

# The Regulation of Drug and Biological Products

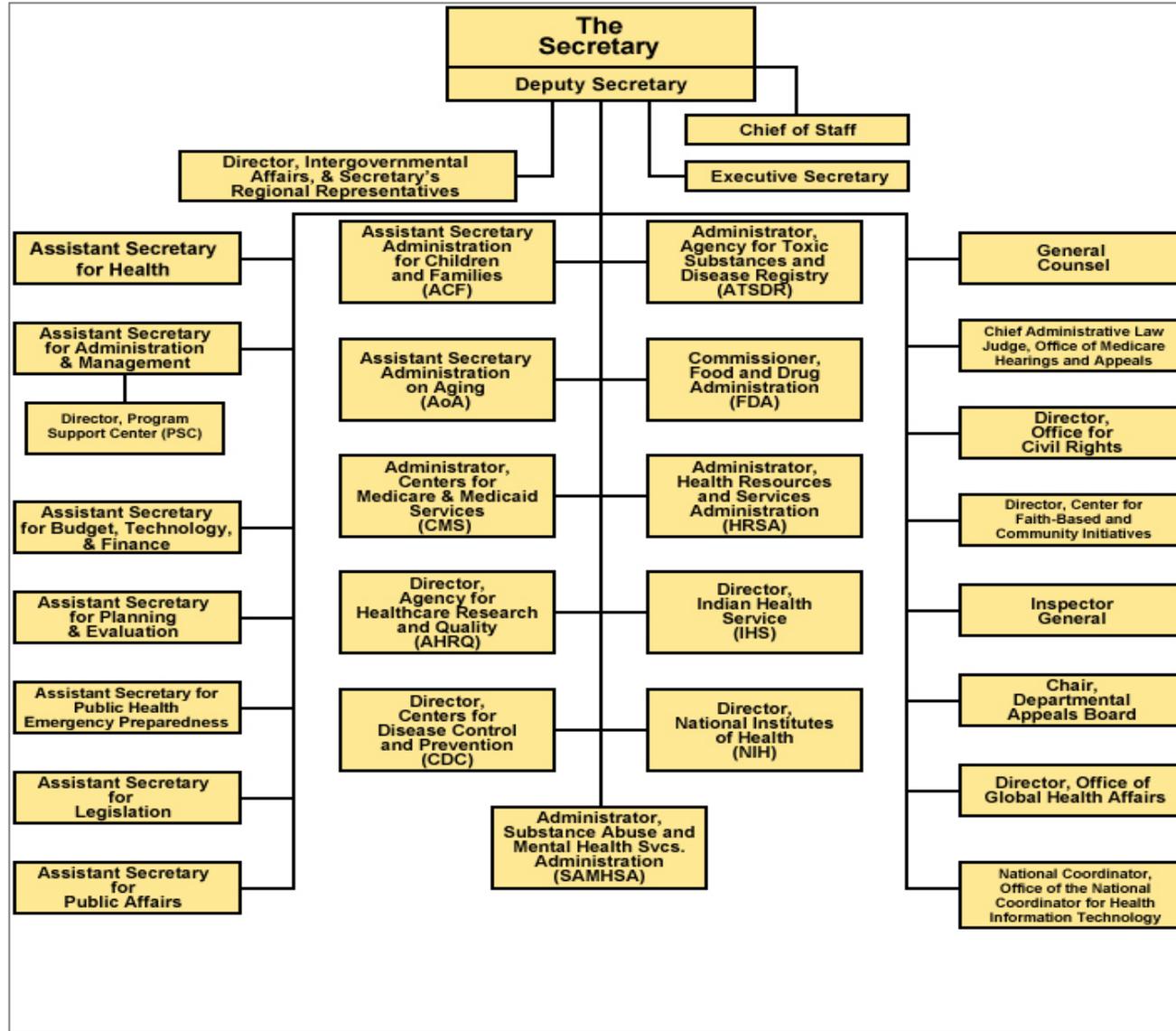
## Introduction to the Principles and Practice of Clinical Research



FDA White Oak Campus

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**Center for Biologics Evaluation and Research**  
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# WHERE IS THE FDA? DHHS



# Food and Drug Administration

Commissioner:

Andrew von Eschenbach, M.D.



