Overview of Drug Development:
the Regulatory Process

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Background:

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- Ph.D., Biochemistry and Pharmacology, University of Melbourne, Australia
- Visiting Fellowship, Eicosanoids, NIEHS, RTP
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- Assistant Professor, Biochemistry and Internal Medicine, EVMS, Norfolk
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- Senior Scientist, Drug Development, Cato Research, Durham
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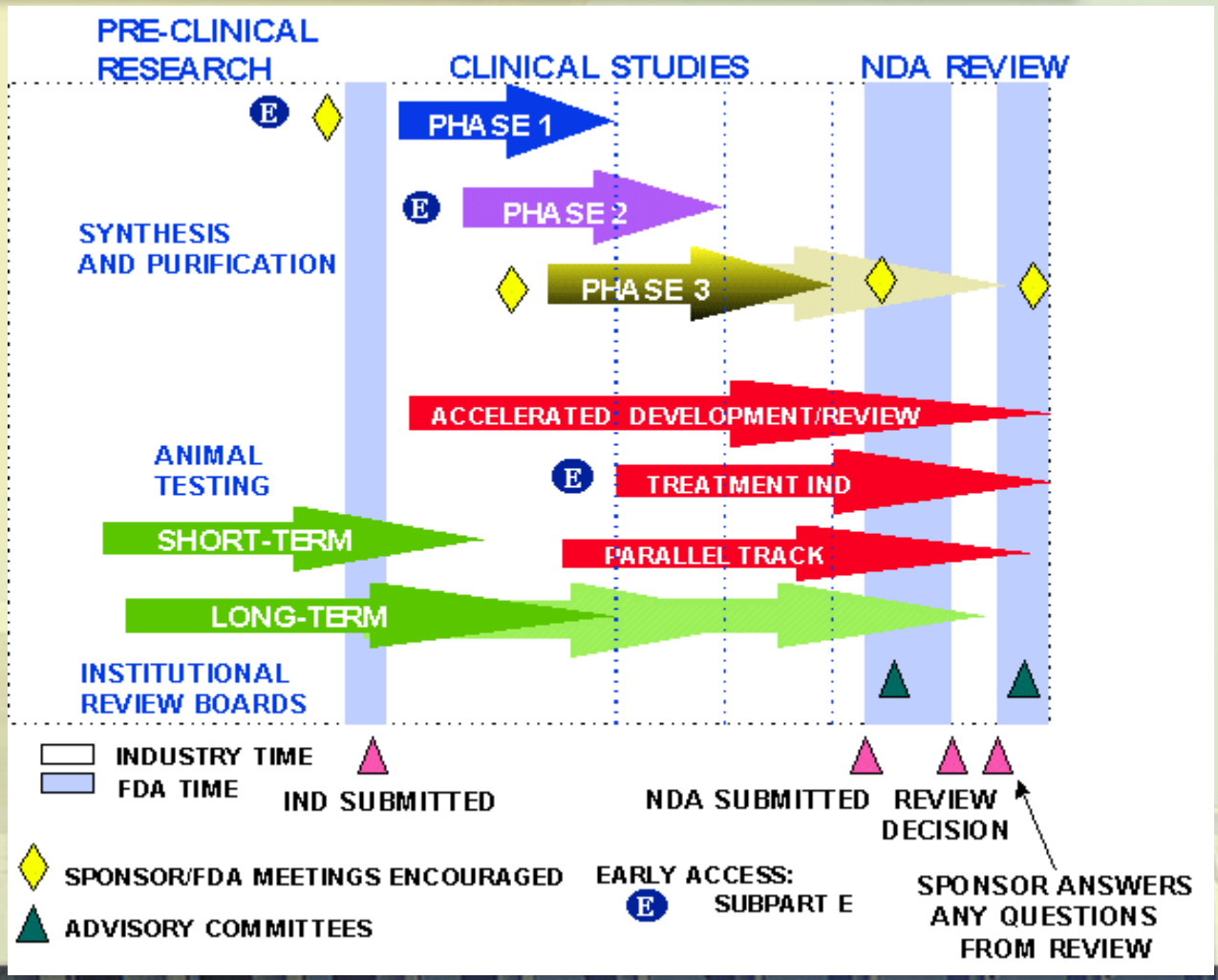
The New Drug Development Process (www.fda.gov/cder/handbook/develop.htm)



Basic Disciplines of Drug Development

Clinical Trials									
	Preclinical Testing		**Phase I**	**Phase II**	**Phase III**		**FDA**		**Phase IV**
Years	3.5		1	2	3		2.5	12 Total	
Test Population	Laboratory and animal studies	File IND at FDA	20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	File NDA at FDA	Review process / Approval		Additional Post marketing testing required by FDA
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				
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

