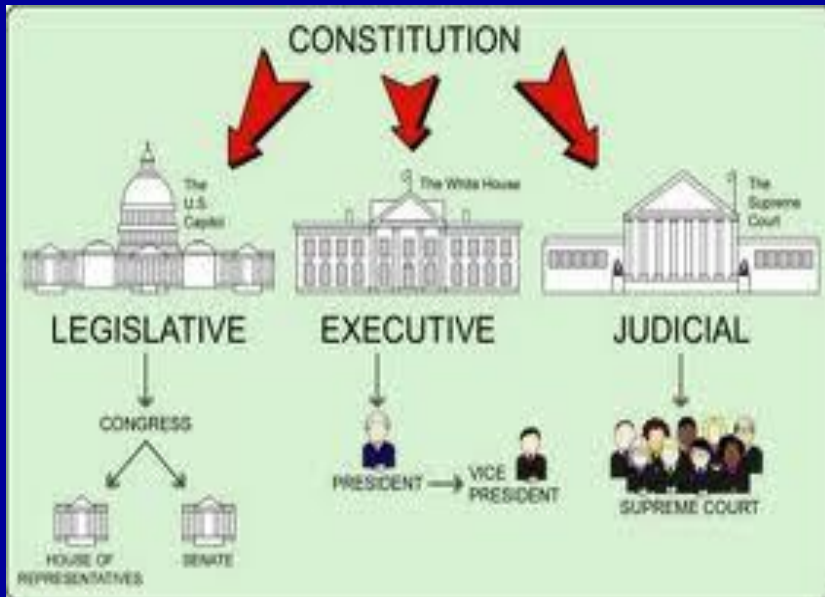


Overview of Regulatory Issues in Clinical Research

John Farley, MD, MPH

What do the initials CFR mean?

