Expectation vs Reality for Regulatory Filings

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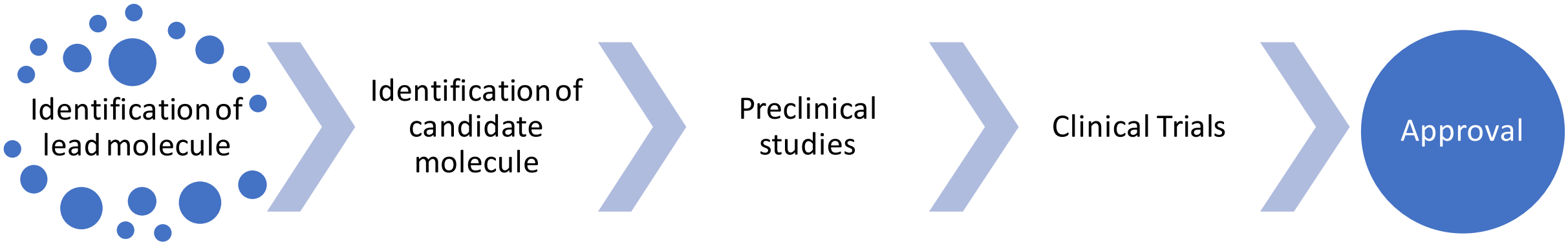
*Views are from my personal perspective and not that from Denali Therapeutics

Agenda

- Target Safety Assessment
- Taking a molecule through the drug development process (to IND and beyond): Toxicology questions asked at each phase
- Cross functional preparation for an IND application
- Decision process for pre-IND meeting
- Toxicology in clinical phase

Drug Development Timeline



Setting the Stage with Target Safety Assessment

- Purpose:
  - **Synthesizing all potential unintended adverse consequences of target modulation into an actionable set of recommendations for a safety evaluation strategy is critical to its successful application in early discovery programs.**

- When is this needed?
  - Throughout drug development process:
    - At discovery stage to scope out target
    - During toxicology studies to characterize toxicities observed
    - In clinical trial to understand emerging risks

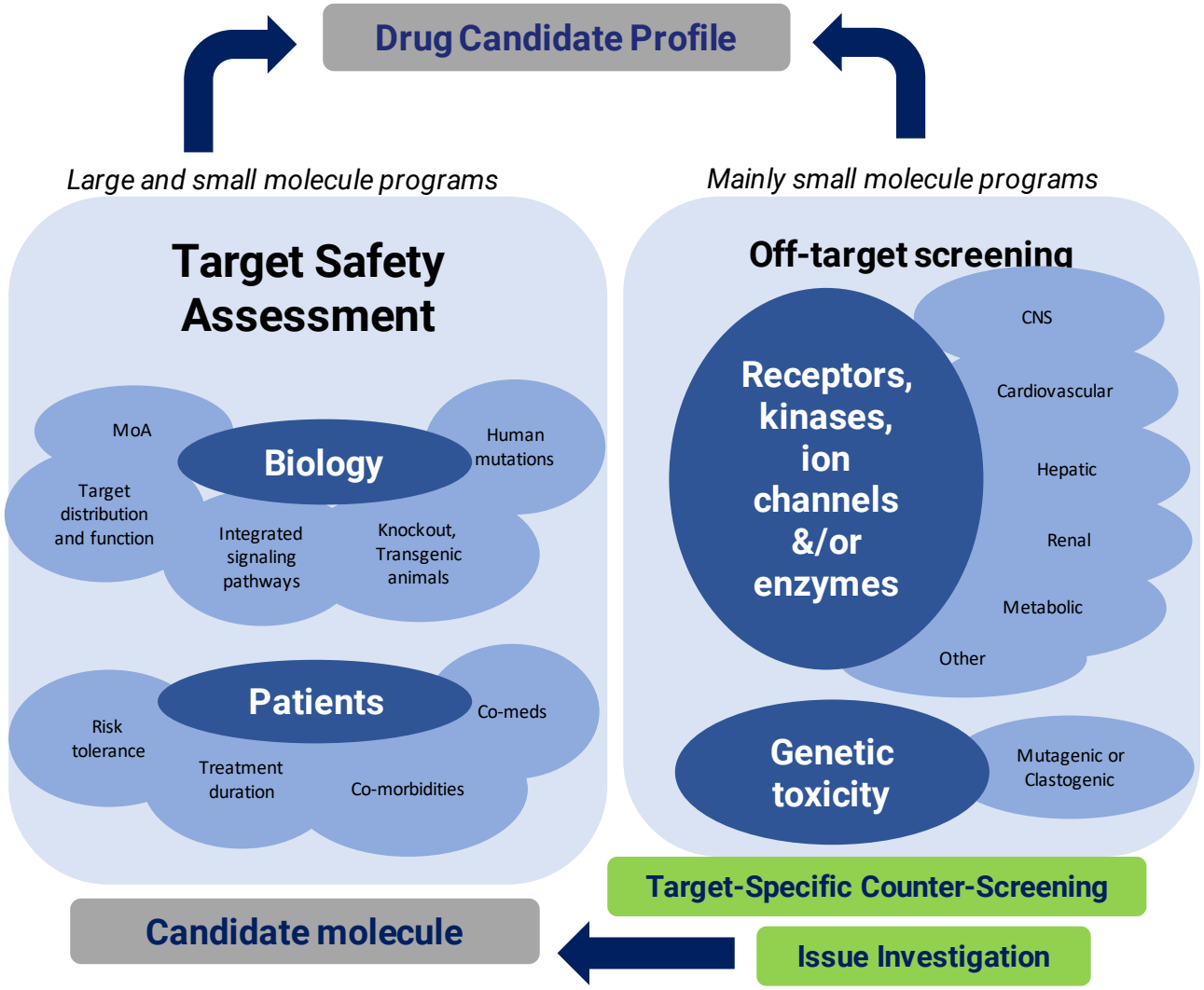
*Brennan et al 2017 Target Safety Assessment Strategies Review

