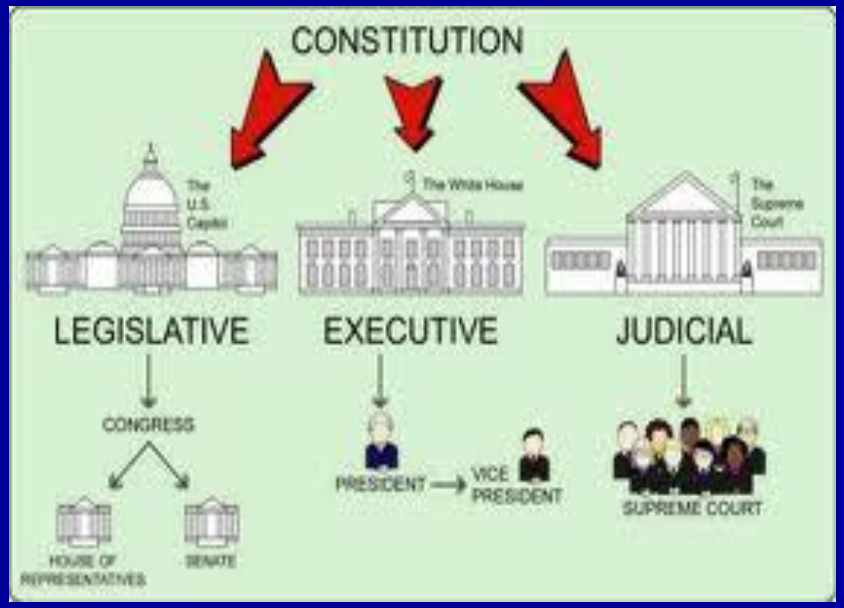
Overview of Regulatory Issues in Clinical Research

John Farley, MD, MPH

What do the initials CFR mean?