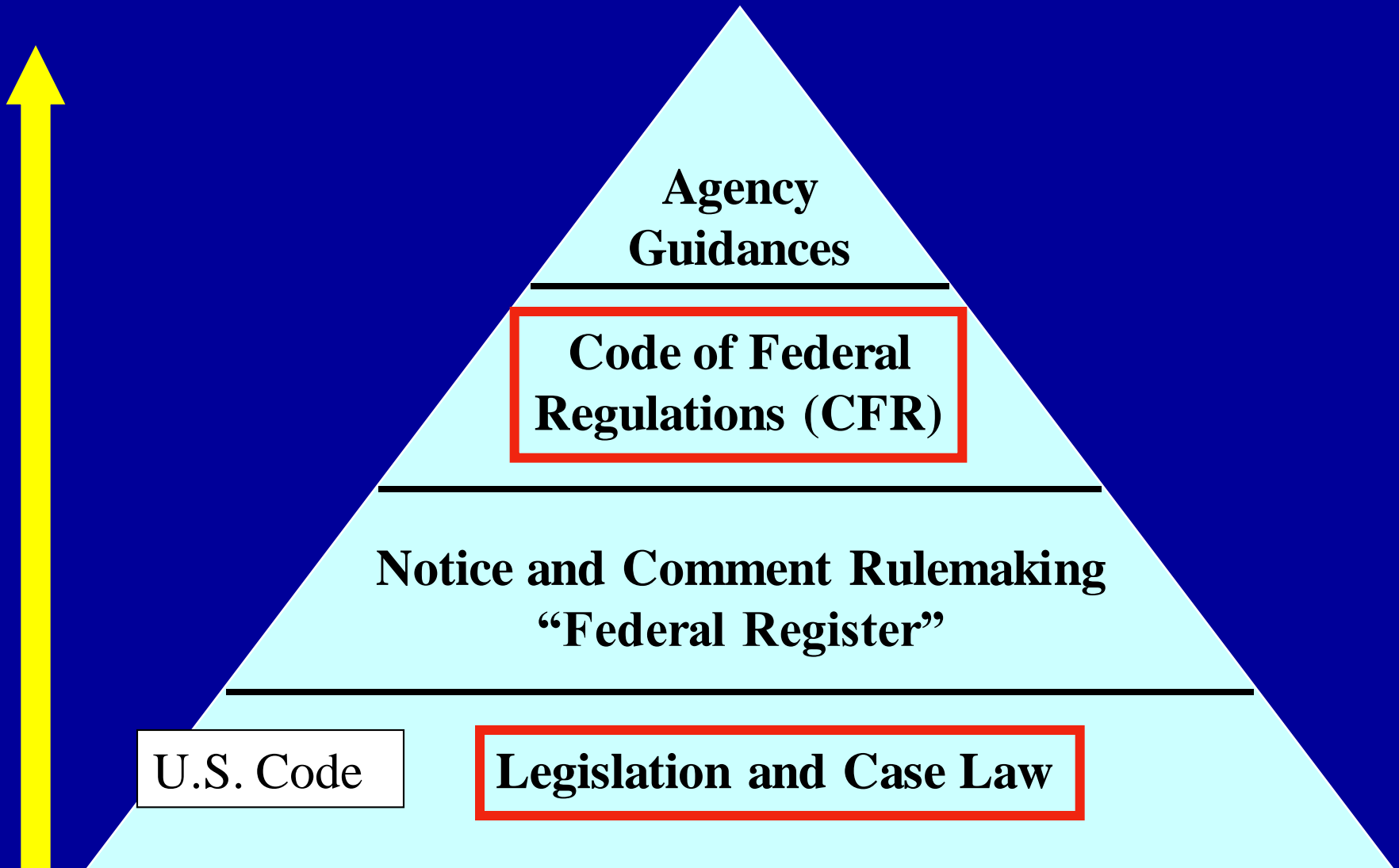


I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

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



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



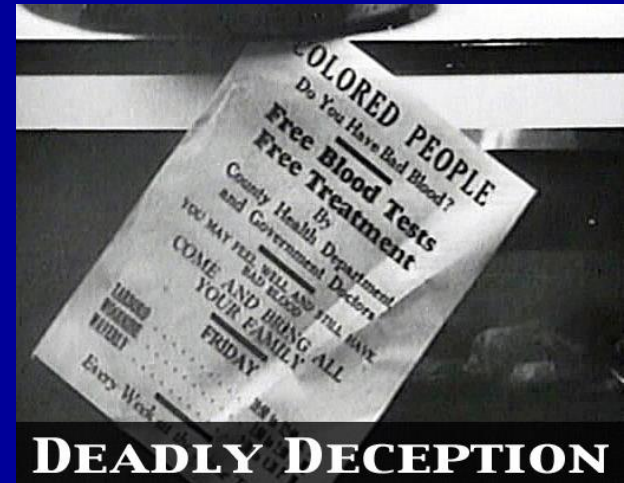
From 1963 through 1966, studies were carried out at a New York State institution for “mentally defective persons.” These studies were designed to gain an understanding of the natural history of Hepatitis A and subsequently to test the effects of gamma globulin in preventing or ameliorating the disease.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

Criticisms: Feeding live virus to mentally disabled children (respect for persons), children before adults, inadequate consent of parents, coercion of parents, duty to improve care setting

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.



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

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



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”

