FDA Regulation

Don’t Drown in the Regulatory Sea?

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Who Am I

20 years in IRB World

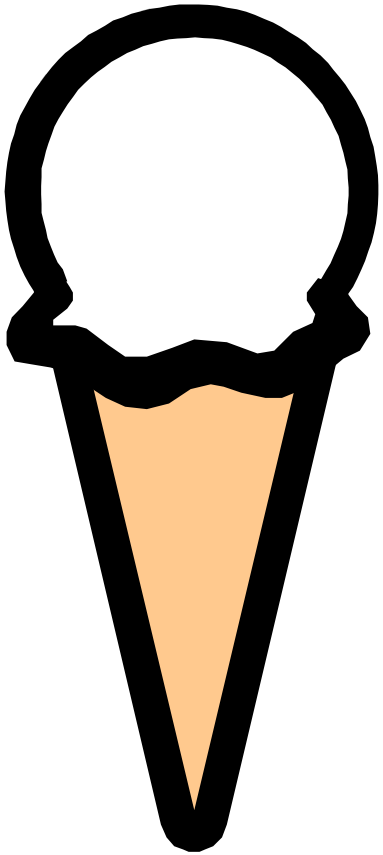
BCH Human Subjects Committee

HSPH IRB, and BUMC IRB

For Fun

Plain Vanilla FDA

- INDs, IDEs
  - What are they?
  - When appropriate
- Sponsor-Investigator Duties
- Food Product Research
- Institutional Policies



1820

United States Pharmacopoeia

to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage.

Some Products from the 1820 USP Continue in Use Today

Acacia

Belladonna (atropine)

Aloe

Digitalis

Castor Oil

Ipecac

Opium

1906

U.S. Federal Food and Drugs Act

..USP standards recognized and imposed standards of purity and strength

1937

Sulfanilamide Tragedy

Sulfanilamide, a drug used to treat streptococcal infections had been available only in pill form

Harold Cole Watkins, of Massengill experimented and found that sulfanilamide would dissolve in diethylene glycol {DEG}

DEG is a chemical cousin to antifreeze and > 100 people died

to realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that that medicine which I had used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm in Tennessee: well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive.
Dr. A.S. Calhoun