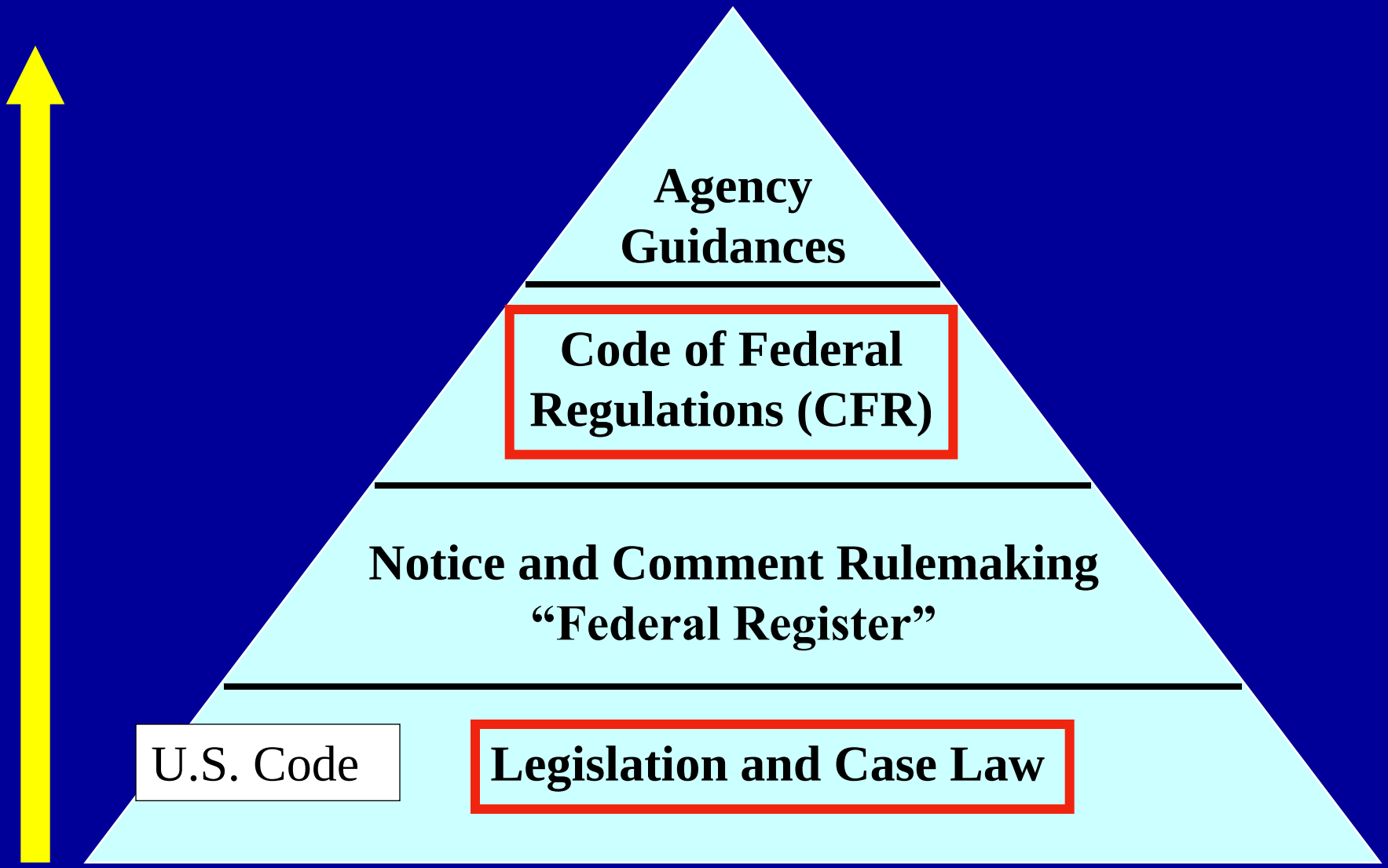


I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

Laws vs. Regulations in the United States

- Laws are passed by Congress.
- Related laws are grouped together and organized in the United States Code (USC)
- Regulations are written by U.S. government agencies and address how laws will be enforced/implemented. Regulations are printed in the Code of Federal Regulations (CFR)

Laws and Regulations in the United States



This former estate / former conference center is located in Elkridge MD. Why is it important in the history of clinical research?

1970: Criticism of Hepatitis A Experiments Conducted at the Willowbrook State School

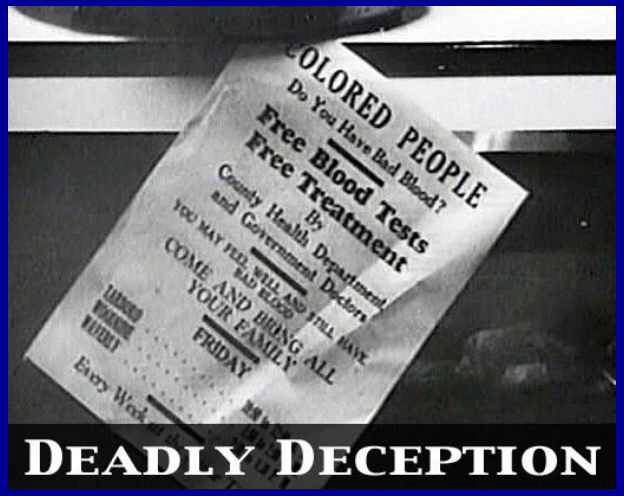
From 1963 through 1966, studies were carried out at a New York State institution for "mentally defective persons." These studies were designed to gain an understanding of the natural history of infectious hepatitis and subsequently to test the effects of gamma globulin in preventing or ameliorating the disease. Some subjects, all children, were deliberately infected with hepatitis A, then received gamma globulin.

Criticisms: Unacceptable to infect subjects, benefit for others only, inadequate consent of parents, coercion of parents

1972: Tuskegee Study Revelation in the U.S.

Since the 1930s, approximately four hundred black men in Tuskegee, Alabama, had been involved, without their knowledge, in a lengthy study of the natural history of syphilis. These men were systematically denied penicillin even after its introduction as the standard treatment for the disease.

28 men died of syphilis, 100 men died from related complications, at least 40 wives were infected, 19 children born with congenital syphilis.



The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men.

