Design of Clinical Drug Development Programs

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Disclaimer

The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA.

Introduction

- By way of …
  - Small
  - Medium and
  - Large Pharma
  - & the FDA
    - OND\CDER\DNP (Div Neurology Products)

Objectives

- What is Drug Development
  - What is Clinical Development
- Why *Develop* Drugs
- How does one *develop* a drug
  - A walk through the process
    - Lab bench to post-approval…since what you do in the beginning should be directed at where you want to go in the end

Acknowledgement…it's a big question

Aim of Drug Development

- **CMC [21 CFR 312.23(a)(7)]:**
  To assure the proper identification, quality, purity, and strength of the investigational drug.
- **Preclinical [21 CFR 312.23(a)(8)]:**
  To assure that it is reasonably safe to conduct the proposed clinical investigations.
- **Clinical [FD&C Act Sec. 505]:**
  To establish efficacy and safety of a drug for use in humans, in a dose range and schedule that provides an acceptable risk benefit relationship.

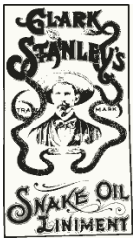
Why Develop Drugs Clinically

Landmark Legislation Affecting Clinical Development

- Pure Food and Drug Act (1906)
- Food & Drug Cosmetic Act (1938)
- Durham-Humphrey Amendment (1951)
- Kefauver Harris Amendments (1962)
- Pharmaceutical Drug User Fee Act (1992)
- Food & Drug Administration Modernization Act (1997)
- Pharmaceutical Research Equity Act
- Best Pharmaceutical in Children Act
- Food and Drug Administration Amendment Act (2007)

Snake Oil

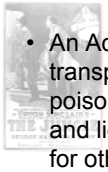
Resveratrol is the plant compound found in red wine linked to better health and longer life. Ricardo Dearatanha/ Los Angeles Times

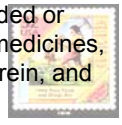


- mineral oil
- 1% fatty oil (presumed to be beef fat)
- red pepper
- turpentine
- camphor

*On the March 24th Oprah show, Dr Oz recommended the anti aging resveratrol supplement. "**This Extreme life extension pill could add up to 30 years on our life expectancy**." Dr Oz also discussed the benefits of calorie restriction and its affects on the aging process.*

Pure Food and Drug Act (1906)





- An Act for preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes
  - **Drug** – all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals
  - **Adulterated** – it differs from the standard of strength, quality, or purity, as determined by the test laid down in the United States Pharmacopoeia or National Formulary official at the time of investigation
  - **Misbranded** – any statement, design, or device regarding such article, or the ingredients or substances contained therein which shall be false or misleading

1938 Federal Food, Drug and Cosmetic (FD&C) Act

- The introduction of this act was influenced by the death of more than 100 patients due to a sulfanilamide medication where diethylene glycol was used to dissolve the drug and make a liquid form. It replaced the earlier Pure Food and Drug Act of 1906.
- Pre-clearance of drugs for safety
- Grandfathered Drugs – New drug/old drug concepts
  - Marketed prior to 1938
  - Not covered by requirements of the Act
  - Cannot change formulation or labeling
- No NDA approval action

Substantial Evidence

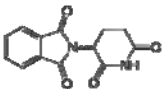
- The term "substantial evidence" is defined in § 505(d) of the Act, which provides:
  - "As used in this subsection and subsection (e), of this section, the term `substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

1951 Durham-Humphrey Amendment

- Separated the prescription drugs from OTC products
  - A drug that does NOT meet the following criteria:
    - Habit-forming
    - Need for physician's supervision
    - Limitations set by an effective NDA for the drug

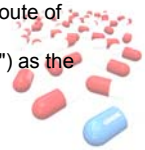
1962 Kefauver Harris Amendments

- Added a requirement that drugs be shown to be effective
- Required a positive act of approval before a new drug could be marketed
- Required that the FDA review all drugs that had become since 1938 for effectiveness



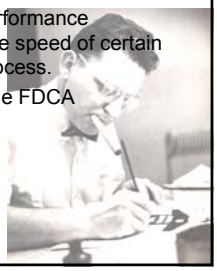
1984 Drug Price Competition and Patent Term Restoration Act

- *More commonly known as the "Hatch-Waxman Act*
- Extended the patent exclusivity terms of new drugs
  - tied extensions, in part, to the length of the FDA approval process for each individual drug
- Created new approval mechanism, the Abbreviated New Drug Application (ANDA), in which generic drug manufacturers need only demonstrate that their generic formulation has the same active ingredient, route of administration, dosage form, strength, and pharmacokinetic properties ("bioequivalence") as the corresponding brand-name drug.