# Food and Drug Administration

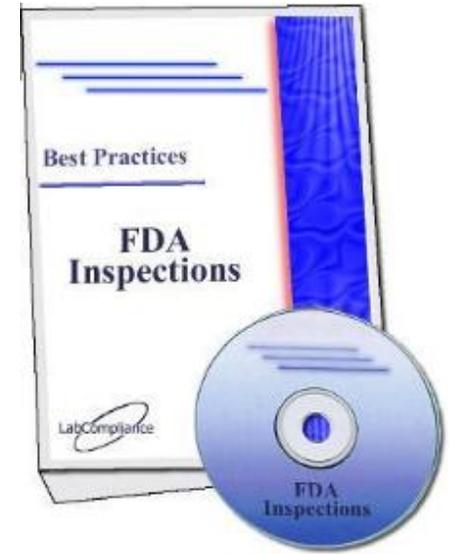


Nutrition Facts	
Serving Size 1 cup (236ml)	
Servings Per Container 1	
Amount Per Serving	
Calories 80	Calories from Fat 0
% Daily Value*	
Total Fat 0g	0%
Saturated Fat 0g	0%
Trans Fat 0g	
Cholesterol Less than 5mg	0%
Sodium 120mg	5%
Total Carbohydrate 11g	4%
Dietary Fiber 0g	0%
Sugars 11g	
Protein 9g	17%
Vitamin A 10%	Vitamin C 4%
Calcium 30%	Iron 0% • Vitamin D 25%

\*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

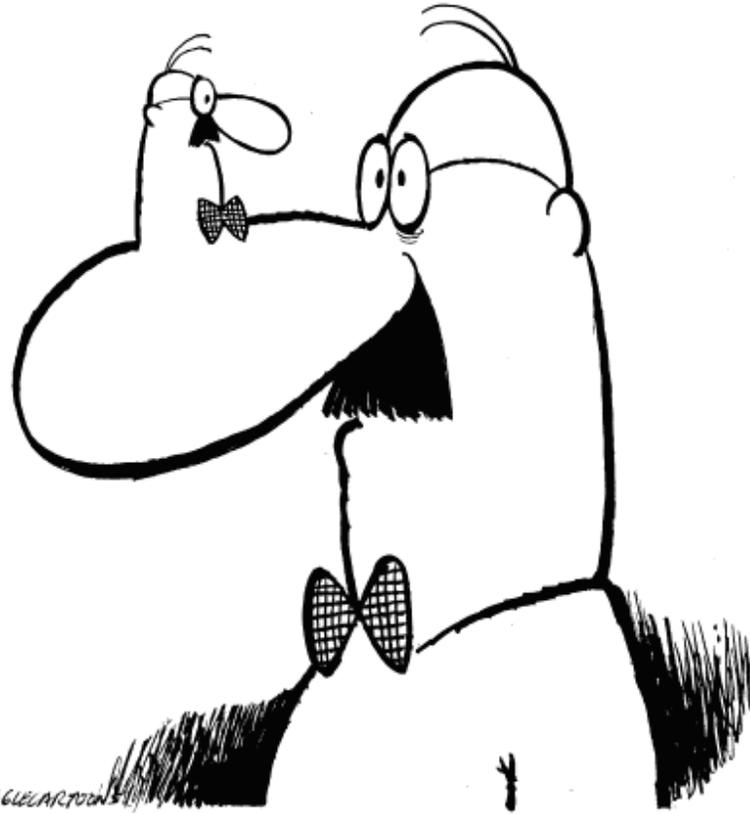
- \* Center for Biologics Evaluation and Research
- \* Center for Drug Evaluation and Research
- \* Center for Food Safety and Applied Nutrition

# Food and Drug Administration



- \* Center for Devices and Radiological Health
- \* Center for Veterinary Medicine
- \* National Center for Toxicological Research
- \* Office of Regulatory Affairs

THE FDA HAS ANNOUNCED  
THAT EATING CLONED ANIMALS  
IS SAFE, WITH THE POSSIBILITY  
OF SOME SIDE EFFECTS



WAGNER THE SON  
WIM WAGNER CARTOON

# Mission of the FDA

- a. **REVIEW:** Promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner.
- b. **SAFE AND EFFECTIVE:** With respect to such products, protect the public health by ensuring that: foods are safe, wholesome, sanitary, and properly labeled; human veterinary drugs are safe and effective; there is reasonable assurance of the safety and effectiveness of devices intended for human use; cosmetics are safe and properly labeled; and the public health and safety protected from electronic product radiation.