Acronyms

- FDA
- IND
- NDA
- sNDA
- ANDA
- BLA
- PLA
- ELA
- 510(k)
- IDE
- PMA
- CMC
- GMP
- GLP
- GCP
- QC
- QA
- AWC
- EMEA
- HPB
- MHW
- ICH

Organization of the FDA

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)

Basic Disciplines of Drug Development

- Chemistry, Manufacturing, and Controls
- Nonclinical
- Clinical

Basic Disciplines of Drug Development

- Chemistry, Manufacturing, and Controls
  - Discovery (serendipity, folk medicine, random screening, rational drug design)
  - Chemistry (synthesis, purification, scale-up)
  - Analytical (chemical structure and activity, excipients, purity and stability)
  - Pharmaceutical (dosage form, route of administration, packaging and labeling)
  - Good Manufacturing Practice (GMP):
    - Guidelines related to manufacturing practices and specifications
    - Focus on impurities
    - Necessary to ensure quality of drug product (finished dosage form) and drug substance (bulk ingredients)

Basic Disciplines of Drug Development

- Nonclinical
  - Testing in laboratory (in vitro) and in animal models (in vivo) to assess safety and efficacy
  - Objectives:
    - To develop the pharmacological profile
    - To determine the acute toxicity in at least 2 animal species
    - To assess toxicity with studies ranging from 2 weeks to several months
  - Good Laboratory Practice (GLP):
    - Guidelines related to studies in animal models
    - To ensure the quality and integrity of data by establishing basic standards for the conduct and reporting of nonclinical safety studies

Therapeutic Index

The **therapeutic index** (also known as **therapeutic ratio** or **margin of safety**), is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxic effects. Quantitatively, it is the ratio given by the dose required to produce the toxic effect divided by the therapeutic dose. A commonly used measure of therapeutic index is the lethal dose of a drug for 50% of the population (LD_{50}) divided by the effective dose for 50% of the population (ED_{50}).

$$Therapeutic\ ratio = \frac{LD_{50}}{ED_{50}}$$

Investigational New Drug (IND) Application

- Pre-IND Meeting Request
- Pre-IND Meeting package
- Pre-IND Meeting
  - Pre-IND Meeting Package
    - 25-75 pages
    - Agenda/Attendees/Objective
    - Questions
    - CMC information
    - Nonclinical information
    - Phase 1 protocol summary
    - Clinical development plan (at least 1 year)
    - Previous human experience