1974: National Research Act

- Established the modern IRB system
- Established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
  - Belmont Report published 1979

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

The Belmont Report

Part B: Basic Ethical Principles:

1. **Respect for Persons**: acknowledges the dignity and autonomy of individuals
2. **Beneficence:** protect individuals by maximizing potential benefits and minimizing harm
3. **Justice:** subjects should be carefully and equitably chosen so that one class of individuals is not systematically selected or excluded

"Respect for Persons"

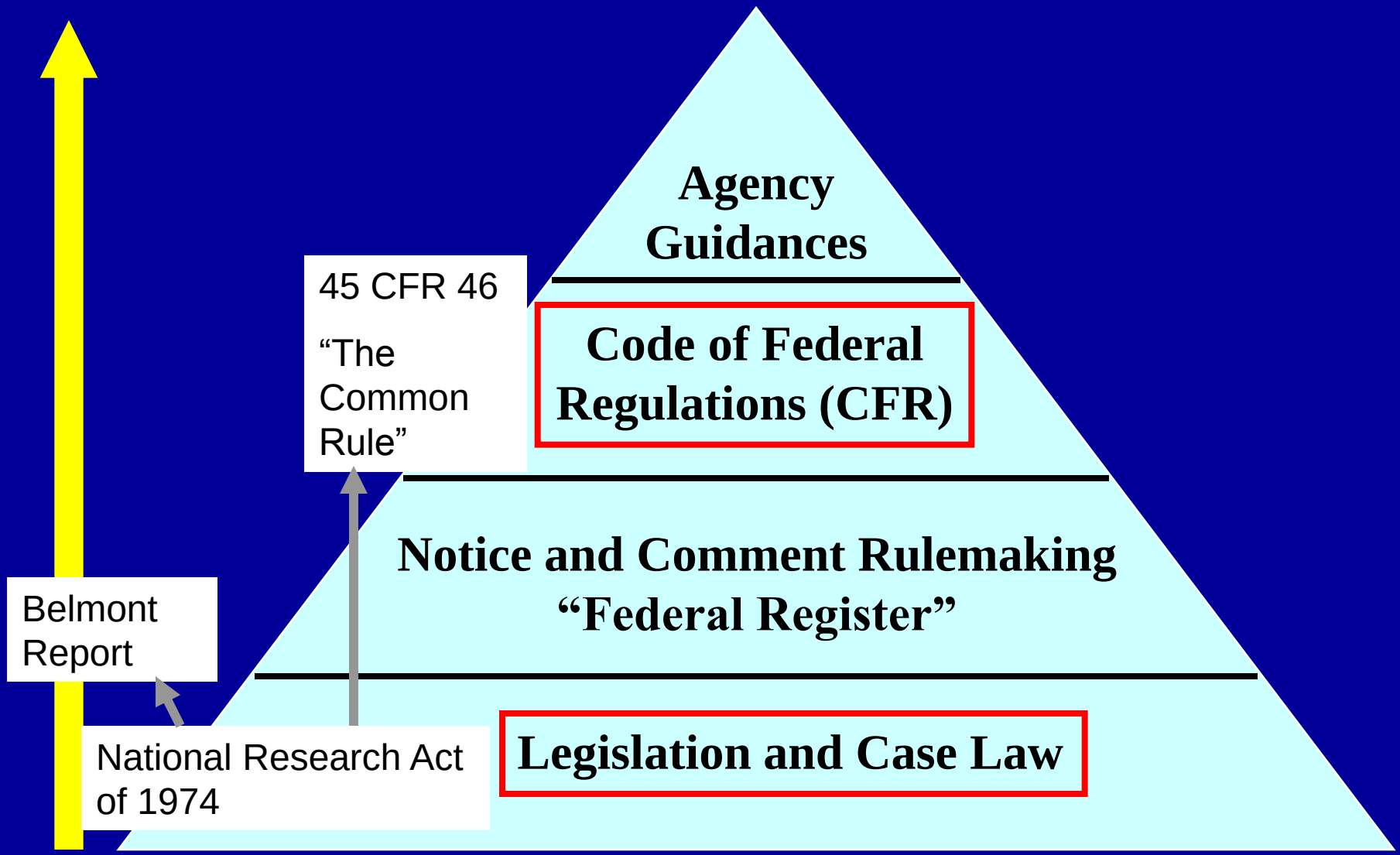
The Belmont Report

- "Respect for persons incorporates at least two ethical convictions: first, that **individuals should be treated as autonomous agents**, and second, that **persons with diminished autonomy are entitled to protection**.
- "…not every human being is capable of self-determination. **The capacity for self-determination matures during an individual's life**…"