# Mission of the FDA

- c. **HARMONIZATION:** Participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements.
- d. **CONSULTATION:** As determined to be appropriate by the Secretary, carry out paragraphs (a) through (c) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.



One of the first bottles (1895) of diphtheria antitoxin produced at the Hygienic Laboratory.

# Tragedies lead to Legislative and Regulatory Actions



## Tragedy

- \* 14 children die of tetanus in 1901
- \* Cure-all claims for worthless and dangerous patent medicines
- \* 100 died due to ethylene glycol in elixir of sulfanilamide in 1936
- \* Cutter incident, several children contract polio and/or die from Salk vaccine in 1955

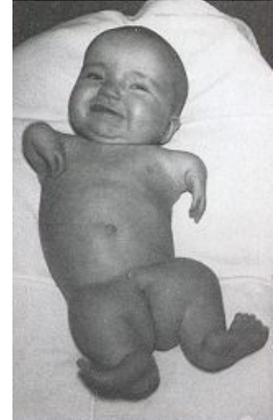
## Legislation

- \* Biologics Control Act of 1902
- \* Food and Drug Act of 1906
- \* Federal FD&C Act of 1938
- \* Division of Biological Standards Created

# Tragedies lead to Legislative and Regulatory Actions

## Tragedy

- \* Thalidomide, sleeping pill, causes severe birth defects in thousands of babies in western Europe in 1962
- \* Cyanide poisoning via Tylenol capsules in 1982



## Legislation

- \* Kefauver-Harris Drug Amendments of 1962
- \* Federal Anti-Tampering Act of 1983

# Statutory and Regulatory Authorities

Pharmaceutical Product	<i>Food Drug &amp; Cosmetic Act</i>	<i>Public Health Service Act</i>	<i>Interstate Commerce Act</i>	<i>Foreign Commerce</i>	<i>Component Jurisdiction</i>	<i>Generic Equivalence</i>	<i>Good Manufacturing Practices</i>	<i>PDUFA*</i>	<i>FDA Modernization Act 1997</i>
Drug	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>					
Biologic	<input checked="" type="checkbox"/>								

\* Prescription Drug User Fee Act

# Regulations for Medical Products Title 21, Code of Federal Regulations (CFR)

- \* Part 201, 202 - Labeling & Advertising
- \* Part 312 - Investigational New Drug (IND) and Part 314 - New Drug Application (NDA)
- \* Parts 600-680 Biologics [Public Health Service Act]
- \* Part 800-861 Devices & In Vitro Diagnostics



# **Regulations for Drug & Biological Products Title 21, Code of Federal Regulations (CFR)**

- \* Part 25 - Environmental Impact Considerations
- \* Part 50 - Protection of Human Subjects
- \* Part 54 - Financial Disclosure by Clinical Investigators
- \* Part 56 - Institutional Review Boards
- \* Part 58 - Good Laboratory Practices for Non-Clinical Laboratory Studies

# Guidance Documents

- \* Developed with input from many sectors: academia, other government components, industry, public forums, e.g., workshops, meetings, ICH
- \* Good Guidance Practices
- \* Flexible and allow for case-by-case assessment
- \* Example: **Guidance for Industry**

