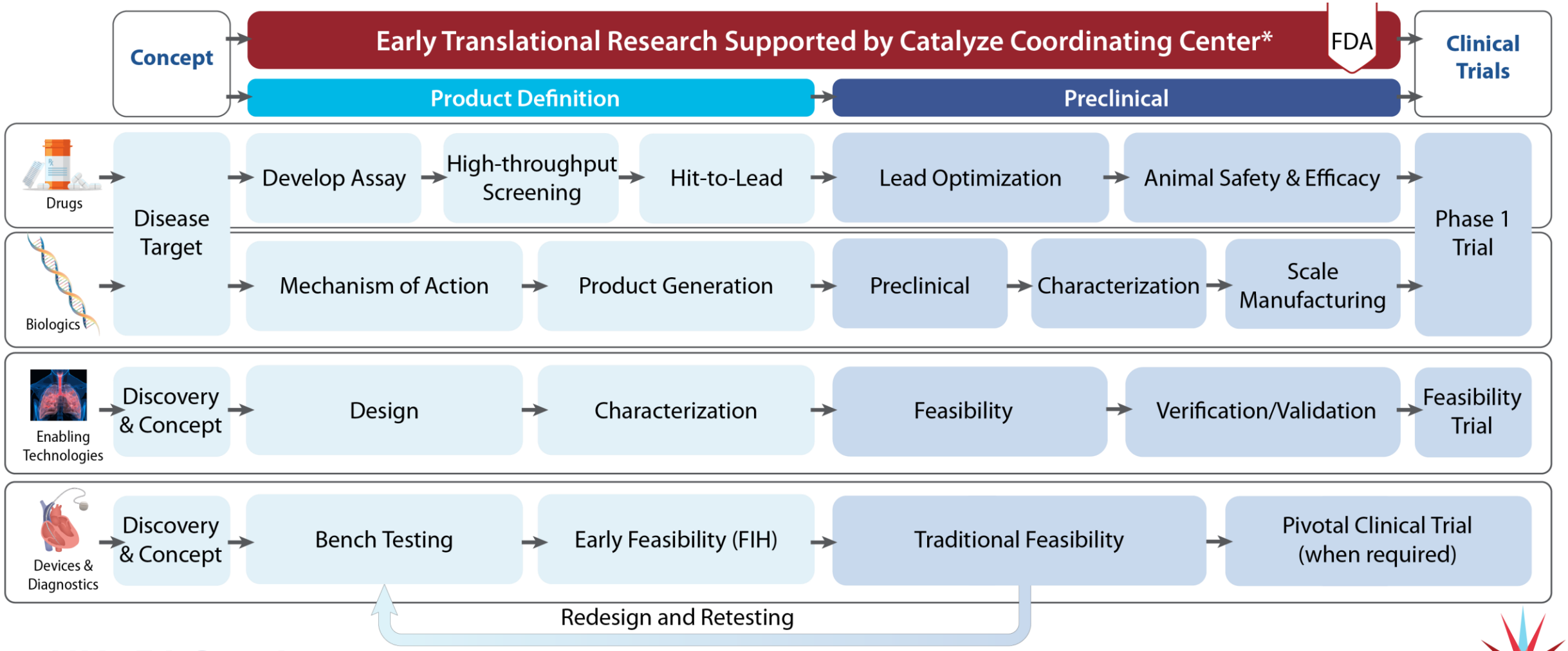
Catalyze Program Components



NHLBI Catalyze

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Product Definition Due Nov 21, 2023

- Grant Mechanism R61/R33
- Technology Readiness Level 1-3

- **Online submission through GRANTS.GOV**

- **Five Funding Opportunities**
  - Two for therapeutics
  - Two for devices, diagnostics, and tools
  - One for enabling technologies and transformative platforms

- **Special Application Requirements**
  - Project Management
  - Milestones and Timeline
  - Intellectual Property and Regulatory Strategy
  - Rigor and Reproducibility
  - Matching Funds Expectation (R33 only)
  - Accelerator Partner (R33 only)

Preclinical Services Due Nov 17, 2023

- Preclinical Services (not funds) through RTI
- Technology Readiness Level 3-8

- **Online Application to Request Services (EOI, full application)**
  - Focus on gap filling studies:
    - PK / PD, toxicology
    - Manufacturing
    - Engineering validation/verification
    - Regulatory support/submissions
  - Awardees will be expected to achieve negotiated commercial milestones

- **Special Application Requirements**
  - Competitive Landscape
  - Market Size
  - Regulatory Path (FDA communications)
  - Intellectual Property
  - Reimbursement

Questions?