1992 'Prescription Drug User Fee Act' (PDUFA)

- Allowed FDA to collect fees at time a New Drug Application (NDA) was submitted from Sponsor to fund approval process
  - FDA is required to meet certain performance benchmarks, primarily related to the speed of certain activities within the NDA review process.
  - Is renewed in cyclical updates to the FDCA



(1997) Food & Drug Administration Modernization Act

- Added fast-track approval for priority medications
- Added pediatric exclusivity for study in children

Pediatric Legislation

- Best Pharmaceuticals for Children Act of 2002
- Pediatric Research Equity Act of 2003

The Carrot and Stick of Peds Drug Development

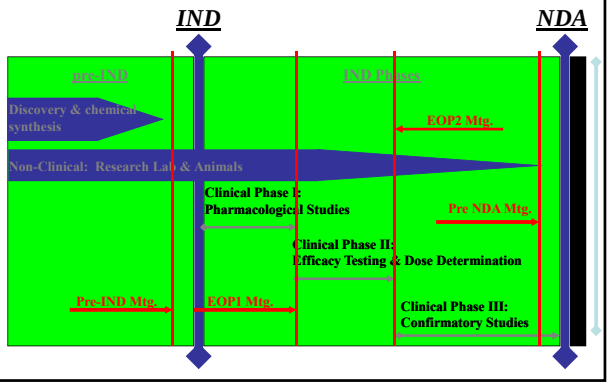
…More on this later!!

The Food and Drug Administration Amendments Act (FDAAA)

- Signed September 27, 2007
- Huge law – includes PDUFA IV, many others
- New authorities, FDA can require
  - Safety-related labeling changes
  - Postmarketing clinical trials and epi studies
  - Risk Evaluation and Mitigation Strategies

How is Clinical Development Done?

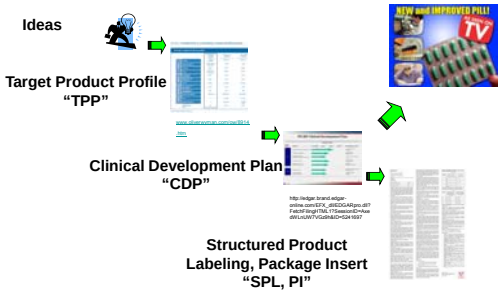
Drug Development Process



Stages of Clinical Development

- **Planning**
  - Developing the Target Product Profile
  - Designing your Clinical and Strategic Development Plans
- **Investigational New Drug**
- **Clinical**
- **New Drug Application (NDA)**
- **Postmarketing**

Planning Clinical Development



Target Product Profile

- A contract with the Corporation regarding the desired attributes of the Product
  - Determines estimate of Net Present Value
  - Forms the basis of Go-No Go Criteria
  - Forms the basis of the clinical development plan (CDP;and probably all other DPs) and draft label

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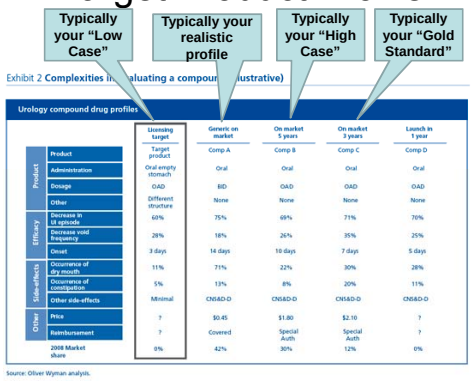
Target Product Profile



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Target Product Profiles

Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

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Prototypic Clinical Development Plan

(Modified Release Type)

Study \ Year	2010	2011	2012	2013	2014	2015
Pilot SD (w pilot Fed arm)						
Pilot MD						
IND						
Rel BA						
Dose Prop						
Dose Lin						
Food Effect						
Bridge API						
Peds PK						
Ph3a						
NDA						
Launch						

GANNT Chart

– Allows review of timetables
  - Allows one to double check assumptions
– Identification of resources
– Allows recognition of critical interdependencies
  - e.g., need to clear a product with QA before shipping
  - Forms the basis of Go-No Go Criteria
– Identifies critical path tasks
  - **Critical path** – the sequence of activities that add up to the longest overall project duration. This determines the shortest time possible to complete the project. Any delay on the critical path directly impacts the planned project completion date. Those activities that can be done at anytime are "not on the critical path"