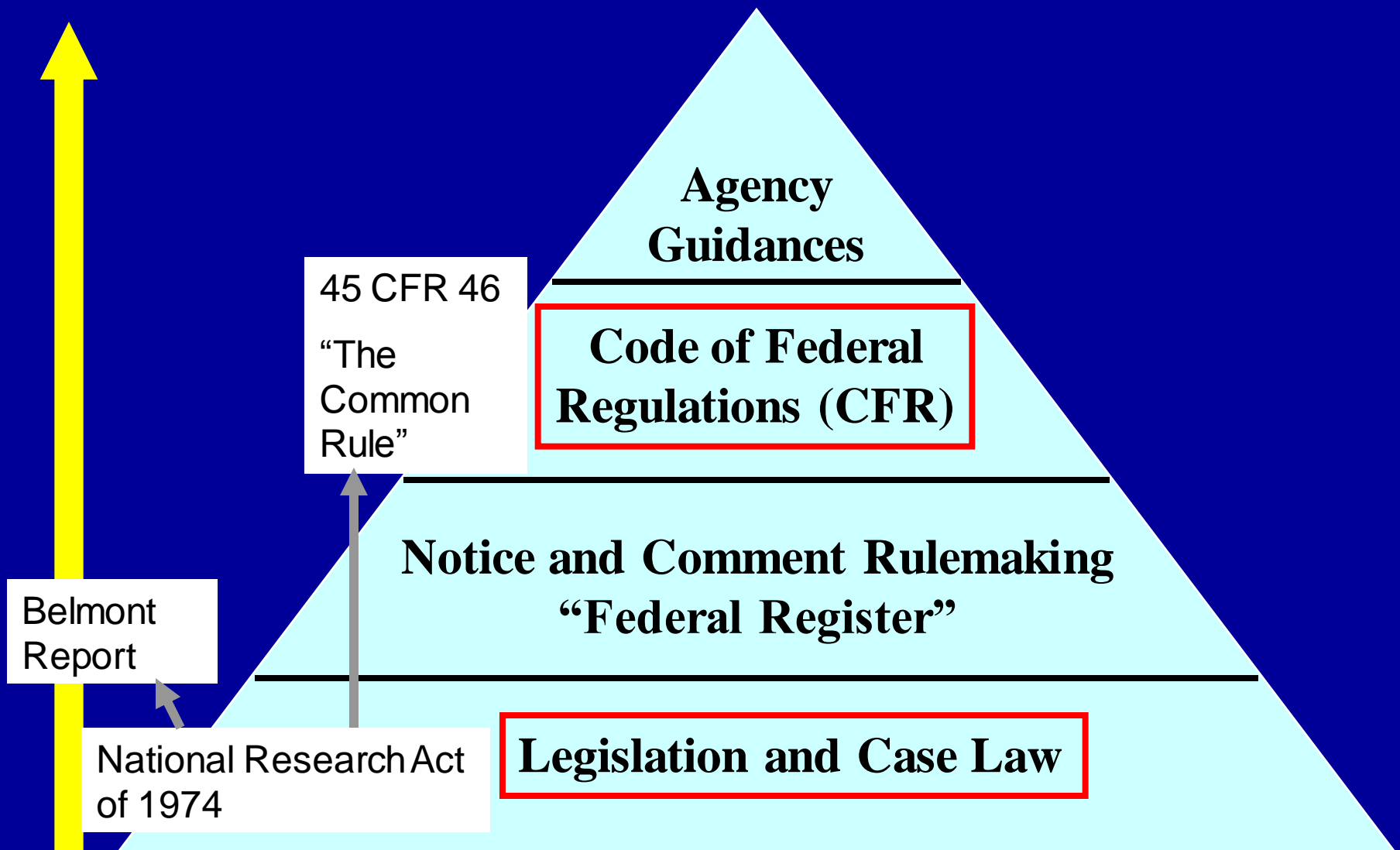
The Belmont Report

- “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: accepted by multiple USG Agencies, applies to all institutions receiving federal funds for research (e.g. 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”?**

**Bonus Question –
What happened
with the Common
Rule on January
21, 2019?**



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) obtains

- (1) Information or biospecimens through intervention or interaction with the individual and uses, studies, or analyses information or biospecimens.
- (2) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

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?**



Human Research Protections Program

Phone: (410) 706-5037

Email:

HRPO@umaryland.edu

Web:

www.umaryland.edu/hrp

**What is one of the
first things I
should read?**

Investigator Manual

Revised April 8, 2017

Human Research Protection Program Plan

Revised February 10, 2016

Sulfanilamide Elixir

- In 1937, a pharmaceutical manufacturer, created a preparation of sulfanilamide using diethylene glycol as a solvent.
- At least 100 deaths were attributed to the medication.

