



ATHEROGENICS, INC.<sup>SM</sup>

Dr. Russell M. Medford  
President & Chief Executive Officer

The Review & Approval Process

**FDA & Pharma**

# PROFILE

- Scientific co-founder of AtheroGenics, Inc.
- President & CEO at AtheroGenics, Inc since 1995 after serving as Executive Vice President from 1993-1995
- A Director of the following companies/organizations:
  - ✱ Inhibitex, Inc.
  - ✱ Biotechnology Industry Organization
  - ✱ Chair, GABIO (Georgia Biomedical Partnership)
  - ✱ SEBIO (Southeast BIO)
- Previously Associate Professor of Medicine & Director of Molecular Cardiology at Emory University School of Medicine
- Education:
  - ✱ Cornell University (B.A.)
  - ✱ Albert Einstein College of Medicine (M.D./Ph.D.)
  - ✱ Fellow in cardiology at the Brigham & Women's Hospital and Harvard Medical School, where he also served on the faculty



# What We'll Discuss Today ...

- A summary of the drug approval process between:
  - ✱ The FDA (Food & Drug Administration) and Pharma/Biotech companies
  
- A clear pathway of how the process works:
  - ✱ PreClinical Approvals
  - ✱ Filing an IND
  - ✱ Phase 1
  - ✱ Phase 2
  - ✱ Phase 3
  - ✱ Filing an NDA
  - ✱ New Drug Approved for Marketing
  
- Q&A

# REVIEW:

## What Is A Drug?

FDA definition:

A drug is an article (other than food) intended for the use in the diagnosis, cure, treatment or prevention of disease in man or other animals



As presented by: Troy L. ZumBrunnen, PharmD, BCPP  
Clinical Pharmacology  
Solvay Pharmaceuticals, Inc.

# How It All Begins ...

A Company's perspective ....