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GANNT Chart

ID	Task Name	Duration
1	**Preclinical Phase**	**54 wks**
2	Laboratory API Synthesis and Analysis	12 wks
3	API Physicochemical Evaluation and Preformulation Activities	10 wks
4	GMP Synthesis and Analysis of API	14 wks
5	Preclinical Formulation	2 wks
6	Mutagenicity Studies	14 wks
7	Acute Toxicity Studies	8 wks
8	Repeat-Dose Toxicology Studies	24 wks
9	ADME/PK Evaluation Pre–Phase 1	26 wks
10	Safety Pharmacology Package	18 wks
11	Drug Product Formulation (GMP)	12 wks
12	Regulatory Review (CTA/IND) for Phase 1 Study	4 wks
13	**Phase I**	30 wks
14	Basic Phase I Studies	30 wks
15	Additional tox. (if required), e.g., 3m to support Phase II/III	26 wks
16	Tox. Reproduction: Embryotoxicity (2 Species)	36 wks
17	Drug Product Optimization/Manufacture Phase 2	22 wks
18	API Process Development	26 wks
19	**Phase II**	104 wks
20	Proof-of-Concept Efficacy Trial	32 wks
21	Dose-finding Clinical Trials	72 wks
22	Clinical Pharmacology, e.g., QTc study & interactions	26 wks
23	Long-Term Repeat Dose Toxicology Studies	70 wks
24	Tox. Reproduction: Fertility and Peri/Postnatal	22 wks
25	Carcinogenicity	150 wks
26	Drug Product (Phase 3) Scale-Up and Validation	26 wks
27	Stability of Drug Product (Final Formulation)	110 wks
28	**Phase III**	120 wks
29	Pivotal Phase 3 Efficacy Trials	120 wks
30	Long-Term Safety Evaluation	120 wks
31	Special Population Studies	40 wks
32	Marketing Approval (MAA/NDA) Submission	0 wks

Year 1 Year 2 Year 3 Year 4 Year 5 Year 6 Year 7
Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2

Project: Project plan
Date: 31 Aug '07

Early Start · Late Start · Critical Task · Milestone · Summary

Strategic Development Plan

Adapted from Kennedy's "Pharmaceutical Project Management"

Plan section	Pages	Content	Comment
Executive summary	4	The approval sought (scope of activities, funds, and resources) Development strategy Key risks/risk management Go/no-go checkpoint and criteria High level Gantt chart	A template often used so that the oversight committee has consistent "view" of the projects being presented
Target product profile(s)	2	Refer to Table 3	The detail increases during development phases
Business strategy	5	Market definition Marketing assumptions Pharmacoeconomics strategy	Current and future market structure and constraints to access
Clinical strategy	5	Clinical strategy Clinical studies tabulation Clinical Gantt chart Clinical issues/issue management	High level extract from a functional clinical plan
Regulatory strategy	3	Regulatory strategy Regulatory plan Regulatory risks/risk management	Defines regulatory strategy/plans for the major markets
Technical strategy CMC	3	Drug substance plan Drug product plan Analytics plan Key issues/issue management	The manufacturing strategy for sourcing and supply detailed in functional plans
Scientific summary	4	Scientific rationale Preclinical plan ADME plan Key issues/issue management	High-level status summary and forward activity plan
Development costs	2	Estimated costs by stage Estimated costs by activity type	Standardized analyses for portfolio
Financial analysis	4	5th-yr revenues Financial assessment of project	Standardized analyses for portfolio

Abbreviations: CMC, chemistry, manufacturing and controls; ADME, absorption, distribution metabolism, excretion.

Stages of Clinical Development

- **Planning**
- **Investigational New Drug (IND)**
  - Preparation and Application
  - Commensurate with Preclinical Phase
- **Clinical**
- **New Drug Application (NDA)**
- **Postmarketing**

IND Package

- Cover letter
- CV (check for qualifications)
- Investigator's brochure
- General investigational plan
- **Clinical protocol (s)**
- Clinical pharmacology (dose, drug interactions, etc.)
- Pharm / Tox (safety signals)
- CMC (chemistry)

Grounds for Imposing a Clinical Hold: Phase 1

- 21 CFR 312.42 (b)(1)
- Human subjects at unreasonable and significant risk
- Unqualified investigator(s)
- Investigator brochure misleading, erroneous or incomplete
- Insufficient information to assess risk
- Exclusion by gender if for life-threatening condition

Clinical Trials: Human Protection

- Assure that the rights, safety, and well-being of human trial subjects are protected.
- 21 CFR 56: Institutional Review Boards (IRB)
- 21 CFR 50: Protection of Human Subjects (Informed Consent)

