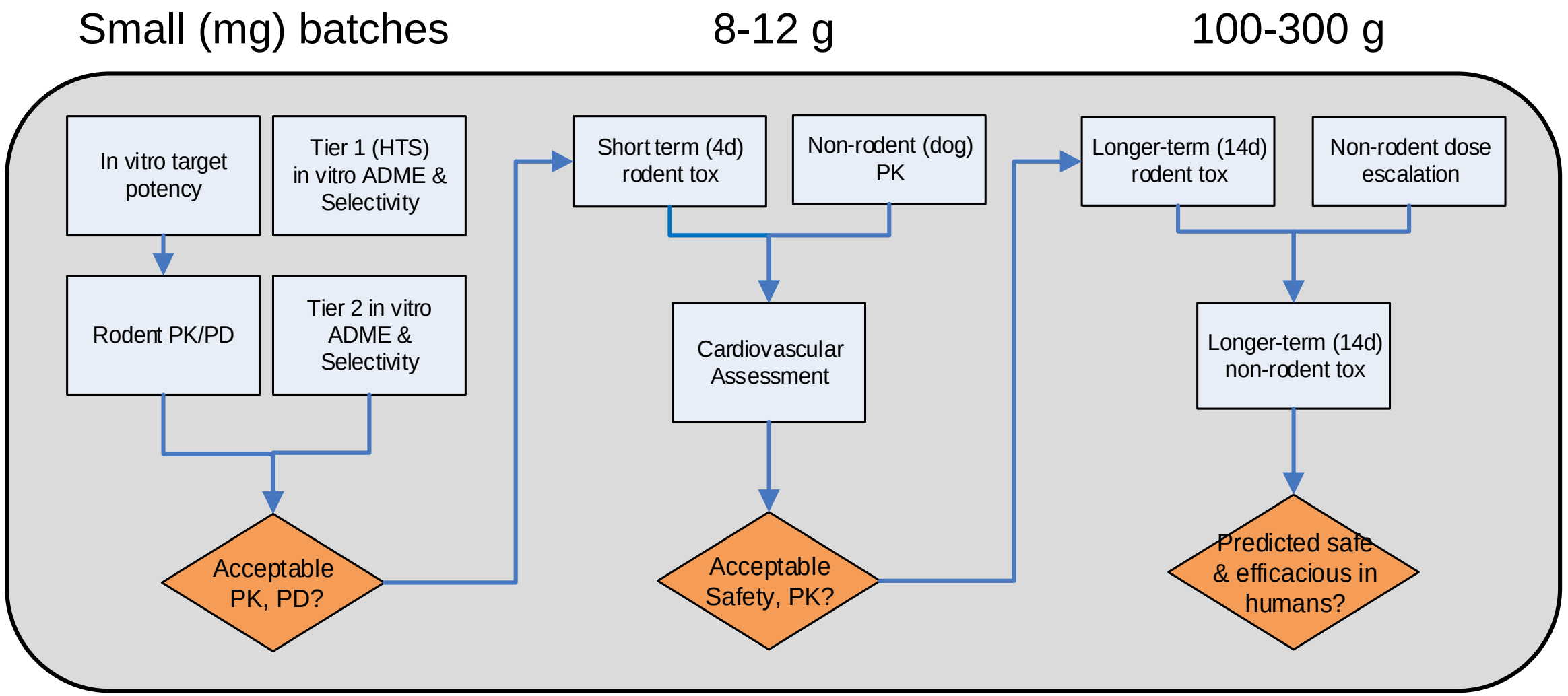
- Pharmacology:
  - Estimate of efficacious plasma concentrations (i.e. PD biomarker)
  - Drives dose selection and initial estimates of safety margin

- Pharmacokinetics:
  - PK profile in nonclinical species (eg. AUC, Cmax, half-life, etc)
    - Informs dose selection for toxicology studies
  - Metabolite profile
    - Risk of reactive metabolites (e.g. hepatotoxicity risk)