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Catalyze (nhlbicatalyze.org)

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Preparing to Partner with a Contract Research Organization: What You Need to Know for an Effective and Efficient Relationship for the Development of Your Nonclinical Program

Sharon Daily, PhD, DABT - RTI

NIH National Heart, Lung, and Blood Institute

Preface

This presentation is in regard to nonclinical animal studies provided to support an investigational new drug (IND) application for various scenarios and approaches. There are a number of other aspects to the medical product development process that may not be covered.

There is not a ‘one size fits all’ approach to designing a nonclinical development plan for an IND package. Rather, nonclinical studies in support of an IND must be tailored to the specific investigational agent and the proposed clinical trials.

Drug Discovery to IND

Target Identification and Validation	Hit Identification	Lead Identification	Lead Optimization	Preclinical Development
Molecular target proposed/identified	High-Throughput Screening of compound library	Medicinal chemistry effort to turn “hits” into “leads”	Extensive med chem to improve potency and selectivity	GLP-compliant toxicology and PK studies
Biological hypothesis relevant to disease	Virtual or *in silico* screening	Potency and selectivity	*In vivo* efficacy in additional models	GLP-compliant safety pharmacology studies
Genetic models to demonstrate proof of concept	Confirm potency and selectivity of “hits” in 1º and 2º assays	*In vitro* PK: CYP inhibition, metabolic stability	*In vivo* PK characterization	Drug formulation
	Initial *in vitro* pharmacokinetic (PK) assessment	*In vivo* efficacy in relevant animal models of disease	Initial dose-ranging toxicology studies	Pre-IND meeting with FDA

Nonclinical Development Program

- Once a lead molecule (candidate compound) is identified, a specific nonclinical development strategy should be prepared. Nonclinical studies seek to answer the following questions:
  - Does it work? (Efficacy assessment)
  - How can it be delivered and how does the body react? (ADME profiling)
  - Is it safe? (Toxicology/safety, pharmacology assessment)
  - Is the manufacturing process viable and controllable? (CMC activities)
- **Nonclinical development studies and activities continue throughout the life-cycle of the product.**

Types of Nonclinical Studies Needed for Phase 1 Studies

Type of Study	Aim of Study
Primary & secondary pharmacodynamics	In vivo and/or in vitro studies, assessing mode of action/effects of candidate compound on the target.
Safety pharmacology	Assess effects on central nervous system, respiratory, cardiovascular systems.
Pharmacokinetics / toxicokinetics	Assess ADME components; exposure data
General toxicology	Expanded acute and repeated dose data in two mammalian species
Genetic toxicology	Assess mutations and chromosomal damage

What Is Needed Before You Do Nonclinical Studies

- Species selection
  - Metabolic profiles
  - Pharmacology
- Vehicle / Formulation
  - Solution vs. suspension
  - Concentration
- Methods
  - Analytical – Dose Formulation Analysis (DFA)
  - Bioanalytical - Toxicokinetics
  - Immunological for biopharmaceuticals
- Clinical plan

Nonclinical Toxicology Package Overview

- Evaluate 1 rodent (usually rat) and 1 non-rodent (usually dog) species
- Should be pharmacologically active (at least one species)
- Should have some ADME information for each
- Monkey usually only used after de-selection of dog

Range Finding Studies:

- **Goal:** Select doses for definitive studies; usually non-GLP
- Observe general toxicity, survivability, target organs, and TK (toxicokinetics)
- Define non-toxic & toxic dosages
- Ideally define the maximum tolerated dose (MTD)
  - Make sure to push the dose