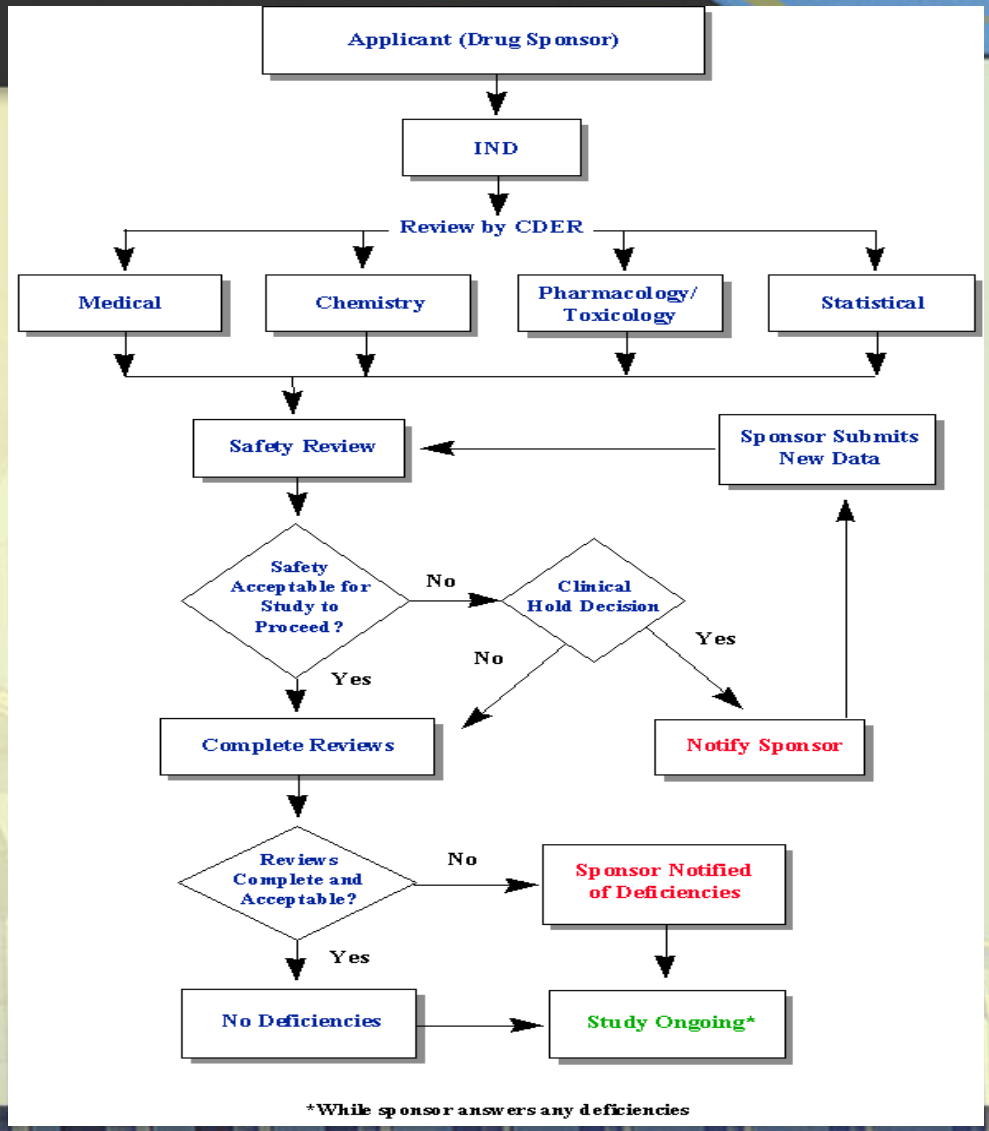
Basic Disciplines of Drug Development

- Clinical Investigation
  - Submission of the IND
  - Conduct of Clinical Studies
    - Phase 1
    - Phase 2
    - Phase 3
    - Phase 4 (post-marketing studies)

Basic Disciplines of Drug Development

- IND Submission
  - Tantamount to a request for permission from FDA to begin testing the product in humans
  - Compilation of the following:
    - Data obtained during nonclinical investigation stage and from previous human experience
    - Chemistry, manufacturing, and control data
    - Protocol
    - Detailed description of proposed studies
  - 30-day review period at FDA

IND Review Process



Basic Disciplines of Drug Development

- Clinical Studies
  - Conducted in healthy volunteers or in patients
  - Three phases (1-3) during this stage of development and one phase (4) following marketing approval
  - Takes an average of 6 years to complete the first three stages

Basic Disciplines of Drug Development

- Phase 1 Clinical Studies
  - Initial assessment of safety, drug tolerability, and dose range in humans
  - Usually involve healthy volunteers
  - Usually involve a single administration of the product or a placebo
  - Small subject population (10-80)
  - Usually last 6 months to 1 year (30% of drugs fail Phase 1 testing)
- Objective of Phase 1 Clinical Studies
  - Final objective of Phase 1 studies is to have determined the maximum-tolerated dose with potential toxicities well-defined

Basic Disciplines of Drug Development

- Phase 2 Clinical Studies
  - Initial assessment of efficacy (proof-of-concept) and further assessment of safety
  - Involve patients who have the indicated disease or condition
  - Small patient population (100-300)
  - Usually last 2 years (37% of drugs fail Phase 2 testing)

- Objective of Phase 2 Clinical Studies
  - Final objective of Phase 2 Studies is to have rigorously defined the dose regimen of the drug that elicits the desired therapeutic benefit and that outweighs the observed clinical risks

Basic Disciplines of Drug Development

- End-of-Phase 2 Meeting
  - Type “B” meeting with FDA
  - Package received 30 days before scheduled date
  - Outstanding Nonclinical/CMC issues
  - Proposed Phase 3 adequate and well-controlled study design and analysis plan
  - Obtain agreement from FDA on Phase 3 adequate and well-controlled study design and analysis plan

- Adequate and well-controlled study
  - Has agreed-upon adequate and well-controlled design
  - Provides the data the FDA will base its go/no-go decision on (pivotal)
  - Must meet high scientific standards: controlled, blinded, randomized, adequate size

Basic Disciplines of Drug Development

- Phase 3 Clinical Studies
  - Large-scale studies aimed at verifying efficacy establishing safety, and establishing the optimum dosage
  - Involve a larger number of patients (500-2000)
  - Usually last 3 years (6% fail Phase 3 testing)

- Objective of Phase 3 Clinical Studies
  - To provide the data sufficient to convince the FDA of the favorable benefit/risk ratio of the drug under investigation

Basic Disciplines of Drug Development

- Pre-IND/BLA Meeting
  - Type “B” Meeting
  - Package received 30 days prior to scheduled date
  - Questions to which you desire answers
  - Obtain written documentation to all decisions and commitments (minutes)
  - Obtain agreement on submission format
  - Obtain agreement on submission plan

