Pharmacy Law Educators Session: Teaching Federal Pharmacy Law

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Declarations

- *Any opinions expressed are my own and* ***do not reflect those of my employer or any other governmental or professional organization***.
- I declare that neither I nor any member of my immediate family have a financial arrangement or affiliation with any corporate organization offering financial support or grant monies for this continuing education program, nor do I have a financial interest in any commercial product(s) or service(s) that may be discussed during this presentation.
- This presentation is intended for education and is NOT intended to endorse any particular teaching product or publication

Opening thoughts …

- Thank you to ASPL officers and leaders for providing the opportunity for this forum.
- Thank you - Nathela and Janet for their assistance with logistics related to this conference and presentations.
- I am deeply indebted to Bill Stilling for his many years of friendship and collegiality. He has been and continues to be a great mentor.
- Continuing on that dimension, I am also very grateful for the example that all of you set in leading our profession toward serving patients, students, and society at large. I am truly honored for this opportunity to share thoughts and learn from all of you today.
- I know there are some who choose may take a much more formalized approach to classroom instruction, I hope that my informality is not offensive, as I respect there are a variety of ways to delivery this content
- Hoping to facilitate a forum for robust discussion and sharing of ideas & best practices.

Background

- JD, PharmD, BS Pharmacy, BS Biochem/Biology
- Associate Professor – Univ. of Utah
  - Joined academia full-time in 2009, adjunct faculty previous 15 years
  - Teach pharmacy law, ethics, compounding (795/797)
  - Co-chair, Hospital Ethics Committee – Univ. of Utah
  - Compounding Task Force Member, Utah State Board of Pharmacy
- Pharmacist experience
  - Neuroscience clinical & research pharmacist – Epilepsy, MS, Movement Disorders, ALS
  - Pharmacy Administrator - Home Infusion pharmacy at Univ. of Utah Health Care
  - Hemophilia Case Management Program / 340 B Programs
  - Retail and Hospital experience – wards, ICUs, IV/Admix, Drug Info, Poison Control
- Legal experience
  - Intellectual Property – prosecution (4 years)
  - Health care consultant and Supervisor Pharmacist for probationers

Objectives

1. Understand what other instructors teach professional pharmacy students regarding Federal Pharmacy Law.
2. Compare and contrast selected references on Federal Pharmacy Law content.
3. Implement various resources for teaching Federal Pharmacy law content to pharmacy students.
4. Compare an inductive and deductive teaching style for conveying a Federal Pharmacy Law content.
5. Implement applicable ACPE accreditation standards when teaching about Federal Pharmacy Law.

Roadmap

- General approaches to teaching law
  - General demographics
  - Educational philosophies
  - Teaching and learning styles
  - Reference and instructional texts
- Handout/module guide used at Univ. of Utah
  - The handout is reproduced for you
  - Slide content (including turning point data) will be made available to all attendees
- Assessment Questions / Formats
  - Some of these mixed into the handout discussion

General Approaches to Teaching Law

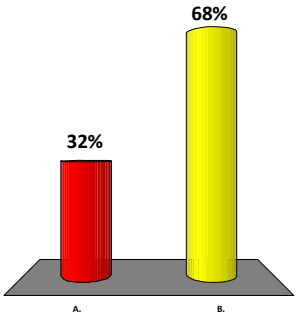
- I view teaching law as being a great privilege
  - It is an opportunity to shape young and emerging professionals into being tremendous advocates for their patients, themselves, and the profession
- I am not qualified to speak for anyone except myself, but I feel my views are similar to thoughts and aspirations shared by all of us in this room
- Our intent is the same, our pathways can have different look and feel

Audience Response / Clickers

- Planning to use clickers for many slides – hopefully to enrich our discussion
- Data collected will be made available to attendees of this teacher's session, but will otherwise be kept confidential and will NOT be reproduced or published
- You MUST (SHALL) return clicker at end of discussion, or if you need to leave early, just leave on you desk, and I'll collect it at the end of the session
- I am informed by my institution that replacement fee per clicker is $4321 and a new car of their choosing.

In my teaching, I use clickers and/or a similar audience response technology.

A. Yes
B. No

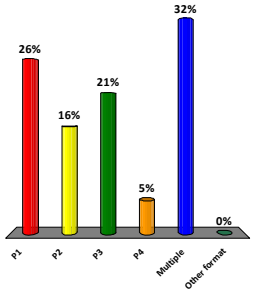


Pharmacy Law Course

- Taught during P2 year, but next fall moving to P1
- 60 students per class
- 3 credit hours, but taught 4 hours/week
- 6 modules
  1. Intro to Law
  2. Federal Laws
  3. Controlled Substances
  4. State Laws
  5. Civil Liability
  6. Intro to Ethics
- Instructor(s)
  - Three (Jim 87%) (Bill 10%) (Jeanne 3%)
- Teaching style is mixture of didactic/discussion and Socratic (lite)
- The Univ. of Utah has separate courses in:
  - Advanced Law Seminar
  - Health Care Policy
  - Ethical Dilemmas in Pharmacotherapy & Health Care

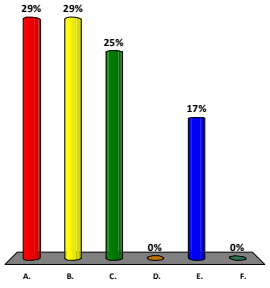
Year(s) in which Pharmacy Law is taught at my institution.

A. P1
B. P2
C. P3
D. P4
E. Multiple
F. Other format



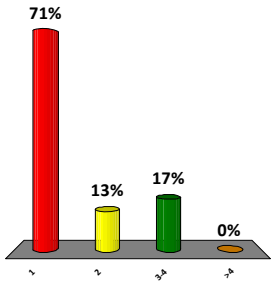
Number of credit hours pharmacy law instruction at my institution.

A. 2
B. 3
C. 4
D. More than 4
E. Law is taught in multiple courses
F. Law is taught in an intensive block/module format



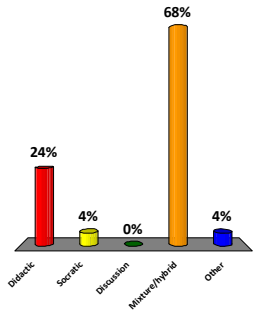
Number of instructors involved in teaching pharmacy law at my institution.

A. 1
B. 2
C. 3-4
D. >4



General style of instruction in pharmacy law at my institution is ____.

A. Didactic
B. Socratic
C. Discussion
D. Mixture/hybrid
E. Other



Course Objectives

- Two fundamental goals of the pharmacy law class
  - Facilitate career-long learning skills in understanding and applying principles of pharmacy law
  - Provide foundation for the Multistate Pharmacy Jurisprudence Examination (MPJE)
- This course is intended to prepare you in the law as a pharmacist and health care provider, and NOT to prepare you to be an attorney

Learning Law

- Similar to learning about drug effects
- Drug, Setting, (mind)Set
  - There is no short cut to learning the laws/regs
    - Although many have tried to isolate and perfect the alchemy of the law
  - There are many settings in which we learn law
    - Classroom
    - Practice
    - Advocacy
  - Mind set and pre-conception can have a big influence in students knowing and understanding the law

Eliciting student perspectives

- Students have many perspectives on learning the law
  - Total ignorance of the law
    - (….well, except for that one thing that happened in high school, but that's now off my record)
  - Open minded to learning, but this content kind of scares me
  - "you cannot teach me anything I don't already know, after all, I've been a pharmacy technician for____ years"
  - I want to be a pharmacy administrator someday, so I need to know the law
  - I am from a country not named the United States of America. I know very little about US law and political system and I have low confidence about being able to learn this subject

May the force be with you…

- I suggest to students there are some in the profession who may try to persuade you that pharmacy law is the dark side of the force
  - You also may be led to believe that law prevents or otherwise serves as a barrier to pharmacists providing optimal health care
  - Don't be fooled…

Pharmacy Law

- A good foundation and understanding of the law is a very powerful tool that you can harness for great effect in your individual practice
- Knowledge of the law helps you to be an informed and valuable advocate for health care and the profession
- As a condition of your drivers license you are expected to know the laws of the road. This is no different for those holding professional licenses

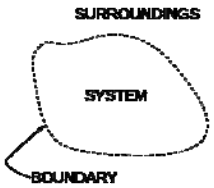
Foundations for Teaching Federal Law

- **Systems approach**
- **Relationships**
- **Communication**
  - **"you are embarking on learning the language of love … pharmacy law"**
  - **There are many dialects, some of you have differing skill levels in conversation**
  - **This is an immersion course and intended to get you "conversational" as quickly as possible**
  - **However, it may take much time for you to become fully conversational**
  - **It just takes practice …**
    - **In the words of Allen Iverson… "we talking 'bout practice, man"**