Content in Target Safety Assessment

Information Included	Purpose	Source
General gene function	Physiological role of target	NCBI Gene database KEGG Gene Ontology
Gene and protein sequence comparison	Similarity in gene and protein sequence between human and preclinical model species (species selection for tox studies)	NCBI HomoloGene
Tissue Distribution and Expression	Where target is expressed High level of expression in particular organ, tissue, or cell type may indicate increased likelihood of adverse effects (pay attention to these organs in exploratory safety studies)	BioGPS Protein Atlas (include ones I use)
Biological interactions and pathways	Holistic view of biological neighborhood of target, particularly with respect to which functions downstream of the target are likely to be affected by changes in its activity	Reactome Kyoto Encyclopedia of Genes and Genomes Comparative toxicogenomics database Pathway Commons MetaCore
Knockout/transgenic models	Gain/loss of function implications	Mouse Genome Database PubMed
Competitive Information	Clinical trials – outcomes (efficacy, but also adverse events)	Clinicaltrials.gov SBoAs Press Release

*Brennan et al 2017 Target Safety Assessment Strategies Review

Target Validation to Identifying Candidate: Role of Toxicologist



Key Scientific Questions

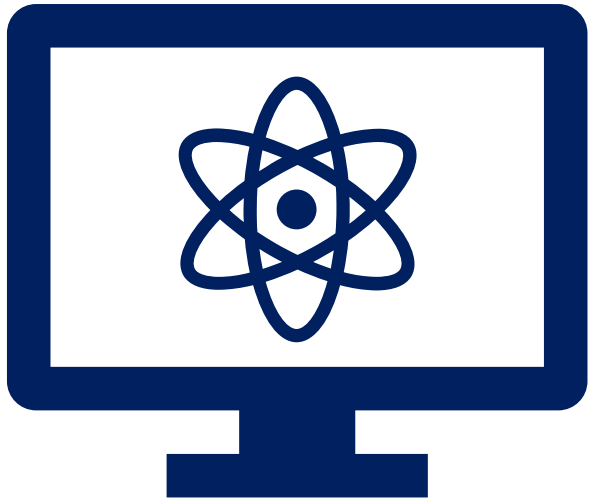
- Is this a **tractable target** from a safety perspective?
- **Potential undesired target / pathway modulation**: what do we want to evaluate early on and rule out?
- **Acceptable selectivity** (low off-target potential)?
- **Acceptable anticipated safety margins** for key causes of attrition due to safety?
- Identify potential targets that might have safety concerns (as determined from Target Safety Assessment); a particularly concerning off-target toxicology based on sequence homology or known concerns based on structural similarity
- Identify appropriate in vitro/in vivo toxicology assessment to prepare for IND enabling phase