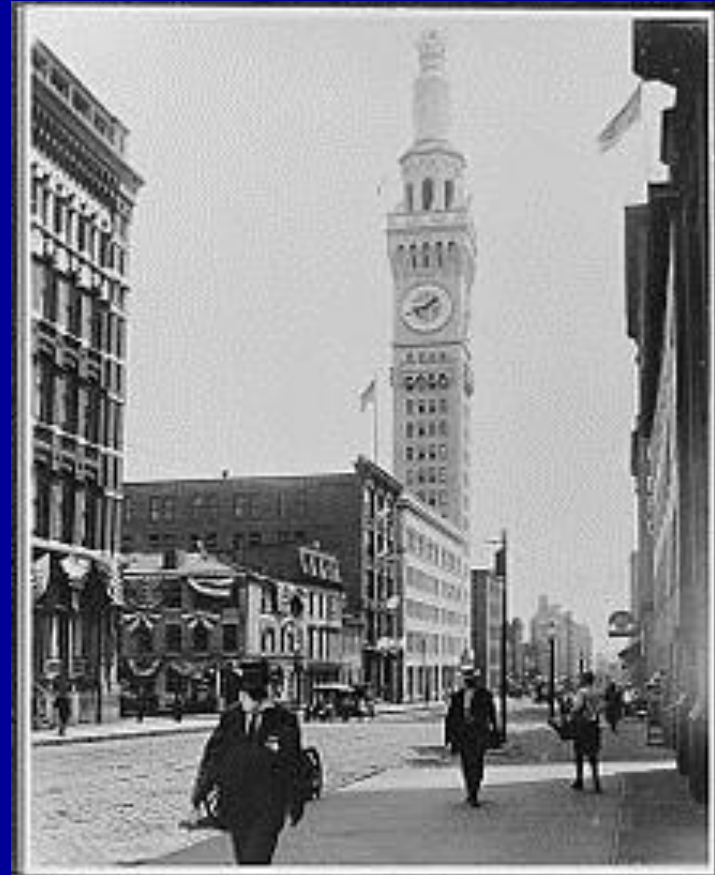


History of the FDA



- 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)

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 and acetanilide
- Original marketing targeted “nerves”, headache, “hangover”
- Bromides were withdrawn from the U.S. market in 1975 due to toxicity, and Bromo-Seltzer was discontinued.
- Re-introduced in 1990s for with the contents of acetaminophen, sodium bicarbonate, and citric acid



137

FIGHT HEADACHES

3 ways at same time!

Break Headache's Vicious Circle this proved, sensible way

• A splitting headache disturbs your *nervous system*; with jumpy nerves often goes an *upset stomach*—all tending to aggravate the headache. *That's headache's "vicious circle."*

That's why a mere single-acting pain reliever may prove so unsatisfactory. It may deaden the *pain*, and still leave you feeling dull, sickish.

Millions break headache's vicious circle with Bromo-Seltzer because it works *3 ways at the same time*; not only helps **STOP THE PAIN**, but also **CALM THE NERVES** and **SETTLE THE STOMACH**. Next time you get a headache, try Bromo-Seltzer.*

*Just see as directed on the label. For persistent or recurring headaches, see your doctor.

phil-ere-go.blogspot.com

TENSE MOMENTS

CREW

Columbia-Navy racing, and Husing on the spot with a second-by-second account. "When headache has me on the spot," he says, "I race for Bromo-Seltzer."

GOLF

Down the fairway goes the ingenious Husing. He follows the golfers from a motorized lawn mower! He says, "Bromo-Seltzer doesn't leave me dragged out—it leaves me more alert."

WHEN HEADACHE COMES, I THINK OF MY NERVES—TAKE BROMO-SELTZER

says TED HUSING

Voted most popular sports announcer in a nation-wide poll, 8 years in a row, Ted Husing's job is colorful, tense! "Believe you me," he says—"I can't let a headache make me jumpy. Bromo-Seltzer relieves the headache fast, calms my nerves."

I RELIEVE HEADACHE AND CALM YOUR NERVES!

MILLIONS TAKE...

HEADACHE strains your NERVES

Headache disturbs your nervous system. That's why it's best treated with a remedy made to do at least 2 things . . . ease *pain*—steady *nerves*. Bromo-Seltzer does both. Tests by a group of doctors proved this. Take Bromo-Seltzer!* At drugstores, soda fountains. Keep it at home!

*For frequently recurring or persistent headache, see a doctor. For ordinary headache, take Bromo-Seltzer!

BROMO-SELTZER

What is an IND? (or IDE)?

The image shows a screenshot of a web browser displaying the FDA Form 1572 (Statement of Investigator) form. The browser's address bar shows the URL: <http://inside.fda.gov/9003/downloads/AdministrativeForms/FDA/UCM022770.pdf>. The form is titled "STATEMENT OF INVESTIGATOR (TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)" and is issued by the "DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION".