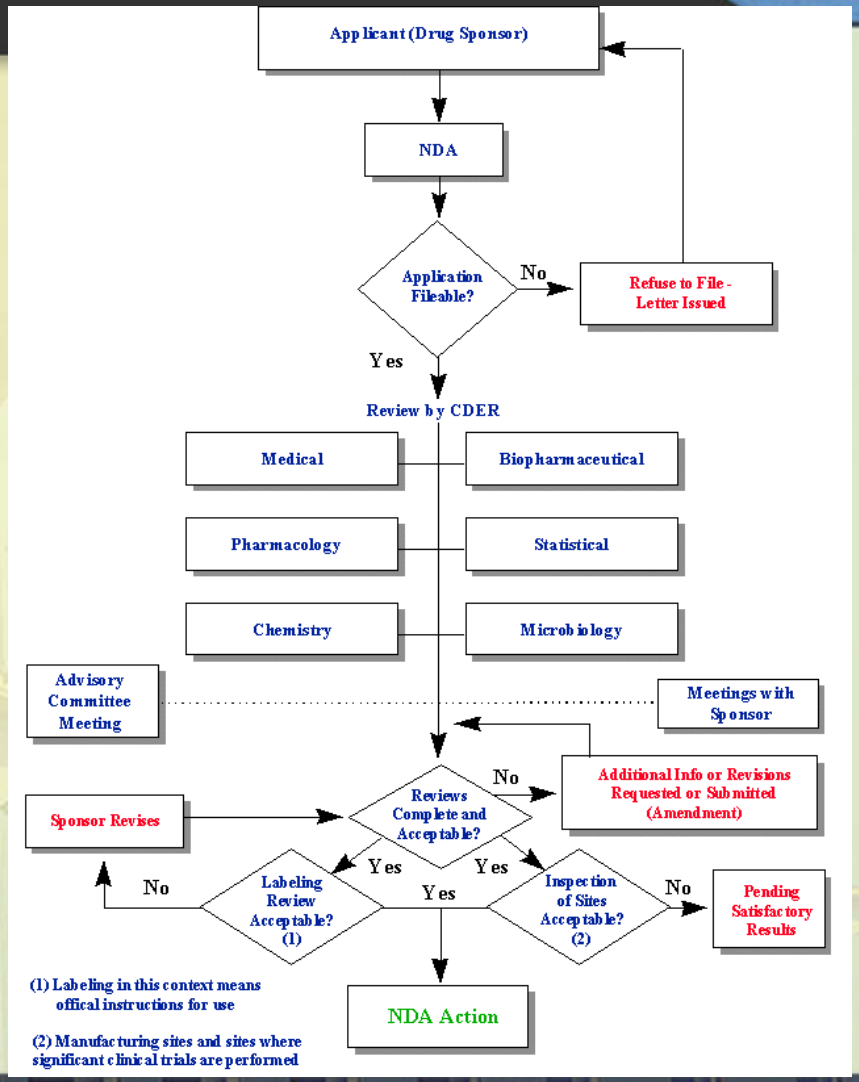
- Good Clinical Practice (GCP)
  - Minimum standards for conducting clinical research
  - Regulations hat seek to accomplish the following:
    - Ensure the quality and integrity of the data and ensure that the FDA’s decisions based on these data re informed and responsible
    - Protect the rights and safety of subjects
  - ICH E6 – GCP: Consolidated Guideline

Basic Disciplines of Drug Development

- Marketing Applications
  - NDA, sNDA, ANDA for drugs
  - BLA (=NDA), PLA, ELA for biologics
  - 510(k), PMA for devices

- Drugs: New Drug Application (NDA)
  - 80% of an NDA is clinical data
  - Includes the following:
    - Results of animal and clinical studies
    - Any foreign clinical and marketing data
    - Detailed chemistry, manufacturing, and control data

NDA Review Process



Basic Disciplines of Drug Development

- Phase 4 Clinical Studies
  - Conducted after approval to market has been granted by FDA
  - Designed to confirm the safety of the product in large patient populations
  - Involve AE reporting by physicians

Devices

- Before marketing a medical device the manufacturer must submit a premarket notification [510(k)] or a premarket approval (PMA) application to FDA
  - A Premarket Notification [510(k)] is a marketing application submitted to FDA to demonstrate that the medical device is as safe and as effective or substantially equivalent to a legally marketed device. Most devices are cleared for commercial distribution in the U.S. by the 510(k) process (Class II devices).
  - Premarket Approval (PMA) is the process of scientific review by FDA to evaluate the safety and effectiveness of Class III devices. Clinical studies in support of a PMA are subject to the investigational device exemption (IDE) regulations.

Links to web

- The U.S. Drug Approval Process: A Primer
  http://www.thememoryhole.org/crs/more-reports/RL30989.pdf
- The New Drug Development Process
  http://www.fda.gov/cder/handbook/develop.htm
- Content and Format of INDs for Phase 1 Studies of Drugs
  http://www.fda.gov/cder/guidance/clin2.pdf
- Center for Devices and Radiological Health
  http://www.fda.gov/cdrh/

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