Characterizing Candidate Molecule

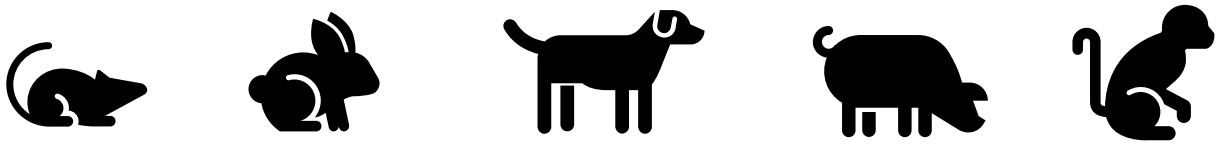
Goal: Identify molecule that meets drug candidate profile and is ready to advance into the next phase.

Key scientific questions addressed at this stage:

- Which are the best species to conduct toxicity studies?
- What are the dose-limiting toxicities?
- For key findings, conduct risk assessments:
  - Mechanism? On- or off-target?
  - Human-relevance?
  - Expected to be monitorable and reversible in the clinic?
  - Reasonable safety margin?
  - Acceptable for the intended patient population?



In Vivo Tox Assessment: Objectives and Considerations

Objectives:	Considerations:
Select appropriate species 1 rodent, 1 non-rodent	 Target homology, cellular potency, metabolite profile, achieve adequate exposures (PK), biological relevance related to known/potential toxicity concerns
Pilot toxicity studies Address key concerns (on-target, off-target)	• Identify **dose-limiting toxicities (target organ systems)** and maximum tolerated dose (MTD) • Characterize **exposure-response** with toxicokinetics
Conduct risk assessment and **design investigative studies** if needed	For adverse findings that occur with multiple molecules and are potentially impactful (small therapeutic index/possibly on-target), address key scientific question: **mechanism, pathogenesis, monitorability, reversibility, human-relevance?**

Design of Pilot Toxicology Studies

Goal: Identify dose-limiting toxicities (target organ systems), MTD, and understand exposure-response

Standard dosing duration : 5-14 days			
Dose group	Number of Animals		Target exposure multiple*
	Rodent	Non-rodent	
1. Vehicle control	4 per sex	2 per sex	N/A
2. Low dose	4 per sex	2 per sex	1-3X
3. Medium dose	4 per sex	2 per sex	5-15X
4. High dose	4 per sex	2 per sex	10-50X +

*Multiple (X) above projected human efficacious exposure, as determined by potency and pharmacology assessments; different considerations for small and large molecules

What are the standard endpoints included?

- Toxicokinetics
  - Drug concentration in plasma/tissues; determine AUC, Cmax, Tmax associated with dose and any toxicities
- Clinical Observations: evaluate animal for abnormal physical signs or behaviors
- Clinical Pathology
  - Hematology: red cell count, white cell count(s), platelet counts
  - Serum chemistry: liver and kidney function, electrolytes, serum proteins and lipids
- Necropsy/Histopathology: macroscopic and microscopic evaluation
- **Additional endpoints identified in TSA**

Conducting Toxicology Studies with CRO

Manage the conduct of Toxicology and Safety Pharmacology (non-GLP and GLP) studies

- Align on study protocol (it's all in the details!)
- Ensure study materials arrive at CRO (contract research organization) on time
- Deal with unexpected events (e.g., sick animals, test article in control samples)
- Review data and collaborate with Study Director on interpretation of results

Other responsibilities

- Forecasting studies – keeping an eye out for CRO availability with internal timelines
- Managing CRO relationship

Relevant Guidances for a Toxicology Package

Regulatory/Health Authority expectations (GLP and ICH) Main applicable guidances are provided under **I**nternational **C**onference on **H**armonisation (**ICH**), members include US, EU, Japan (but are generally accepted worldwide).