1938

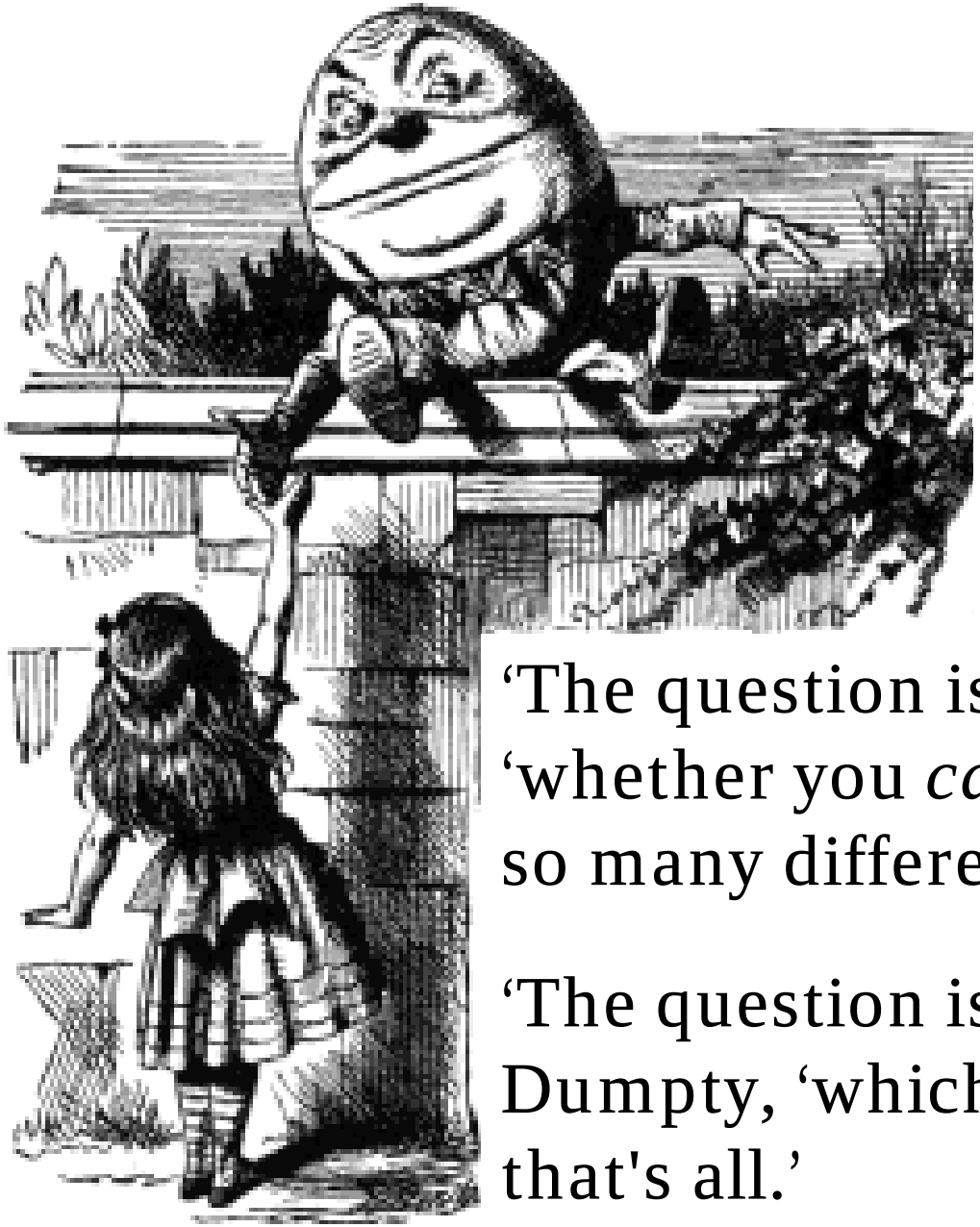
U.S. Federal Food, Drugs and Cosmetics Act

..Safety criterion was added and devices were added and regulated like drugs

1962

Kefauver Amendments

Effectiveness criterion added



‘When I use a word,’ Humpty Dumpty said, in rather a scornful tone, ‘it means just what I choose it to mean -- neither more nor less’

‘The question is,’ said Alice, ‘whether you *can* make words mean so many different things.’

‘The question is,’ said Humpty Dumpty, ‘which is to be master -- that's all.’

Test Article

any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product," or any other article subject to FDA regulation

What Is An IND?

- Notice of claimed investigational exemption for a new drug
  - Investigational New Drug (IND) application

An IND is a Stay Out of Trouble Card

- The law
  - No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug
- Investigational Exemption

When is an IND required?

- In general drugs for human use must be approved as safe and effective
  - Investigational use exemption
- All clinical investigations on drugs or biologicals, including those that are approved/licensed, require an IND unless an exemption applies.

Types of INDs

- Commercial IND
  - product under development for general marketing to the public (typically pharmaceutical or biotechnology company sponsors. or National Institute of Health institute)
- Non-Commercial IND
  - Investigator Sponsored IND (can come under commercial classification if that is intent of investigator
  - Treatment IND
  - Emergency Use

Sponsor

- The initiator of an IND application [**FDA Form 1571**]
  - may be a pharmaceutical company, a private or academic organization, or an individual (including an investigator)
- Sponsor's Duties
  - Investigator selection
  - Maintaining records

Other Sponsor Duties

- Study monitoring
- Obtaining investigator commitment to compliance: FDA Form 1572
  - Conducting study in accordance with protocol
  - Ensure requirements of IRB review, informed consent are met
  - Reporting AEs to the Sponsor

The 21 CFR 312.2(b) IND Exemption

- **Investigation--**

  is not intended to be reported to FDA in support of a new indication for use or significant change in the labeling for the product;

  – **is not** intended to support a significant change in the advertising for the product;

  – **does not** 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 the use of the drug product;

The 21 CFR 312.2(b) IND Exemption - 2

- is conducted in compliance with IRB review and informed consent regulations . (See 21 C.F.R. Parts 50, 56) AND
- **is conducted in compliance** with the rules against promotion of and charging for investigational drugs. (See, 21 C.F.R. 312.7).