# From Science to Medicine: An Idea to Product Paradigm

The Scientific Discovery



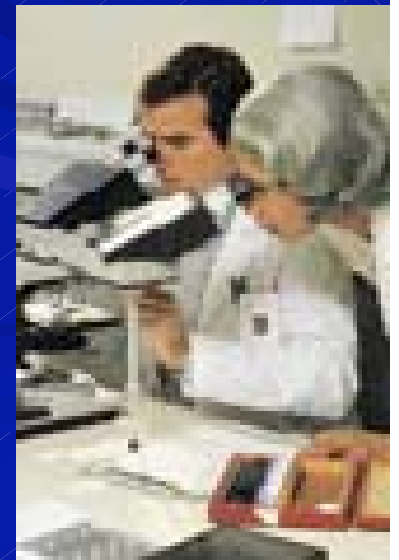
And then  
a miracle happens



New Treatments for  
Human Disease

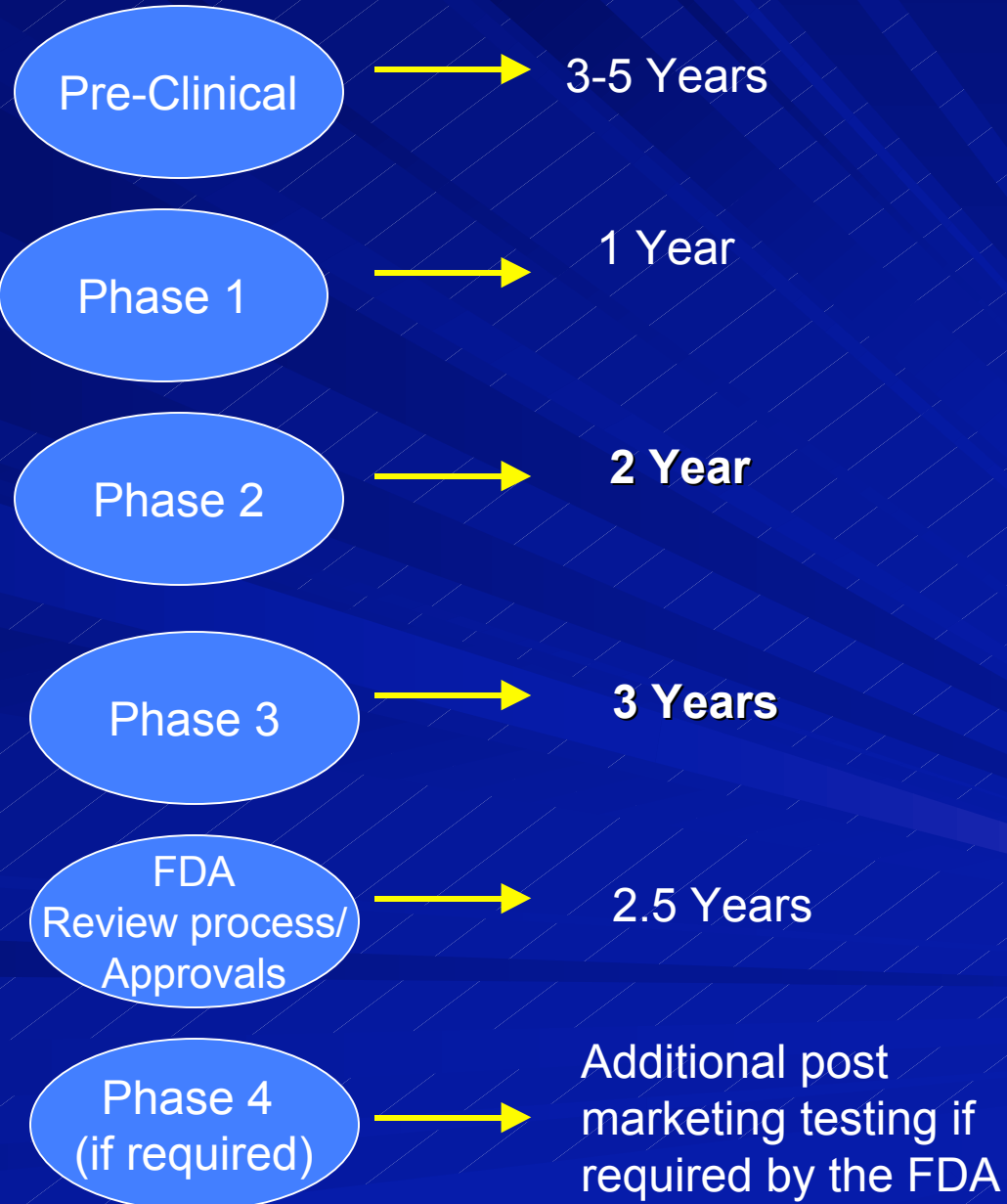
# The Facts About Drug Approvals

- The Federal Drug Administration (FDA) estimates that it takes approximately 8 \_ years to study and test a new drug before it can be approved for the general public.
- This estimation includes:
  - ✱ Early laboratory testing
  - ✱ Animal testing
  - ✱ Clinical trials in human subjects



Source: Food & Drug Administration  
Center for Drug Evaluation & Review

# Phases of Product Development



## Product Development (continued)

- It takes 12 years from bench to pharmacy
- Est. cost per drug: 1 Billion

Pre-Clinical



# Early Pre-Clinical Reviews

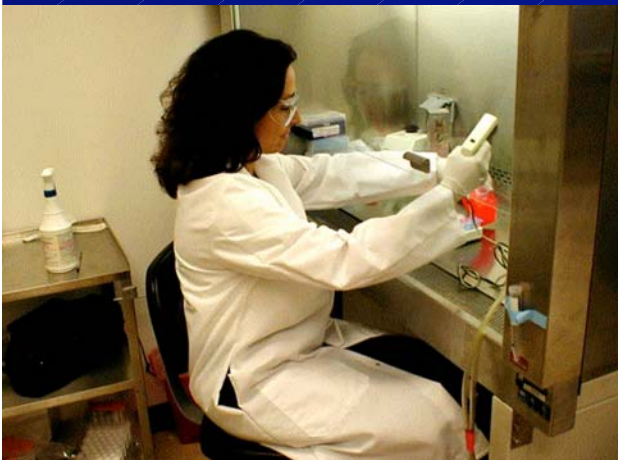
**Drug Companies use animal testing to measure:**

- How much of the drug is absorbed into the blood
- How it is broken down chemically
- The toxicity of the drug
- The time the drug and its metabolites are excreted from the body