- General Nonclinical Safety Studies guidance, ICH M3 R2
- Biotechnology Products guidance, ICH S6

Other relevant, more specific guidances that are considered:

To support design of FIH studies (Phase 1)

- Safety Pharmacology, ICH S7 (effects to cardiovascular, central nervous, and respiratory systems)
- Genotoxicity, ICH S2 (mutagenicity and clastogenicity)
- Photosafety evaluation, ICH S10 (effects of photoreactivity on skin and eye)
- Immunotoxicology, ICH S8 (effects of immunosuppression on risk of infections and neoplasia)
- Oncology guidance, ICH S9

To support design of studies, generally beyond FIH studies

- Reproductive toxicology, ICH S5 (effects to fertility, embryo-fetal and postnatal development)
- Pediatric medicines, ICH S11 (effects in developing, juvenile animals)
- Carcinogenicity, ICH S1

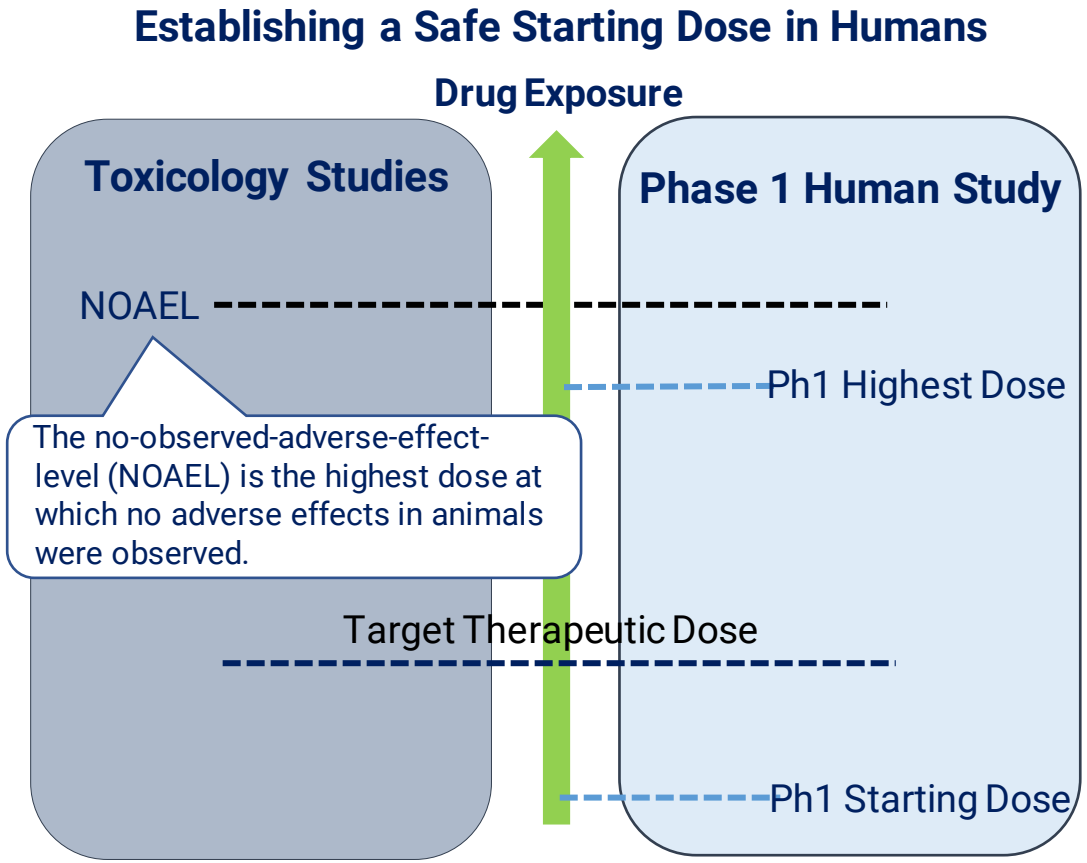
Toxicology Strategy Prior to First In-Human Studies

Goal: Determine if investigational drug is safe to proceed into humans, help establish clinical monitoring plan and a safe human starting dose by utilizing relevant animal models and validated procedures.

Toxicologists develop a **Pre-IND Toxicology Strategy** according to the needs of each program that enables the Clinical Development Plan and according to Health Authority guidelines and requirements.