Elements of Consent Documents

- Statement that study involves research
- Description of risks or discomforts
- Description of any benefits from research
- Disclosure of any alternative procedures or treatments available
- Description of confidentiality of records
- Compensation for injury
- Contact for questions
- Conditions of participation
- Circumstances of participation termination
- Any costs to subject
- Consequences & procedures to withdraw
- Significant new findings
- Number of subjects involved in the study

Stages of Clinical Development

- **Planning**
- **Investigational New Drug**
- **Clinical**
  - Disposition of Drug
  - Characterization of Pharmacodynamics
  - Proof of Efficacy and Safety
- **New Drug Application (NDA)**
- **Postmarketing**

Phases of Clinical Studies

- **Phase 1** (first in human): small size, healthy volunteers, single dose, determine pharmacology and tolerability
- **Phase 2** (exploratory, proof-of-concept): moderate size, "healthy" target population, multiple dose, dose-finding, short term safety
- **Phase 3** (confirmatory safety and efficacy): large size, target population, mimic use in real-life

The division into phases (esp 2 vs. 3) is somewhat artificial; the law states that you must prove your efficacy and safety through adequate and well controlled trials although one could require the development of the drug's dose response under the guise of "safe" dosing. More on this later..

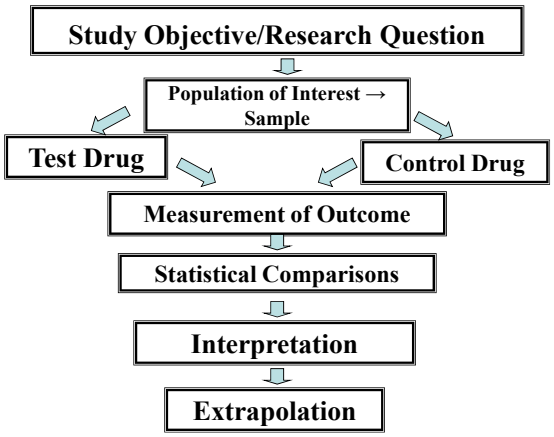
Types of Phases 1 Studies

Name (Acronym)	Objective	Design	Dosing
Single Ascending Dose (SAD)	First in human; PK and Safety	Single Dose (SD); 1/10 NOAEL ⇧; parallel	
Single Dose (SD)	Formulation screening	SD vs. ref. drug; Highest dose that's safe to take; crossover	
Multiple Ascending Dose (MAD)	PK and Safety; Maximal Tolerated Dose (mtd)	MD to mtd; parallel	
Multiple Dose (MD)	PK and Safety; NDA req for Rel Bio of MRs	MD to mtd or top of known dose range vs ref drug (1 dose level)	
Food Effect (FF or FE)	Effect of food on bioavailability (BA)	SD fed and fasted; crossover	
Dose Linearity and Proportionality	Uniformity of the BA from dosage units	1 vs 2 vs 4 mg (sd) vs. 4x1mg, 2x2mg, 1x4mg; crossover	
Drug Interaction	Effect of drug on other drug BA or visa versa	SD (A) ± steady state dosing of (B) and visa versa	
Special Populations (elderly, gender, renal or hepatic impairment)	BA of drug under various conditions	Often SD but may vary	
ADME	Disposition of drug (labeled chemical)	SD of labeled drug in bottle	

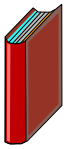
Pharmacokinetics in drug development : clinical study design and analysis / Peter Bonate, Danny Howard.
p. cm.
Includes bibliographical references and index.
ISBN 0971176764 (v. 1)

Design of Phase 2/3 Studies

- A study in the patient population testing a hypothesis regarding the efficacy of a drug
- When done as part of a regulatory package, the study should support ("map to") the indication and dosing guidance in terms of the
  - Primary endpoint + Population ☛ Indication
  - Doses and dosing regimen ☛ Dosing guidance



Special Protocols

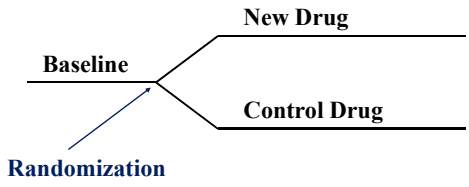


- Implements Section 119(a) FDAMA
  - Special Protocol Assessment (SPA)
- Requires FDA to meet with sponsors for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim in marketing applications. Also available for carcinogenicity and stability protocols.