## **Guidance for Industry**

**Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases**

**DRAFT GUIDANCE September 2006**



# **21 CFR 312 Investigational New Drug Application and Good Clinical Practice Consolidated Guideline (ICH E6)**

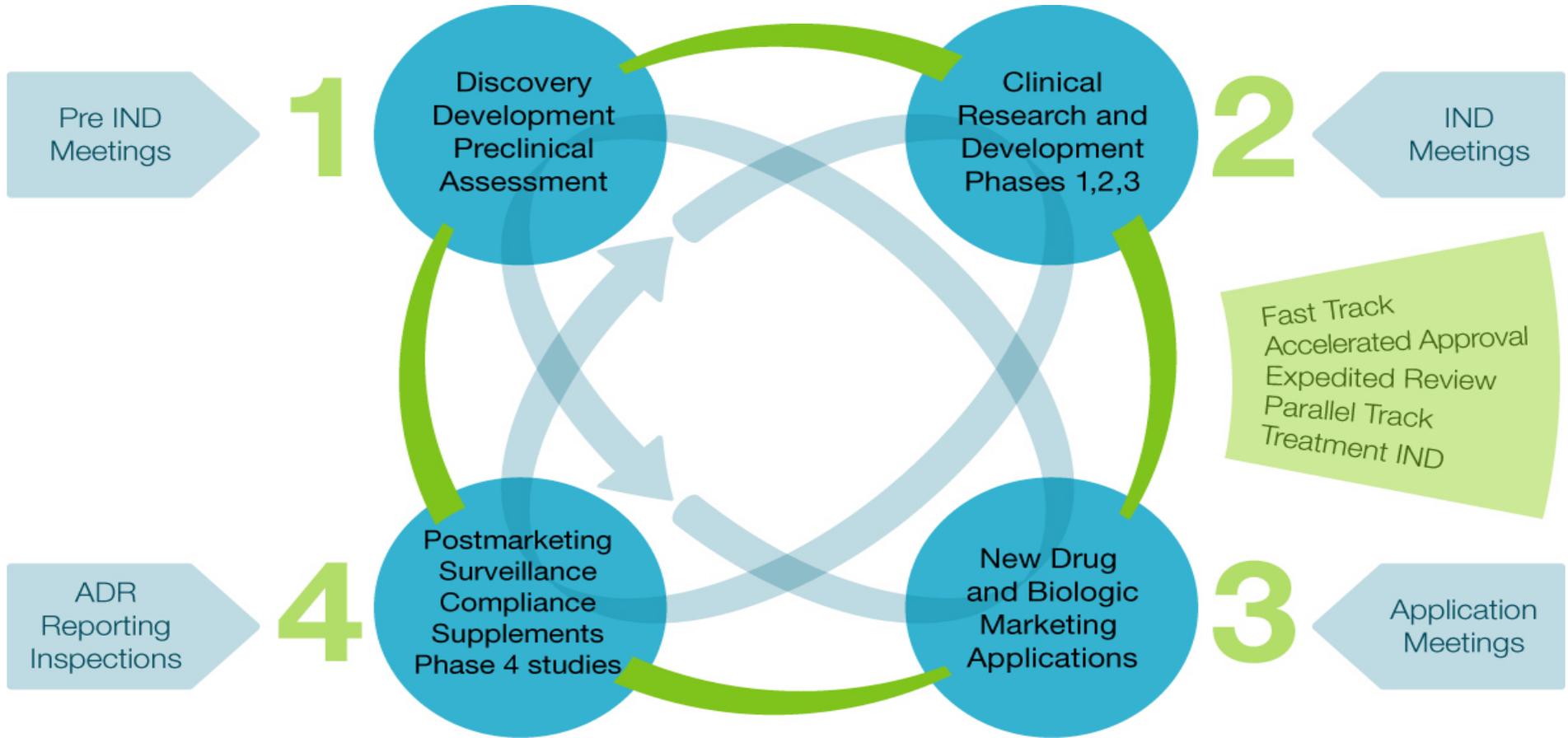
- \* Unified standard for designing, conducting, recording & reporting clinical trials.
- \* Content and Format of IND and the Investigator's Brochure (IB):
- \* Essential documents for clinical trial & data evaluation.

# Investigational New Drug Application

## 21CFR 312 Subpart B

- \* Requirement for an IND
- \* Phases of Investigation
- \* General Principles of the IND Submission
- \* IND Content and format
- \* Protocol and Information Amendments
- \* IND Safety and Annual Reports
- \* Treatment Use of an Investigational New Drug
- \* Emergency Use of an Investigational New Drug
- \* Withdrawal of an IND

# Drug and Biologic Product Life Cycle



# Phases of a Clinical Investigation

- \* Phase I Studies
  - Small number of subjects, generally less than 50
  - Focus on safety
- \* Phase II Studies
  - Generally up to a few hundred subjects
  - Safety and dose selection
  - Activity assessment
- \* Phase III Studies
  - Pivotal safety and efficacy studies
  - Size is dependent on disease, population and study design



# Fast Track Drug Development Program

- \* Guidance for Industry:  
September 1998, revised  
2004
- \* Criteria for Qualification
  - Serious or Life-threatening  
Condition
  - Potential to Address  
Unmet Needs
- \* Process for Designation
- \* Programs for Expediting  
Development and Review



# Accelerated Approval

- \* 21CFR 314.510 and 601.41
- \* FDA approval can be based on a surrogate endpoint that is reasonably likely to predict clinical benefit or clinical effects that are not the desired ultimate benefit but are reasonably likely to predict such benefit.