Professional Perspectives

- KISS
  - Keep It Simple and Straightforward
- Society is dynamic and complex
  - Continuous evolution
  - Engineered [illegible]/health care delivery systems
    - Health Care Professionals
    - Health Care Organizations / Facilities / Payers / Employers
    - Regulators
    - Legislators and Legislative Staff
    - Administrative Agencies
    - Legal Advisors
    - Law Enforcement / Judicial Systems
    - Patients / Caregivers
  - Hopefully, we all have the same common goal -
    - Promote the best interests of the patient

Professional Perspectives



- Thermodynamic system
  - Macroscopic volume in space
    - Surroundings
    - Walls/Barriers
  - Can be described with state variables
    - Temperature
    - Pressure
    - Internal energy
      - Often examined as movement
    - Entropy
      - Measure of disorder in a system

en.wikipedia.org/wiki/Thermodynamic_system#mediaviewer/File:System_boundary.svg

Basic Professional Philosophies

- Our role is largely centered on our relationships
  - Professional-Patient
  - Professional-Professional
  - Professional-Employer
  - Professional-Society
  - Professional-Self/Family/Personal or Spiritual Belief systems
- When relationships break down, or are not optimal, society must compensate

Communication is Key

- How we communicate is key to reducing risk and maximizing our relationships
  - Internal (self) communication regarding capabilities
  - To the best degree possible, achieving a "meeting of the minds"
    - Professional-Patient communications
    - Professional-Professional
    - Professional-Society communications
  - Frequently, the complexity of society does not allow for efficient/effective communication
    - Breakdown in relationships
- Important to emphasize willingness to re-engage anytime there is lack of understanding

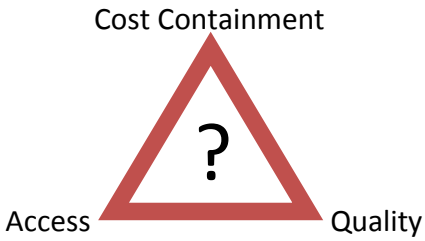
Challenging Times

- Relationships and communication skills are essential elements in our professional success
- Trying to function in a complex, multi-component system
  - Basic principles of societal engineering indicate we can never have a perfect system
  - But we try to continually improve
  - There are incredible amount of details
  - Keeping a macroscopic view of our roles
- Ultimately, we are trying to achieve the same goals

Foundations for Teaching Federal Law

- History
  - Substantial federal legislation often follow public crisis or societal tragedy
  - While society generally tries to resist govt interference in life, sometimes a consensus calls for intervention
- Health Care Policy
  - I feel it is Impossible to teach federal law without educating on health care policy
    - Every so often, Federal elected/appointed leaders change
    - Can result in sometimes sudden, dramatic changes in enforcement of statutes/regulations or agenda for public policy

Iron Triangle of Health Care



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Text and Exam Prep Books

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- Nielsen JR. Handbook of Federal Drug Law. Philadelphia: Lippincott, Williams & Wilkins;1992.
- Fink JL, Vivian JC, Reid KK. Pharmacy Law Digest. 40th ed. Philadelphia: Lippincott, Williams & Wilkins;2005.
- Strauss S. Federal Drug Laws and Examination Review. 5th ed. London: CRC Press;2000.
- Reiss BS, Hall GD. Guide to Federal Pharmacy Law. 8th ed. Boynton Beach, FL: Apothecary Press;2013.

Pharmacy Law:

Federal Pharmacy Law

September 2014

Objectives

- Review historical development of key Federal Drug Laws
- Introduce general organization and structure of FDA
- Introduce general organization and structure of FDCA
- Discuss, Compare, Contrast key definitions: drugs, devices, foods, dietary supplements
- Understand key proscriptions in the FDCA: adulteration and misbranding; and mechanisms for preventing or mitigating these actions – cGMP, adequate directions for use, adequate information for use, market enforcement (criminal penalties, recalls, seizure, court orders)
- Discuss the drug approval process for New Drugs and Generic Drugs
- Discuss and apply key federal legislation on drug dispensing
  - Durham-Humphrey, Kefauver-Harris, Poison-Prevention Pkg, Prescription Drug Marketing Act, OBRA 90, FDA Modernization Act, DQSA
- Identify key laws in health care reimbursement and understand actions that might violate the anti-kickback statute, federal false claims act, or Stark laws

Roadmap

I. History of drug reg.
II. Food-Drug definitions
III. Prohibited acts, penalties, enforcement
IV. New Drug approval
V. Generic drugs
VI. Biologicals
VII. Med watch/reporting
VIII. Medical devices
IX. Cosmetics
X. Drug Ad/Promotion
XI. Durham-Humphrey amend
XII. Unlabeled use of drugs
XIII. Compounding v manufacturing
XIV. Orange book
XV. PDMA
XVI. Inspections
XVII. Alcohol in pharm practice
XVIII. Poison Prevention Pkg Act
XIX. Pharmacy Advertising
XX. Affordable Care Act
XXI. FDA Safety & Innovation Act
XXII. Drug Quality and Safety Act

Other Federal Laws Which Impact Pharmacy Practice
I.Government Reimbursement Programs
II.Federal Regulation of Long-Term Care
III.Anti-Trust Laws
IV.? HIPAA

Federal Regulation of Drugs

- Can be traced back to the early 1800s
  - Technological advances
    - Microscopy and public health
  - Indirect Regulation
    - Focused on information dissemination to public
    - 1906 Pure Food and Drugs Act
  - Direct Regulation
    - Paternalistic paradigm that takes decisions away from consumer
    - Frequently uses a "licensing" mechanism to prohibit unauthorized products in the market

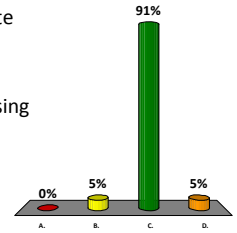
As discussed in class, which of the following choices would best describe the current philosophy of federal regulation of drugs in the US?

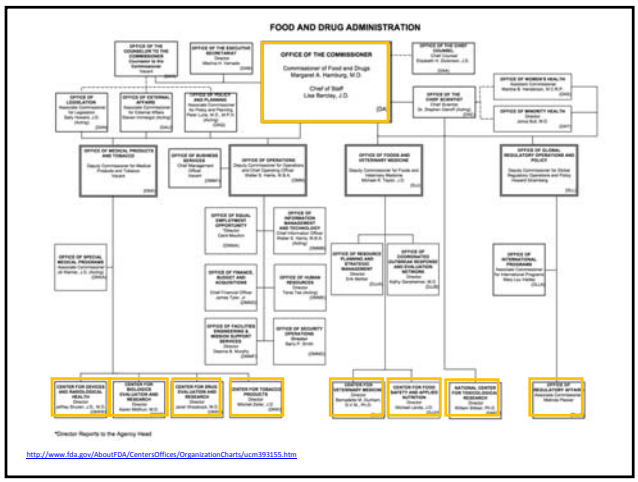
A. **Free Market Regulation** – let the market regulate itself – *Caveat Emptor*

B. **Indirect Regulation** – Simply facilitate information to the public

C. **Direct Regulation** – paternalistic paradigm that takes decisions away from the consumer and uses a licensing mechanism

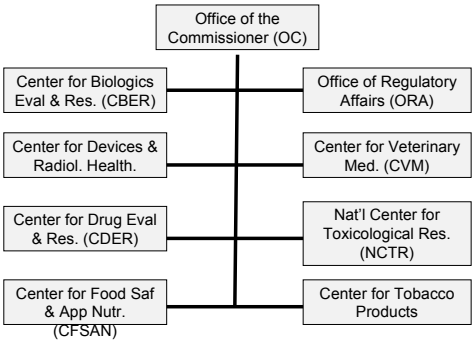
D. **Strict Scrutiny Regulation** – unconstitutional, unless narrowly tailored to meet a compelling governmental interest





http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm393155.htm

FDA Organization & Structure



Food Drug and Cosmetic Act 1938

- Nine Chapters
  - I: Short Title
  - II: Definitions
  - III: Prohibited Acts and Penalties
  - IV: Food
  - V: Drugs and Devices
  - VI: Cosmetics
  - VII: General Authority
  - VIII: Imports and Exports
  - IX: Miscellaneous
- 910 or 399 sections
  - "§" -- depending on cross-reference

