

# Candidate Selection Tips for Developability

# Characterization Helps Development

	Oral	IV	SubQ
Chemical stability	Y	Y	Y
Some BA in animal	Y	Y	Y
Aqueous solubility / pH profile	Y	Y	Y
LogP & LogD	Y		Y
Permeability determination (CACO2 or PAMPA screen)	Y		
Export pump substrate liability (PgP, BCRP)	Y		
Preliminary Polymorphic form(s),	Y	Y	Y
Crystalline?	Y	Y	Y
Does it change?	Y	Y	Y
Solubility across polymorphic forms	Y	Y	Y

- All relatively low cost and quick
- Biologics considerations – more focus on physical stability
- Implications of NOT considering – open to risk of
  - Poor dose/exposure relationship in dose range tox
  - Inability to achieve DLTs in tox
  - Long delays in moving to tox and GMP manufacturing
  - *Can have great pharmacology / biology and only 2% BA*

# Early Safety Pre-CAN Nomination

- On top 1 or 2, non-GLP – most are weeks not months duration
  - Understand Cardiac Liability – (hERG, Nav 1.5, Cav 1.2)
  - CYP screening (metabolism pathway, inhibition, induction)
  - Plasma protein binding to provide hERG, CYP context
  - Microsomal/hepatocyte clearance, metabolite profile across species
  - Embellishing rodent efficacy studies to make sure you have a therapeutic index
    - Safety labs
    - PK (exposure-efficacy relationship)
    - Body weight monitoring
- Dose range tox with exposures in rat as part of candidate nomination
- Implications of NOT considering
  - Fail to ID poor therapeutic index prior to CAN nomination
  - Failure to ID serious DDI liability

# Identify Initial Target Indication Early

- Prioritizes route of administration
- Directs PK studies (oral vs parenteral, distribution studies –CNS, etc.)
- Informs tox exposure duration to enable human POC study
- Provides context to therapeutic index and importance of DDI, cardiac liability, etc.
- Oncology vs non-oncology indications
  - Tox package differs (definition of human starting dose, need for day-for-day multidose coverage, mutagen and repro studies)
  - FIH studies in cohort or normal volunteers

# We hope this was helpful!

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