# Special IND Programs

- \* Drugs Intended to Treat Life-threatening and Severely Debilitating Illnesses 21CFR 312 Subpart E
- \* Treatment use of an investigational new drug 21CFR312.34 and 312.35
- \* Parallel Track: a mechanism to permit wider availability of experimental agents



# Priority Review



- \* Center for Biologics Evaluation and Research
  - A significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a severe and life-threatening illness
- \* Center for Drug Evaluation and Research
  - A significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease
- \* Complete review of a marketing application within 6 months (90% goal)

# Clinical Hold (21 CFR 312.42)



## ***IND* Phase 1**

- \* Subjects exposed to an unreasonable and significant risk of illness or injury
- \* Clinical investigator is not qualified
- \* Investigator's Brochure is misleading, erroneous or materially incomplete
- \* IND does not contain sufficient information to assess risk
- \* Women or men excluded to avoid potential for reproductive or developmental toxicity

# Clinical Hold

## ***IND* Phase 2 and 3**

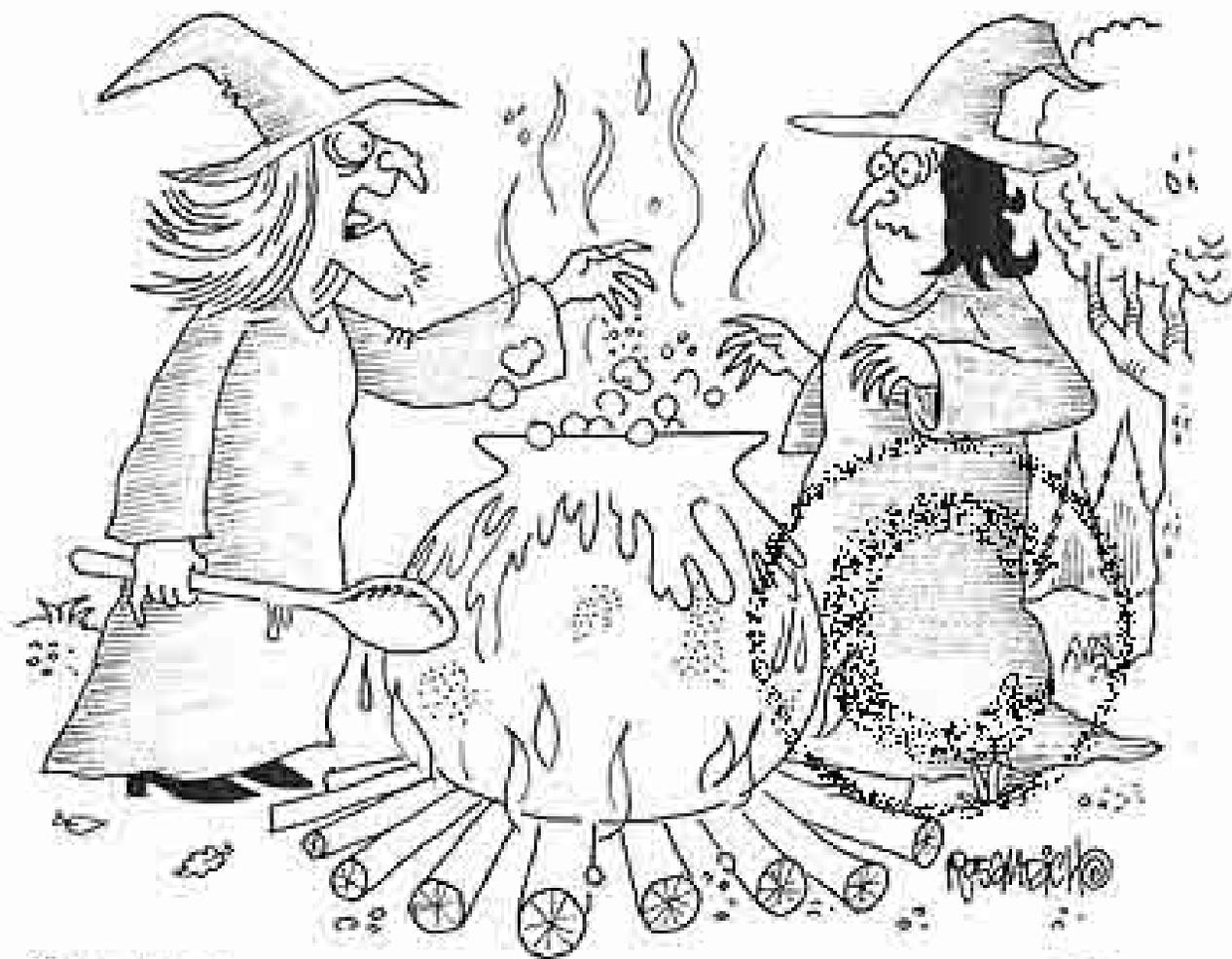
- \* All the Phase 1 reasons
- \* Protocol is clearly deficient in design to meet its stated objectives