I. Historical Overview

Law	Abbreviation	Year
Pure Food and Drug Act		1906
Federal Food Drug and Cosmetic Act	FDCA or FFDCA	1938
Durham-Humphrey Amendment		1951
Food Additives Amendment		1960
Color Additive Amendments		1962
Kefauver-Harris Amendments		1962
Comprehensive Drug Abuse Prevention and Control Act – "Controlled Substances Act"	CSA	1970
Poison Prevention Packaging Act	PPPA	1970
Medical Device Amendments		1976
Orphan Drug Act		1983
Drug Price Competition and Patent Term Restoration Act	Hatch-Waxman Act	1984
Prescription Drug Marketing Act	PDMA	1987
Nutritional Labeling and Education Act	NLEA	1990
Prescription Drug User Fee Act	PDUFA	1992
Dietary Supplement and Health Education Act	DSHEA	1994
Food and Drug Administration Modernization Act	FDAMA	1997
Medicare Modernization Act	MMA	2003
Combat Methamphetamine Epidemic Act	CMEA	2005
Dietary Supplement and Nonprescription Drug Consumer Protection Act		2006
Food and Drug Administration Amendments Act	FDAAA	2007
Patient Protection and Affordable Care Act	PPACA / ACA	2010
Food and Drug Administration Safety and Innovation Act	FDASIA	2012
Drug Quality and Safety Act	DQSA	2013

I. Historical Overview

- Pure Food and Drug Act 1906
  - US v. Johnson
- Federal Food Drug & Cosmetic Act (FDCA) 1938
- Durham-Humphrey Amendment 1951
- Kefauver-Harris Amendments 1962
- Medical Device Amendments 1976
- Orphan Drug Act 1983
- Drug Price Competition & Patent Term Restoration Act 1984
- Prescription Drug Marketing Act 1987
- Nutrition Labeling & Education Act 1990

I. Historical Overview

- Prescription Drug User Fee Act 1992
- Dietary Supplement & Health Education Act 1994
- Food and Drug Administration Modernization Act 1997
- Medicare Modernization Act 2003 / DRA 2005
- Food and Drug Administration Amendments Act 2007
- Patient Protection and Affordable Care Act 2010
- Food and Drug Administration Security & Innovation Act 2012
- Drug Quality and Safety Act 2013
- Milestones in Drug Law History
  - http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/default.htm

II. Definitions

- Statutory definitions are found at 21 USC § 321
  - Drug 21 USC § 321(g)(1)

    (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and

    (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

    (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

    (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

II. Definitions

– "New Drug" 21 USC § 321(p)

(1) Any drug - the composition of which is such that this drug is **not generally recognized**, among experts qualified by scientific training and experience to evaluation the safety and effectiveness of drugs, **as safe and effective for use** under the conditions presented, recommended, or suggested in the labeling thereof; or

(2) Any drug - the composition of which is such that this drug, as a result of investigation to determine is safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to material extent or for a material time under such conditions.

II. Definitions

- Prescription Drug 21 USC 503(b)(1)
  - A drug intended for use by man which:
    (1) is a habit-forming drug; or
    (2) because of its toxicity or other potential for causing a harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such a drug; or
    (3) is limited by an approved application – to use under the professional supervision of a practitioner licensed by the law to administer such a drug.

-Definition introduced by the Durham-Humphrey Amendment (1951) to the Food Drug and Cosmetic Act

II. Definitions

- Definitions also depend on what type of CLAIMS are made by manufacturer (supplier)
- Example Cases
  - *Action on Smoking & Health v. Harris (DC Cir 1980)*
    - Cigarettes are not drug, unless therapeutic claims made
  - *FDA v. Brown & Williamson (US Sup Ct 2000)*
    - FDA does not have jurisdiction over cigarettes
    - Congress reacted in 2009 – Family Smoking Prevention and Tobacco Control Act
  - *National Nutritional Foods Assn v. Mathews (US Dist 1977)*
    - High dose Vit A & D are not drugs without therapeutic claims
    - If no scientific support for higher doses, this does not automatically default to drug classification

II. Definitions

- Food v. Drugs
  - *Nutrilab v. Schweiker (7th Cir 1983)*
    - Starch blocker is a drug because
      - Intended to affect structure/function of the body, active ingredient was derived from kidney beans, but this does not automatically mean it is a food
  - Special dietary foods 21 USC § 350(c)(3)(A)
    - Different from dietary supplements
    - Key: food intended for persons with a particular "condition"
      - Disease, convalescence, pregnancy, obese, etc.

II. Definitions

- Medical Foods 21 USC § 360EE
  - Foods prescribed under medical supervision, for oral use to manage a disease requiring specific nutrients
    - Flavocoxid (Limbrel) for osteoarthritis
- Nutritional and Functional Foods
  - No definitions in statutes/regs
  - Commonly associated with Dietary Suppl
    - Often used in marketing slogans

II. Definitions

- Health Claims for Foods
  - US v. Article of Drug Labeled as Exachol (SDNY 1989)
    - Various nutritional compounds intended for prevention of coronary thrombosis events
      - Intended for persons already with the condition
    - Could be regulated as drug or special dietary food
    - If special dietary food, pre-market approval not required by FDA. Advantage to company to be designated as special dietary food

II. Definitions

- Dietary Supplements
  - Nutrition Labeling Education Act (1990)
    - Prohibits disease prevention claim in food labeling, unless FDA approves the claim
    - Essentially required supplements to have same claim standards as drugs
    - Mfg can make disease prevention claims, if there is "significant scientific agreement"
      - In Pearson v. Shalala (DC Cir 1999), court said "significant scientific agreement" was too vague to provide guidance for industry/consumers. Therefore FDA must come up with less burden definition

II. Definitions

- Dietary Supplement (DS) defined 21 USC § 321(ff)
  - Product intended for ingestion
  - Product to supplement diet
  - Contains one or more:
    - Vitamin
    - Mineral
    - Herb or other botanical
    - Amino acid
    - For use by man to increase total dietary intake
    - Concentrate, metabolite, extract, of the above

II. Definitions

- *Pharmanex v. Shalala (10th Cir 2000)*
  - Red yeast rice product contains lovastatin
  - Product was not marketed prior to approval of Mevacor
  - Court found that if whole product or any active ingredient in DS was previously approved as a drug, then active ingredient cannot be marketed as DS

II. Definitions

- Dietary Supplements –
  - Definitions changed to exempt DS as drugs, when associated with certain types of claim
  - Can be in variety of dosage forms, but must still be given _____
  - Label must explicitly state "dietary supplement"
  - FDA has burden to prove product is adulterated
    - Significant or unreasonable risk of illness if used according to labeling
    - HHS Secretary declares an ingredient poses imminent hazard to public health
    - Product contains poisonous or deleterious ingredient

II. Definitions

- Labeling exemption
  - Labeling does not apply to publications if those publications:
    - Not false or misleading
    - Do not promote a particular manufacturer
    - Presented with other subject matter to present balanced view
    - Physically separate from the DS
    - Do not have appended other info by sticker or other method

II. Definitions

- Permissible Claims
  - DS Benefit related to classical nutrient deficiency disease (must disclose prevalence)
    - Vitamin D for ricketts
  - Describes role of DS intended to affect structure/function of body
    - "calcium builds strong bones"
    - "Fiber helps maintain bowel regularity"
  - Characterizes mechanism by which DS works
    - Anti-oxidants to prevent free radicals, and promote cell repair
  - Describes general well-being from consuming DS
    - Ginko for general well-being

II. Definitions

- Dietary supplement labels
  - Must state: "This product has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

A large multi-marketing corporation that is located in Utah has decided to create a new line of oral supplements that are focused on "health and wellness." The company has developed a new supplement ["HEFFALUMP"] that will be the lead product in this new marketing effort and company sales program. The company claims HEFFALUMP will promote general well-being by reducing stress and general anxiety that results from living in a complicated society. HEFFALUMP is derived from a marine mollusc that is primarily found in the Caribbean region. Sometimes these molluscs are referred to as conch. HEFFALUMP is commercially provided as small granules that are seasoned and placed into shaker containers. Customers are instructed to gently shake the container once or twice over their evening meal (similar to a salt shaker) to dispense the product for consumption. Recently, the FDA has determined that HEFFALUMP contains moderate levels of Lithium carbonate. Lithium carbonate is an inorganic compound that is FDA approved to treat mania and bipolar depression.

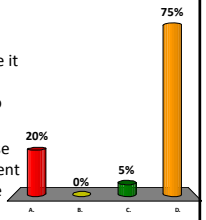
In view of class discussion on *Pharmanex v. Shalala* (10th Circuit Court of Appeals, 2000), which of the following choices best describes what will happen to HEFFALUMP?

