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

Jui Shah, PhD
Sr. Regulatory Officer
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)

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

- DAIT Office of Regulatory Affairs Staff
- Contract Research Organization (CRO)
- Individual Consultants
  - GLP toxicology
  - GMP quality
  - GMP facilities
The “Good Practices”

<table>
<thead>
<tr>
<th>GCP</th>
<th>GLP</th>
<th>GMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensures Quality of Data Obtained from Clinical Testing, and Protects the Rights and Safety of Clinical Subjects</td>
<td>Ensures Quality of Preclinical Testing and Data Obtained</td>
<td>Ensures Quality of Drugs Based on Standards Applicable for All Manufacturing Facilities</td>
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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

<table>
<thead>
<tr>
<th>Pre-clinical testing</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>FDA</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1</td>
<td>2</td>
<td></td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Test population</td>
<td>Laboratory &amp; Animal Studies</td>
<td>20 to 80 patient volunteers</td>
<td>100 to 300 patient volunteers</td>
<td>1,000 to 3,000 patient volunteers</td>
<td>9</td>
</tr>
<tr>
<td>Purpose</td>
<td>Assess safety and biological activity</td>
<td>Determine safety and dosage</td>
<td>Evaluate effectiveness. Look for side effects.</td>
<td>Verify effectiveness, monitor adverse reactions from long-term use.</td>
<td>Expedited Review: Phases II and III combined to shorten approval process on new medicines for serious and life-threatening diseases.</td>
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</tbody>
</table>
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
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**

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<thead>
<tr>
<th>Preclinical</th>
<th>CMC</th>
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<tbody>
<tr>
<td>Chronic Tox or</td>
<td>Must use GMP material</td>
</tr>
<tr>
<td>Expected Use</td>
<td></td>
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<tr>
<td>scenario</td>
<td>Must use validated release tests</td>
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<tr>
<td>Reproductive</td>
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<tr>
<td>Toxicity*</td>
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<td>Carcinogenicity*</td>
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<td>Local Tolerance*</td>
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<td>Immunotoxicity*</td>
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<td>Human Safety Studies</td>
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<td><strong>SD in Healthies</strong></td>
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<tr>
<td><strong>Repeat</strong></td>
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<tr>
<td><strong>Dose/continuous</strong></td>
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<td><strong>administration if</strong></td>
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<td><strong>reqd</strong></td>
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<tr>
<td><strong>PK, PD, safety &amp;</strong></td>
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<tr>
<td><strong>Tolerability</strong></td>
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<tr>
<td><strong>Other eg. radiation</strong></td>
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<tr>
<td><strong>oncology populations</strong></td>
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New Drug Application (NDA) or Biologic License Application (BLA) include:

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

- IND Regulations: Code of Federal Regulations, Title 21, parts 312 and 50.

- ICH E6 Good Clinical Practice: Consolidated Guidance

- ICH

- Small Business Assistance
  - [http://www.fda.gov/cder/about/smallbiz/default.htm](http://www.fda.gov/cder/about/smallbiz/default.htm)
The End