# Quality and Safety Issues Associated with Biological Products

- \* Manufacturing
  - Raw materials and seed banks
  - Production, e.g. fermentation, harvesting, purification, storage of the bulk, formulation, final fill
  - Characterization
  - Process validation
  - Testing
- \* Pharmacology and Toxicology
- \* Clinical





"THE FDA DIDN'T APPROVE THE USE OF EYE OF NEWT!"

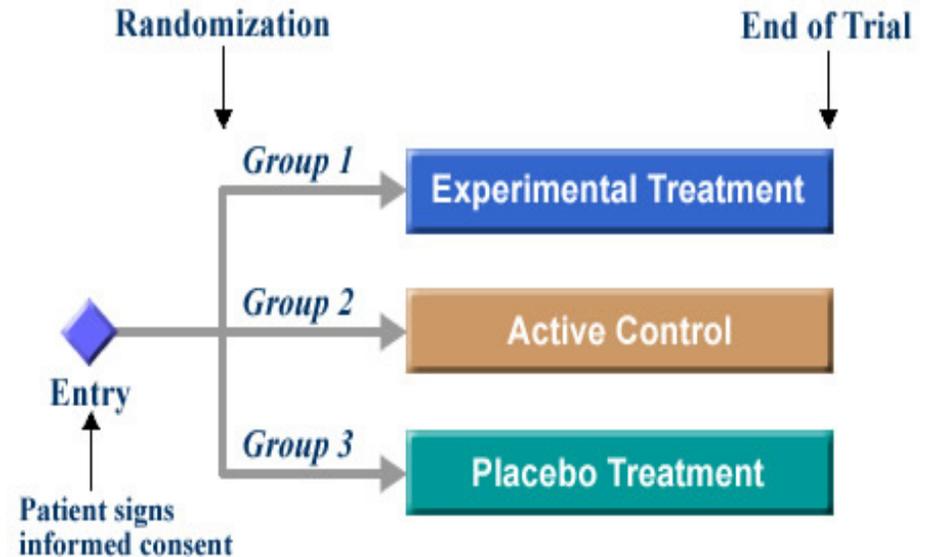
# Pharmacology and Toxicology Issues

- \* Data
- \* Immunogenicity Data  
Planned Clinical  
Evaluation
- \* Selection of Relevant  
Animal Model
- \* Animal Pharmacokinetic



# Clinical Issues

- \* Clinical Trial Design and Analysis
- \* Conduct and Monitoring of Clinical Trial, e.g. immunogenicity
- \* Adverse Event Reporting



# Principles of Good Clinical Practice

- \* A clinical trial should be conducted in accordance with ethical principles which are consistent with GCP and applicable regulatory requirements

Initiated and continued only if the anticipated benefits justify the risks, with the individual trial subjects safety prevailing over the interests of science and society

Supported with adequate clinical and non-clinical investigational product information