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

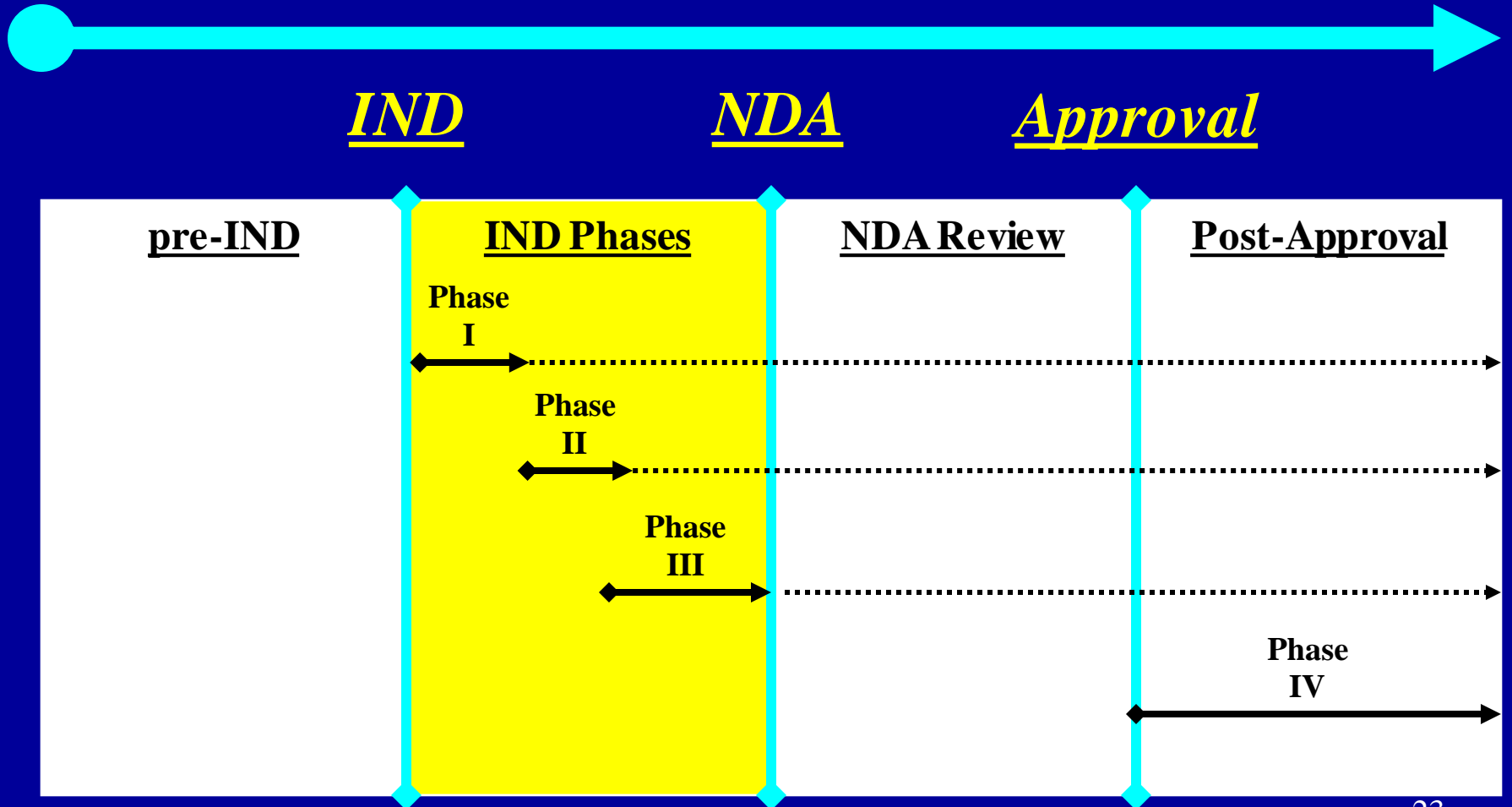
ZIP or Postal Code

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.)