1991: "The Common Rule"

- 45 CFR (Code of Federal Regulations) part 46: applies to all institutions receiving federal funds for research (ex. NIH grants)
  - Subpart A: Federal Policy for the Protection of Human Subjects
  - Subpart B: Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research
  - Subpart C: Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
  - Subpart D: Additional DHHS Protections for Children Involved as Subjects in Research

Laws and Regulations in the United States



Why is the "Common Rule" common?
What are the common themes in the "Common Rule"?

45CFR46 Subpart A mandates:

- **Review of research by an IRB considering:**
  - Risks to the subjects
  - Anticipated benefits to the subjects and others
  - Importance of the knowledge that may reasonably result
  - The informed consent process to be employed

- **Informed consent of subjects**

- **Institutional assurances of compliance**

Office of Human Research Protections (OHRP) (under DHHS) oversees. (Previously called the Office for Protection from Research Risks (OPRR)).

What groups are identified in the CFR as "vulnerable"?

- Pregnant women/human fetuses and neonates (45CFR46 Subpart B)
- Children (45CFR46 Subpart D)
- Prisoners (45CFR46 Subpart C)
- Mentally disabled "Decisionally Impaired" (45CFR46.107(a),111(a))
- Handicapped (45CFR46.107(a)), Economically or educationally disadvantaged (45CFR46.111(a)), "Subordinate individuals" (no reference)

Am I engaged in human subject research?

(f) ***Human subject*** means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or
(2) Identifiable private information.

45 CFR 46.102

(d) ***Research*** means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Who should I contact if I have questions?

UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

Human Research Protections Program

Phone: (410) 706-5037
Fax: (410) 706-4189
Email:
HRPO@umaryland.edu

What is one of the first things I should read?

Investigator Manual
Revised January 5, 2015

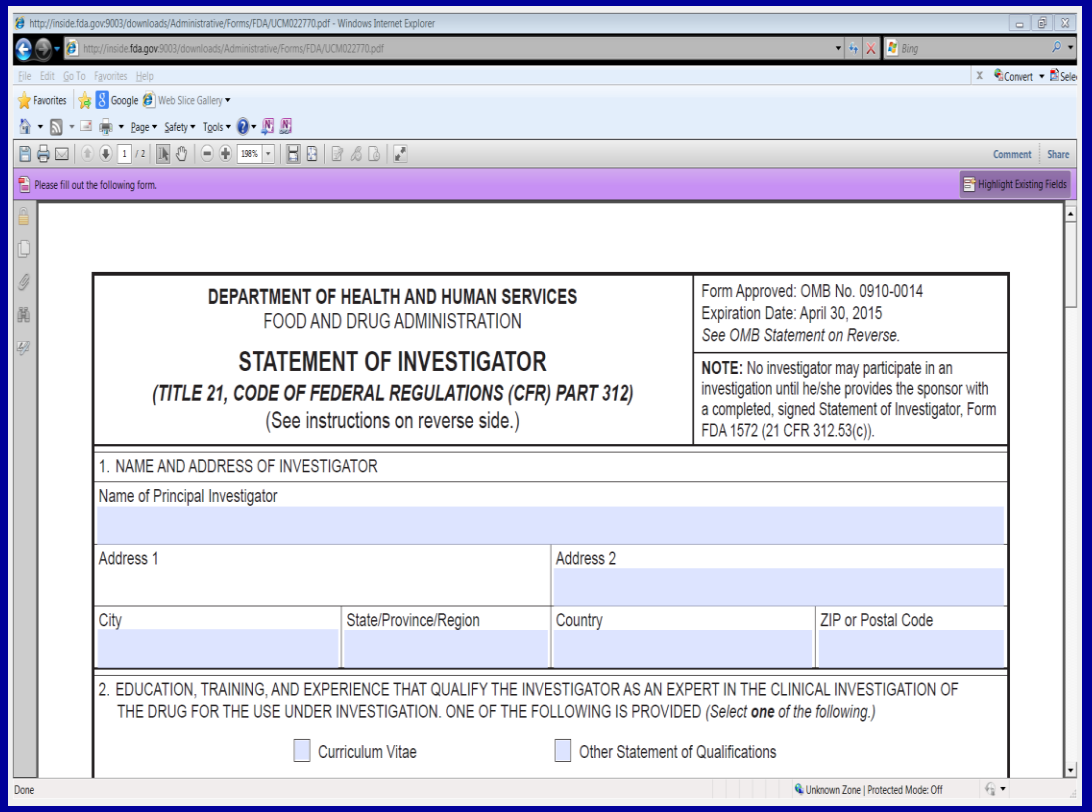
This nearby edifice was built in 1911 and significantly modified in 1936. What does that have to do with our topic today?