A. HEFFALUMP will be classified as a "Dietary Supplement" because it is taken orally, and because the company is claiming the product for general well-being

B. HEFFALUMP will be classified as a "Food" because it is derived from an animal source and put into a salt form which shaken over and consumed with another food product

C. HEFFALUMP will be classified as a "Cosmetic" because it is being used to reduce stress, which will reduce wrinkles and make the user appear more attractive to other members of the general public

✓ D. HEFFALUMP will be classified as a "New Drug" because lithium carbonate is an active pharmaceutical ingredient in another FDA approved medication. In addition, the product is being claimed to reduce general anxiety



II. Definitions

- DS safety issues
  - Ephedra (EDS – ephedra alkaloid DS)
  - High profile deaths
    - Two professional athletes
  - FDA determined significant or unreasonable risk of injury if used as directed in labeling
  - Challenged by mfg. 10th Cir. sided with FDA
    - Nutraceutical Corp.
  - Congress passed: Dietary Supplement and Non-prescription Drug Consumer Protection Act 2006
    - New requirements for reporting DS adverse events
    - New mandates for investigation of DS safety

II. Definitions

- DS
  - FDA regulation issued in 2007 requires DS mfgs to comply with cGMP.
  - Implications for pharmacists
    - As appropriate, direct consumer to DS products that comply with compendial references
    - Do not promote products on the basis of unapproved claims
    - Try to provide balance of information to consumer and remain in compliance with the law

II. Dietary Supplements

- Sept 2014 FDA warning to Utah based DS Company
  - Young Living Farms and associated distributors
  - Claims directed to protection against Ebola

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm416023.htm (accessed 24 September 2014)

II. Definitions

- Drugs v. Devices
  - Devices do not impart their affect through chemical action, nor depend on metabolism of product to achieve affect
  - Is a pregnancy test a drug or device?
    - US v. Article of Drug Ova II (414 F.Supp 660 (NJ 1975))
    - A test for pregnancy is not a test for the diagnosis of disease. It is no more than a test for news, which may be either good news or bad news, depending on whether pregnancy is wanted or not

II. Definitions

- Drugs v. Devices
  - Factors used by FDA:
    - Product intended to deliver drugs to patient, but is not pre-filled with drug
    - Product has drug component solely for safety of product
    - Product has drug component intended to have therapeutic effect

II. Definitions

- Drugs v. Cosmetics
  - If cosmetic makes therapeutic claim, it's a drug
  - Examples of warning letters:
    - http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/ComplianceEnforcement/WarningLetters/ucm081086.htm
    - Lancome example

II. Definitions

- Label and Labeling 21 USC 321(k) 21 USC 321(m)
  - **Label**: display of written, printed, or graphic matter, **upon immediate container**
  - **Labeling**: all labels and other written material **either upon container or accompanying an article**
- Official Compendia 21 USC 321(j)
  - United States Pharmacopoeia (USP)
  - National Formulary (NF)
  - Homeopathic Pharmacopoeia (HPUS)

III. Prohibited Acts, Penalties, Enforcement

- 21 USC §331
- (a) introduction or delivery into interstate commerce of any food, drug, device, or cosmetic that is **adulterated** or **misbranded**
- (f) refusal to permit entry or inspection
- (i)(3) doing of any act which causes a drug to be a counterfeit drug, or the holding for sale or dispensing a counterfeit drug
- (k) Alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling …
- Introduction of an unsafe dietary supplement into interstate commerce

III. Prohibited Acts, Penalties, Enforcement

- Essentially, two (2) major offenses:
  - (1) adulteration
  - (2) misbranding
- Considered to be strict liability offenses
  - These activities are crimes, regardless of the knowledge or intent of those who committed the activities
- FDCA [21 USC 333(c)] indicates that pharmacist should not be held liable for adulteration or misbranding, so long as acting in good faith, and assists regulatory authorities in identifying source of good

III. Prohibited Acts, Penalties, Enforcement

- FDA Investigations Manual

- Criminal Penalties (fines and Imprisonment)
- Seizures
- Injunctions

III. Prohibited Acts, Penalties, Enforcement

- Liability
  - Criminal statutes typically require two elements (unless strict liability, then only action)
    - *Actus reus* (guilty act)
    - *Mens rea* (guilty mind)
  - FDCA imposes criminal penalties on corporate officers even if they do not have personal knowledge of violations
    - *US v. Park, 421 US 658 (1975)*
    - *US v. Dotterweich, 320 US 277 (1943)*

US v. Sullivan

332 US 689 (1948)

- Parties
  - United States of America v. JJ Sullivan
- Procedural history
  - Convicted at Trial Court, Overturned at Appellate Court, US appeals to SCOTUS
- Issue
  - Whether misbranded provisions apply only to first sale, or throughout retail course of the product

US v. Sullivan

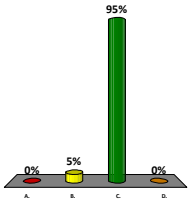
332 US 689 (1948)

- Facts
  - RPh bought stock bottles of sulfathiazole
  - Removed tablets and put into pill box. Boxes not labeled in accordance with Federal Law
- Standard of Review
  - Regular review
- Result / Reasons
  - Circuit court reversed, conviction reinstated

Pharmacist in the State of Old York, USA, places order for *Smackrolimus* (a prescription only medication used to treat college football fans with a condition called "negativity hyperexpressiveness"). The medication is manufactured in Massachusetts, advertised nationally, and distributed by only one wholesale company. There is an upcoming college game and he feels it wise to obtain extra supplies. The shipment will not arrive in time for the game, so he travels to the distributor's main warehouse, located about 100 miles away, but still within the state boundaries of Old York. He receives 5 containers (1000 count each), which is enough to treat several hundred patients. On his way back to his pharmacy, he realizes just how valuable the medication is, so he covers the manufacturer labels on the bottles with a label that has only the words, "suppository base and wart retardant." Unintentionally, he exceeds the speed limit while traveling back to his pharmacy and he is pulled over by a police officer. The officer notices the bottles resting on his back seat. The police officer has made many drug busts in his career and does not believe these containers have "suppository base and wart retardant" as this is a common ruse to mask illegal drug activity. The FBI is called in to investigate and the pharmacist is subsequently charged with violation of the misbranding provisions of the Federal Food Drug and Cosmetic Act. In his defense, the pharmacist asserts that the Federal Food Drug and Cosmetic Act does not apply because the product was moving in commerce within the State of Old York and thus was not subject to regulation under Federal Laws as a product held for sale in interstate commerce.

Based on your knowledge of the case of US v. Sullivan, 332 US 689 (1948) [case involving pharmacist who received sulfathiazole stock bottles from wholesaler, and subsequently sold tablets in pill boxes with only the term "sulfathiazole" and no other warning labels or directions] – what answer choice best describes the likely outcome of this current case?

A. Innocent because this was entirely intrastate activity
B. Guilty of misbranding – did not properly store in his car trunk
C. ✓ Guilty of misbranding – any activity which obliterates, defaces, or removes mfg. label
D. Innocent because he is a pharmacist and specifically exempted from misbranding and adulteration laws



III. Prohibited Acts, Penalties, Enforcement

- Product Recalls
  - Prior to 2007, FDA had no ability to force recall – "negotiation" process to entice voluntary recall
    - Now FDA can use seizure authority
  - Classifications
    - Class I – Serious health effects or death
    - Class II – Reversible health effects/remote serious effects
    - Class III – unlikely to cause adverse health effects
      - http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2010/default.htm

III. Prohibited Acts, Penalties, Enforcement

- Product Recalls
  - Manufacturer is responsible for notifying sellers of the recall
  - Sellers are responsible for contacting consumers
    - Written notices required for Class I/II recalls
  - Pharmacist responsible for knowing which drug products have been recalled.
    - Furnishing a recalled product to a patient may violate FDCA
    - May also be subject to civil liability
  - FDA Recall Page

III. Prohibited Acts, Penalties, Enforcement

- **Adulterated Drugs** 21 USC 351
  - *Primary intent: ensure purity of products*
  - *Focused on manufacture and storage of goods*
    - *"physical conditions"*
  - Poisonous, insanitary, unsafe ingredients
    - Decomposed, putrid, filthy materials
    - Unsanitary conditions for packing/storing
    - Poisonous container
    - Unsafe color additive
  - Strength, quality, purity differ from compendium
  - Not in conformance with GMP
  - Varies from compendium, but not stated on label

III. Prohibited Acts, Penalties, Enforcement

- Current Good Manufacturing Practice (cGMP)
  - 21 CFR 211
  - Intended to ensure drug meets quality and purity requirements
  - Firms (mfgs) typically inspected every 2 years
  - cGMP do not apply to compounding pharmacies, unless they are acting as manufacturer … however, DQSA changes some of that, stay tuned…
  - Sample warning letters

III. Prohibited Acts, Penalties, Enforcement

- Misbranding 21 USC 352
  - Labeling is false or misleading in any particular
    - Primarily related: **representations** about a drug
  - Label does not state name and address of mfg and accurate statement of quantity
  - Information not prominently displayed
  - Brand name less than ½ font size of generic name
  - Does not identify proportions of API and other ingredients required to be listed

III. Prohibited Acts, Penalties, Enforcement

- Misbranding 21 USC 352
  - Labeling does not bear "**adequate directions for use**" and "adequate warnings against use"
    - Prescription agents required to have "**adequate information for use**"
  - Drug listed in USP, but not packed according to USP standards
  - Subject to deterioration, but not labeled
  - Endangers health if used as labeled
  - Mfg not registered with FDA
  - Fails to bear symbol: "Rx only"