**The pharmacology/toxicology review team is staffed by pharmacologists and toxicologists who:**

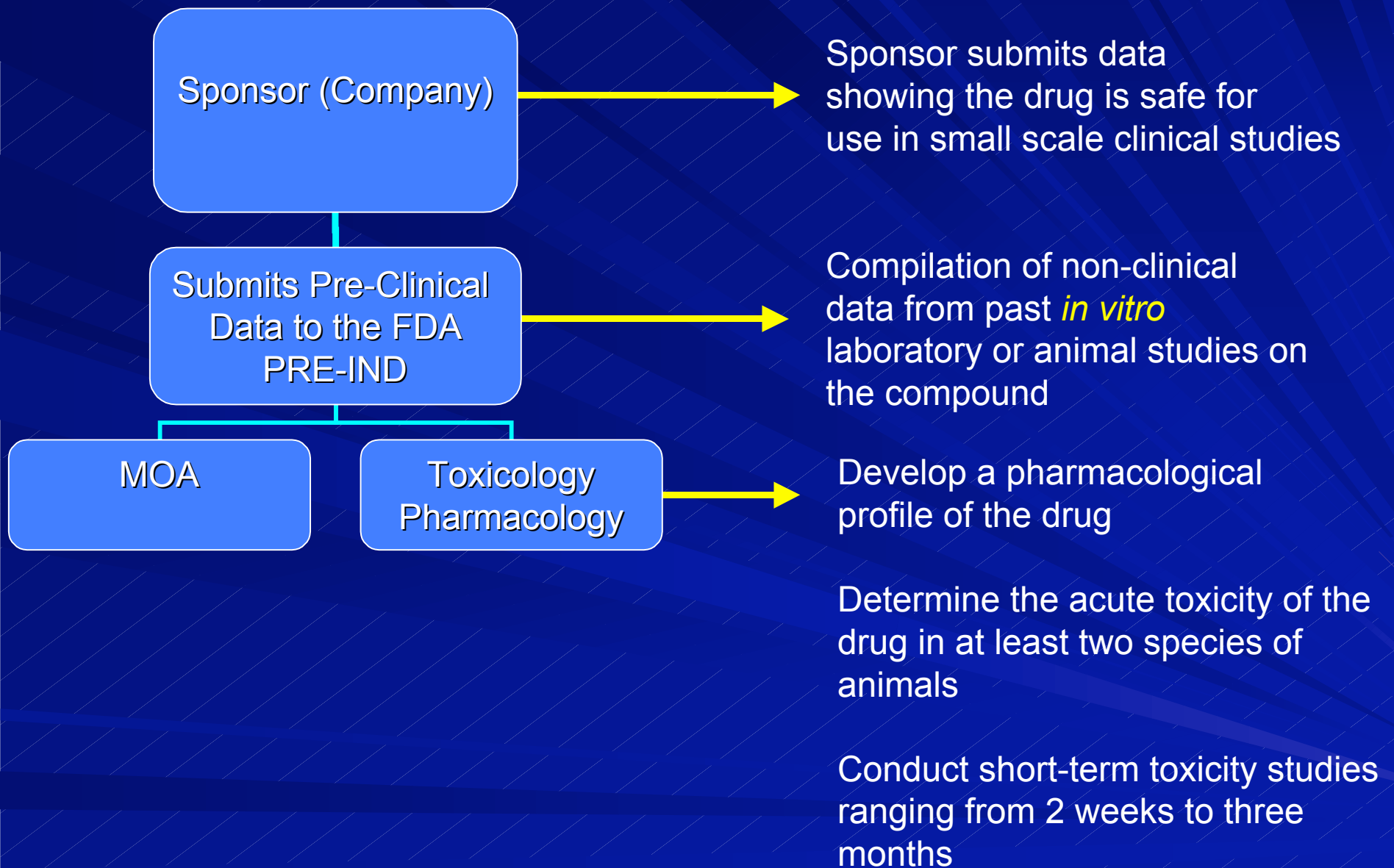
- Evaluate the results of animal Testing
- determine the relation of the animal drug effects to potential effects in humans



Source: Food & Drug Administration ([www.fda.gov](http://www.fda.gov))  
Center for Drug Evaluation & Review

# FDA Review of Pharmacology & Toxicology Information

- The Sponsor is required to submit specific pharmacology and toxicology information to the FDA to address:
  - ✱ Description of the pharmacologic effects and MOA (mechanism of action of the drug in animals)
  - ✱ Information on the absorption, distribution, metabolism and excretion of the drug



**Note: This is the minimum that the FDA will require be submitted for preclinical review**

Source: Food & Drug Administration ([www.fda.gov](http://www.fda.gov))  
Center for Drug Evaluation & Review