- Originally marketed in 1888 by the Isaac E. Emerson drug company of Baltimore.
- Effervescent granules which were mixed with water before ingestion
- Original formula included sodium bromide
- Bromides were withdrawn from the U.S. market in 1975 due to toxicity, and Bromo-Seltzer was discontinued.
- Re-introduced in 1990s with the contents of acetominophen, sodium bicarbonate, and citric acid

History of the FDA

- 1906: Pure Food and Drug Act (misbranding)
- 1933: FDA formally established
- 1938: Federal Food, Drug, and Cosmetic Act (safety)
- 1962: Kefauver-Harris Drug Amendment (safe *and effective*, establishes IND process, clinical trial design, manufacturing sites inspected, FDA may pull drugs from the market, FDA controls labeling and advertising

What is an IND? (or IDE)?



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: April 30, 2015
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Principal Investigator

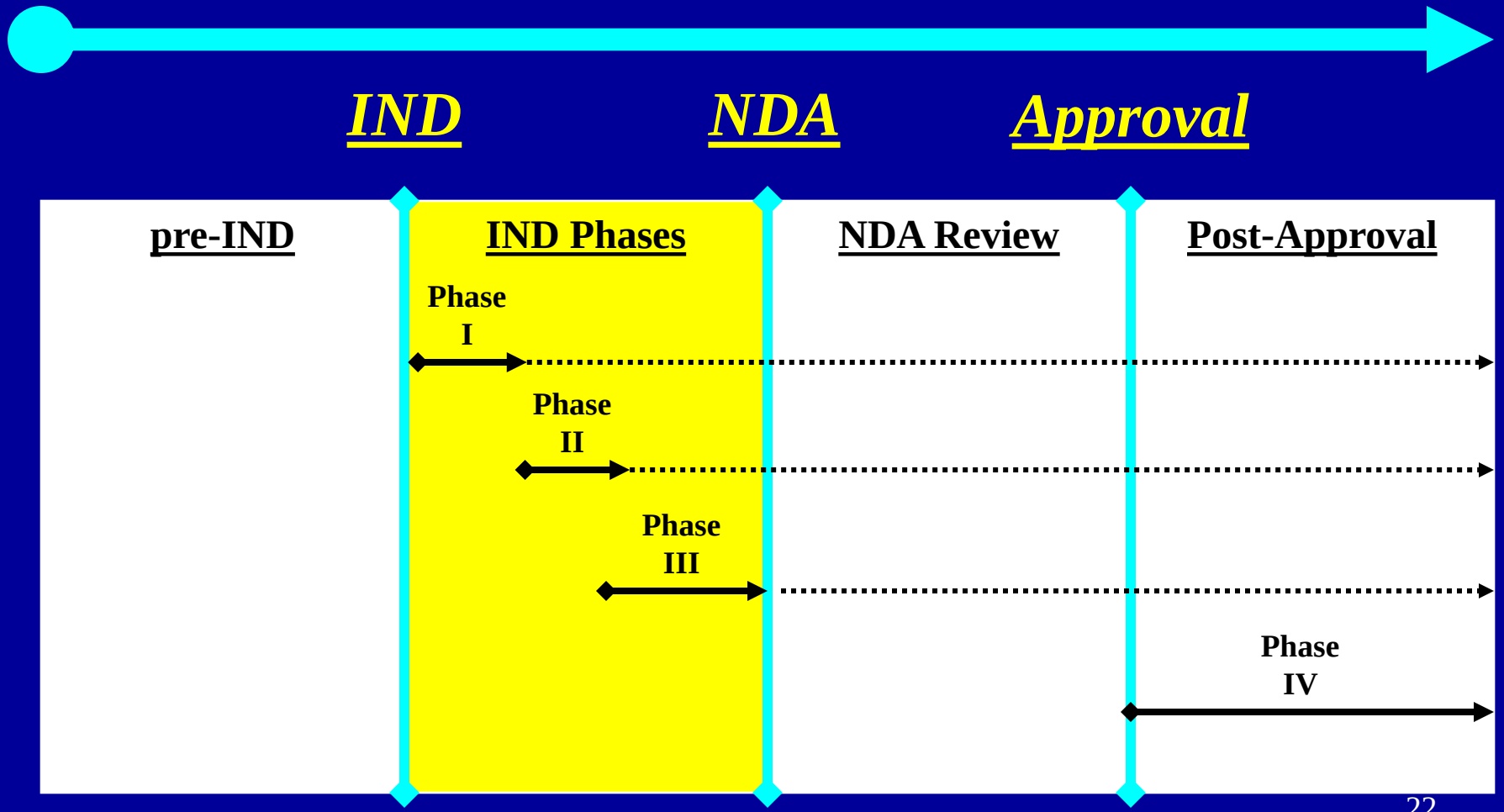
Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