III. Prohibited Acts, Penalties, Enforcement

- Adequate Directions for Use 21 CFR 201.5
  - Directions under which a layperson can use a drug safely and for the purpose for which it was intended
  - 6 required pieces of information
    - Quantity or dosage for each intended use and for persons of different ages and physical conditions
    - Frequency of administration or application
    - Duration of administration or application
    - Time of administration or application (e.g. relation to meals)
    - Route or method of administration or application
    - Any preparation necessary for use (e.g., shaking, dilution)
  - Basically applies to all OTCs

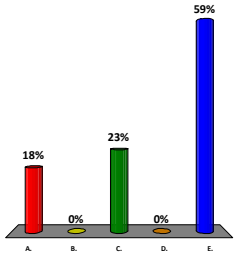
III. Prohibited Acts, Penalties, Enforcement

- Adequate Information for Use 21 CFR 201.100
  - Directions under which a prescriber can use a drug safely and for the purpose for which it was intended in a patient
  - 6 required pieces of information
    - Drug indications
    - Side effects
    - Dosages
    - Routes, methods, frequency, duration of administration
    - Contraindications
    - Other warnings, as needed, to enable practitioner to administer, prescribe or dispense the drug safely
  - Applies to all prescription drugs

Which of the following statements is/are CORRECT regarding "adequate directions for use?"

I. Must be provided by manufacturer and written in terms a layperson can understand to use the drug safely
II. Includes quantity or dosage for each intended use and for persons of different ages and physical conditions
III. Must include frequency, duration, time and route of administration

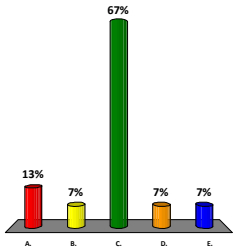
A. I only
B. II only
C. I and II only
D. II and III only
E. ✓ I, II, and III



Which of the following statements is/are CORRECT regarding "adequate information for use?"

I. Included with prescription drugs, intended for prescribers
II. Was introduced as part of the 1906 Pure Food and Drugs Act
III. Must include drug indications, side effects, dosage, routes, methods, frequency, duration of administration, contraindications and any other required warnings for the prescriber

A. I only
B. II only
C. ✓ I and III only
D. II and III only
E. I, II, and III



III. Prohibited Acts, Penalties, Enforcement

- Non-prescription Drug Labeling
  - New user friendly label
  - Required elements
    - Identity of the product name, pharmacologic category or principal intended action(s)
    - Name and address of mfg, packer, or distributor
    - Net quantity
    - Cautions and warnings needed to protect consumer
    - Adequate directions for use
    - "Drug Facts" panel

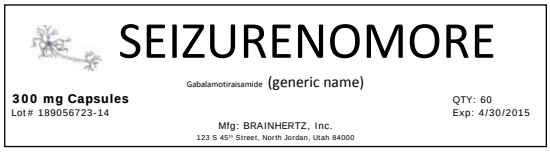
III. Prohibited Acts, Penalties, Enforcement

- Commercial Container Label
  - Name & address of mfg, packer, distributor
  - Established name of product
  - Ingredient information (quantity & proportion of each api)
  - Names of inactive ingredients
  - Statement of identity
  - Quantity in terms of weight or measure
  - Net qty of container
  - Recommended or usual dosage or reference to PI
  - "Rx only" symbol, or federal legend:
    - "caution: Federal Law Prohibits dispensing without prescription"

III. Prohibited Acts, Penalties, Enforcement

- Commercial Container Label
  - Route of administration, if it is not for oral use
  - Identifying lot or control number
  - Statement directed to the pharmacist specifying type of container to be used in dispensing
    - "dispense in tight, light-resistant container…."
  - Expiration date, unless exempted
    - If expressed as Month/Year, then expiration date is last day of the month

In view of class discussion about adulteration and misbranding, which of the following choices best describes the following mfg label?

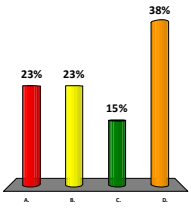


A. nothing wrong, product label meets all label standards

✓ B. product is misbranded because generic name not correctly formatted on label

C. product is adulterated because bottle label does not include temperature information

D. product is unfit for use because bottle label does not include dosage instructions



III. Prohibited Acts, Penalties, Enforcement

Package Insert (official labeling) 21 CFR 201.56

- Indications and usage
- Dosage and administration
- Dosage forms and strengths
- Contraindications
- Warnings and precautions
- Adverse reactions
- Drug interactions
- Use in special populations
- Drug abuse and dependence
- Overdose
- Description
- Clinical pharmacology
- Nonclinical toxicology
- Clinical studies
- References
- How supplied/storage and handling
- Patient counseling information

IV. New Drug Approval

- New Drug: 21 USC 321(p)
  - "Any drug - the composition of which is such that this **drug is not generally recognized**, among experts qualified by scientific training and experience to evaluation the safety and effectiveness of drugs, **as safe and effective for use under the conditions presented**, recommended, or suggested in the labeling thereof…"

IV. New Drug Approval

- Grandfathered drugs:
  - Anything on the market prior to 1938 was exempted from this definition, so long as the drug is marketed in accordance with the regulations as they existed at the time of first approval
  - Examples:
    - Aspirin, codeine, digoxin, hydrocodone, hydromorphone, morphine, nitroglycerin, phenobarbital, potassium salts, phosphate salts, et al.

IV. New Drug Approval

- Approved as new drugs
  - Drug also considered new if:
    - Contains a new substance
    - New combination of previously approved drugs
    - Proportion of ingredients changed
    - Established drug, in new dosage forms, new dosage levels, or new packaging
    - Established drug with new claims (indications)

IV. New Drug Approval

- Route to New Drug Application (NDA)
  - Evidence of Safety/Efficacy must come from animal and human clinical studies
    - Cannot move in interstate commerce
  - Notify FDA of intent to study
    - IND (investigational new drug) exemption
    - License granted by FDA to ship "new drug" in commerce, … for purposes of research.

IV. New Drug Approval

- Phases of Drug Testing
  - Phase I
    - Small number of subjects, tox, metabolism, adme
  - Phase II
    - Initial trials on limited number of subjects with condition to be treated, dose ranging studies
  - Phase III
    - Large number of subjects, formal studies for safety and efficacy, usually d-b RCT
  - Postmarketing
  - FDA may terminate trial at anytime

IV. New Drug Approval

- Prescription Drug User Fee Act (PDUFA)
  - Has cut the average approval time from 4-6 years down to about 1-2 years
  - Requires mfg to pay "fees" to FDA
    - Applications
      - Requiring clinical data $2,169,00
      - Not req clinical data $1,084,550
      - Supplemental applications $1,084,550
    - Establishments $554,600
    - Products $104,060

IV. New Drug Approval

- Risk Evaluation and Mitigation Strategies (REMS)
  - Initiated in 2007
  - Mfg must ensure benefit outweighs risk of particular products
  - REMS is overall strategy (plan)
    - Part of REMS is a "medication guide" (Med Guide)
- REMS program is controversial
  - Many argue that program is not effect and consumers ignore information

V. Generic Drugs as New Drugs

- Kefauver-Harris Amendments (1962)
  - Required that drugs be proven efficacious as well as safe
  - What to do with drugs approved between 1962 and 1938?
    - **DESI study** (Drug Efficacy Study Implementation)
    - Systematic evaluation of drugs approved between 1938-1962
      - Use available in the medical literature
      - Give 1 of 6 designations:
      - Effective, Probably Effective, Possibly Effective, Ineffective, Effective "but", Ineffective combo

V. Generic Drugs as New Drugs

- Drug Competition and Patent Term Restoration Act (1984)
  - Often referred to by sponsors:
    - Hatch-Waxman Act
  - Essentially provided the economic incentive to fuel the Generic Drug Industry
  - Mfg can obtain approval based on bioequivalence and bioavailability studies
    - Must be for same indication as innovator (brand) drug
      - Within 90% Confidence Interval
  - 1st generic approved gets 180 day period of exclusivity

V. Generic Drugs as New Drugs

- OTC Drug Review
  - DESI have also reviewed 100-500 K OTC products
  - Instead of looking at each product, created "therapeutic categories"
  - These have turned into "OTC Monographs"
  - Three Categories of OTC products
    - Cat I – GRAS
    - Cat II – not GRAS
    - Cat III – insufficient data

V. Generic Drugs as New Drugs

- Patient Treatment with Investigation Drugs
  - Do we have constitutional access to investigational drugs?
  - Should we have this access?
  - Abigail Alliance v. Von Eschenbach 445 F.3d 470 (CADC 2006)

Abigail Alliance v. Von Eschenbach

- Parties
  - Abigail Alliance – advocacy group to promote access to exp drugs v. Von Eschenbach
- Procedural history
  - En banc rehearing in DC Circuit App. Ct.
  - Subsequently SCOTUS declined to hear
- Issue
  - Do terminally ill patients have a fundamental right of access to unproven drugs?

