Drug Development Overview

FDA: Basic Research to Clinical Use

12 June 2012

Lucie Yang, MD, PhD
Division of Medical Imaging Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Outline

• Therapeutic Drug vs Diagnostic Imaging Agent Development

• Preclinical Research to Clinical Studies
  – Appropriate FDA submission(s)
  – Introduction of upcoming talks in this session
Therapeutic Drugs

Basic Research, Target ID, Lead Selection
Chemical Synthesis, Screening, Lead Selection
Preclinical Testing & Optimization
Phase 1-3 Trials
NDA Review & Approval
Post-marketing Surveillance

$800 million, 14 years

$3.4 B annual revenue

Diagnostic Imaging Agents

Chemical Synthesis
Assays & Preclinical Testing
ID of Diagnostic Opportunity
Lead Selection
Preclinical Testing & Optimization
Phase 1-3 Trials
NDA Review & Approval
Post-marketing Surveillance

$150 million, 10 years

$400 M annual revenue

adapted from Agdeppa (2009) AAPS Journal 11:286
New Drug Development Process

PRE-CLINICAL RESEARCH

- synthesis & purification
- animal testing

CLINICAL STUDIES

- Phase 1
- Phase 2
- Phase 3

NDA REVIEW

POST MARKETING

= meetings with FDA

= Applicant orientation meeting

= Advisory Committee
Transitioning from eIND to Traditional IND

-- Dr. Siham Biade --
10:00 AM

What are the preclinical requirements for toxicology / pharmacology?

• PK and
• proof of mechanism / concept
• toxicity
• translation to humans
New Drug Development Process

PRE-CLINICAL RESEARCH

- synthesis & purification

Considerations:
- target affinity
- selectivity
- metabolism
- lipophilicity
- molecular weight / size
- signaling moiety selection / incorporation
- how the radiolabel is integrated into the imaging agent

CLINICAL STUDIES

Phase 1

CMC Issues in Radiopharmaceutical INDs

-- Dr. Ravindra Kasliwal --
10:45 AM

- Radioactive drug substance
- Radioactive drug product
New Drug Development Process

PRE-CLINICAL RESEARCH

synthesis & purification
animal testing

What do I submit to FDA before starting human studies?

CLINICAL STUDIES

Phase 1

What do I submit to FDA before starting human studies?
Which submission is most appropriate?

- PET drug
  - RDRC
  - IND
    - Exemption
      - research or investigational use
    - IND
Definitions

Research use
• For basic science research
• Not using for immediate therapeutic, diagnostic, or similar purpose
• No intent to determine safety or effectiveness for clinical use

Investigational use
• To establish the safety or effectiveness of a new use of the drug to support approval
Which submission is most appropriate?

PET drug

- RDRC
  - research use
- IND
  - Exemption
  - investigational use
- IND
RDRC NOT for 1st in human study!

IND not needed if study is approved by a Radioactive Drug Research Committee (RDRC)

RDRC research limited to:

- Basic science
- Not for diagnostic or therapeutic purpose
- Not an evaluation of drug’s safety/efficacy
- Dose known not to cause any pharmacologic effect
- Radiation dose within specific limits
IND Exemption

Before December 12, 2015

**Criteria**

- PET drug used in the trial is made at a facility included in a submitted NDA/ANDA
- No intent to support new indication, labeling change, or advertising change
- No intent to promote/commercialize the drug
- No significant risk increase (e.g. dose, route of administration, patient population)
  - Compliant with IRB/consent process
IND Exemption

**After December 12, 2015**

**CRITERIA**

- PET drug used in the trial is included in an approved NDA/ANDA
- No intent to support new indication, labeling change, or advertising change
- No intent to promote/commercialize the drug
- No significant risk increase (e.g. dose, route of administration, patient population)
  - Compliant with IRB/consent process
Which IND type is most appropriate?

PET drug

- RDRC
- IND Exemption
  - Exploratory IND
  - Traditional IND
- IND
# Exploratory IND

## Purpose

- An early Phase 1 approach to help distinguish earlier in the process those candidates that hold promise from those that do not.

