The Drug Development Process and the Role of DAIT's Office of Regulatory Affairs

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Presentation Overview

- DAIT Office of Regulatory Affairs Staff
- How Can We Help You (the PI)
- Traditional Drug Development Pathway for an NME
- Resources

Office of Regulatory Affairs (ORA)

Name	Title	Previous Employment
Christine Czarniecki, Ph.D.	Chief, Office of Regulatory Affairs	Genentech, ICOS, AXYS, InterMune
Julia Goldstein, M.D.	Senior Regulatory Affairs Officer	MedImmune Inc., SAIC Food and Drug Administration
Steven Adah, Ph.D.	Senior Regulatory Affairs Officer	Food and Drug Administration
Jui Shah, Ph.D.	Senior Regulatory Affairs Officer	Food and Drug Administration
John Guzman, M.S.	Senior Regulatory Affairs Officer	Nabi Biopharmaceuticals Food and Drug Administration Quintiles
Sheila Phang, R.N.	Regulatory Affairs Specialist	NHLB, NIH Metropolitan Healthcare
Tomeka Templeton	Quality Assurance Specialist	Hemagen Diagnostics, Inc. Alpha Therapeutic Corporation
Richard Legg	Program Specialist	NIMH Endocrinology Clinic US Army

Regulatory Affairs

- **DAIT Office of Regulatory Affairs Staff**
- **Contract Research Organization (CRO)**
- **Individual Consultants**
  - **GLP toxicology**
  - **GMP quality**
  - **GMP facilities**

The “Good Practices”

GCP

Ensures Quality of Data Obtained from Clinical Testing, and Protects the Rights and Safety of Clinical Subjects

GLP

Ensures Quality of Preclinical Testing and Data Obtained

GMP

Ensures Quality of Drugs Based on Standards Applicable for All Manufacturing Facilities

Role of Regulatory Affairs

- **Develop regulatory strategy for the project**
- **Anticipate the needs of the FDA and other Health Authorities**
- **Communicate those needs to the team**
- **Monitor the conduct and reporting of trial activities to ensure that the needs are being met**
- **Assemble and submit documents in a form that can be effectively reviewed by FDA**
- **Manage the FDA document review process and lead negotiations with FDA to achieve successful outcome**
- **Compliance with all regulatory requirements**
- **Newly issued regulatory requirements**
  - **Analyses**
  - **Communication**
  - **Implementation**
- ***Serve as the Sponsor's authorized representative***

Ongoing Projects

- **Communications with Health Authorities**
  - **Verbal (Telephone)**
  - **Face-to-Face Meetings**
  - **Written Submissions**
    - **New INDs**
    - **Amendments: SAE Reports, Annual Report, Response to FDA questions**
- **Communications with study drug manufacturers**
- **Compliance**
  - **Problem solving with team**
  - **"Sponsor" study files**
    (clinical & regulatory)