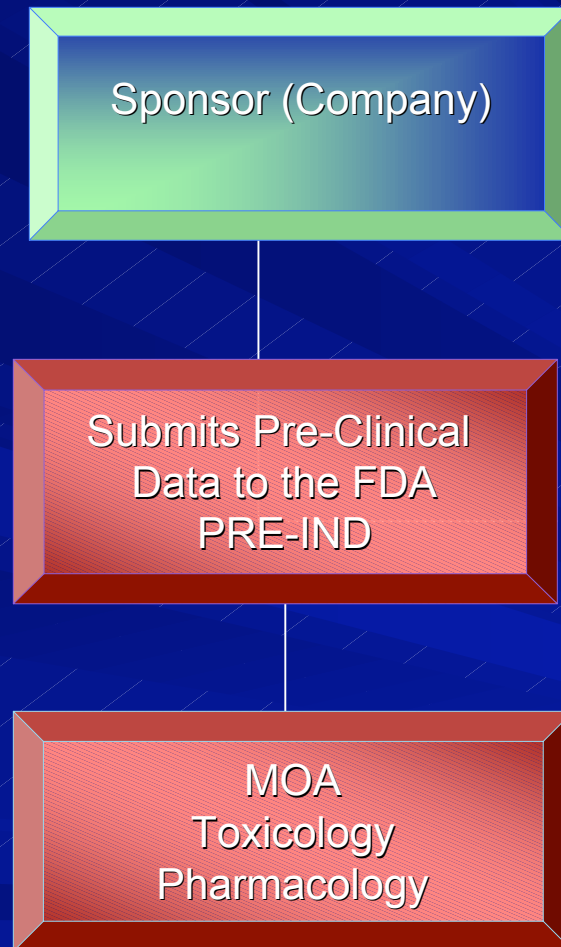
# FDA

## Chemistry & Manufacturing Review Team

**Each review division employs a team of chemists responsible for reviewing the chemistry & manufacturing control sections of drug applications.**

**Sponsors should describe any chemistry and manufacturing differences between the drug product proposed for clinical use and the drug product used in the animal toxicology trials that formed the basis for the sponsor's conclusion that it is safe to proceed with the proposed clinical study.**

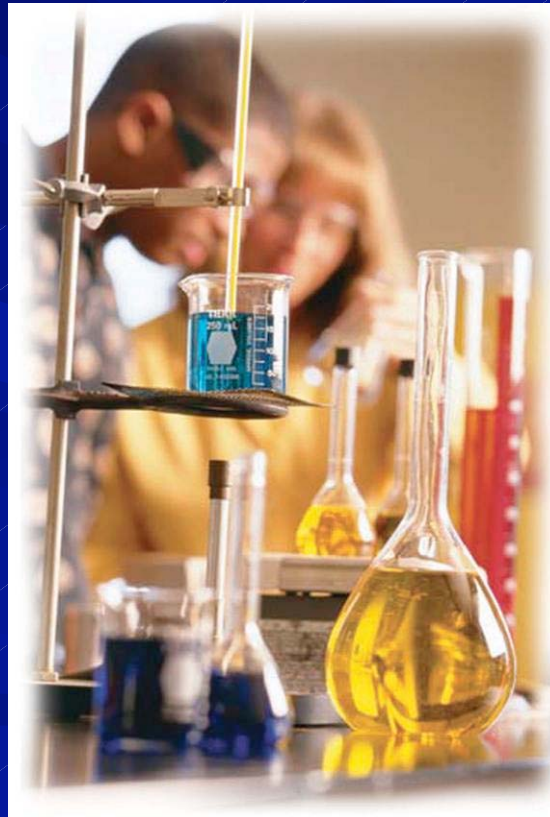
# PATHWAY TO APPROVAL



File IND

# IND

## Investigational New Drug



# Investigational New Drug Application (IND)

## ■ *What is an IND?*

- ✱ An IND is the result of a successful preclinical development program.
- ✱ It is the vehicle through which the sponsor (company) advances to the next stage of drug development (known as clinical trials) in human subjects.

# What Data Should the Sponsor (Company) Provide To The FDA In Order To File For An IND?

## ✱ Animal Pharmacology & Toxicology Studies

- ◆ This is the preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans

## ✱ Manufacturing Information

- ◆ Information pertaining to the composition, manufacture, stability and controls used for manufacturing the drug substance and the drug product.
- ◆ This information is assessed as to ensure the company can adequately produce and supply consistent batches of the drug.

