Drug Development Process

CTSC Clinical Research Training

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Module Objectives

At the end of this module participants should be able to:

- Understand differences between regulatory and financial sponsors
- Identify phases of clinical trials
- Define Investigational New Drug Applications (IND) and New Drug Applications (NDA)
- Describe the post-marketing surveillance process
Clinical Trials at SOM (2009 data)

~1600 human subject protocols received by the Investigational Review Board

Out of them 526 were new

- 289 Full Committee
- 237 Expedited/Exempt

289 full committee protocols were initiated by various sources:

- 130 by Pharma (industry-sponsored clinical trials)
- 48 by Cooperative groups
- 101 by investigator (paid for by Foundations, Departments, NIH, State)
Financial Sponsor

*Provides funding for the study*

Industry, Feds, Department, State, donors

May or may not carry regulatory responsibilities

Regulatory Sponsor

*Originates the protocol*

Files the regulatory paperwork with the FDA

Industry, cooperative groups, investigator (sponsor-investigator)
An investigator from Cancer Center wants to study an FDA approved drug in the new clinical trial. The investigator wrote the protocol, and a company provided the drug at no cost.

Who is Regulatory Sponsor?
Who is Financial Sponsor?
Pharmaceutical Product Development Stages

**Discovery**
- Basic Research
- Pre Clinical

**Development**
- Clinical Testing
- I
- II
- III
- IV

**Commercialization**
- Marketing
- Product Launch
- Sales

RA775
Time and Money

Pre Clinical | Phase I | Phase II | Phase III | Phase IV

3.5 years | 1 year | 2 years | 3 years

FDA Approval Process
2.5 years

10-12 years

~ $ 200 M
Depends on Indication

All drugs:

Clinical Phase 5.9 years
Approval phase 1.4 years

Categories:

Neuro (7.5+1.5 years)
Endocrine (8+1 year)
Respiratory (5.2 +2.25 years)
AIDS (3.25 years+ 4 mos)
Clinical Trial Phases

Studies performed under an Investigational New Drug Application (IND) are often classified into phases as if they are separate and distinct steps in the process. In reality the phases overlap and trials in one phase are often conducted simultaneously with trials in other phases.

21 CFR Part 312.21 Phases of an investigation

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.21

- Phase I – First Stage in human subjects, metabolism, pharmacology
- Phase II – Effectiveness, safety, side effects
- Phase III – Large, Randomized, Blinded trial to test clinical outcomes
- Phase IV – Post-marketing to assess side effects or additional uses
Phase I

Conducted to determine the appropriate dose range with regard to safety and toxicity

Pharmacokinetics and pharmacodynamics

Conducted in a limited number (usually 20-80) healthy volunteers or in patients with diseases such as cancer or AIDS

Many compounds are abandoned in Phase I testing because of problems with safety or toxicity.
Phase II

Conducted in a limited number of subjects (usually 100-300) who have the disease/condition to be treated

May focus on dose-response, maximum safe dose, dosing schedule, or other issues related to preliminary safety and efficacy

Explore therapeutic efficacy

Define target population

Focus on desired claims
Phase III

Conducted in a larger number of subjects (thousands to tens of thousands) and in more diverse patient groups

Makes comparisons between the new treatment and standard therapy/placebo; can also be uncontrolled

Studies risk-benefit relationship by gathering addtl. info on safety and effectiveness

Extrapolating the results for general population: Product Labeling and Package Insert

Sometimes called Pivotal Studies (if well-controlled, randomized, double blind)
Phase IV (postmarket)

These trials may be conducted to provide additional information such as:
• Testing new doses
• Evaluating patient subgroups (minorities or children)
• To assess additional uses

Phase IV studies can further establish the safety and efficacy of the drug and thereby gain greater market acceptability for the product.

Expanding the Product Label
The Plan of Drug Development

Begin with the end in mind

What label is desirable?
How do we get there?