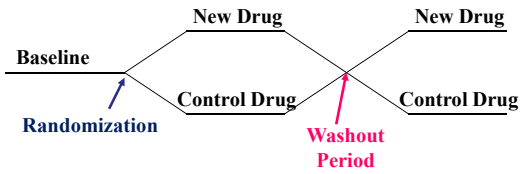
Common Study Designs

- Case-Control Study
  - Retrospective Observational Study
- Cohort Study
  - Prospective Observational Study
- **Controlled Clinical Trial**
  - **Prospective Experimental Study**
  - **Best design to study causality**
  - **Design of confirmatory trials**

Parallel Study Design



Cross-over Study Design



What you want to show with this trial?

Efficacy

- New drug is more efficacious than sham treatment - placebo controlled (superiority) trial
- New drug is as efficacious as the current therapy - active controlled equivalence trial trial
- Combination of new drug and existing drug (or two existing drugs) is better than no treatment and better than each component drug - combination trial

What you want to show with this trial?

- Do better with this drug prior to treatment - baseline controlled trial
  - Not typically accepted because of changes in disease over time
- New drug is more efficacious than past medical practice - historically controlled trial

Safety Studies

- That new drug is as safe (regarding specific endpoint) as current therapy or placebo
  - Should assess efficacy and safety simultaneously

Assignment - Randomization

- Randomization attempts to assign individuals to groups (or vise-versa) without bias.
  - Protects Against Selection Bias
  - Balances Treatment Groups
    - With respect to factors known or suspected to influence outcome.
    - With respect to factors which are not known to affect outcome.
  - Insures the Validity of Statistical Tests

Blinding or Masking

- Double Blind - Neither the patient nor the investigator know group assignment (test or control)
- Single Blind - The patient does not know group assignment
- Open Label – Group assignment known by patient, investigator, etc.

Study Sample

What is the population of interest?

- All people who have the target disease
- A subset of the general population
  - Only patients in a certain age group
  - Only patients who have a certain severity of the disease
  - Only patients with (or without) certain other diseases
  - Only patients who are taking (or are not taking) certain other medications

Control Group

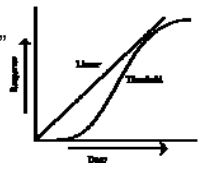
- The drug, device, or test procedure administered in a clinical trial that serves as a standard against which experimental group are evaluated.
- For non-life-threatening diseases, the control group can be a placebo.
- For life-threatening diseases, the control group is often the standard care for the disease.
  - May be historical; placebo rate of similar trials

Study Size?

- Adequate to demonstrate the desired outcome
- Factors which determine sample size:
  - + the size of the Type I error
  - + the size of the Type II error (power)
  - + the variability of the responses (variance)
  - – the expected improvement in the treated group minus the control group (clinical significance)

The Dose Response

- The most typically accepted study design is the parallel fixed-dose study
- What you should know about your dose range
  - The "maximum tolerated dose"
  - The minimum dose that gives the maximal effect (MED)
  - The shape of the curve leading up to the MED
  - The effect of titration on the drugs tolerability



Dose Response Rationale

TABLE 1

DATA OF MATERSON

Fall in blood pressure (systolic/diastolic) from baseline in erect and supine position with each of four dose levels of chlorthalidone and placebo.

Dose	Fall in Blood Pressure (mmHg) Supine	Standing
Placebo	0/2	0/0
12.5 mg	5/4	6/4
25 mg	11/5	15/7
50 mg	10/6	14/5
75 mg	11/6	14/6

Endpoints

- The primary goal in choosing endpoint(s) is to select definitive and appropriate measures of the condition being studied
  - Should be clinically relevant
  - Should coincide with current medical practice
  - Should be measurable/interpretable
- **NEED A CENTRAL *or* PRIMARY ENDPOINT**…this drives design, analysis, etc
  - ☹ …to study X and Y and Z and AA…
  - ☹ …to study the efficacy and safety of Drug X

Choice of Endpoints

- Numeric, Categorical, Ordinal
  - Change in weight
  - Yes vs No
  - None, Mild, Moderate, Severe…
- Single vs. composite
  - Composite endponts – Is one component driving outcome?
- Objective or subjective
  - Time until asleep
  - I slept good/bad

Statistics is never having to say you're certain

There are lies, damn lies and statistics

-Mark Twain

Analysis

- Compare group results using appropriate statistical methods
  - Test the primary hypothesis to draw conclusions regarding populations based on sample studied
  - Measure the size of the differences between the groups or the strengths of the relationships between variables (*estimation*)
  - Frequentist vs. Bayesian methods
- Remove the effect of confounding variables if necessary

Types of Analyses

- T Test
- Fishers Exact Test
- Chi Square Test
- ANOVA
- ANCOVA
- Linear Regression
- Logistic Regression
- Non-parametric analysis (e.g., CMH)
- Survival Analysis

Vary by type of variable, nature of the data, and the question you want to answer

Who do you analyze?