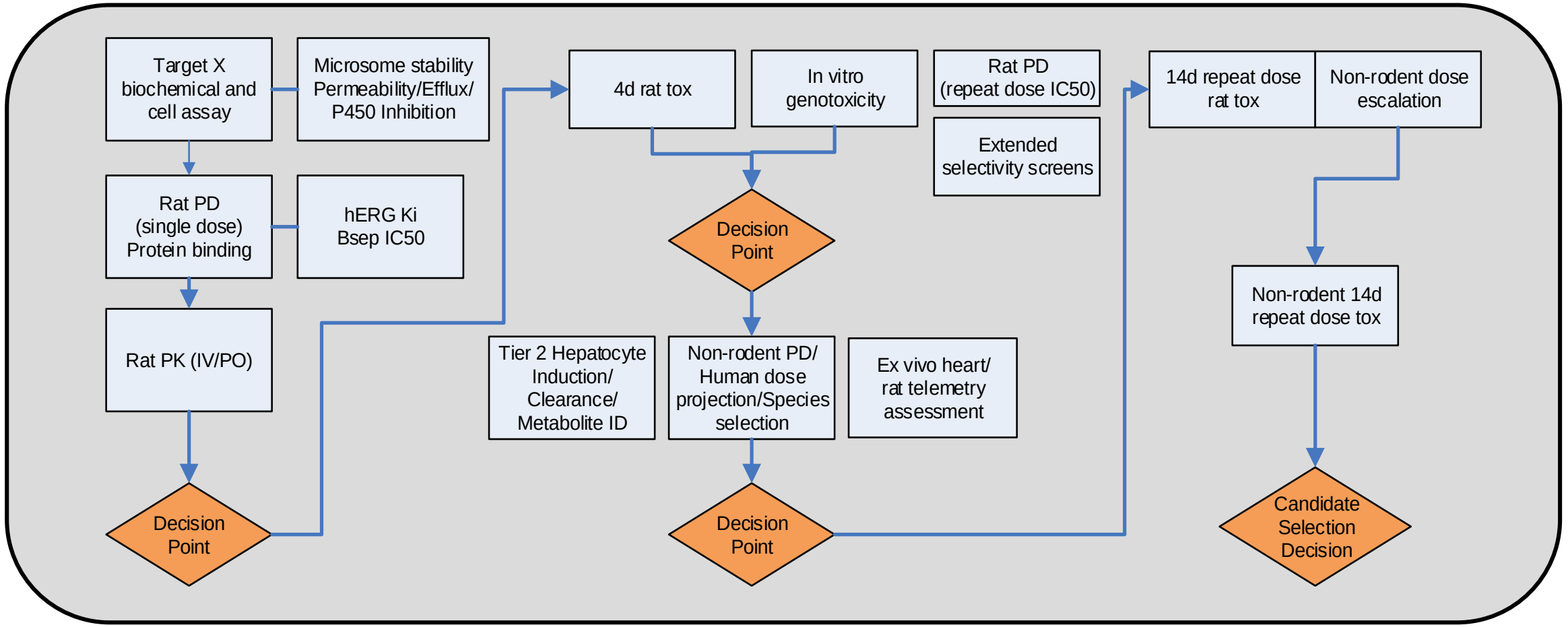
What is a Lead Optimization Flow Scheme

- An outline for how molecules will be evaluated for PD, PK and safety
- Establishes the order of testing, and typically the desired criteria to advance molecules to the next stage of testing
  - Goal is to fail fast
- Helps project teams understand
  - Resources for assays and studies needed
  - Timing considerations
  - Compound needs (how much, and when)

Conceptual LO Flow Scheme



“Real Life” Example of LO Flow Scheme



In Vivo Study Design Considerations

- Rat and dog are typical small molecule test species
  - Practical, large historical database, readily available
- 4 to 14 days in duration
  - Assumes 28-day GLP study needed to support Phase 1
- Dosing designed to establish maximum tolerated dose
  - Up to limit dose (1000 mg/kg) or saturation of exposure