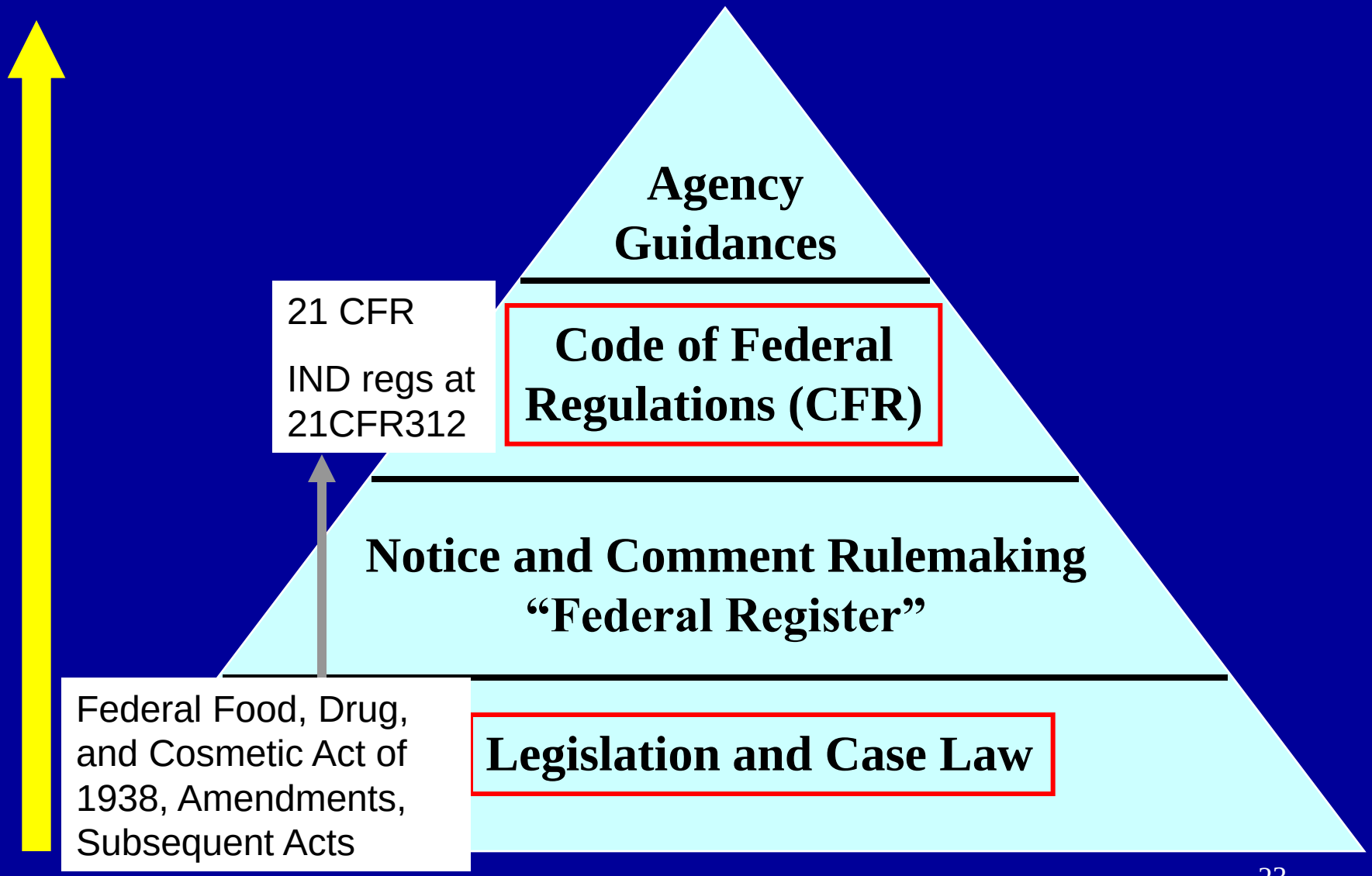
2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select **one** of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