- If patients drop out of the study, whether related to treatment or not, they must be accounted for - especially if patient losses were disproportionate between groups.
  - All randomized patients - Intent-to-treat (ITT)
  - Randomized patients meeting baseline criteria or other study criteria of interest –modified ITT
  - Only patients who have complete data who complied with all provisions of the protocol – Per Protocol

Statistical Terms

P-value:

- Probability of observing a test statistic (difference, ratio, etc.) as extreme or more extreme, than that observed, if the null hypothesis were actually true
  - P < .05 = less than 5% of the time, the result would have gone the other way
  - *The value for which P=0.05, or 1 in 20, is 1.96 or nearly 2; it is convenient to take this point as a limit in judging whether a deviation ought to be considered significant or not. Deviations exceeding twice the standard deviation are thus formally regarded as significant. Using this criterion we should be led to follow up a false indication only once in 22 trials, even if the statistics were the only guide available. Small effects will still escape notice if the data are insufficiently numerous to bring them out, but no lowering of the standard of significance would meet this difficulty* (Fisher, p.44 13th ed. SMRW).
- small p-values give more evidence against the null hypothesis

Statistical Terms

Confidence Interval

A 95% confidence interval is a set of parameter values formed by procedure, which is repeated many times, will contain the true population parameter 95% of the time.

Significant Results

Clinical Significance

The amount of difference or relationship between treatments that assures that the results are clinically meaningful.

Sometimes a scale of the Global Clinical Impression (severity or improvement) is performed to assess this; the details around investigator or patient instructions are critical

Adverse Reactions

- Adverse Reactions
  - Undesirable effect reasonably associated with use of drug
- Serious Adverse Reactions
  - Any adverse event occurring at any dose that results in any of the following outcomes:
    - Death
    - Life Threatening
    - In-patient Hospitalization or Prolongation of Existing Hospitalization
    - Persistent or Significant Disability/Incapacity
    - Congenital Anomaly/Birth Defect
    - Important Medical Events -Based on Medical Judgment
      - may jeopardize the patient or subject and
      - may require medical or surgical intervention to prevent one of the other outcomes
      - Examples: allergic bronchospasm requiring ER or home treatment; convulsions that do not result in inpatient hospitalization

Stages of Clinical Development

- **Planning**
- **Investigational New Drug**
- **Clinical**
- **New Drug Application (NDA)**
  - Preparation and Submission
- **Postmarketing**

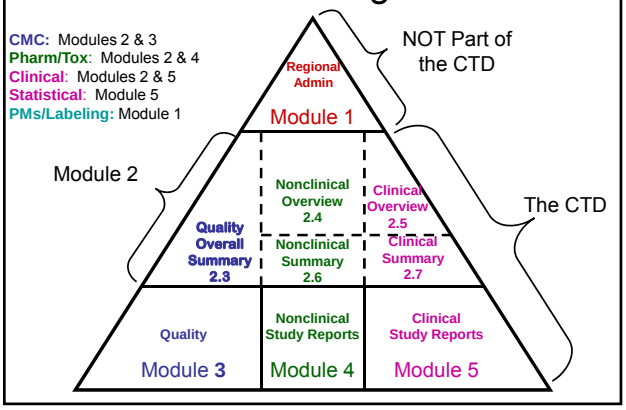
Types of NDAs
(as of 1984)

- 505(b)(1) - Applicant must own or have a right of reference to all of the investigations relied upon by the applicant to support approval of the NDA
- 505(b)(2) - An NDA that relies on investigations not conducted by or for the applicant and for which the applicant does not have a right of reference; references the FDAs finding of safety and efficacy
- 505(j) – Approval of generic drugs (Abbreviated NDA)
- 507 (repealed by FDAMA in 1997)

Examples of Changes to a Previously Approved Application Made in a 505(b)(2) NDA

- Dosage form
- Strength
- Route of Administration
- Substitution of an active ingredient in a combo
- Formulation
- Dosing regimen
- Active ingredient
- New molecular entity
- Combination product
- Indication
- Rx/OTC switch
- OTC monograph
- Naturally derived or recombinant active ingredient
- Bioequivalence

CTD Triangle



Exclusivity

- Administered by the FDA
- Provides incentive for innovation
- Protects innovator competition from 505(j) and 505(b)(2) applicants for a proscribed period of time
- Types
  - New chemical entity – 5 yr
  - Innovations to previously approved products – 3 yr
  - Generic drug – 180 d
  - Orphan drug – 7yr
  - Pediatric – 6 mo

What is Labeling? Or Why are we doing all of this?