The Clinical Development Plan drives the strategy

- **Understand the patient perspective** to assess risk tolerance.
  - For example, cancer will have a higher **risk tolerance** compared to a patient with rheumatoid arthritis, a disease with decades-long life expectancy and better quality of life.
- **Match or exceed the duration** dosed in clinical trials.
  - Typically, 28-day tox studies are conducted in the Pre-IND phase to enable FIH studies. Longer tox studies (6-9 months) are conducted in parallel with early clinical development to enable Ph2/3.
- **Same route of administration** as planned for human trials.



Toxicologists Interpret Tox Data to Protect Patient Safety

Conduct a Risk Assessment of the Key Finding(s)

Toxicologists work closely with Biologist, Pathologist and Clinical Scientists to review and interpret the data. The objectives are to:

- Define the **NOAEL**s and associated **safety margins**
- Determine if findings are **monitorable, manageable, reversible** in a clinical setting.

Risk Management

Monitoring for early signs of toxicity in patients may be implemented in a clinical trial based on the animal toxicology findings. The findings need to be deemed **monitorable, manageable, reversible** in humans and be appropriate for the risk tolerance of the patient population.

Risk Communication

Findings are shared with Clinical Investigators and Regulatory Authorities via the **Investigator's Brochure**. Findings are shared with patients via the **Informed Consent Form** which patients review and sign with consultation from their site's PI.

Typical Assessments conducted in Toxicology Studies

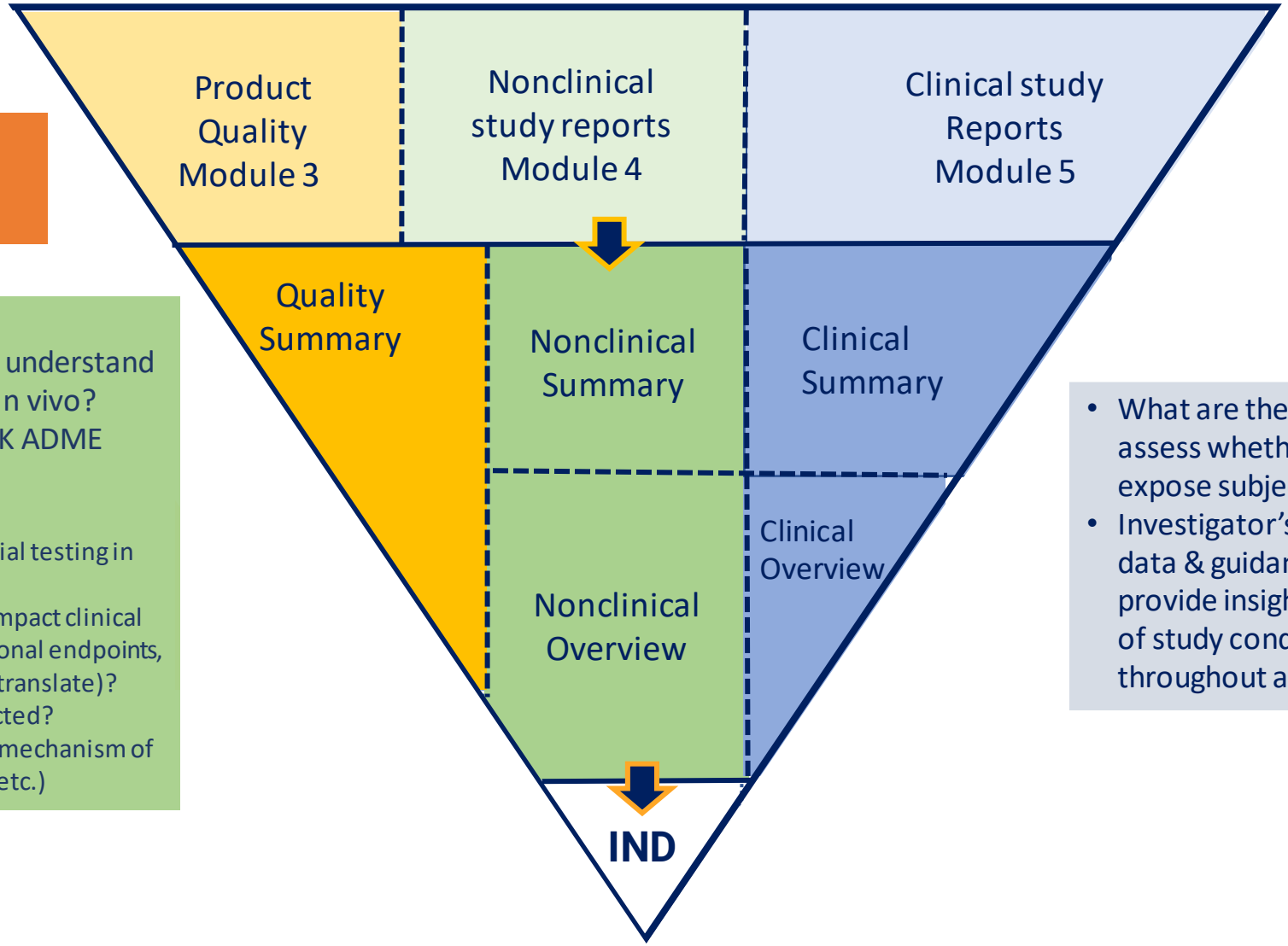
In-life Observations	• Behavioral observations • Food Intake • Body Weight
Hematology, Serum Chemistry	• Measure effects to red and white blood cell populations • Assess Organ Function
Pathology	• Macro- and Microscopic examination of organs and tissues