# What Data Should the Sponsor (Company) Provide To The FDA In Order To File For An IND? (continued)

## ✱ Clinical Protocols and Investigator Information

- ◆ Detailed protocols for proposed clinical trials
- ◆ Any risks associated with the initial phase trials
- ◆ Information on the qualifications of clinical investigators (professionals) who will oversee the administration of the experimental compound

# During the IND Review Process:

- CDER (Center for Drug Evaluation and Research, Department of the FDA), may request meetings with the Company (Sponsor)
- Through the course of reviewing an application, CDER usually communicates often with sponsors about:
  - ✿ Scientific, medical and procedural issues that may arise during the review process
    - These communications may be:
      - By Phone
      - Letters/faxes
      - Face-to-face meetings



Source: Food & Drug Administration ([www.fda.gov](http://www.fda.gov))  
Center for Drug Evaluation & Review

# The FDA Review Team



- Medical / clinical reviewers, often called medical officers are responsible for:
  - ✱ Evaluating the clinical sections of submissions
    - ◆ Safety of the clinical protocols in an IND
    - ◆ Results of the testing submitted in the NDA (new drug application)
- Clinical reviewers take the “lead role” in the IND or NDA review which will formulate the overall basis for a recommended Agency action on the application
  - ✱ Responsible for synthesizing the results of the animal toxicology
  - ✱ Human pharmacology
  - ✱ Clinical reviews

Source: Food & Drug Administration ([www.fda.gov](http://www.fda.gov))  
Center for Drug Evaluation & Review

# Conclusion of CDER's Review & Process of notification to Sponsor

## ■ NOT APPROVAL LETTER

Lists the deficiencies in the application and why the Application cannot be approved



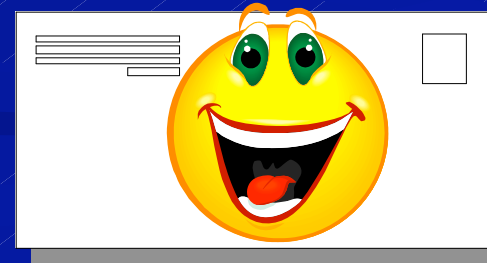
## ■ APPROVABLE LETTER

Signals that, ultimately the drug can be Approved. Lists minor correctable Deficiencies (often labeling changes and Possibly requests commitment to do post-Approval studies)



## ■ APPROVAL LETTER

States that the drug is approved!  
May follow an approvable letter,  
But can also be issued directly