- FD&C Act section 201k
  - Label= Written, printed, or graphic matter on the immediate container of the drug product
- FD&C Act section 201m
  - Labeling= All labels, as well as other written, printed, or graphic matter accompanying the product

Highlights

- Limitations Statement
- Product Names and Date of Initial US Approval
- Boxed Warning (20 lines)
- Major Recent Changes
- Indications and Usage
- Dosage & Administration
- Dosage Forms & Strengths
- Contraindications
- Warnings & Precautions
- Adverse Reactions – include Reporting Contact Info
- Drug Interactions
- Use in Specific Populations
- Patient Counseling Information Statement
- Revision Date

Contents and FPI

Boxed Warning
1 Indications & Usage
2 Dosage & Administration
3 Dosage Forms & Strengths
4 Contraindications
5 Warnings & Precautions
6 Adverse Reactions
7 Drug Interactions
8 Use in Specific Populations
9 Drug Abuse & Dependence
10 Overdosage
11 Description
12 Clinical Pharmacology
13 Nonclinical Toxicology
14 Clinical Studies
15 References
16 How Supplied/Storage & Handling
17 Patient Counseling Information

Boxed Warning

- Contraindication or serious warning particularly leading to death or serious injury
- Usually based on clinical data
- Placement
  - "Old" regs: FDA decision
  - PLR: Beginning of full prescribing info

Pediatric Research Equity Act

(PREA)

- Applies to BOTH drugs and biologics!!!
- Requires submission of pediatric studies for certain applications types:
  - New indication
  - New dosage form
  - New route of administration
  - New dosing regimen
  - New active ingredient

- Orphan indications/products EXEMPT
- Requirement may be deferred or waived
- Failure to comply may result in misbranding

Best Pharmaceuticals for Children Act (BPCA)

- Does NOT apply to biologics!
- Renews Pediatric Exclusivity provision established under FDAMA
  - If a drug has existing patent or marketing exclusivity ("on-patent drug"), the FDA may issue a Written Request for studies
  - If a Sponsor conducts the study and submits the data fairly responsive to WR, they qualify for 6 months of exclusivity

PREA vs. BPCA

- Studies mandatory
- Studies required only on product & indication being reviewed
- Studies not required for orphan indications
- Standard review – *unless it qualifies for priority*
- Pediatric studies must be labeled
- Drugs and biologics
- Sunsets 10/1/12

- Studies voluntary
- Studies on entire active moiety
- WR may be issued for orphan indications
- Priority review
- Pediatric studies must be labeled
- Drugs only
- Sunsets 10/1/12

Stages of Clinical Development

- **Planning**
- **Investigational New Drug**
- **Clinical**
- **New Drug Application (NDA)**
- **Postmarketing**
  - Market Expansion (Phases 3b/4)
  - Over-the Counter
  - Generics

http://www.fda.gov/cder/otcmonographs/rulemaking_index.htm: OTC Monograph
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm: NDA

What are OTC drugs?

OTC Drug Products

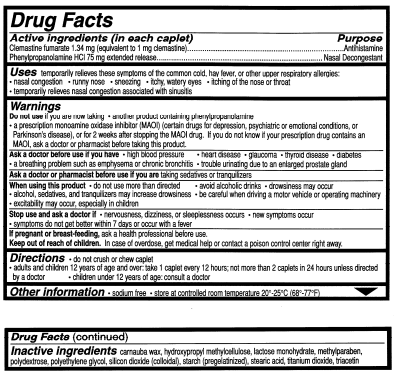
General Concepts

- Need to ensure that consumers can:
  - Diagnose the underlying condition
  - Determine whether drug is appropriate for them
  - Self-administer safely and effectively
  - Avoid potential serious consequences
  - Recognize when to see a physician or seek emergency assistance
- Label comprehension is key to approval
  - All labeling directed to the consumer

NDA vs. OTC Drug Monograph

NDA Process	OTC Monograph Process
Pre-market approval	No pre-market approval
Confidential filing	Public process
Drug product-specific	Active ingredient-specific ■ OTC drug category
May require a user fee	No user fees
Potential for marketing exclusivity	No marketing exclusivity
Mandated FDA review timelines	No mandated timelines
May require clinical studies ■ label comprehension ■ actual use	May require clinical studies ■ label comprehension and actual use studies not required

After Drug Facts



Drug Facts

Active ingredients (in each caplet) — **Purpose**
Clemastine fumarate 1.34 mg (equivalent to 1 mg clemastine) ..... Antihistamine
Phenylpropanolamine HCl 75 mg extended release ..... Nasal Decongestant