Ultimate Decisions on IND Need Are Fact Specific

Because assessing the risks involved in specific uses of a product depends on a number of variable factors, the agency cannot in advance describe precisely the degree to which particular drug products might be altered through dosage level changes, dosage form changes, or changes in the intended patient population and stay within the exemption

What Role Does GRAS Play in Determining Whether You Need an IND For Clinical Research?

Food Additive GRAS

- FDA Food Additive Amendment of 1958
  - Response to consumer concerns about increasing use of “chemicals” in foods
- Factors in GRAS Determination
  - Long use in food history
  - Nature of the substance (e.g. spices)

Food Additive GRAS (2)

  - Customary or projected use
  - Information generally available to scientists
- GRAS determination that product is safe under conditions of their intended use
  - Scientific procedure
  - Common use GRAS

The Crucial Fact about GRAS

under section 201(s) of the act, it is the use of a substance, rather than the substance itself, that is eligible for the GRAS exemption.

“Safe” is a Qualified Term

Safe or *safety* means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. . . .

Factors in Safety Determination

- The probable consumption of the substance and of any substance formed in or on food because of its use.
- The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.
- Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

Use is King

Substances that do not qualify for GRAS food additive status require FDA premarket approval

Monograph Products

- Certain over the counter (OTC) drugs do not require premarket approval
- In May 1972, the monograph regulation was finalized
- 21 CFR Part 330

Monographs are Recipes

- A special marketing approval category
- Monograph products are recognized as generally safe and effective (GRAS/E) if they meet each requirement of Part 330 and the applicable monograph

GRAS Status Does Not Determine Whether an IND is Needed

- For food additive substances the issue is whether the product is being used as a drug
- For OTC products marketed under an monograph, the inquiry is whether any IND exemption under 312.2 applies

IDE

- Investigational Device Exemption
  - Has similar function to IND, but different regulatory scheme
  - Devices are placed in classes (I-III) based on risk level
    - Classification determines whether testing is required for marketing approval
  - Devices also receive a Category A or B designation for Medicare program

The IDE is Also a Stay Out of Trouble Card

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution.

Class	Controls	PREMARKET Notification or Approval	Marketing Requirement
Class I	General Controls	Exempt	General Controls
		Not Exempt	510(k)
Class II	General Controls Special Controls	Exempt	General & Special Controls
		Not Exempt	510(k)
Class III	General Controls	Not Exempt	PMA
	PMA		510(k): qualifying pre1976 devices

When Is an IDE Required?

- **Simple Inquiries**-specifically addressed in either IDE regulation or SR/NSR guidance
  - Marketed device studied per labeling would be IDE exempt
  - Study of device on the list of NSR devices in the SR/NSR guidance

FDA, *Procedures for Handling Inquiring Regarding the Need for an Investigational Device Exemption Application for Research Involving Medical Devices* (10-26-01)

When Is an IDE Required?-2

- **Inquiries Requiring Interpretative Response**
  - Two marketed devices investigated in combination per labeling
    - Relevant factors
      - Are safety and efficacy being evaluated?
      - Risks of device combination
  - NSR listed device used non-conventionally or has been modified

When Is an IDE Required?-3

- **Complex Inquiries**
  - Study of cleared device that has been modified to collect date for nutritional study
  - Study of a device used to collect basic physiologic information about the progression of a disease or condition

Nonsignificant Risk Devices

- An NSR device is one that does not meet the Significant Risk Device definition
- Be Careful!
  - An NSR study is not automatically a minimal risk study

Significant Risk Device

- A device that presents a potential for serious risk to the health, safety, or welfare of a subject and
  - is an implant; or
  - is used in supporting or sustaining human life; or
  - is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
  - otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

