Design of Clinical Drug Development Programs

Christopher D. Breder, MD PhD

The Center for Drug Evaluation and Research

The Food and Drug Administration

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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

Photograph of two wine glasses partially filled with what appears to be wine and another wine glass filled approximately half full with capsules. Under the photograph it says “Resveratrol is the plant compound found in red wine linked to better health and longer life. Ricardo Dearatanha/Los Angeles Times”.

What appears to be a reproduction of an old ad is shown that reads as follows:

Clark Stanley’s Snake Oil Liniment.

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

Two apparently faded photos of stamps are depicted.

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

There is a photograph of an old, dark, glass bottle of a drug apparently from the early 1930s.

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

A photograph of Herbert Humphrey is shown.

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

Chemical structure

Photograph of a baby with a deformed foot is shown.

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.

Photographs of Senator Orrin Hatch and Representative Henry A. Waxman

A photograph of some capsules is also shown.

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

A photograph is shown of a man holding a pencil and writing or drawing with a T-square while smoking a cigar.

(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

Two photographs are shown, one of a baby sucking on a carrot and the other of a young child holding a big stick.

…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

A flow chart is shown of this process from pre-IND through NDA.

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

A flow chart is shown starting with ideas (a cartoon is shown of a man holding a light bulb) →

Target Product Profile →

“TPP” (a reproduction of a page is shown) →

Clinical Development Plan “CDP” ” (a reproduction of a page is shown with the web address of http://edgar.brand.edgar-online.com/EFX_dll/EDGARpro.dll?FetchFilingHTML1?SessionID=AxedWLnUW7VGz9h&ID=5241697 →

A depiction of an ad is shown for a “New and Improved Pill! As seen on TV” with a photograph of capsules →

A photograph of a typed page is shown with illegible print. “Structured Product Labeling, Package Insert “SPL, PI”

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

Target Product Profile

A chart is shown of a target product profile.

Target Product Profiles

A reproduction of the cover page of Guidance for Industry and Review Staff is shown. It is entitled

Target Product Profile – a Strategic Development Process Tool

Draft Guidance

This document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Jeanne M. Delasko at 301/796-0900.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2007
Procedural

Prototypic Clinical Development Plan
(Modified Release Type)

An example of this type of plan is shown.

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”

GANNT Chart

A photograph is shown that is probably of Henry Gannt, the originator of the GANNT chart.

An example of a GANNT chart is shown.

Strategic
Development
Plan

An example is shown adapted from Kennedy's "Pharmaceutical Project Management".

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 doses, 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, and Dosing are also shown)

Single Ascending dose
(SAD)

Single Dose (SD)

Multiple Ascending
Dose (MAD)

Multiple Dose (MD)

Food Effect (FF or FE)

Dose Linearity and
Proportionality

Drug Interaction

Special Populations
(elderly, gender, renal
Or hepatic Impairment)

ADME

Pharmacokinetics in drug development : clinical study design and analysis/Peter Bonate, Danny Howard. P. cm. Includes bibliographical references and index. ISBN 09711767-4-4 (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

Study Objective/Research Question

Population of Interest →

Sample

↓ ↓

Test Drug **Control Drug**

↓ ↓

Measurement of Outcome

↓

Statistical Comparisons

↓

Interpretation

↓

Extrapolation

Special Protocols

A cartoon illustration of a book is shown.