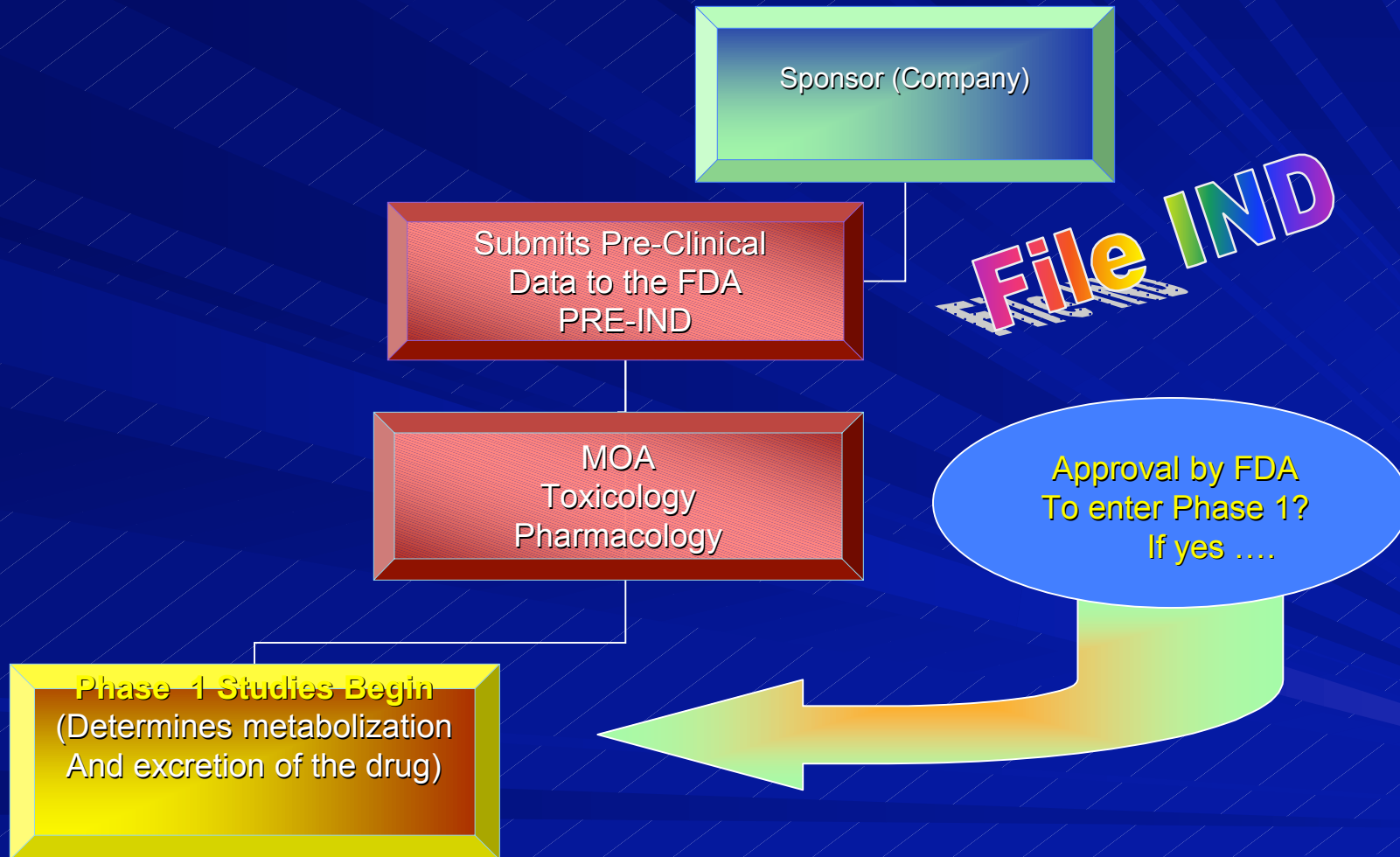
Source: Food & Drug Administration ([www.fda.gov](http://www.fda.gov))  
Center for Drug Evaluation & Review