Abigail Alliance v. Von Eschenbach

- Holding
  - Nation's history and tradition does not establish a substantive due process right to unapproved drugs with some limited data on safety, but unproven effectiveness
  - common law doctrine of necessity, tort of intentional interference with rescue, right to self-defense, do not establish a right to self-preservation
  - FDA policy of limiting access to investigational drugs is rationally related to the legitimate government interest of protecting the public from potentially unsafe drugs

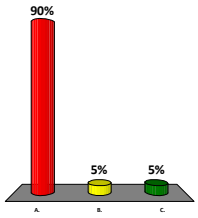
You are a pharmacist on duty at a community pharmacy. A customer approaches you and relates the following information: Her 23 year old son has recently been diagnosed with an advance stage cancer. He does not qualify for any of the cancer trials that are being conducted in Utah. The customer has recently learned of a medication that has just completed a Phase I trial in Texas for the same stage of cancer of which her son is suffering. The family does not have enough money to send her son to Texas. The customer indicates that this medication represents the only chance that her son would have to achieve a remission or cure from his cancer. The Phase I trial was conducted in 12 patients and the published results indicate that liver transaminases must be closely monitored because the drug appears to have potential for hepatotoxicity. However, the FDA has cleared the medication to progress into Phase II clinical trials. The customer says to you, "We know there are risks, but we're willing to accept those risks. There is a cancer doctor here at the hospital that said he would prescribe the medication if it was available. You're a pharmacist, please tell me, doesn't my son have a right to obtain this medication?"

Based on your knowledge of the Abigail Alliance Case [Abigail Alliance v. Von Eschenbach, 495 F.3d 695 D.C. Cir. App. 2007] Which of the choices below would be the best answer to communicate to this customer?

✓A. Unfortunately, the federal court system has ruled that patients do not have a fundamental right to unproven medications. The FDA and the manufacturers are not under any obligation to provide an unapproved medication which may have some limited safety information, but otherwise has no proven effectiveness for the condition. However, your physician may be able to arrange access to the agent directly with the pharmaceutical company.

B. You are fortunate. There is a relatively new court case that specifically compels the FDA to provide unproven medications free of charge to patients who do not qualify for enrollment in a clinical trial

C. As a condition of the FDA granting an investigational new drug license to the manufacturer for conducting clinical research, the manufacturer is required to provide the medication to all those who do not qualify for a formal research Phase II or Phase III trial.



V. Generic Drugs as New Drugs

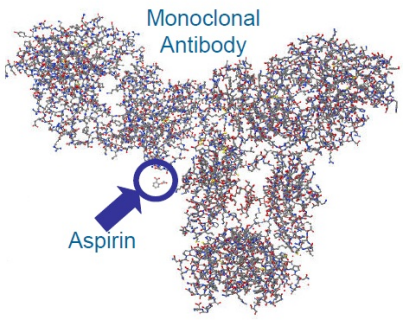
- Patient Treatment with Investigation Drugs
  - Other mechanisms for access to investigational agents
    - Serious / "life-threatening" disease
    - No satisfactory treatment available
    - Ongoing or completed clinical trials
    - Sponsor pursuing FDA approval
    - Sufficient evidence of safety
  - Parallel Track
    - Under mfg protocol for individual patient
    - Compassionate plea use
  - Expedited Approval ("fast-track")
    - FDA may approve early if drug addresses unmet need and intended to treat life-threatening disease

VI. Biologicals

- Biologicals 42 USC 262(j)
  - "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings
  - Licensing previously granted through Public Health Service, now shifting to FDA – CBER

VI. Biologicals

- Biosimilars
  - "Branded" biologics are approved through the submission of a Biological License Application (BLA)
  - But what to do with "generic" biologics … biosimilars
    - Section in Affordable Care Act directs FDA to create an approval pathway for biosimilars
      - Biologics Price Competition and Innovation Act (BPCIA)
    - Risk based "totality of the evidence" standard
    - Analytical evaluation of physical-chemical properties of biosimilar compared to innovator
    - There is much controversy about whether we can be assured of the equivalence between the Biologic and Biosimilar



http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM292463.pdf

VIII. Medical Device Act (1976)

- Medical Device
  - Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, … which is:
    - Recognized in NF or USP
    - Intended for use in diagnosis, or cure, mitigation, treatment, or prevention of disease in man, or other animals, or
    - Intended to affect the structure or any function of the body of man or other animals which does not achieve primary intended purpose through chemical action…

VIII. Medical Device Act (1976)

- Types of Medical Devices
  - Class I
    - Least regulated
      - stethoscopes, toothbrushes
  - Class II
    - Meet specific FDA performance standards
      - Insulin pumps, thermometers, tampons
  - Class III
    - Most regulated; life-supporting
      - Catheters, pacemakers, etc.
      - Pre-market approval required
      - 510(k) application

IX. Cosmetics

- Articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body … for cleansing, beautifying, promoting attractiveness, or altering the appearance
- No premarket approval needed
- Mfg must substantiate safety of product
- Compliance with GMP not necessary
- Still subject to adulteration / misbranding
- If therapeutic claim made, then it's a drug

X. Drug Advertising and Promotion

- Does Commercial Speech enjoy the same rights as regular speech under 1st amendment?
  - Central Hudson Factors 447 US 557 (1980)
    - Commercial Speech can only be limited if:
      - it is not misleading or related to unlawful activity
      - Governmental interest is substantial
      - Limitation directly advances the government interest
      - Limitation is not more extensive than necessary to achieve the interest
  - Factors applied in WLF v. Friedman

X. Drug Advertising and Promotion

- Prescription Drug Advertising: Mfg to Professional
  - "Drug Promotion"
    - Drug is misbranded, unless "**true statement**"
      - Established name of drug
      - Formula, showing each ingredient
      - "Brief Summary" of other info, SE, C/I, Efficacy
    - Advertising must present "**fair balance**" between side effects and effectiveness
  - "Reminder Advertisements"
    - Mentions drug, but not indications or dosage
  - "Help-Seeking" advertisements
    - "see your doctor for ____" ads
  - Sample Ads

X. Drug Advertising and Promotion

- Prescription Drug Advertising: Mfg to Consumer

  "Direct-to-Consumer" ("DTC") ads

  –Educational -
    - no mention of drug name, just manufacturer

  –Product specific
    - Must include summary of risks
    - Can also provide full info through other sources:
      - Toll-free number
      - Internet address
      - Referral to current ad in a printed publication
      - Referral to a health care provider

  –Merck Policy

X. Drug Advertising and Promotion

- Promoting Prescription Drugs for Off-Label Use
  - Federal (and State) laws do not limit off-label prescribing by practitioners
    - Even though not regulated, civil liability may apply to off-label use
  - Food & Drug Admin Modernization Act (FDAMA)
    - "liberalized" off-label advertising to
      - Professionals, PBMs, Insurance, Health Plans, Govt
      - Allowed company to place info in peer-reviewed articles for scientific and medical journals
      - Ads to be followed-up by subsequent application to FDA for new indication

XI. Durham-Humphrey Amendment

- 1951 Amendment to FDCA
- Created two classes of drugs:
  - OTC
    - Safe for use without medical supervision
    - label to give "adequate directions for intended use"
  - Prescription (Legend)
    - Unsafe without medical supervision
    - Prescriber determines which patients to get drug, therefore "adequate information for use"
    - Label must contain "Rx only" legend

XI. Durham-Humphrey Amendment

- Granted FDA authority to categorize drugs as Rx only
  - Subject to New Drug Application process
- Allowed prescriptions to be in written or oral form (amended again to allow electronic prescriptions)
  - If transmitted orally, must be promptly reduced to written form by pharmacist
  - Also provided authority to include refills

XI. Durham-Humphrey Amendment

- Exempts pharmacists from same label requirement as manufacturers
  - Minimum stds for prescription drug label
    - Prescriber's name
    - Name and address of pharmacy
    - Rx number
    - Date of filling or date of prescription
  - If stated on Rx, label must also include:
    - Name of patient
    - Directions for use
    - Cautionary statements

XI. Durham-Humphrey Amendment

- Expiration or Beyond Use Dating (BUD)
  - Usually required by states, FDA does not require
  - USP sets stds for BUD
    - Multi-unit containers, not later than:
      - (a) expiration date on mfg container, or
      - (b) 1 year from dispensing date
    - Non-sterile solid/liquid dosage forms repackaged into containers
      - 1 year from date of repackaging or
      - Expiration date on original bulk package