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

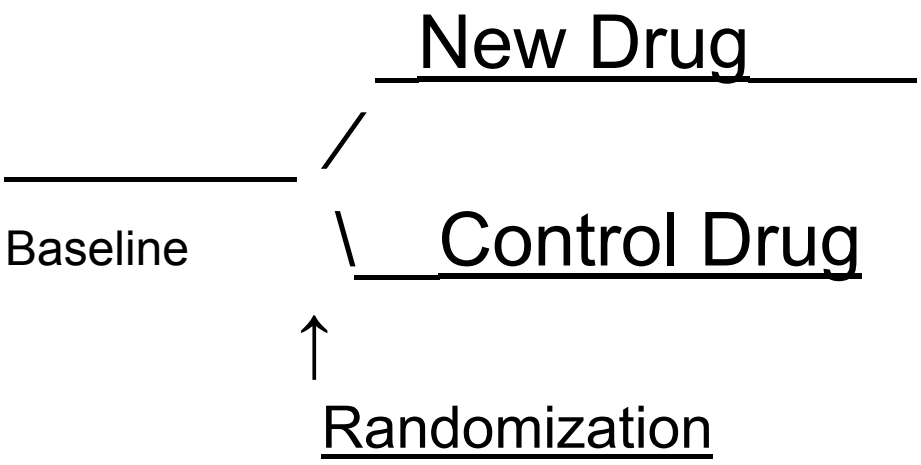
Cohort Study

Prospective Observational Study

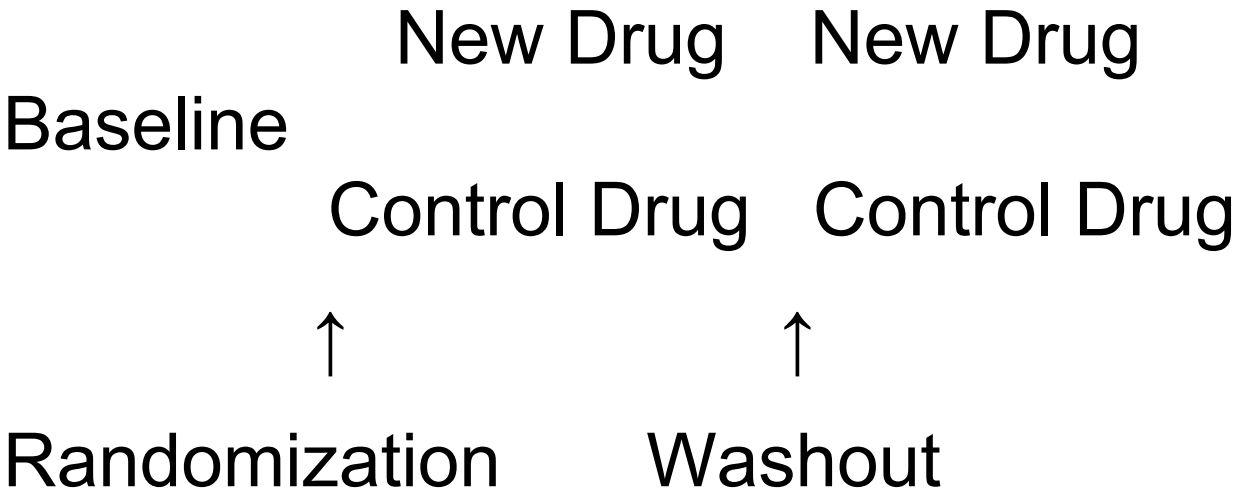
Controlled Clinical Trial

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 vice-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

There is a plot showing the Linear and Threshold responses over dose. The response for both increases with the amount of the dose although the response for the Threshold starts more slowly and eventually levels off whereas the Linear plot continues steadily upwards.

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.

	Fall in Blood Pressure (mmHg)	
Dose	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

CMC: Modules 2 & 3

Pharm/Tox: Modules 2 & 4

Clinical: Modules 2 & 5

Statistical: Module 5

PMs/Labeling: Module 1

A drawing of pyramid is shown with Module 1 at the top, Module 2 beneath it, and Modules 3, 4, and 5 on the bottom.

Module 1 – Regional Admin. NOT part of the CTD

Module 2 – Quality Overall Summary 2.3

Nonclinical Overview 2.4

Nonclinical Summary 2.6

Clinical Overview 2.5

Clinical Summary 2.7

Module 3 – Quality

Module 4 - Nonclinical Study Reports

Module 5 - Clinical Study Reports.

Modules 2, 3, 4, and 5 are the CTD

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

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

There is a photograph of the head and showers of a female child smiling. There is another photograph of the head and shoulders of a younger child with a thermometer in her mouth, one of her hands on her forehead, and an unhappy expression on her face.

Best Pharmaceuticals for Children Act (BPCA)

There is a photograph of a young smiling boy with his arms raised and he is apparently holding softball mitts in both hands.

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

What are OTC drugs?

http://www.fda.gov/cder/otcmonographs/rulemaking_index.htm: OTC Monograph

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm: NDA

Photographs of a variety of over the counter products are shown, some with “New Drug Application (NDS)” printed as a heading in front of them (Aleve, Imodium A-D, Colgate Total toothpaste, Commit, Pepcid AC, and Claritin) and others with “OTC Drug Monograph” printed as a heading in front of them (Tylenol Extra Strength, Listerine, head and shoulders intensive solutions, Dulcolax, Colgate Cavity Protection toothpaste, Robitussion DM, Speed stick, and Coppertone 8).

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 marking exclusivity	No marketing exclusivity
Mandated FDA review timelines	No mandated timelines
May require clinical studies	May require clinical studies
Label comprehension	label comprehension and actual use studies not required

After Drug Facts

Reproduction of a drug label that lists the drug facts, purpose, uses, active ingredients in each caplet, warnings, directions, other information, and inactive ingredients.

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

ALLERTENALL[BM] For the prevention of yawning and head bobs during training and lectures

There is a flow chart showing the process from IND submission through post-approval and ANDA Submission.

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