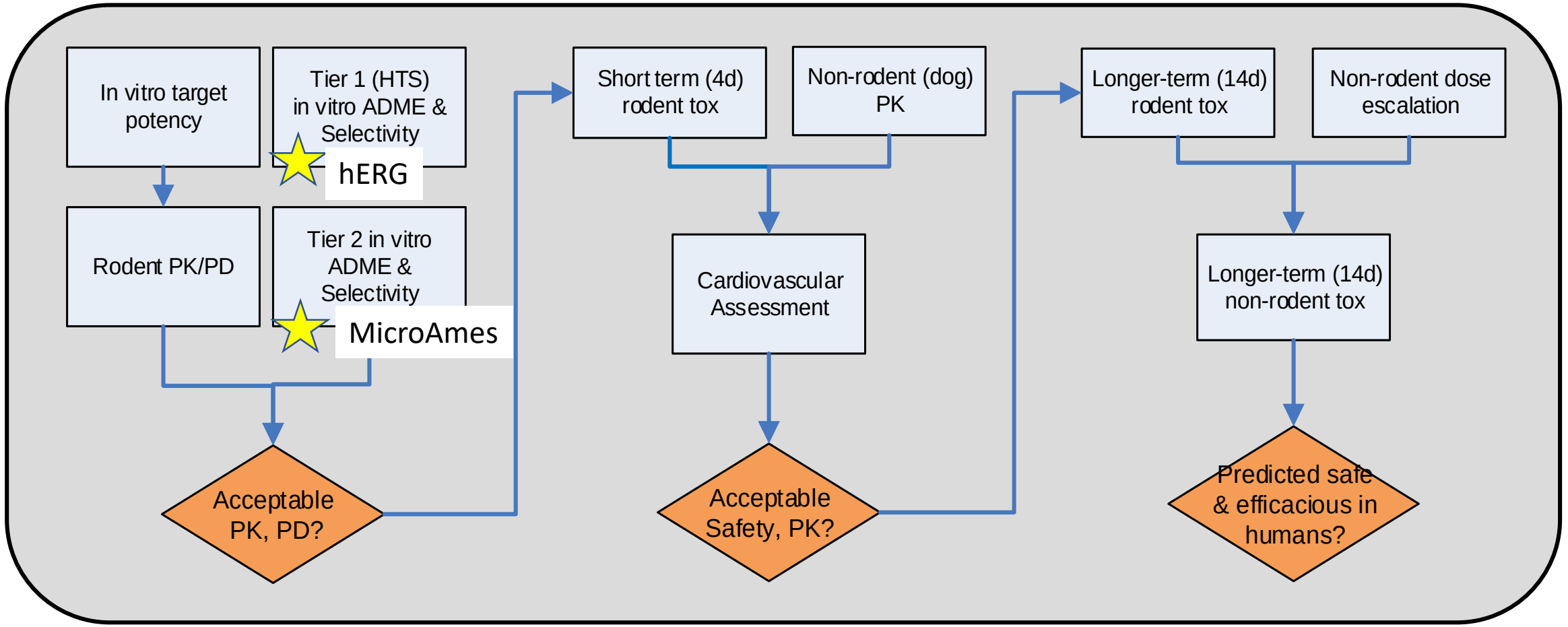
Additional Safety Considerations During LO

- On-target liabilities
  - Non-standard endpoints to inform target liabilities
- Phototoxicity
  - Absorbance, and potential in vitro evaluations (see ICH S10)
- Teratogenicity risk
  - Early assessment if outcome is critical for clinical indication
- Other safety endpoints important for clinical differentiation
  - E.g. better selectivity versus competition

Case Study 1: CV and Mutagenicity Liabilities

- Issue: chemical series has moderate affinity for hERG, and many tested compounds are mutagenic in Ames
- Project Goal:
  - Ensure an adequate safety margin to QT prolongation
  - Eliminate the mutagenicity
- Approach:
  - Front load the in vitro hERG assay and micro Ames assay prior to investment in significant compound scale-up or in vivo tests
  - Confirm safety margin to QT prolongation in whole heart/whole animal CV model according to in vitro risk