IRB's Role

- Sponsor has initial responsibility for making the case that a study involves an NSR device
- IRB is FDA surrogate in making the NSR (deemed IDE) determination
- IRB may disagree with Sponsor's assessment

NSR Sponsor Responsibilities

- NSR device studies require a Sponsor
- Sponsor requirements are termed “abbreviated,” but actually quite extensive

January 2006: Guidance on NSR Devices

- NSR
  - Low Power Lasers for treatment of pain
  - Electroencephalography
  - Manual Image Guided Surgery
  - Ureteral Stents
- SR
  - Surgical Lasers
  - Organ Storage/Transport Units
  - TMJ Prosthesis
  - Computer Guided Robotic Surgery

In Vitro Diagnostic Devices

- Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions or to determine state of health, in order to cure, mitigate, treat, or prevent disease or its *sequelae*
  - Used to collect prepare, and examine specimens taken from the human body
  - Normally do not require IDE if method of obtaining specimen is non-invasive


Food Supplements
Medical Food

Dietary Supplement

- A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
- a vitamin;
- a mineral;
- an herb or other botanical;
- an amino acid;
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- a concentrate, metabolite, constituent, extract, or combination of any ingredient described in (A), (B), (C), (D), or (E);

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Additional Definition

- Product
  - is intended for ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form; or
  - if not intended for ingestion in such a form, is not represented as conventional food and is not represented for use as a sole item of a meal or of the diet;
  - is labeled as a dietary supplement; and

Critical Exclusion for Certain Investigations

- includes products previously classed as supplements that subsequently received approval as drugs, but excludes products approved as new drugs or test articles being investigated for drug, antibiotic, or biological use

Permissible Supplement Claim

- Statements limited to characterizing documented mechanism “by which nutrient or dietary ingredient acts to maintain . . . structure or function”

No supplement may claim to “diagnose, mitigate, treat, cure, or prevent disease

- No explicit or implicit claims that product
  - has an effect of specific disease or class of disease;
  - has an effect on characteristic signs or symptoms of specific disease or class of diseases;
  - has an effect on abnormal condition associated with a natural state or process, if abnormal condition is uncommon or can cause significant or permanent harm;

Disease Claims, 2

- has an effect on disease through the
  - product name
  - statement about FDA regulation as a drug or known to consumers for claimed disease use
  - **citation of a publication referring to disease use**
  - uses the term disease
  - pictures, symbols, vignettes;

Disease Claims, 3

- belongs to a product class intended to diagnose, mitigate, treat, cure, or prevent disease;
- is a substitute for a product that is disease therapy;
- augments a particular therapy or drug action;
- has a role in the body's response to disease or to a vector of disease

Disease Claims, 4

- treats prevents or mitigates adverse events associated with a therapy for disease, if the adverse events are diseases;
- otherwise suggests an effect on disease

When Is an IND Required?

- An IND is required for clinical research when a supplement is being investigated for disease claims

Medical Foods

- Until 1972 medical foods were regulated as prescription drugs
- FDA considers the statutory definition of medical foods to narrowly constrain the types of products that can be considered to fall within this exemption

What is a Distinctive Nutritional Requirement?

Distinctive nutritional requirements can be used in two ways:

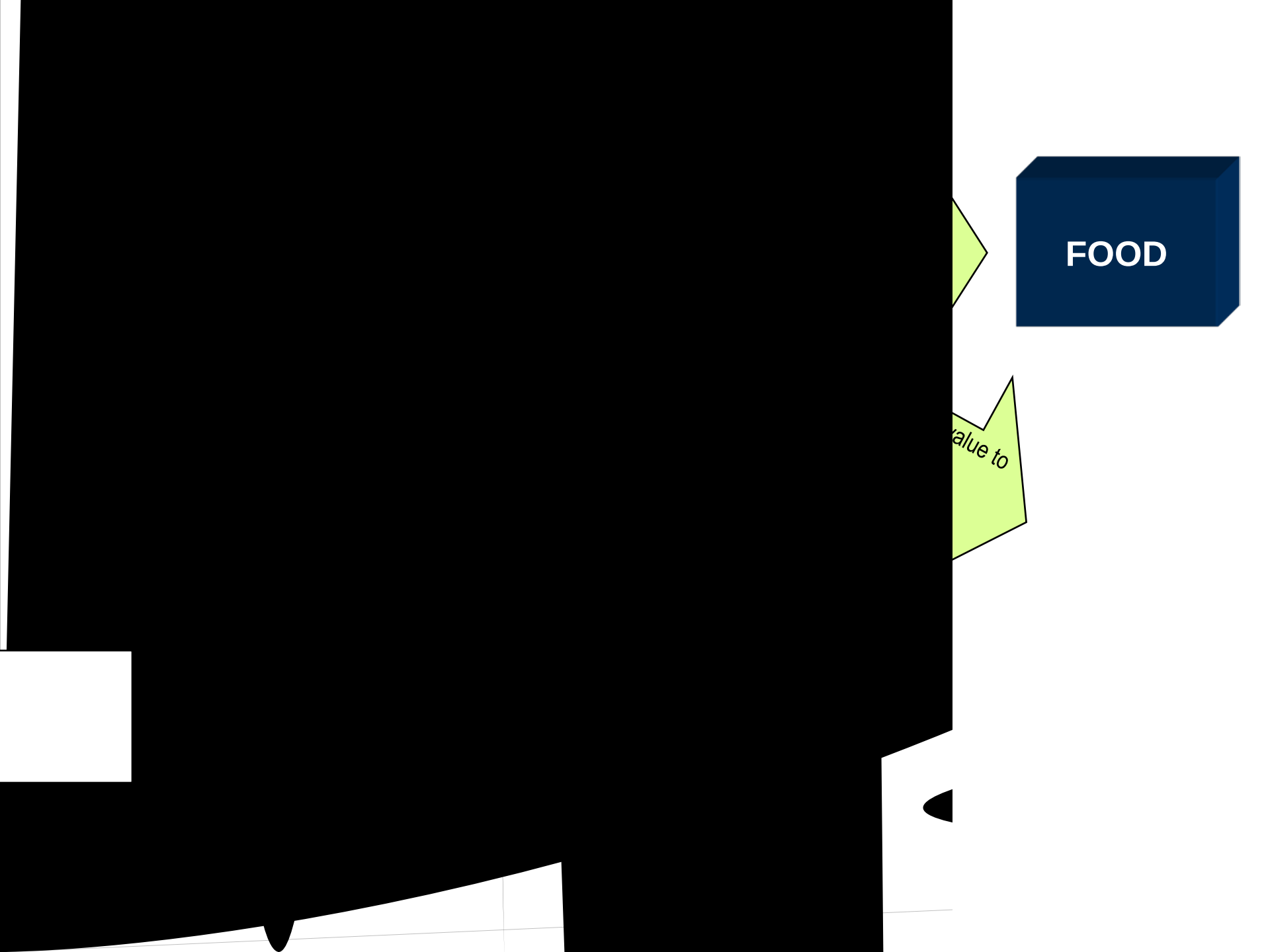
- distinctive nutritional needs associated with a disease reflect the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism, and excretion.
  - requirements may be greater than, less than, or in a narrower range of tolerance than for an otherwise healthy individual.
- "Distinctive nutritional requirement" can mean physical or physiological limitations in a person's ability to ingest or digest conventional foods, as well as distinctive physiological nutrient requirements.

Where is the Line?

- A “medical food” is not authorized to claim that it will cure, mitigate, treat, or prevent a disease.
  - Such a claim makes the product a “drug”
- A “medical food” is permitted only to make a claim to address a patient’s special dietary needs that exist *because of a disease*; this is a distinct and different claim from a claim to treat or prevent the disease itself

When Is an IND Required?

