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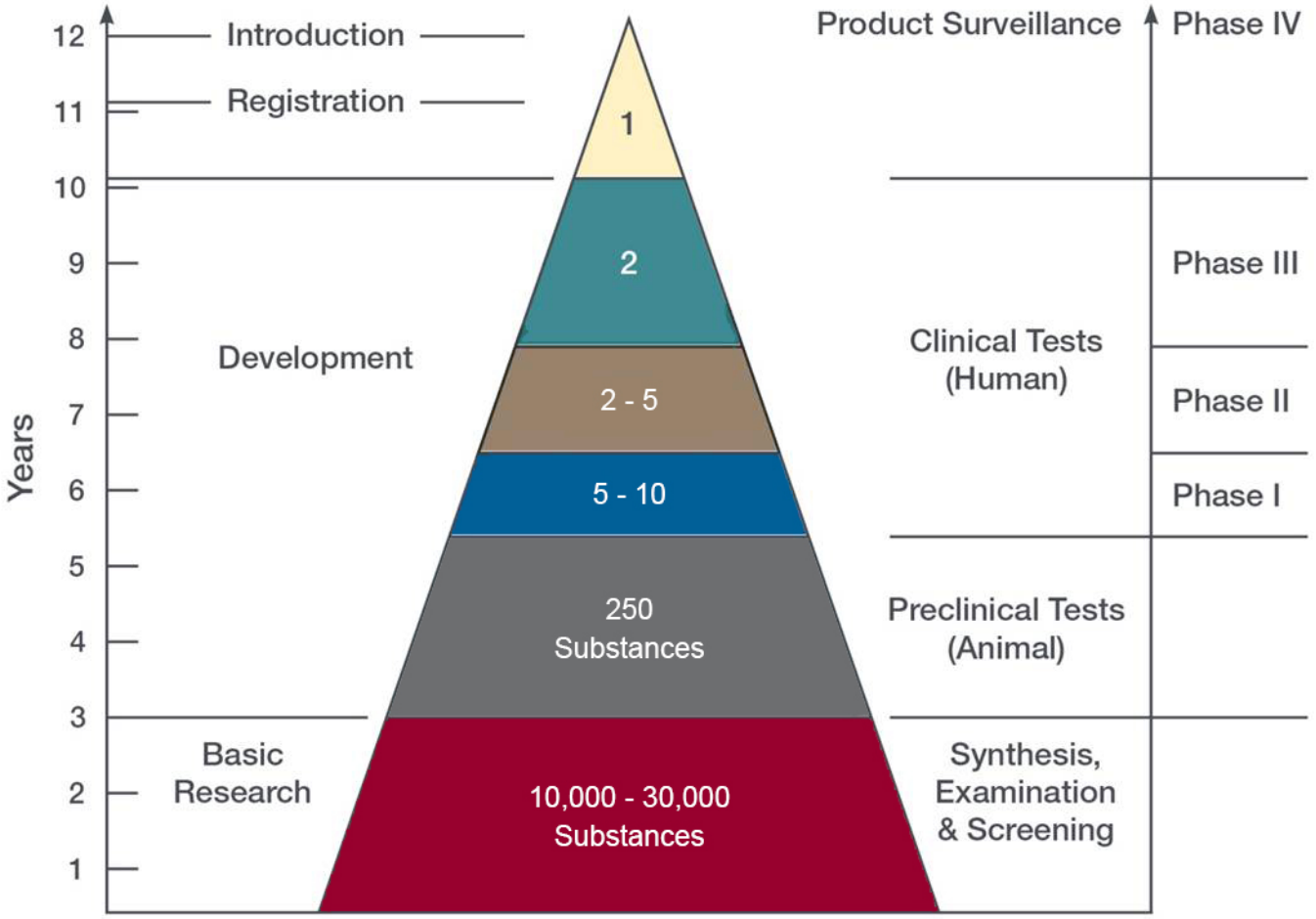
REGULATED BIOANALYSIS & DMPK

Virtual Drug Development in Southern California, A Pre-Clinical Focus

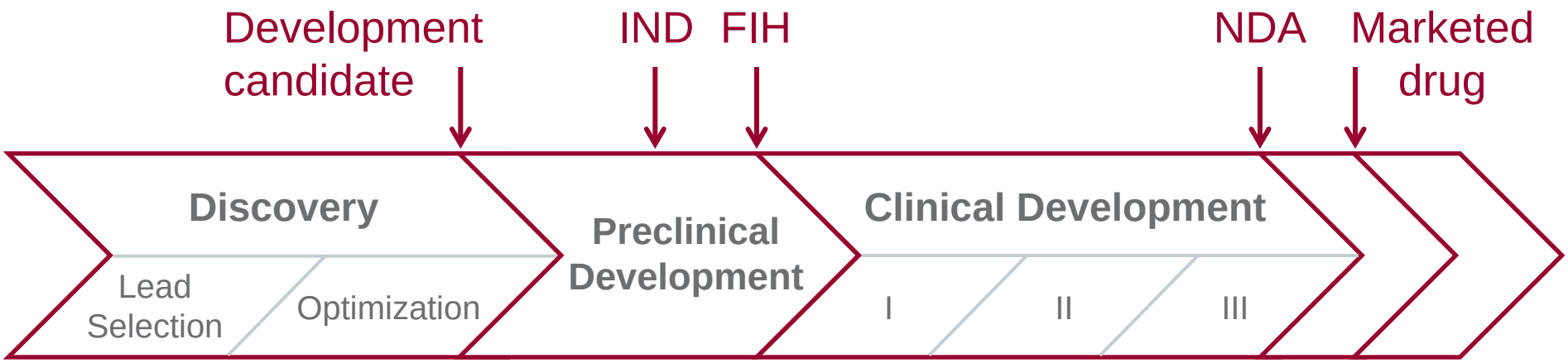
in vitro tests to support IND submissions