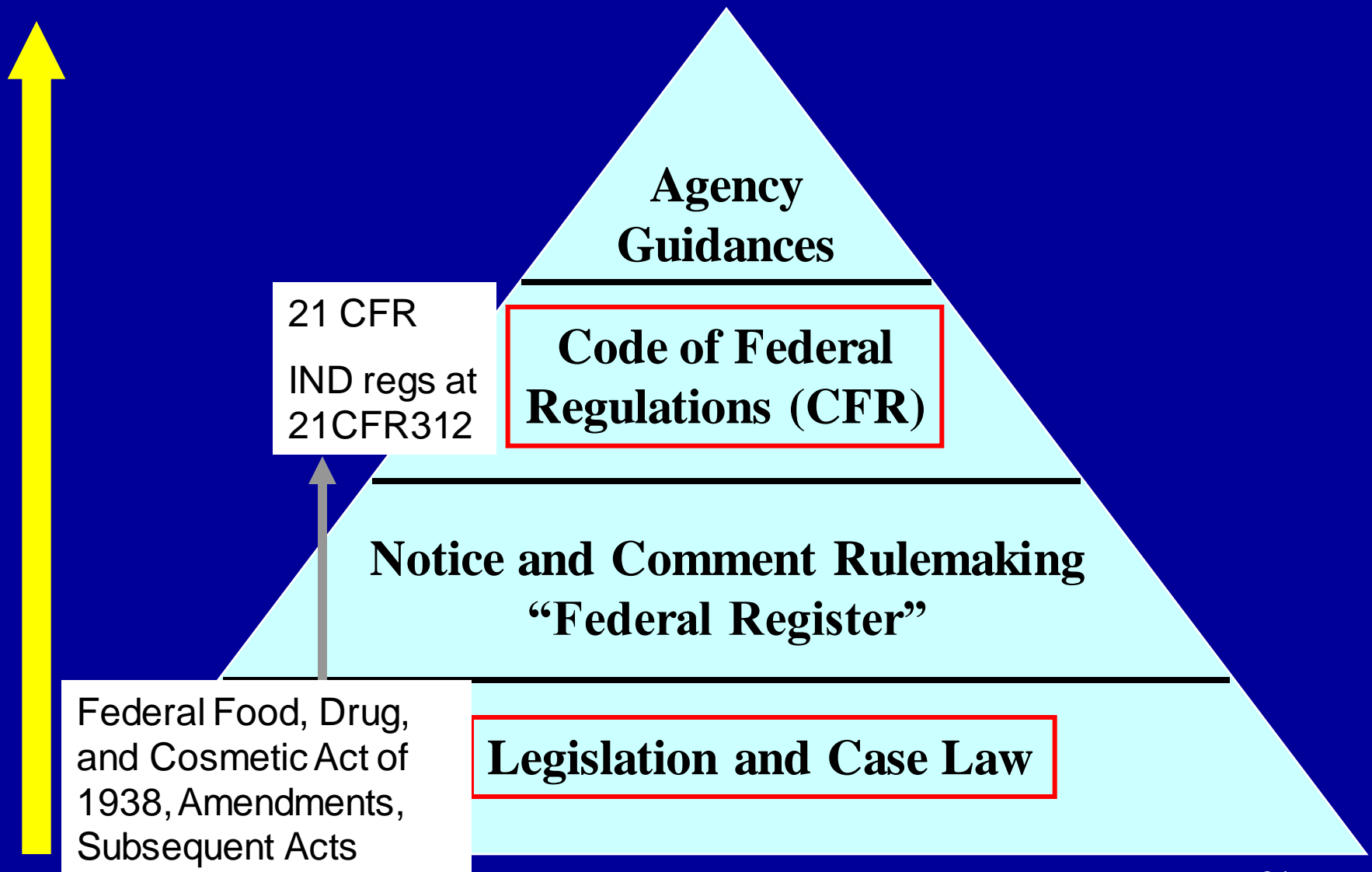
Curriculum Vitae

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

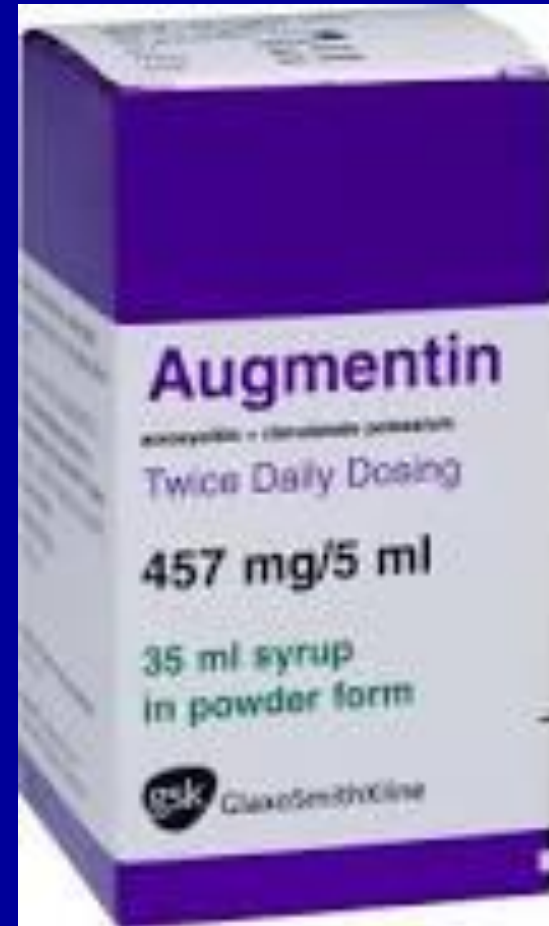
Investigator Responsibilities – IND Studies

- 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?