**FDA  
*IND*  
APPROVAL**



**Phase 1**

# PATHWAY TO APPROVAL

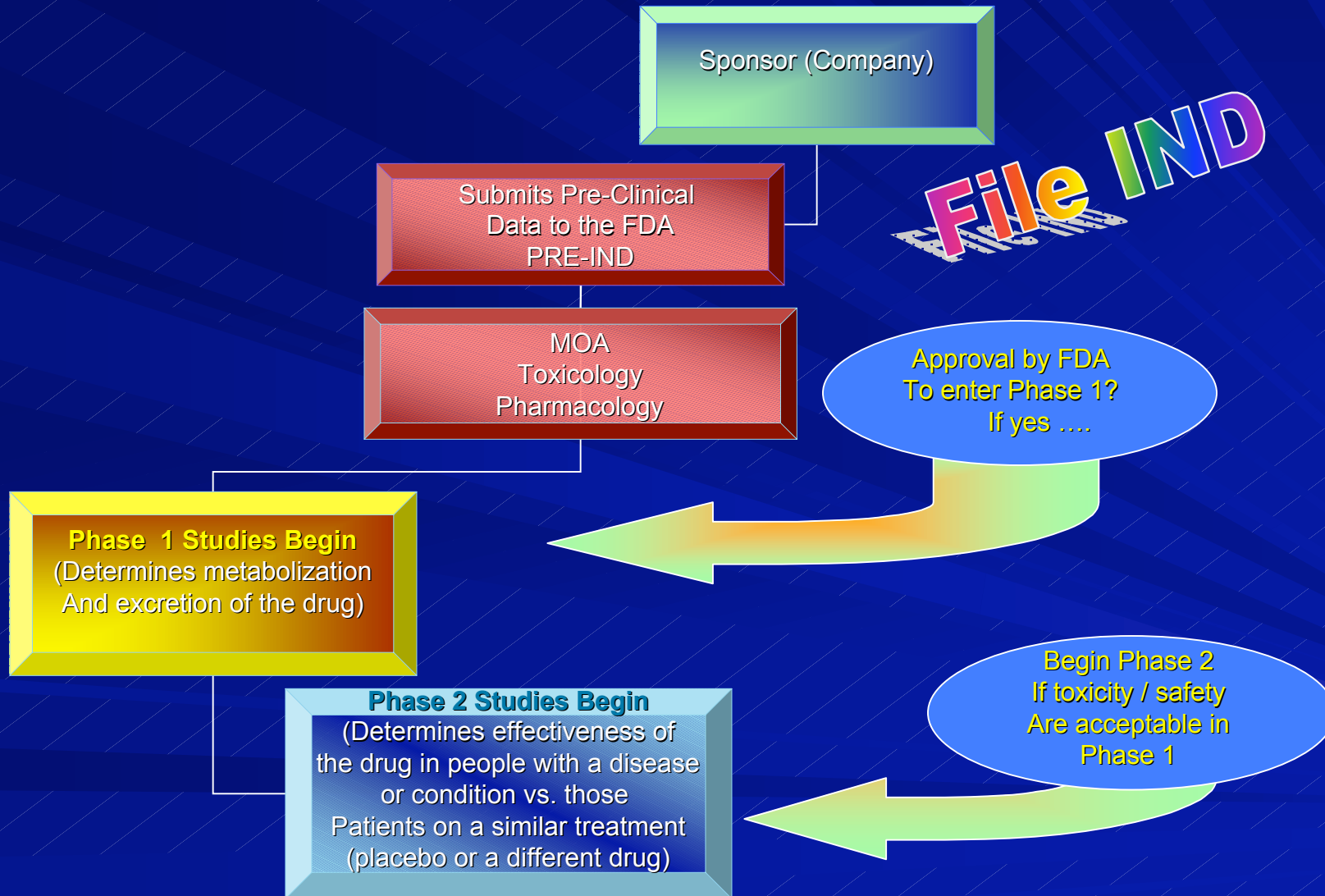


# Phase 1 Studies

- Phase I studies usually include from 20 – 80 patients or healthy volunteer subjects
- The studies are designed to:
  - ✱ Determine the metabolic and pharmacologic actions of the drug in humans
  - ✱ Side effects associated with increasing doses
  - ✱ To gain early evidence on the effectiveness of the drug
  - ✱ Evaluate drug metabolism and Mechanism of Action in humans

# Phase 2

# PATHWAY TO APPROVAL



# Possible Delays in the Approval Process?

## ■ *FDA issues a clinical hold on the program*

- ✱ An order issued by the FDA to the applicant of an IND to delay a proposed clinical investigation or to suspend an ongoing clinical investigation

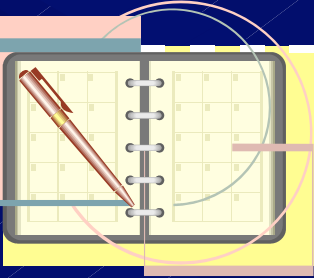
### ✱ Complete Clinical Hold:

- ◆ A delay or suspension of all clinical work requested under an IND. However ....

- *The FDA and sponsor have 30 days to agree on an alternative protocol*

### ✱ Partial Clinical Hold:

- ◆ A delay or suspension of only part of the clinical work requested under the IND (specific protocol or part of a protocol is not allowed to proceed)



# Timing of Clinical Hold Delays?

- There is a 30 day response time from the sponsor after receiving a full or partial clinical hold from the FDA
- The FDA is required by the Modernization Act to respond in writing to the applicant within 30 calendar days after receipt of the applicant's complete response to a clinical hold

# Phase 2 Studies

- Phase 2 studies usually include several hundred patients or healthy volunteer subjects
- Testing in a larger group to assess clinical efficacy and to continue Phase 1 assessment
- Phase 2 include:
  - ✱ Early controlled clinical studies conducted to obtain preliminary data on effectiveness of the drug
  - ✱ To determine the particular indication(s) in patients with the disease or condition
  - ✱ Determines the common short-term side effects and risks associated with the drug
- These studies are usually well-controlled and closely monitored

# Institutional Review Boards

- Under FDA regulations, an **Institutional Review Board** is a group that has been formally designated to review and monitor biomedical research involving human subjects.
- In accordance with FDA regulations, an IRB has the authority to:
  - ✱ Approve
  - ✱ Review modifications
  - ✱ Disapprove research
- The purpose of the IRB review is:
  - ✱ To assure that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research