- An IND should be sought when investigating a use that is beyond the permissible claims for a medical food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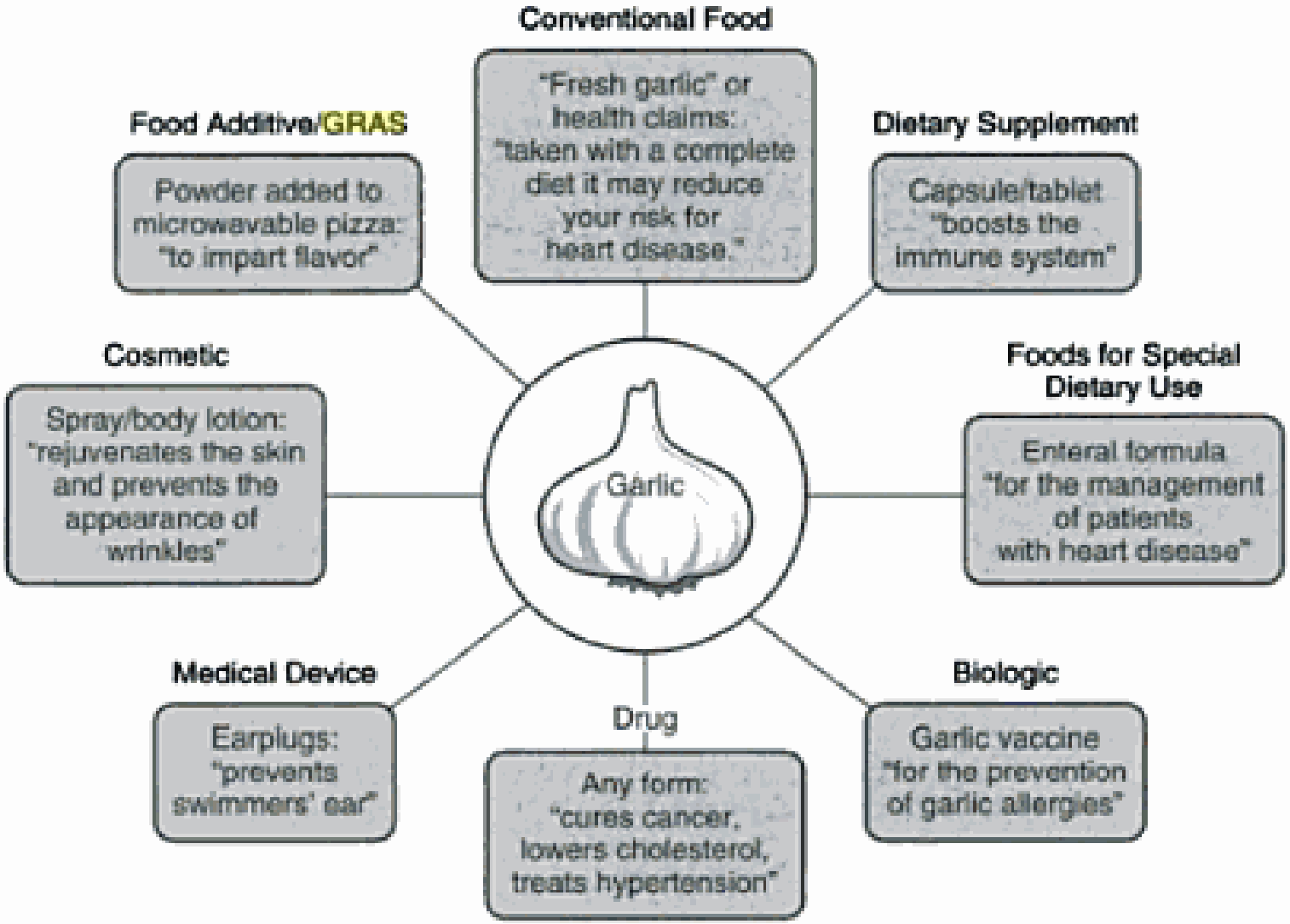

Fig. 15-2. The U.S. Regulatory Classification (e.g., claims for garlic products). (Courtesy Freddie Ann Hoffman, M.D., and Thomas Garvey IV, J.D.)

Legal Medicine, American College of Legal Medicine (6th Ed. 2004), p 168