May 9, 2013

Development of a Successful New Drug



Drug Development Path / Lifecycle



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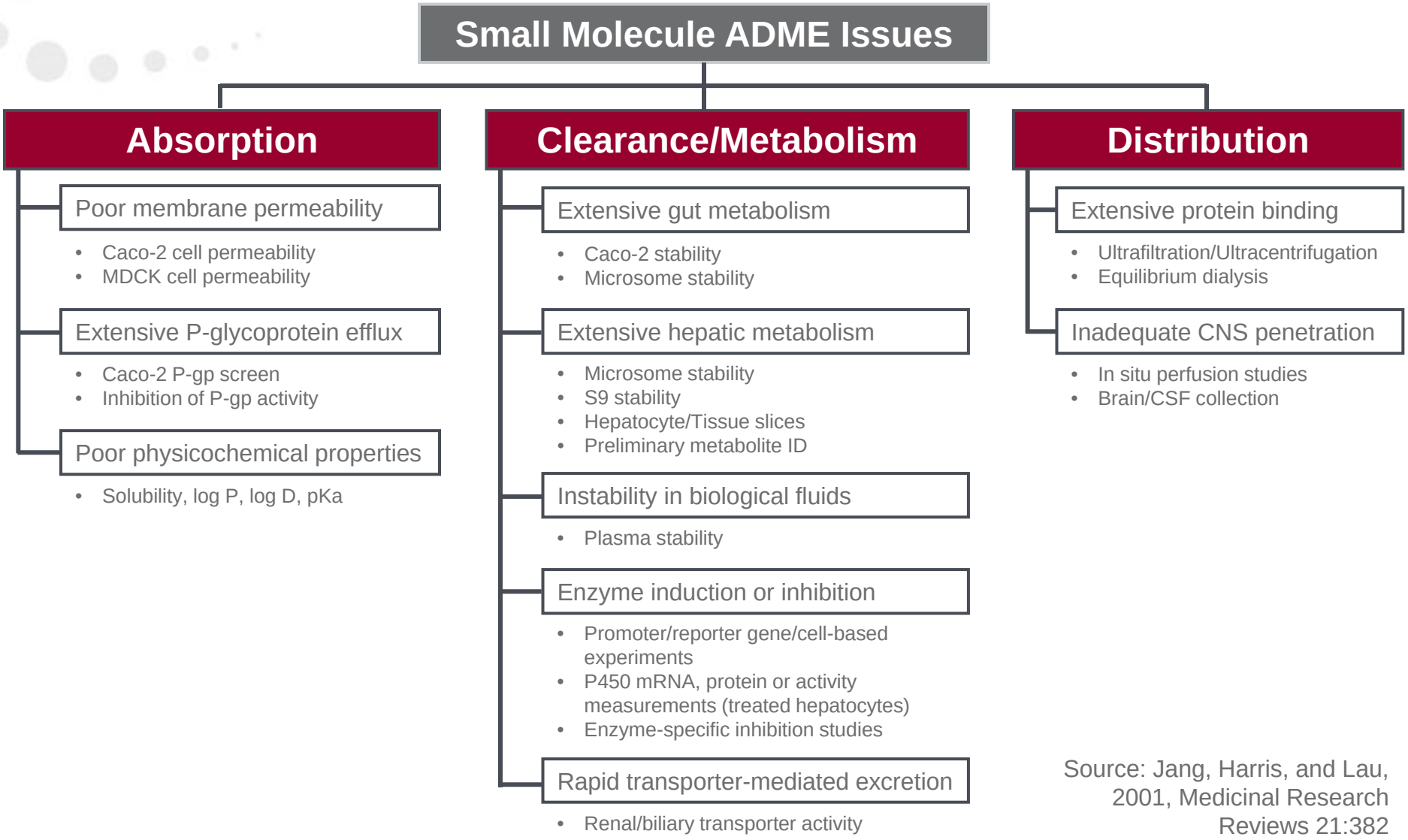
Ideal Drug Candidate Wish List

FROM A DMPK PERSPECTIVE

- Good aqueous solubility for i.v. formulation and oral absorption
- High bioavailability and acceptable PK characteristics for intended route/dosing regimen
- Small first-pass effect
- “Balanced” clearance:
  - Renal excretion of intact drug
  - Biliary elimination of intact drug
  - Metabolism to limited number of products
- Moderate plasma protein binding (<90%)
- Minimal P-450 inhibitory potential (especially mechanism-based)
- Metabolism should be catalyzed by multiple CYP enzymes, e.g., CYP3A4, 2C9, 1A2
- Metabolism should not depend largely on polymorphically-expressed P-450, e.g., CYP2D6, 2C9, 2C19
- Key human metabolites also present in tox species

Source: Carlson, Tim (Amgen). *In vitro ADME Assays & Techniques*, CACO/BAADME Workshop, March 28, 2013.

ADME Issues & *in vitro* Studies to Address Them



Source: Jang, Harris, and Lau, 2001, Medicinal Research Reviews 21:382

Primary Components of an IND Application

The IND application must contain information in three broad areas:

- **Animal Pharmacology and Toxicology Studies** - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- **Manufacturing Information** - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- **Clinical Protocols and Investigator Information** - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Source: http://www.fda.gov/cder/Regulatory/applications/ind_page_1.htm

DMPK Studies Typically Included in IND Submissions

- Plasma Protein Binding
  - Used to assess free fraction
- Drug-Drug Interaction (DDI) Studies
  - CYP inhibition / induction
  - Reaction phenotyping
  - Transporter inhibition / substrate
- Metabolite Profiling

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Thank You

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