Described in a clear, detailed protocol which is scientifically sound



# Principles of Good Clinical Practice

Conducted in compliance with the protocol which has prior IRB/IEC approval

Conducted by qualified individuals with only qualified physicians responsible for medical decisions made on behalf of the subjects

Initiated only after obtaining informed consent from each subject prior to enrollment

Protected from invalidation by the proper recording, handling and storage of trial information allowing accurate reporting, interpretation and verification



# Principles of Good Clinical Practice

Conducted in accordance with the regulatory requirements on confidentiality of records which protect subjects identity

Conducted using investigational products manufactured, handled and stored in accordance with GMPs and the approved protocol

Systemized with procedures that assure the quality of every aspect of the trial

# Investigator's Responsibilities

- \* Qualifications
- \* Resources
- \* Medical Care
- \* Protocol compliance
- \* Communication with Institutional Review Board (IRB)
- \* Record keeping and retention
- \* Progress reports
- \* Safety reports
- \* Premature termination
- \* Final report

# Investigator's Responsibilities

- \* Investigational product
- \* Randomization and unblinding
- \* Informed consent
- \* Emergency research-additional protections



# Sponsor Responsibilities

- \* Investigator/institution selection
- \* Notification/submission to regulatory authorities
- \* Adequate monitoring
- \* Interactions with FDA
- \* Ensuring direct access to records with consent
- \* Act on investigator non-compliance
- \* Notification of premature termination or suspension
- \* Study reports

# Sponsor Responsibilities

- \* Ongoing safety assessments, notifying investigators
- \* **Adverse Event Reporting**
- \* Quality Assurance/Quality Control, Standard Operating Procedures
- \* **Trial and data management**
- \* Allocation of duties and functions
- \* **Auditing**
- \* Investigational product



# Sponsor Responsibilities

## FDA Amendments Act of 2007

- \* **Expansion of clinical trials registry**

  - broader scope of trials,  
more required information

  - ClinicalTrials.gov: <http://www.clinicaltrials.gov>

- \* **Include Certification Form with every submission to FDA**

  - [http://www.fda.gov/cder/regulatory/FDAAA\\_certification.htm](http://www.fda.gov/cder/regulatory/FDAAA_certification.htm)

  - <http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf>

# Monitoring



- \* Purpose

  - to verify that rights and well-being of human subjects are protected

  - reported data are accurate, complete, verifiable

  - compliance with protocol, GCP, regulations

- \* Sponsor must select qualified monitors and train appropriately

# Institutional Review Board

## (21 CFR 56)

- \* Review and Approve All Protocols to Assure that:
  - Risks to subjects are minimized and reasonable
  - Selection of subjects is equitable
  - Informed consent will be sought and documented
- \* At least five members with varying backgrounds



# **IND Safety**

## **Reporting Requirements**

(62 FR 5237)

- \* Expedited Reports
- \* Annual Reports or Information Amendments

# Written Reports: §312.32 (c)

- \* Any AE associated with use of the study drug that is both serious and unexpected
- \* Any findings from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity
- \* Sponsor to notify FDA and all participating investigators as soon as possible but no later than 15 calendar days after receipt of the information

# Telephone/Facsimile Safety Reports §312.32 (c)

- \* “The sponsor shall also notify FDA by telephone or facsimile of any unexpected fatal or life threatening experience associated with use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor’s initial receipt of the information.”

# Bioresearch Monitoring

- \* To ensure the quality and integrity of data submitted to FDA in support of an IND / IDE or BLA / NDA / PMA / other application
- \* To ensure that the rights and welfare of the human research subjects are protected



# Standards of Licensure

- \* Safety
- \* Purity
- \* Potency
- \* Stability
- \* cGMP Compliance



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**"The secret to happiness is awaiting F.D.A. approval."**

# Post Marketing Surveillance and Compliance

- \* Adverse Event Reporting  
(21CFR 600.80)  
15-Day “Alert Reports”  
(21CFR 314.80)
- \* Inspections
- \* Enforcement
- \* Education



# Resources for FDA Documents

- \* FDA's Home page : [www.fda.gov](http://www.fda.gov)
- \* ICH Guidance Documents: [www.ich.org](http://www.ich.org)
- \* Code of Federal Regulations:  
[www.gpoaccess.gov/cfr/index.html](http://www.gpoaccess.gov/cfr/index.html)

**THANK YOU**