## Potential Advantage over Traditional IND

- Involve fewer resources than traditional IND;
- Sponsors can move ahead more efficiently with the development of promising candidates.
## Exploratory IND

**Criteria**

- Early Phase 1 study
- Assesses feasibility for further drug development
- Involves very limited human exposure
- Has no therapeutic or diagnostic intent (e.g. screening study, microdose study)
How Can an Exploratory IND Study Help Sponsors?

• Determine mechanism of action: same in humans and experimental system?

• Provide pharmacokinetics information

• Select most promising lead product

• Explore biodistribution
New Drug Development Process

**PRE-CLINICAL RESEARCH**
- synthesis & purification
- animal testing

**CLINICAL STUDIES**

Phase 1

**What do I submit to FDA before starting human studies?**

**ANSWER:**

For *investigational use*, options are
- Exploratory IND (if qualify)
- Traditional IND

For *research use*, RDRC

**RDRC: NOT 1st in human!**
New Drug Development Process

CLINICAL STUDIES

--- WHAT? ---
- initial human studies
- evaluate safety
- determine radiation absorbed dose
- determine safe mass dose
- determine metabolism
- determine pharmacokinetics
- gain early evidence of efficacy

--- WHO? ---
- small group of people (20-80)
- healthy participants and/or patients

for radio-pharmaceutical

Phase 1

clinicaltrials.gov
Radiation Dose: What Do We Want?
-- Dr. Orhan Suleiman --
10:15 AM

How is human radiation dose estimated?
New Drug Development Process

------ WHO? ------
- larger groups of people
- patients with disease or condition under study

------ WHAT? ------
- controlled clinical study
- evaluate efficacy of drug for a particular indication
- determine common short-term side effects and risks
- refine dose, population
- develop image reading method

Phase 2

clinicaltrials.gov
WHO?  
- even larger groups of people  
- for imaging agent

WHAT?  
- expanded controlled and uncontrolled trials  
- **confirm efficacy**, monitor side effects  
- compare to commonly used treatments  
- evaluate overall benefit-risk relationship of the drug  
- gather data to inform adequate basis for labeling

though the sample size may depend on the study design
New Drug Development Process

- **PRE-CLINICAL RESEARCH**
  - Clinical Trial Efficacy Endpoints
    - Dr. Qi Feng
    - 10:30 AM

- **CLINICAL STUDIES**
  - Phase 3

- **NDAR REVIEW**

What should the primary endpoint be?
New Drug Development Process

CLINICAL STUDIES

Phase 1

Phase 2

Phase 3

----------- Phase 4 trial -----------

• post-marketing study
• delineate additional information including the drug’s risks, benefits, and optimal use

clinicaltrials.gov
New Drug Development and Review Process

The mission of FDA’s Center for Drug Evaluation and Research (CDER) is to assure that safe and effective drugs are available to the American people. This section has definitions and interactive charts which provide basic information for small business and others who are unfamiliar with the new drug development and approval process.

American consumers benefit from having access to the safest and most advanced pharmaceutical system in the world. The main consumer watchdog in this system is CDER. The center’s best-known job is to evaluate new drugs before they can be sold. The center’s evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both brand-name and generic, work correctly and that their health benefits outweigh their known risks.

Drug companies seeking to sell a drug in the United States must first test it. The company then sends CDER the evidence from these tests to prove the drug is safe and effective for its intended use. A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the company’s data and proposed labeling. If this independent and unbiased review establishes that a drug’s health benefits outweigh its known risks, the drug is approved for sale. The center doesn’t actually test drugs itself, although it does conduct limited research in the areas of drug quality, safety, and effectiveness standards.

Before a drug can be tested in people, the drug company or sponsor performs laboratory and animal tests to discover how the drug works and whether it’s likely to be safe and work well in humans. Next, a series of tests in people is begun to determine whether the drug is safe when used to treat a disease and whether it provides a real health benefit.
Thank you!
**New Drug Development Process**

<table>
<thead>
<tr>
<th>PRE-CLINICAL RESEARCH</th>
<th>CLINICAL STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>synthesis &amp; purification</td>
<td>Phase 1</td>
</tr>
<tr>
<td>animal testing</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

- ♦️ = meetings with FDA
- 🔼 = Applicant orientation meeting
- 🔻 = Advisory Committee

**NDAR REVIEW**

**POST MARKETING**