Pivotal Toxicity Studies

Goals:

- Identify toxicities to guide clinical monitoring
- Identify no-observed-adverse-effect-level (NOAEL)
- Calculate safety margins relative to intended clinical exposures
- Set safe starting doses in the clinic

Study Design:

-3 Dose groups and vehicle control
-Generally half-log spacing of doses (based on TK exposures –AUC)
-N = 10/sex/group for rodents (could be larger for longer studies)
-N = ~4/sex/group for non-rodents

Endpoints:

-Clinical pathology, ophthalmology, cardiovascular evaluations (non-rodent)
-Terminal necropsy –full histopathology
-Recovery groups (Control and HD; optional);
N=5/sex/group rodents; 2/sex/group non-rodents

Genotoxicity Studies

Goal: To test for mutagenicity and clastogenicity (strand break) potential

- Generally conduct the following 3 tests:
  - *In vitro* Ames –mutation test in multiple strains of bacteria (+/-metabolic activation)
  - *In vitro* micronucleus or mouse lymphoma assay (+/-metabolic activation) –genetic damage
  - *In vivo* rodent micronucleus test –genetic damage

- Flexibility on timing of the studies

Safety Pharmacology Studies

Goal: Evaluate physiologic changes related to pharmacology (PD) that could cause acute effects in Ph1 subjects

- Generally conduct the following assessments:
  - Neurobehavioral toxicity (Irwin test) –rats
    - Functional observational battery; autonomic, sensory/motor, behavior
  - *In vitro* - hERG (human potassium channel), patch-clamp test
  - Cardiovascular - *In vivo* in non-rodents
    - ECG, QTc prolongation, HR, blood pressure, etc.
  - Respiratory–Stand-alone in rodent

Pre-Investigational New Drug Application (pre-IND) Meeting

- A Pre-IND meeting can be a valuable component in planning a development program.
- For companies that have not previously interacted with the FDA in the early stages of a product's development, a pre-IND meeting is an opportunity to receive the Agency's feedback and guidance prior to conducting expensive GLP toxicology studies.
- While FDA guidance documents can provide helpful information, they are broadly applicable to several types of products.
- Regulatory strategy for the overall development program may require a gap analysis.

Benefits of a Gap Analysis

Assessment of the Investigators product development program can reduce time in several ways:

- Ensure that the necessary studies have been conducted
- Identify and avoid unnecessary studies
- Clarify endpoints and goals of the development program
- Costs could be minimized
- Develop a strategy that will gain the support of FDA

❖When the investigator is ready to move forward, a pre-IND briefing document summarizing the available preclinical data and the proposed development plans, e.g. study details of the GLP toxicology studies, will be submitted to the FDA.

Position Your Program To Investors: Leveraging FDA Feedback

- Many investigators use the completion of their initial FDA meeting as a springboard to raise external capital, as the outcome of the Pre-IND meeting can be a useful fundraising tool.

- In order to receive the most useful information from the pre-IND meeting, we encourage investigators to discuss their development plans and to ask questions that are specific not only to the early phase but possibly the next phase of their program.

- By receiving, meaningful and clear recommendations from the Agency, an investigator's pitch to investors, will demonstrate the investigator's ability to de-risk the products development.

Questions Asked by Review Pharmacologist/Toxicologist

- Validity of study design:
  - Was the appropriate animal model used?
  - Were dose(s) and duration sufficient to support the proposed clinical study?
  - Were adequate systemic exposures achieved?
  - Was the route of administration relevant to clinical used?

- Other questions:
  - Did the test system exhibit any effects?
  - Were the effects treatment-related?
  - Are the effects biologically significant?
  - Are the effects reversible?
  - Are the effects clinically relevant?
  - Can the effects be monitored clinically?

Statement of Work/ RFP

Statement of Work: Name of Nonclinical Study

On behalf of the *Insert Sponsor/Company*, RTI International requests a proposal(s) for a name of study for a compound which the *Sponsor* is developing as an oral pro-drug to treat X.