XI. Durham-Humphrey Amendment

- Professional Practice issues
  - Only Prescriber can authorize refills
    - But communication can be delegated to agent
      - How to determine if prescriber authorized?
  - Prescriptive authority
    - Left to states to determine

XI. Durham-Humphrey Amendment

- OTC Plan B and Conscientious Objection
  - covered in last module – ethics
- Patient Package Inserts (PPIs)
  - Required for:
    - Oral contraceptives
    - Oral postcoital contraceptives (DES)
    - Injectable contraceptives
    - Estrogens
    - Progestational drug products

XIII. Compounding v. Manufacturing

- Pharmacies exempt from mfg regulations, as long as they engage in traditional practice of pharmacy
- Historical context
  - 1992 CPG in response to Court cases examining pharmacy exemptions from mfg registration
  - 1997 FDAMA seeks to exempt "compounding" from "New Drug" regulations
  - 2002 CPG (CPG 460.200) published
  - 2011 US v. Franck's Lab

XIII. Compounding v. Manufacturing

- CPG factors:
  1. Soliciting business to compound specific products
  2. Compounding inordinate amounts that are commercially available
  3. Sources unapproved by FDA or do not meet compendia requirements
  4. Using commercial scale mfg equipment
  5. Compounding qty far in excess of prescription volume
  6. Offering compounded drugs at wholesale or for resale
  7. Distributing compounded products out of state
  8. Failing to operate in conformance with state law
  9. Other factors

XIII. Compounding v. Manufacturing

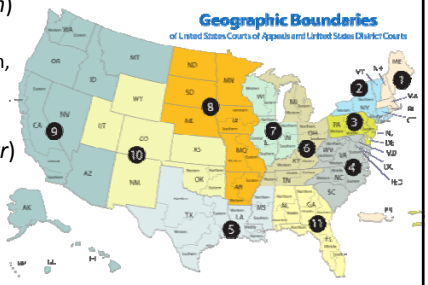
- 1997 FDAMA
  - Section 503 – exemption from NDA
    - Compounding pharmacists given exemption from specific FDCA requirements, as long as they did not "advertise" the compounding practice
      - Adulteration, misbranding, NDA
  - Challenged in courts, based on speech restriction
    - Thompson v. Western States (2002)
    - Medical Center Pharmacy v. Mukasey (2005)
    - Split decision

"Split Decision"

9th Circuit (*Western*)
CA, AZ, NV, OR, WA, ID, MT, AK, HI, Guam, Mariana Islands

5th Circuit (*Med. Ctr*)
TX, LA, MS

Ambiguity in remaining states



Drug Quality and Safety Act (DQSA)

- Signed into law Nov 2013
- In response to numerous compounding failures
  - New England Compounding Center (NECC)
    - Fungal contamination of steroid injections
      - Triamcinolone (preservative-free) for epidural admin
      - 64 deaths / 751 cases, 20 states, 3 lots (about 20,000 doses)
    - Company and executives are being investigated / prosecuted under administrative/civil/criminal law
    - http://www.cdc.gov/hai/outbreaks/meningitis.html

Drug Quality and Safety Act (DQSA)

- DQSA designates two types of "compounders"
  - "Traditional" compounders
    - Independent community pharmacies and other businesses where small-scale compounding is being conducted
  - "Manufacturing" compounders
    - Larger businesses intended as "outsourcing" facilities
    - Enhances registration and inspection reqt's
    - Must comply with GMP

XIV. Orange Book

- FDA Approved Drug Products with Therapeutic Equivalents
  - www.fda.gov/cder/ob/default.htm
  - Rating system for bioequivalence
- Narrow Therapeutic Index (NTI) Drugs
  - Less than two-fold difference between
    - Medial Lethal Dose and Median Effective Dose
    - Minimum Toxic Conc. And Minimum Effective Conc
  - Digoxin, Theophylline, Phenytoin, Lithium, Warfarin, and others

XV. Prescription Drug Marketing Act

- Intent "Drug Pedigree Act"
  - To provide integrity in the drug supply chain
  - To reduce public health risk from adulterated and misbranded drugs
- Limitations
  - Samples limited
    - Prescribers may receive only on written request
    - Pharmacies may not possess samples
- Required detailed records and pedigrees
  - "chain of custody" of medications

XV. Prescription Drug Marketing Act

- Prohibited Reimportation
  - Drugs originally mfg'd in US, but exported, could not be "reimported" from another country
- Directed FDA to develop strategies against counterfeiting of medications
  - RFID, nanotechnology, encryptions
- Substantial penalties for violating act
  - 10 years imprisonment, fines up to $1 million

XVIII. Poison Prevention Packaging Act

- 16 CFR Parts 1700-1702
- Requires household substances to be packaged in child-resistant containers
  - Extends to most drugs (CS, Rx, several OTC)
  - Child-resistant packaging
    - No more than 20% of children are able to open a container within 10 minutes, after being visually shown how to open the container
    - No less than 90% of adults are able to open and reclose a container within 5 minutes, after being visually shown how to open the container
  - exemptions
    - Anti-anginal drugs
    - Selected OTC drugs
    - Express waiver
      - Prescriber or Patient

XVIII. Poison Prevention Packaging Act

Selected substances <u>covered</u> under the PPPA

- Aspirin – any aspirin product for oral use
- Methyl salicylate (>5%)
- Controlled Substances / Rx Drugs
- Na/K OH (≥2%) (10% dry powder)
- Turpentine (≥10%)
- Methyl OH (≥4%) /Ethylene glycol (≥10%)
- Sulfuric acid (≥ 10%)
- Iron-containing products (≥ 250 mg/pkg)
- Acetaminophen (>1 gm/pkg)
- Diphenhydramine (>66 mg base/pkg)
- Ibuprofen (≥1 gm/pkg)
- Loperamide (>0.045 mg/pkg)
- Lidocaine (> 5 mg/pkg)
- Naproxen (≥250 mg/pkg)
- Ketoprofen (≥ 50 mg/pkg)
- Fluoride (>50 mg & 0.5% / pkg)
- Minoxidil (>14 mg/pkg)
- OTC (any agent previously available as Rx drug – oral administration)
- Mouthwash (≥ 3 grams EtOH)

XVIII. Poison Prevention Packaging Act

Selected substances <u>exempted</u> under the PPPA

- OTC product that is subject to PPPA – Mfg can market one (1) product in conventional packaging provided:
  - Packaging has warning statement
  - Not intended for households w/ children
  - Mfg must produce at least one other product with the substance that complies with PPPA
- Nitroglycerin – SL dosage forms
- Isosorbide dinitrate – SL/chew forms (≤ 10 mg)
- EES granules/oral susp (≤ 8 gms/pkg)
- EES tablets (≤16 gm/pkg)
- K supplements (≤ 50 mEq/unit dose)
- Na Fluoride (264 mg/pkg)
- Betamethasone (≤12.6 mg/pkg)
- Mebendazole tabs (≤ 600 mg/pkg)
- Methylprednisolone tab (≤84 mg/pkg)
- Prednisone tab (≤ 105 mg/pkg)
- Cholestyramine powder form
- Colestipol powder (≤ 5 gm/pkg)
- Pancrelipase
- Cyclically administered oral contraceptives in memory-aid packaging
- Hormone Replacement Therapy
  - Progestin or Estrogen based activity

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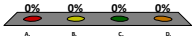
A manufacturer of pharmacy containers submits a new type of container to the Consumer Product Safety Commission (CPSC) for approval under the Poison Prevention Packaging Act. The manufacturer is referring to this revolutionary product as the "Y-tainer" It is blue in color (FOURTH most awesome color, ever!) and is formed in the general shape of the letter "Y." The container is tested in small groups of consumers. One of these groups consists of ten (10) children (all 4 years old), all 10 were able to open the container within 10 minutes after being visually shown how to open the container. Another group consists of ten (10) adults (ages 50-72 years old), eight (8) of whom are able to successfully open and close this container within 5 minutes after being visually shown how to open it. Which of the following choices CORRECTLY describes CPSC's analysis of the "Y-tainer"?

A. Approved for use with Rx medications because 100% of children were able to open and more than 20% of adults were able to open within their allotted time periods

B. Approved for use with Rx medications because 100% of children were able to open and 20% of adults were unable to open within their allotted timer periods

✔ Non-Approved for use because more than 20% of children were able to open during the allotted time period and less than 90% of adults were able to open during the allotted time period

D. Non-Approved for use because of the goofy color and silly shape



XIX. Drug Advertising by Pharmacists

- Previously discussed in relation to compounding
- What about advertising pharmacy drug prices?
- Is this OK?

- *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council*, the U.S.
  - Supreme Court held that the laws prohibiting the advertising prescription drug prices were unconstitutional. The Court noted that the Board of Pharmacy cannot protect "its citizens by keeping them ignorant."