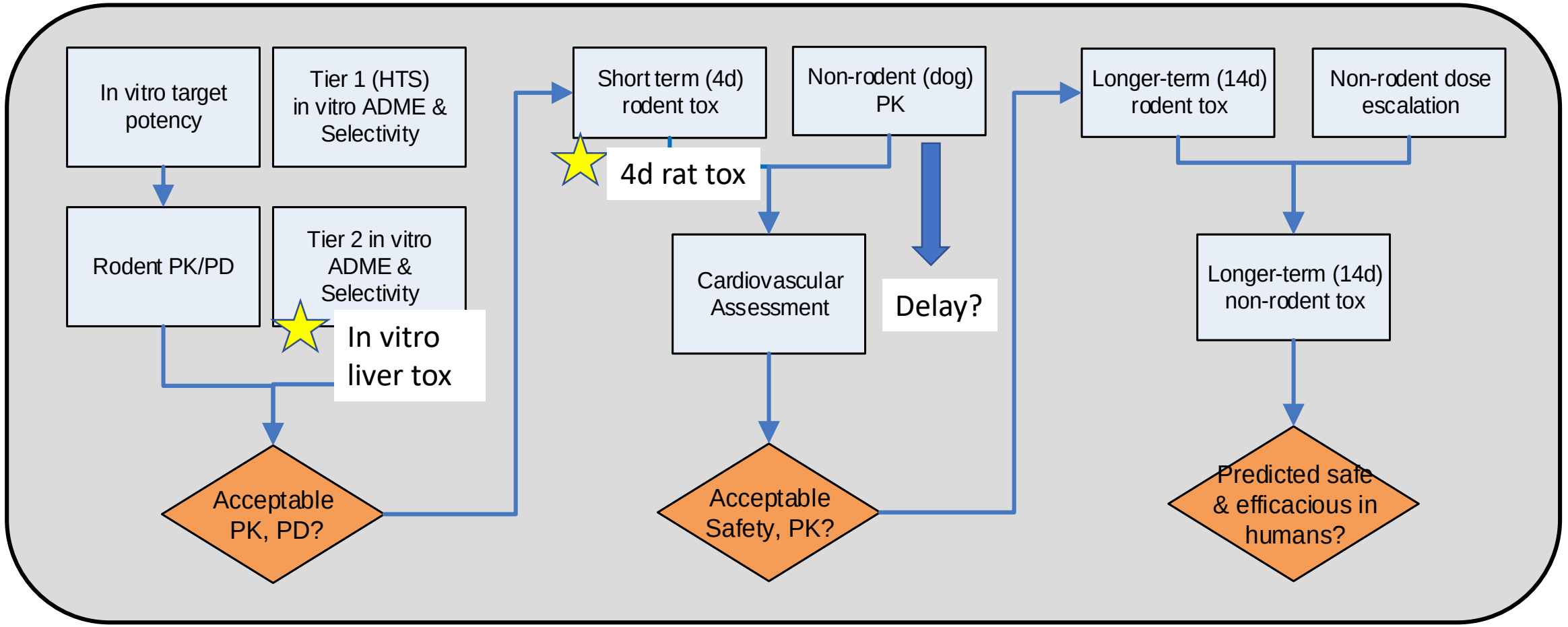
Case Study 1: CV and Mutagenicity Liabilities



Case Study 2: Unanticipated Liver Toxicity

- Issue: unanticipated liver toxicity observed in 4-day rat tox studies
- Project Goal:
  - Screen compounds to identify candidate with no liver tox (or better safety margin)
- Approach:
  - Evaluate mechanisms of liver toxicity to identify in vitro model to counter screen and prioritize compounds for in vivo testing
  - Test compounds in 4-day rat tox studies to confirm

Case Study 2: Unanticipated Liver Toxicity



Decision Making: Is My Drug Safe Enough?

- Severity of toxicity (eg. nausea vs. fatal arrhythmia)?
- Adequate margin of safety?
- Will the toxicity get worse over time?
- Is the toxicity monitorable in the clinic, and reversible?
- Consider the intended patient population and medical need
  - Chronic vs acute treatment?
  - Life-threatening disease?
  - Other treatment options?
- Consult with your clinical stakeholders

Conclusions

- Compound attrition is likely, so plan to fail fast
- LO is a dynamic and flexible process
- LO is a highly integrated process with pharmacology, pharmacokinetics and safety partners
- Identifying the clinical candidate is the starting point for drug development, so think ahead

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