As a reminder, the *Sponsor* is a non-profit philanthropic organization that is highly interested in conserving financial resources and would greatly appreciate any discounts granted from your organization. Please indicate in the proposal any discounts provided and the duration of time that the quoted pricing will be honored. Finally, please note that this is a competitive bidding process.

Prepare for:

Sponsor Name, Ph.D.
Address Title
Email

Send Quotation to:

RTI International
East 3040 Cornwallis Road
Research Triangle Park, NC 27709
www.rti.org

Name
Title
email@rti.org
919-XXX-XXXX

Name
Title
email@rti.org
919-XXX-XXXX

Study Design

The Sponsor is in the process of planning X study. Include other relevant information about study objectives.

Table 1. Study Design (Blank study, ex for a 28-day study with recovery)

Regulatory Compliance	GLP or non-GLP
Species/Strain	
Age at Start of Dosing	
Weight at Start of Dosing	
Dose Regimen	
Dosing Formulation and Preparation	
Dose Analysis	
Design	

Group	Treatment	Dose Concentration (mg/mL)	No. of Animals at Necropsy		TK Satellite Group
			Day 28 (Main)	Day 56 (Recovery)	Day 28
1	Vehicle				
2	Test Article				
3	Test Article				
4	Test Article				
Total No. of Animals					

Assessments	•
Toxicokinetics	
Scheduled and Unscheduled Necropsies	
Statistics	
Final Report	
Other Proposal Requirements	

Estimating Safe Starting Dose for Phase 1

- **Submit with IND**
  - Calculate Human Equivalent Dose (HED) of NOAEL in animals
  - Use mg/m2 conversion factor (km) to account for body surface area differences
  - For certain drugs (e.g., mAbs) –use mg/kg without conversion
    - **ex) rat NOAEL = 200 mg/kg/day; HED = 200 / 6.2 rat km= 32 mg/kg (~1900 mg)**

- First Ph1 clinical dose should be ~10-fold lower than NOAEL HED
  - Apply a greater safety margin in certain cases (e.g., steep dose-response)
  - **ex)**start at 1900/10 = 190 mg
  - Dose-escalate to HED of animal NOAEL (ex, 1900 mg)
  - Not generally allowed to go above the HED of the animal NOAEL

QUESTIONS

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Upcoming Events & Reminders

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CRO/CMO Webinar Series

- **January 2024** – Approaching & partnering with CMOs
- **February 2024** – Device-specific considerations for partnerships with contract orgs

Have a question or want to learn more?

- Visit us online at **nhlbicatalyze.org**
- catalyze_info@rti.org
- NHLBI_Catalyze@nih.gov

Back Up Slides

Guidelines

- ICH
  - Q3A (R2) Impurities in New Drug Substances
  - Q3B (R2) Impurities in New Drug Products
  - Q3C (R4) Impurities Guidelines for Residual Solvents
  - S1A Need for Carcinogenicity Studies for Pharmaceuticals
  - S1B Testing for Carcinogenicity of Pharmaceuticals
  - S1C (R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals
  - S2 (R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
  - S3A Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
  - S3B Pharmacokinetics: Guidance for Repeat Dose Tissue Distribution Studies

Guidelines

- ICH (Continued)
  - S4 Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing)
  - S5 (R2) Detection of Toxicity to Reproduction for medicinal Products & Toxicity to Male Fertility
  - S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
  - S7A Safety Pharmacology Studies for Human Pharmaceuticals
  - S7B The Non-Clinical Evaluation of the Potential for Delayed Ventricular Depolarization (QT interval prolongation) by Human Pharmaceuticals
  - S8 Immunotoxicology Studies for Human Pharmaceuticals
  - S9 Nonclinical Evaluation of Anticancer Pharmaceuticals
  - S10 Photosafety Evaluation
  - M3 (R2) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