Building the IND

- Is the drug produced and supplied in consistent batches?

Nonclinical Sections:

- Pharmacology - What do we understand about the biology? In vitro? In vivo?
- DMPK/ADME - What is the PK ADME profile?
- Toxicology
  - Is the product safe for initial testing in humans?
  - How do our tox findings impact clinical development plan (additional endpoints, things to monitor, does it translate)?
  - Are the tox findings expected? Understanding biology of mechanism of action (target organs and etc.)

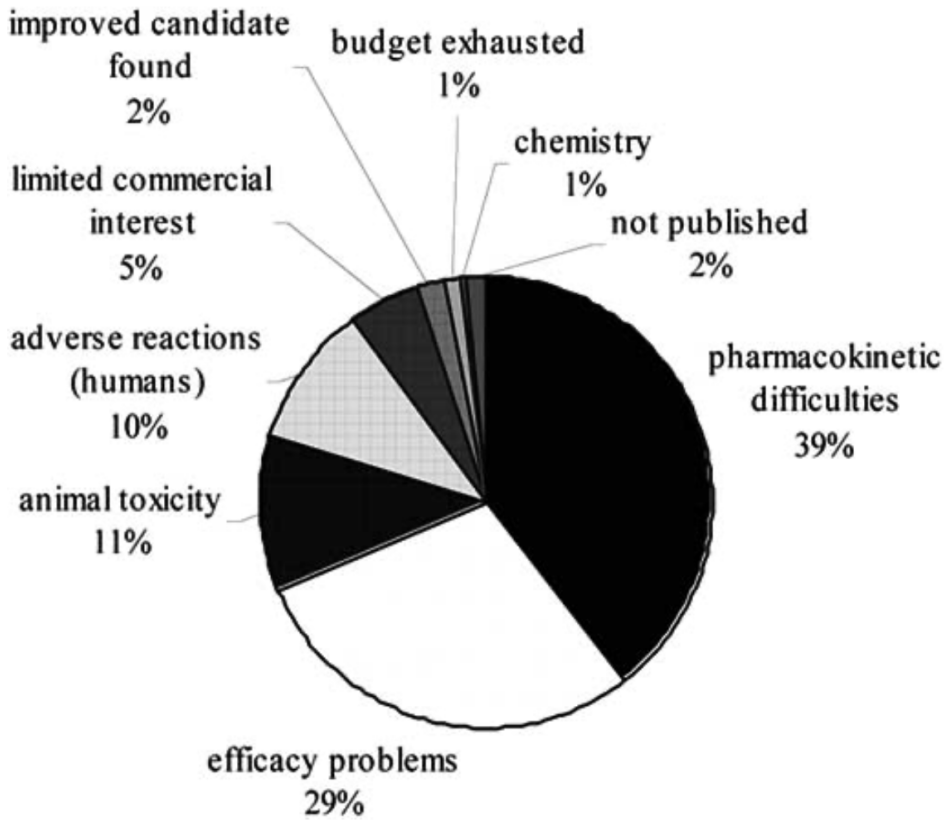


- What are the proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks?
- Investigator's Brochure (IB): Summary of data & guidance for the Investigator to provide insights necessary for management of study conduct & study subjects throughout a clinical trial.