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



Expanded Access to Investigational Drugs for Treatment Use

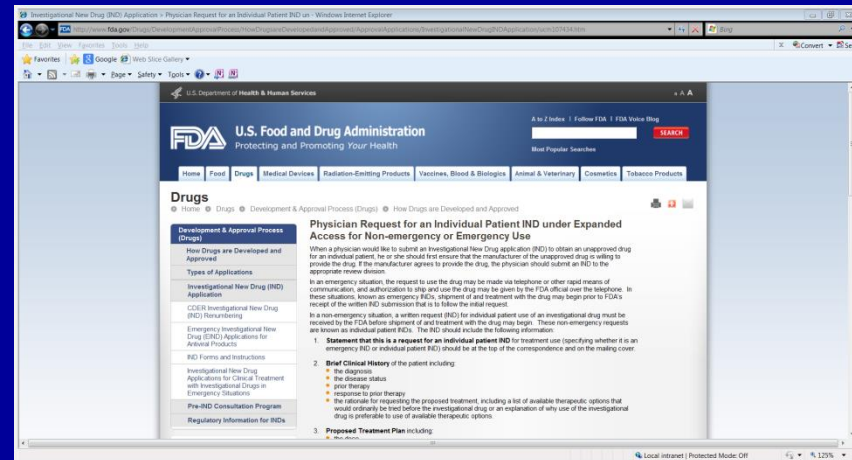
21 CFR 312 Subpart I

Procedure

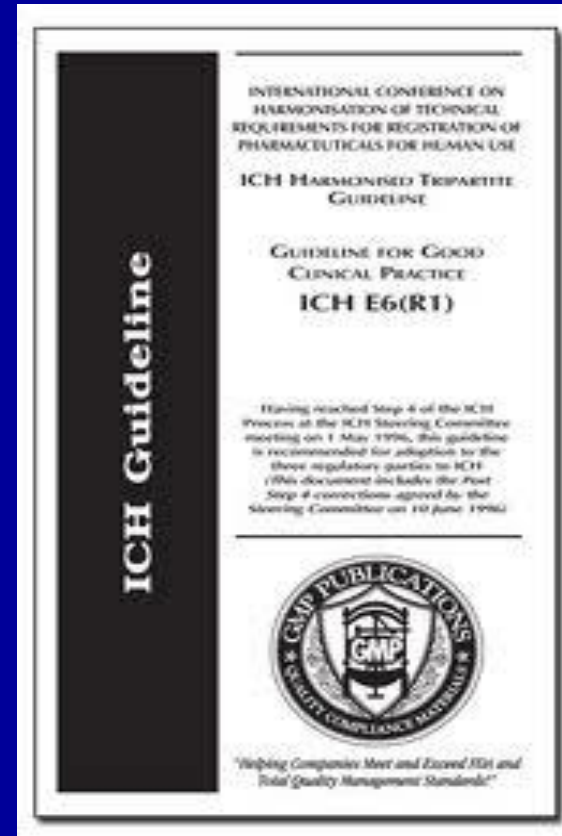
- Contact IRB Chair, HRPO
- Contact FDA (855) 543-3784, or (301) 796-3400

- Individual patients, including for emergency use

- Intermediate-size patient populations
- Treatment IND or treatment protocol



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’

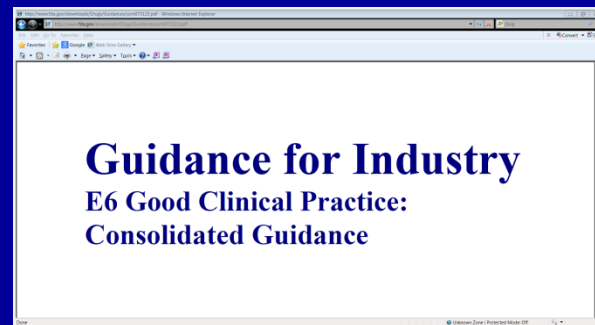
ICH Guidelines Adoption in the United States

- 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 and HRPP. Contact HRPO staff with questions.
- Read 45 CFR 46, pay particular attention to provisions regarding pregnant women, children, and prisoners.
- Read ICH E6 regarding Good Clinical Practice.
- Know if the protocol is being done under IND/IDE or requires submission of an IND/IDE.
- Think about registering for PREV 633