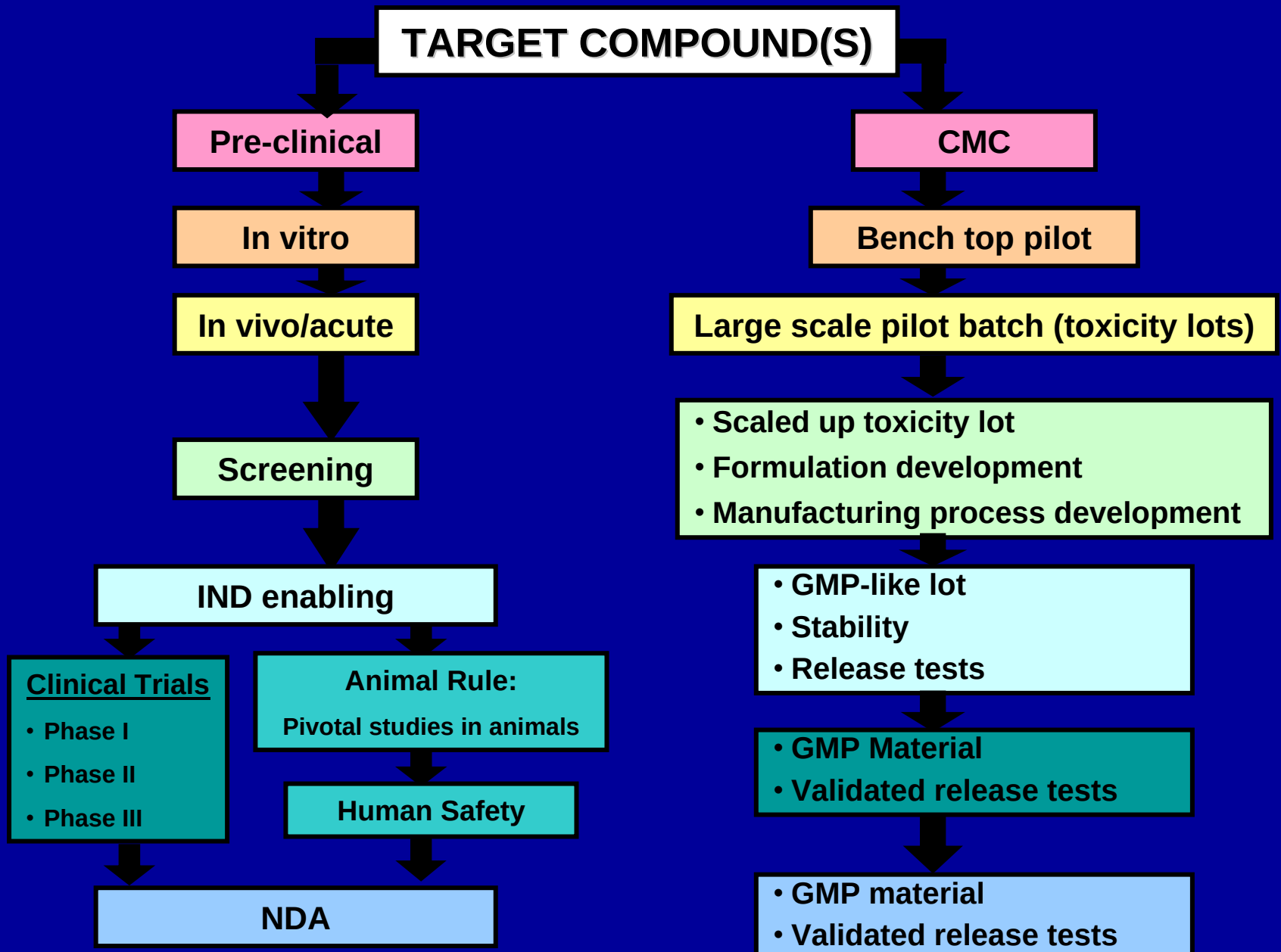
FDA Processes

- PreIND Meeting
  - Meeting Request
  - Questions
  - Package
- IND
  - Ongoing Communications with FDA

Drug Development & Approval Process

	Pre-clinical testing		File IND	Phase I	Phase II		Phase III			File NDA or BLA	FDA		Approval
Year	1	2		3	4	5	6	7	8		9	10	→
Test population	Laboratory & Animal Studies			20 to 80 patient volunteers	100 to 300 patient volunteers		1,000 to 3,000 patient volunteers				Review usually takes about 2-3 years		Post-marketing safety monitoring
Purpose	Assess safety and biological activity			Determine safety and dosage	Evaluate effectiveness. Look for side effects.		Verify effectiveness, monitor adverse reactions from long-term use.						Large-scale manufacturing Distribution Education

Expedited Review: Phases II and III combined to shorten approval process on new medicines for serious and life-threatening diseases.