Considerations for a Pre-IND Meeting

- What goes into the decision of needing one?
  - Any specific input that we want from the Agency?
    - Build relationship with the Agency
    - But biggest benefit is to share information especially when you have to de-risk points that are subjected to interpretation
  - Examples of when one is needed:
    - Input on a complicated clinical plan
    - Share novel biology or novel molecule
    - Difficult toxicity findings from nonclinical toxicology studies; input on toxicology plans during clinical phase (chronic toxicology and repro toxicology plans)
  - Does take extra time, program needs to account for one in the timelines
  - Limited utility if package is very straightforward
    - Disease indication that has lots of experience with a molecule class that has been used before

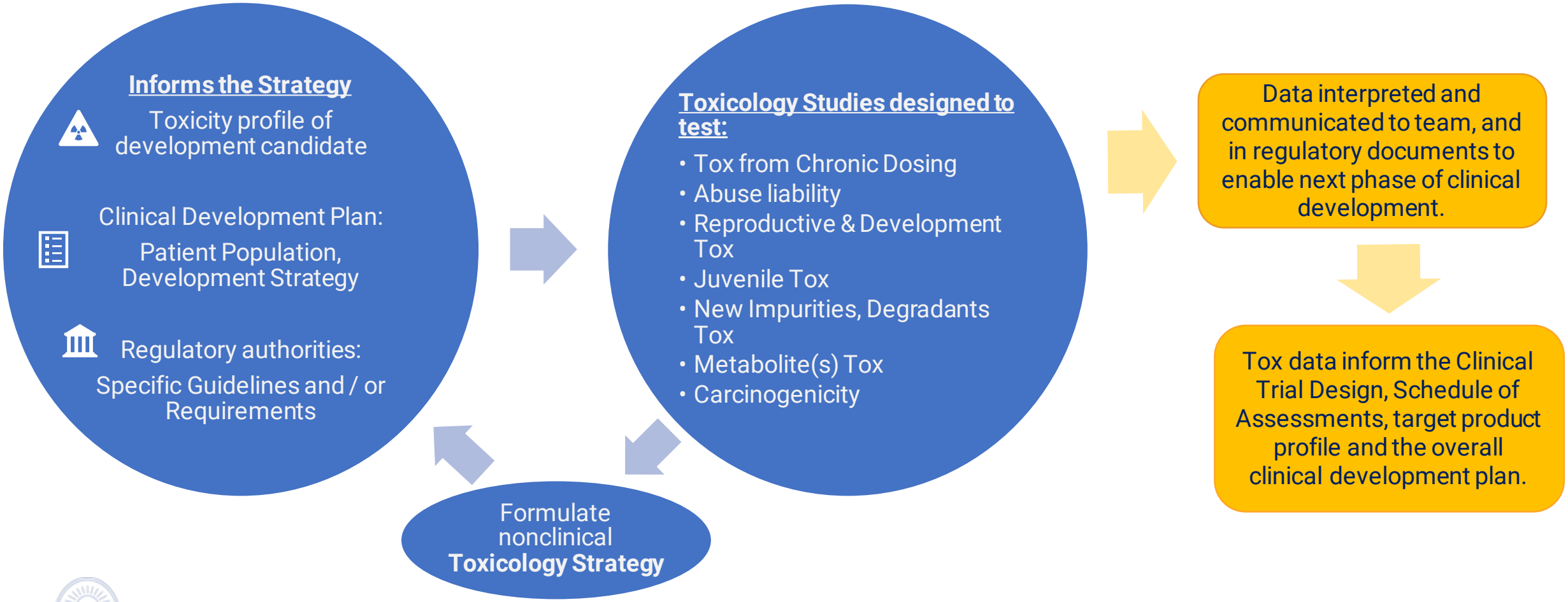
Why are Drugs Terminated?



Reasons for drug development termination

*Schuster et al 2005

Toxicology in the Clinical Phase



Conclusion

- Successful IND starts at the beginning
  - Each molecule and program is unique, all with its own challenges
  - Some guidance exists, but let the science guide your toxicology program
- Toxicology is a multifaceted role interacting with many different functions
  - Internally: chemist, protein science, biologist, DMPK, clinicians, regulatory
  - Externally: CRO, Regulatory agencies

Thank you!