# Phase 3



# Phase 3 Studies

- Studies begin if evidence of effectiveness is shown in Phase 2
- This is a data gathering study to show that the drug is safe and effective in different populations, using different doses
- The number of subjects usually ranges from several hundred to about 3,000 people or in some cases, even more

# Phase 3 Studies

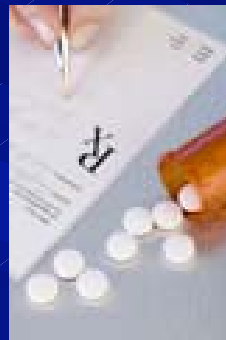
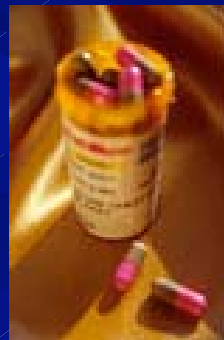
- Phase 3 studies are expanded controlled and uncontrolled trials.
- These are performed after preliminary evidence suggesting effectiveness and safety of the drug has been obtained in Phase 2
- Evaluation of the overall benefit-risk relationship of the drug is determined
- The study also provides adequate basis for gathering the results
- Phase 3 studies usually include several hundred to several thousand people
- *In both Phase 2 and Phase 3, CDER can impose a clinical hold if a study is unsafe or is clearly deficient in design in meeting its stated objective*

# PATHWAY TO APPROVAL



# NDA

# New Drug Application



# New Drug Application - NDA

- At the successful completion of Phase 3, a drug sponsor requests the FDA to consider approving a new drug for Marketing in the United States
- An NDA includes:
  - ✱ All animal and human data
  - ✱ Analysis of these data
  - ✱ Behavior of drug in the body
  - ✱ Manufacturing of the drug



- The FDA has 60 days to make a decision on whether the drug should be filed for further review
- However, an application can be refused by the FDA if incomplete
- The NDA must provide all relevant data and information that a sponsor has collected during the product's research & development

# What information is required by the FDA for an NDA Submission?

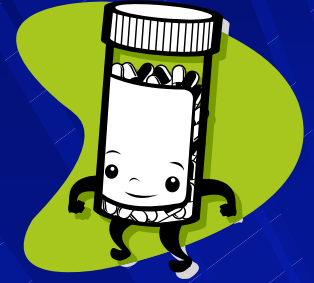
*(note: this may vary with each drug submission)*

- Index
- Summary
- Chemistry, Manufacturing & Control
- Samples, Methods Validation Packaging and Labeling
- Non-clinical Pharmacology and Toxicology
- Human Pharmacokinetics & Bioavailability
- Clinical Data
- Safety Update Report
- Case Report Tabulations
- Case Report Forms
- Patent Certification
- Patent Information
- Other Information

# CDER classifies new drug applications with a code that reflects the following:

- Type of drug being submitted and use intended

1. New Molecule Entity
2. New Salt of Previously Approved Drug
3. New Formulation of Previously Approved Drug
4. New Combination of Two or More Drugs
5. Already Marketed Drug Product
6. New Indication (claim) for already marketed drug (this includes switch in marketing status from prescription to OTC)
7. Already marketed drug product – not previously approved NDA



- Each classification is coded with a review priority

- ◆ **Standard**

- ◆ Review for drugs similar to currently available drugs on the market

- ◆ **Priority**

- ◆ Review for drugs that represent significant advances over existing treatments

# NDA Statistics

- After the sponsor (company) has submitted an NDA to the FDA, the NDA must contain:
  - ✱ Scientific information gathered by the company
  - ✱ Data and files that support the drug demonstrates safety and effectiveness
  - ✱ NDA's size: 100,000+ pages
  - ✱ The FDA is allowed six (6) months to review an NDA
  - ✱ For some medicines, the FDA requires additional studies (Phase IV) to evaluate long-term effects.

# NDA Statistics

- After the sponsor (company) has submitted an NDA to the FDA, the NDA must contain:
  - ✱ Scientific information gathered by the company
  - ✱ Data and files that support the drug demonstrates safety and effectiveness
  - ✱ NDA's size: 100,000+ pages, Labeling review must be justified by data and results submitted in the NDA
  - ✱ The FDA is allowed six (6) months to review an NDA
  - ✱ For some medicines, the FDA requires additional studies (Phase IV) to evaluate long-term effects.

***If after review and approval by the FDA ..... THEN***



Q&A