Target product profile → Product label/claims → Clinical development plan

Plan Backwards

Development plan to deliver the label
Appropriate studies to support the claims
Package Insert

- Contains summary of essential scientific information for safe and effective use of the product.
- Must be based on human clinical experience.
Package Insert – Key areas

- Clinical Pharmacology
- Indications and Use
- Contraindications
- Warnings/Precautions
- Adverse reactions
- Dosage and Administration

Drugs@FDA
Check your understanding

Can this drug be prescribed to pediatric populations? (package insert –Drugs@FDA)
The Development Plan

Non-clinical development plan:

- Studies of a new compound or drug, generally performed in animals, are referred to as "pre-clinical" studies
- Enough safety and efficacy data to move to humans

Clinical Development

- Must provide “substantial evidence” of product’s safety and efficacy in humans
The Development Plan

Pre-clinical plan

- Pre-IND meeting
- Pre-IND meeting

Clinical plan

- Phase I: IND (investigational New Drug Application) submission, 30 day safety review
- Phase II: End of Phase II Meeting
- Phase III: NDA (New Drug Application)
- Phase IV:
The Food and Drug Administration (FDA)

FDA is an agency within the Department of Health and Human Services

Responsible for protecting and advancing human health

Oversees and monitors the drug development process

Sets appropriate regulations and guidelines to ensure that only safe, effective products reach the public
Investigational New Drug Application (IND)

Legal Definition:

Request for exemption from federal statute that prohibits an unapproved drug from being shipped in interstate commerce

Practical Use:

A proposal in which the sponsor attempts to obtain the FDA’s permission to begin clinical testing of a new drug

IND is NEVER “approved”
General Information Required in an IND

- Animal Pharmacology and Toxicology
- Manufacturing information (CMC)
- Clinical Protocols
- Investigator Qualifications
  - **Statement of Investigator, Form FDA 1572**: an agreement by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic.
  - **IND Application Form, Form FDA 1571**: designates Sponsor (or sponsor-investigator)
CTSC offers IND/IDE support for investigators

Clinical and Translational Science Center

Investigational New Drug Application (IND) Process Overview

Introduction

A CTSA Consortium IND IDE Taskforce was formed to focus on enhancing CTSA capabilities to support faculty who were (or were considering becoming) sponsor-investigators. The materials on this website are made available by the members of the IND/IDE taskforce.

As a consequence of investigator-initiated clinical research involving drugs and/or devices, there are numerous institutional considerations to ensure that investigators and their research staff are appropriately...
Do I need an IND?

Drug is not yet approved by the FDA

Drug is approved by the FDA and marketed in the US

I use dietary supplement (botanical product)

Yes

May be …

May be …

… if used for new indications, new disease population or different dose/delivery

… if used to cure, mitigate, diagnose or treat the disease
Botanical products are finished, labeled products that contain vegetable matter as ingredients.

Is IND required for human studies of botanical products that are also lawfully marketed as dietary supplements in the U.S.?

Yes. If a lawfully marketed botanical dietary supplement is studied for its effects on diseases in the proposed investigation (i.e., to cure, treat, mitigate, prevent, or diagnose disease including its associated symptoms), then it is an investigational new drug and will be subject to IND requirements.

This applies to studies in INDs sponsored for both commercial and academic research purposes.
Check your understanding

Is Dandelion juice a drug or dietary supplement?

Drug, when studied for its effect on treatment of the disease

Dandelion juice has been used in herbal medicine for at least 1000 years. Vesicular hand eczema is a rare, but difficult to treat, type of hand eczema. The purpose of this study is to test whether ingestion of dandelion juice could induce a beneficial effect on this type of eczema. (NCT00442091)
IND Holder Obligations

Annual Reports

Adverse Event Reports (Safety)

Deviations, protocol changes, manufacturing changes, new investigator added...
A formal proposal that FDA approves the new drug for sale and marketing in the US

The NDA contains extensive data on the investigational agent, results of the clinical trials conducted, and safety data

15 different sections in the Common Technical Document Format:

Safety and effectiveness
Appropriate labeling
Manufacturing method assurance
NDA Holder obligations

Filing all changes to approved application

Postmarketing reporting of Adverse effects

Other postmarketing reports:
- Periodic Adverse Drug Experience report
- Field alert reports
- Annual reports
Postmarketing Surveillance process

AERS (Adverse Event Reporting Systems)

MedWatch – voluntary reporting

Periodic unannounced inspections of manufacturing facilities

Medication errors report

Management of Drug Shortages

Therapeutic Equivalence reporting
Questions? Comments?

Thank you

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New Drug Development Timeline

Pre-Clinical Testing, Research and Development

- Range: 1–3 years
  - Average: 18 months
- Initial Synthesis

Clinical Research and Development

- Range: 2–10 years
  - Average: 5 years

NDA Review

- Range: 2 months–7 years
  - Average: 24 months

Post-Marketing Surveillance

- Adverse Reaction Reporting
- Surveys/Sampling/Testing
- Inspections

30-Day Safety Review

FDA Time

- 30-Day Industry Time

NDA Submitted

NDA Approved

Short-Term

Long-Term

Phase 1

Phase 2

Phase 3