Uses temporarily relieves these symptoms of the common cold, hay fever, or other upper respiratory allergies:
• nasal congestion • runny nose • sneezing • itchy, watery eyes • itching of the nose or throat
• temporarily relieves nasal congestion associated with sinusitis

Warnings
Do not use if you are now taking • another product containing phenylpropanolamine
• a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have • high blood pressure • heart disease • glaucoma • thyroid disease • diabetes
• a breathing problem such as emphysema or chronic bronchitis • trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers

When using this product • do not use more than directed • avoid alcoholic drinks • drowsiness may occur
• alcohol, sedatives, and tranquilizers may increase drowsiness • be careful when driving a motor vehicle or operating machinery
• excitability may occur, especially in children

Stop use and ask a doctor if • nervousness, dizziness, or sleeplessness occurs • new symptoms occur
• symptoms do not get better within 7 days or occur with a fever

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a poison control center right away.

Directions • do not crush or chew caplet
• adults and children 12 years of age and over: take 1 caplet every 12 hours; not more than 2 caplets in 24 hours unless directed by a doctor • children under 12 years of age: consult a doctor

Other information • sodium free • store at controlled room temperature 20°-25°C (68°-77°F)

Drug Facts (continued)
Inactive ingredients carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate, methylparaben, polydextrose, polyethylene glycol, silicon dioxide (colloidal), starch (pregelatinized), stearic acid, titanium dioxide, triacetin

Definition of Generic Drug

- "Same" as a drug product listed in the Orange Book (the "listed drug")
  - active ingredient(s)
  - route of administration
  - dosage form
  - strength
  - conditions of use recommended in labeling

  OR. . .
- Certain changes from a listed drug if FDA has approved a suitability petition

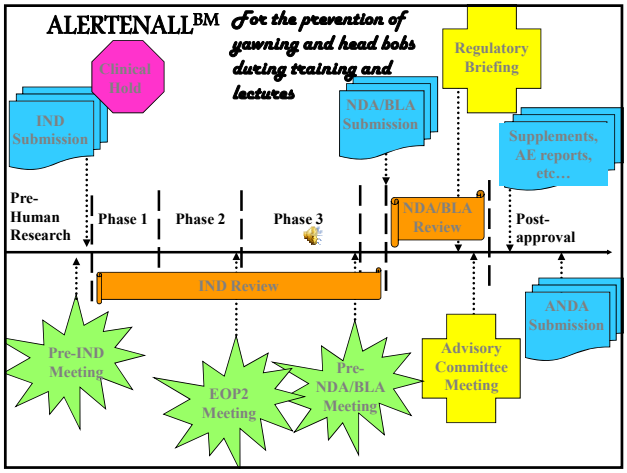
- Labeling same as reference listed drug except for
  - Manufacturer/distributor
  - Indications protected by patent or exclusivity
  - "Voluntary" pieces of approved labeling

Bioequivalence

- Generic drugs must have 90% confidence interval limits from 80% to 125% from AUC and Cmax data after logarithmic transformation

Stages of Clinical Development

- **Planning**
- **Investigational New Drug**
  - Preparation and Application
  - Commensurate with Preclinical Phase
- **Clinical**
  - Disposition of Drug
  - Characterization of Pharmacodynamics
  - Proof of Efficacy and Safety
- **New Drug Application (NDA)**
  - Preparation and Submission
- **Postmarketing**
  - Market Expansion (Phases 3b/4)
    - Over-the Counter
      - Generics



Case 1. Alertenall XR

- Alertenall IR approved for falling asleep in lecture
  - Dosing 25 - 100 mg BID
  - 2 pivotal trials and full clinical pharm and Nonclinical package
- Modified formulation
  - Same technology as Donboremall XR
  - Same clinical doses proposed
  - Cmax 85%; AUC 81%
  - ? Need more tox studies
  - ? Need a clinical trial
  - ? Dose for FF study; When to first study

Case II. Achtungizine

- Achtungizine IR
  - Novel Stelazine-like compound
  - Marketed in Austria for nervousness
    - Marketing stopped 35 y ago
    - 43 trials; many by well respected academicians
  - 200-400 mg QD
  - Application reports a full tox package
  - SAD and MAD; dosing to 400 mg w no AEs

? Will you need to repeat the nonclinical?

? Value of MAD study

? Need to perform pivotal studies?

  ? What would you estimate the biggest mistake in this program was?

  ? What will you look for in the 43 papers to offer as evidence?

  ? What other value are the 43 studies