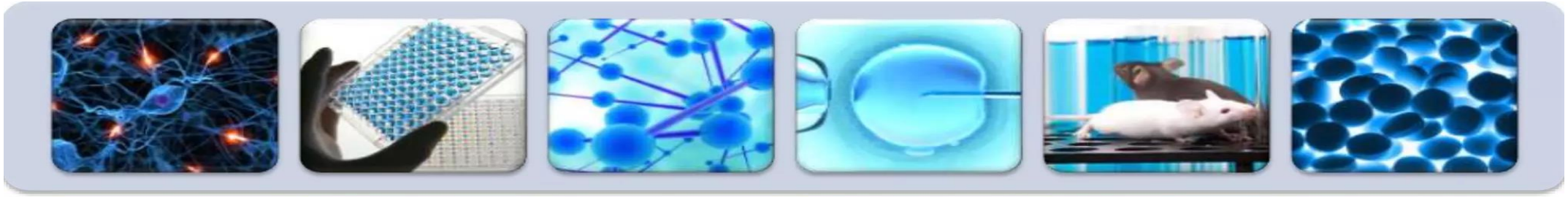
Guidelines

- CDER
  - Animal Models - Essential elements to Address Efficacy under the Animal Rule
  - Developing Medical Imaging Drugs and Biological Products - Part 1: Conducting Safety Assessments
  - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers
  - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches
  - Immunotoxicology Evaluation of Investigational New Drugs
  - Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals
  - Nonclinical Safety Evaluation of Drug or Biologic Combinations
  - Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route
  - Nonclinical Safety Evaluation of Pediatric Drug Products

Guidelines

- CDER (Continued)
  - Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
  - Photosafety Testing
  - Recommended Approaches to Integration of Genetic Toxicology Study Results
  - Reference Guide for the Nonclinical Toxicity Studies of Antiviral Drugs Indicated for the Treatment of N/A Non-Life Threatening Disease Evaluation of Drug Toxicity Prior to Phase I Clinical Studies
  - Safety Testing of Drug Metabolites
  - Single Dose Acute Toxicity Testing for Pharmaceuticals
  - Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals
  - Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs
  - Exploratory IND Studies
  - Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination
  - Applications covered by Section 505(b)(2)

Drug Discovery to IND



Target Selection	Lead Discovery	Medicinal Chemistry	In Vitro Studies	In Vivo Studies	Clinical Trials and Therapeutics
• Cellular and Genetic Targets • Genomics • Proteomics • Bioinformatics	• Synthesis and Isolation • Combinatorial Chemistry • Assay development • High-Throughput Screening	• Library Development • SAR Studies • In Silico Screening • Chemical Synthesis	• Drug Affinity and Selectivity • Cell Disease Models • MOA • Lead Candidate Refinement	• Animal models of Disease States • Behavioural Studies • Functional Imaging • Ex-Vivo Studies	

Types of Nonclinical Safety Studies the Investigator will Need to Conduct for Phase 1 Studies

- Safety pharmacology
- Pharmacokinetics/toxicokinetics (exposure data)
  - Metabolism and transporters
- Expanded acute or repeat dose toxicity studies
  - Rodent and Nonrodent
- Local tolerance
- Genetic toxicity
  - *in vitro* evaluation of mutations and chromosomal damage

Phase I Clinical Trial – IND

- Before starting a clinical trial, an IND must be submitted to the FDA.
- Any trial in humans cannot be initiated until FDA has given approval; the safety of the therapeutic will be a primary factor.
- If the FDA does not approve, then your clinical trial could be put on clinical hold.
- In order to de-risk the possibility of a clinical hold, it might be beneficial to have your development program undergo a gap analysis.
- Often times, the CRO will not be fully be aware of your program and therefore will not have anticipated if all the necessary studies have been conducted prior to IND submission.

CMC for the Nonclinical Scientist

- *Analytical and Bioanalytical Method Development*
  - *Dose Formulation Analysis*
  - *Toxicokinetics*
- *Test article estimates*
- *Non-GMP and GMP*
- *Certificate of Analysis (COA)*

Selection of High Dose

- High dose should show toxicity (adversity)
  - Should be considered the maximum tolerated dose (MTD)
  - Justify based on results in earlier studies
  - Toxicities may occur at lower doses in longer studies

    ex) liver toxicity –generally tolerated, doesn't progress –use same dose

    ex) cardiac toxicity –could get worse –consider lowering the dose

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