Drug Development Timeline



Laws and Regulations in the United States



21CFR

Applies to all clinical investigations regulated by the Food and Drug Administration (FDA) under the Federal, Food, Drug, and Cosmetic Act as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA

(Research usually conducted under IND, IDE)

Investigator Responsibilities – IND Studies

- General responsibilities [21 CFR 312.60]
  - Ensure that the investigation is conducted according to the protocol and applicable regulations
  - Protect the rights, safety, and welfare of subjects
- Control of the investigational drug [21 CFR 312.61]
  - Administer drug only to subjects
  - Do not supply the drug to anyone not authorized to receive it

Investigator Responsibilities – IND Studies

- Recordkeeping and record retention [21 CFR 312.62]
  - Case histories (e.g., Case Report Forms (CRFs) and supporting data, signed and dated consent forms, medical records)
  - Disposition of the investigational drug (i.e. dates, quantity, and use by subjects)
  - Retain records for 2 years after drug is approved for the indication being investigated or 2 years after the investigation is discontinued
  - Permit FDA inspection of records and reports [21 CFR 312.68]

Investigator Responsibilities – IND Studies (similar for IDE 21CFR812)

- Investigator reports to the sponsor [21 CFR 312.64]
  - Progress reports
  - Safety reports
  - Final report
  - Financial disclosure reports
- Assurance of IRB review [21 CFR 312.66]
  - Assure that an IRB is responsible for review and approval of the protocol
  - Report any unanticipated problems involving risk to subjects
  - Not make any protocol changes without IRB approval except to eliminate immediate hazards to subjects

I am doing research with a legally marketed drug. Do I need an IND?

An IND may be required for an investigation involving a lawfully marketed drug product

- Is the investigation intended to be submitted to the FDA in support of a new indication or change in labeling?
- Is the investigation intended to support a significant change in advertising?
- Does the investigation involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the drug product?

21 CFR 312.2(b)

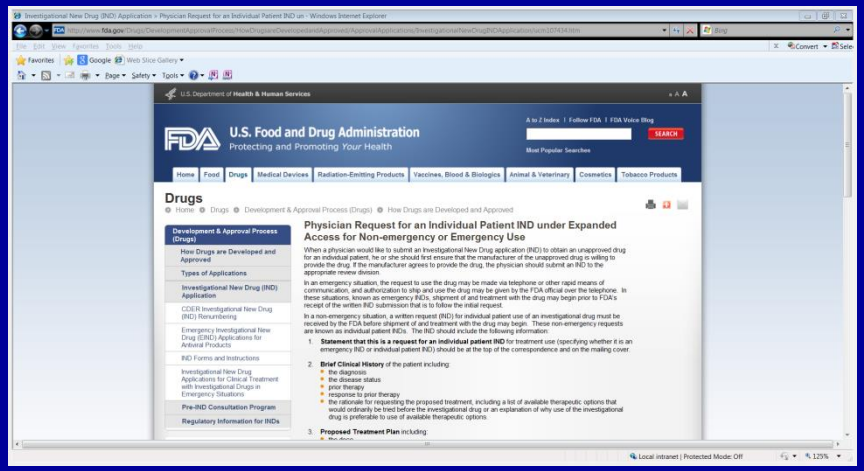
My patient needs access to a drug which is marketed in Europe, but not the U.S. Am I engaged in human research? Do I need an IND?