TARGET COMPOUND(S)
Pre-clinical
In vitro
In vivo/acute
Screening
IND enabling
Clinical Trials
• Phase I
• Phase II
• Phase III
Animal Rule:
Pivotal studies in animals
Human Safety
NDA
CMC
Bench top pilot
Large scale pilot batch (toxicity lots)
• Scaled up toxicity lot
• Formulation development
• Manufacturing process development
• GMP-like lot
• Stability
• Release tests
• GMP Material
• Validated release tests
• GMP material
• Validated release tests

In Vitro Studies

Preclinical

- Preliminary Efficacy Studies
- Dose Response Curves
- Cytotoxicity
- Preliminary In vivo studies

CMC

- Chemical Synthesis
- Isolation of Active
- Small Scale Laboratory Lots
- Physicochemical Properties

In Vivo/Acute Studies

Preclinical

- MTD
- DRC for Radiation Levels
- Sequence & Timing Optimization

CMC

- Small Scale Laboratory Lots
- Tox Lots

Screening Studies

Preclinical

- Pharmacology
  - Efficacy Studies (>1 species)
  - MOA
- ID Clinical Route
- Safety
  - LD50 & MTD
  - Any combination drugs

CMC

- Tox Lots
- Formulation development
- Small Scale Laboratory Lots
- Physicochemical Properties

IND Enabling Studies

Preclinical

- Safety
  - Repeated Dose in 2 species (1 nonrodent)
  - LD50 & MTD
- PK/PD
  - Duration of action
  - Dosing regimen
  - BA/in vitro hemolysis for IV
  - ADME
- Toxicology
  - Genetic Tox*
    - Ames, chromosomal Aberration
    - Micronucleus (for repeat dose clinical trials)
  - Safety Pharm – CNS, CVS, Respiratory

CMC

- Validated process/scale-up
- GMP-like material (lock in material prep and formulation)
- Stability for trial duration
- Release test

Contents of an IND Application

- FDA Form 1571
- Table of Contents
- Introductory Statement
- General Investigational Plan
- Investigator's Brochure
- Clinical Protocol (s)
  - Study Protocols
  - Investigator data
  - Facilities data
  - Institutional Review Board data
- Chemistry, Manufacturing, and Controls
  - Environmental assessment or claim for exclusion
- Pharmacology and Toxicology data
- Previous Human Experience
- Additional Information
- Relevant Information (References)

PHASE 1

First in Man

Safety and Tolerability

Pharmacokinetics

PHASE 2

Proof of Concept

Dose Ranging

Safety/PK in Special Populations and Risk Factors

PHASE 3

Large, Multicentered

Usually Placebo-Controlled

Usually replicated

Primary data to support marketing approval in NDA

Clinical/Pivotal Animal Trials

Preclinical

- **Chronic Tox or Expected Use scenario**
- **Reproductive Toxicity***
- **Carcinogenicity***
- **Local Tolerance***
- **Immunotoxicity***

CMC

- **Must use GMP material**
- **Must use validated release tests**

Human Safety Studies

- SD in Healthies
- Repeat Dose/continuous administration if reqd
- PK, PD, safety & Tolerability
- Other eg. radiation oncology populations

CMC

- Must use GMP Material
- Must use validated release tests

New Drug Application (NDA) or Biologic License Application (BLA) include:

- Pre-clinical studies
- Human clinical studies
- Manufacturing details
- Labeling
- Additional information


FINAL
FINAL

Information Resources

- **IND Regulations: Code of Federal Regulations, Title 21, parts 312 and 50.**
- **ICH E6 Good Clinical Practice: Consolidated Guidance**
  - **www.fda.gov/cder/guidance/959fnl.pdf**
- **ICH**
  - **http://www.ich.org/LOB/media/MEDIA506.pdf**
  - **http://www.ich.org/cache/compo/276-254-1.html**
- **Small Business Assistance**
  - **http://www.fda.gov/cder/about/smallbiz/default.htm**

The End