Expanded Access to Investigational Drugs for Treatment Use
21 CFR 312 Subpart I

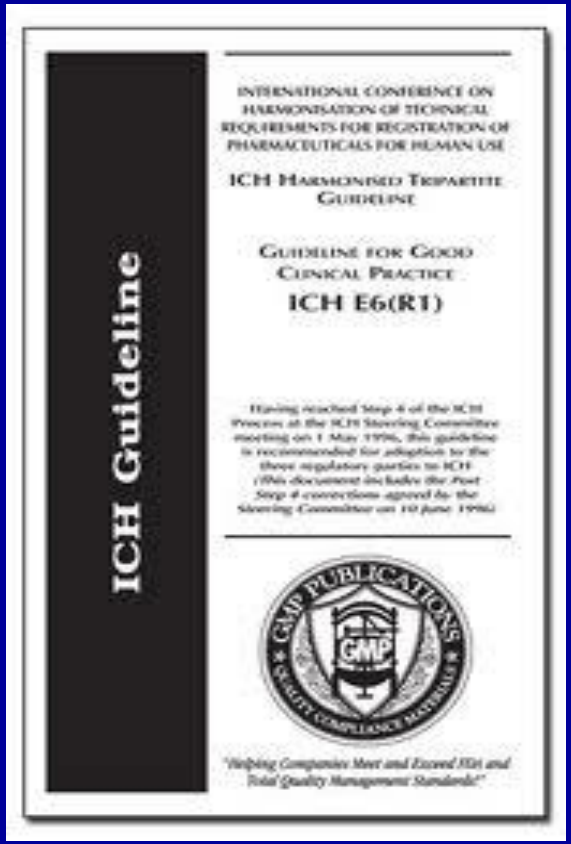
- Individual patients, including for emergency use
- Intermediate-size patient populations
- Treatment IND or treatment protocol

Procedure

- Contact HRPO
- Contact FDA
  (855) 543-3784, or
  (301) 796-3400



What do the initials ICH and GCP stand for?



The International Conference on Harmonization

- Originally met April 1990
- Attendees from the European Union (EU), Japan, and the United States
  - Regulatory/government authorities
  - Industry
- Ongoing meetings and updates of ‘ICH Guidelines’

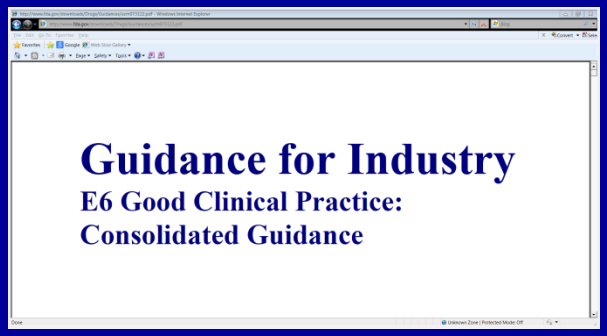
ICH Guidelines Adoption in the United States

- International Conference on Harmonization (international standards) (ICH) major sections published in the *Federal Register* representing FDA 'current thinking')
  - Section E2A, Guideline on Clinical Safety Data Management published *Federal Register* March 1, 1995
  - Section E6, Good Clinical Practice: Consolidated Guideline published *Federal Register* May 9, 1997

Good Clinical (research) Practices (GCPs)

- "International ethical and scientific quality standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects."
- Read More:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf



Advice for Investigators Engaged in Clinical Research

- Read the materials on the HRPO website, particularly the Investigator Manual. Contact HRPO staff with questions.
- Read 45 CFR 46, pay particular attention to provisions regarding pregnant women, children, and prisoners.
- Read the FDA ICH E6 Guidance regarding Good Clinical Practices.
- Know if the protocol is being done under IND/IDE or requires submission of an IND/IDE.