XX. Affordable Care Act

- Main components
  - Expanded access to health insurance coverage
  - Increase Consumer Insurance Protections
  - Emphasize Prevention and Wellness
  - Improve Health Quality and System Performance
  - Promote Health Workforce Development
  - Curb Rising Health Costs

XXI. FDA Safety & Innovation Act

- Eleven Titles
  - Fees relating to Drugs
  - Fees relating to Devices
  - Fees relating to Generic Drugs
  - Fees relating to Biosimilars
  - Pediatric Drugs and Devices
  - Medical Device Regulation
  - **Drug Supply Chain**
  - Antibiotic Incentives
  - Drug Approval and Patient Access
  - **Drug Shortages**
  - Other Provisions

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  - Improve Health Quality and System Performance
  - Promote Health Workforce Development
  - Curb Rising Health Costs

XX. Affordable Care Act

- Expanded access
  - Requires most US citizens/residents to have health insurance
  - Creates state-based health benefit exchanges
- Individual mandate
  - If individual does NOT have qualified coverage, then pay a tax penalty
    - Greater of: $695 (up to $2085) or 2.5% income
    - Phase in, then in 2016 with annual CoL increases
  - Challenged in 2012 – *NFIB v. Sebelius*, 132 S.Ct. 2566
    - SCOTUS ruled constitutional under Congress taxation powers, but not under Commerce clause

XX. Affordable Care Act

- Employer Requirements (mandate)
  - If employer does <u>not</u> offer health coverage, then charged fees:
    - If 50+ employees, $2000/FTE employee
    - First 30 employees excluded from assessment
  - Employers with 200+ employees must automatically enroll employee in health insurance plan offered by employer
    - Employee can "opt out" of coverage

XX. Affordable Care Act

- State Medicaid Expansion
  - Requires states to increase the eligibility of residents upto 138% of poverty level ($15k/$33k)
  - States must do this in order to receive federally matching funds to run state Medicaid program
  - Under 2012 Sup Ct. Case, ruled that States could opt out of ACA provision to expand state Medicaid program, if they could find alternative mechanisms for providing health care benefit up to the 138% poverty level
    - Utah is considering an alternative plan

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  - Other Provisions

XXI. FDA Safety & Innovation Act

- Drug Supply Chain
  - Background: 40% finished drugs imported; 80% APIs foreign sources
  - New rules:
    - FDA given detention authority over imported drugs
    - Higher penalties for adulterated / counterfeit products
    - Enhances manufacturer registration requirements to include UFI
    - Annual reporting of impact of supply chain regulations
- Drug Shortages
  - FDA develop and implement plan to mitigate/prevent drug shortages
  - Numerous shortages are cause significant disruption in health care delivery & threat to public health
  - Enhance communication and transparency between FDA and mfgs
    - Expediting inspections
    - Temporary discretion in FDA to explore alternative sources
    - Work collaboratively with mfgs for root cause analysis of API shortages

Questions

Medicare

- Enacted in 1965
- Title XVIII of Social Security Act
- Provides federal health insurance for:
  - Those 65 years and older
  - Permanent disability
  - End-stage renal disease (ESRD)
  - Exposed to environmental health hazards

Medicare

- Center for Medicare & Medicaid Services (CMS)
  - www.cms.gov
- Four Components to Medicare
  - Part A Hospitalization insurance – no premium
  - Part B Optional plan for Outpatient medical services
    - Diagnostic services – x-rays, lab tests
    - Physical and speech therapy
    - Colostomy supplies
    - Small number of outpatient drugs, that cannot be self-administered
    - DME, certain vaccines, diabetic supplies
  - Part C Combination of A&B in a managed care plan
  - Part D Prescription Drug Benefit

Medicare

- Part D Prescription Drug Benefit
  - 2003 – Medicare Modernization Act (MMA)
    - Partial implementation
  - 2006 – Deficit Reduction Act (DRA)
    - Full implementation
  - Enrollment period
    - Beginning 3 months prior to month turning 65, extending 3 months after month of turning 65.
    - If don't enroll within this window, then late fees
      - 1% per month
    - Open enrollment period each year to move from one plan to another
      - Usually during Fall

Medicare

- Part D Beneficiary Cost
  - Premiums determined by plan
    - Range $15-$132/month, average $30/month
  - Three phases:
    - I: Annual deductible of $325 + 25% co-insurance, from $325 to $2970
    - II: Doughnut hole: $2970 to $6733.75
    - III: Catastrophic coverage 5% co-pay or $2.65 generic or $6.60 brand
  - Under ACA, doughnut hole will be gradually reduced

Medicare

- Covered drugs and plan formularies
  - Covers Rx drugs for medically accepted indications and also biologics, insulin and medical supplies for insulin admin
  - Excluded drugs
    - Weight loss / weight gain drugs
    - Fertility drugs
    - Erectile dysfunction drugs
    - Cosmetic or hair growth drugs
    - Cough and cold drugs used to treat symptoms
    - Vitamins and minerals
    - Outpatient drugs which mfg requires testing or monitoring

Medicare

- Covered drugs and formularies
  - Plans may use drug formularies that include drug tiers
    - Formulary must include all therapeutic categories and classes of drugs determined by USP
    - Formulary needs to include 2 agents from each class
    - Exceptions (all drugs in class must be covered)
      - Antidepressants
      - Antipsychotics
      - Anticonvulsants
      - Antiretrovirals
      - Antineoplastics
      - immunosuppressants

Medicare

- Part D Pharmacy Access
  - Plans must ensure that beneficiaries have access to network of pharmacies
    - Urban – within 2 miles of participating pharmacy
    - Suburban – within 5 miles partic. pharmacy
    - Rural – within 15 miles partic. Pharmacy
  - Previously 90DS only through mail order, however community rx may now disp 90 DS
  - "Any willing provider" law
    - Plan must accept any pharmacy that meets criteria

Medicare

- Part D Pharmacy Reimbursement
  - Reimbursement to pharmacies is set by the Part D plan, not by CMS
  - Dispensing fees are negotiated between plan and networked pharmacies
  - Plans must transmit reimbursement to pharmacies within 14 days of electronic claims and within 30 days for non-electronic claims
  - Plans must update drug cost database weekly

Medicare

- Part D notice for claims not covered
  - Plan must transmit instructions to the pharmacy to provide to the beneficiary for each claim not covered
  - Notice must also instruct beneficiary how to request a coverage determination

Medicare

- Part D Medication Therapy Management
  - Plans required to provide coverage for MTM
  - Pharmacists can receive fees for MTM services
    - Patients with multiple chronic diseases & mult. Rx
    - Patients will likely exceed annual drug costs
    - Idea is for pharmacist to assure covered drugs are appropriately used, optimize outcomes, reduce adverse events
    - Provides for annual drug reviews and face-to-face consultations with pharmacist

Medicare

- DME – Durable Medical Equipment
  - Canes, walkers, wheelchairs, beds, etc.
  - Area that is widely prone to fraud & abuse
  - Providers must achieve DMEPOS credential and be accredited by an independent org
    - DMEPOS – DME, Prosthetics, Orthotics, Supplies
  - Many DMEPOS items may not be covered by Medicare
    - Must give Pt. Advance Beneficiary Notice (ABN)
      - https://www.noridianmedicare.com/dme/forms/advance_beneficiary_notice_of_noncoverage_forms.html

Medicaid

- Title XIX of Social Security Act
- Provides for health care of certain indigents
  - Blind
  - Disabled
  - Aged
  - Members of families with dependent children
- Eligibility determined by income & assets
- Some patients are dual eligible under Medicare Part D & Medicaid
  - Reimbursement is by Part D

Medicaid

- Medicare funds about 90% of Medicaid program for each state
  - Each state must have a comprehensive plan on file with Medicare that determines how the federal funds will be administered and used
- Medicaid provides prescription drug coverage as an optional service
  - In 1975 the MAC program was established
    - Maximum allowable cost
    - Multi-source drugs have a FUL assigned to them
      - "Federal Upper Limit

Medicaid

- Reimbursement for Multi-source drugs
  - FUL reimbursement scheme was devised in response to pharmacist complaints about MAC
    - Some of the reimbursement prices were so low that pharmacies could not even purchase the drugs for the reimbursement
    - FUL drugs reimbursement costs are 150% of published price AWP
    - Many rounds of litigation over these prices
    - Right now looking at 175% of AMP

Medicaid

- Tamper Resistant Prescription Pads
  - 2007 – US Troop Readiness, Veterans' Care, Katrina Recovery and Iraq Accountability Appropriations Act
    - Also included provision that written Rxs must be on a tamper resistant pad
    - Tamper resistant pad to prevent:
      - Unauthorized copying of a completed or blank pad
      - Erasure or modification of information written on the bad
      - Use of counterfeit rx pads
    - Emergency fills permitted, as long as provider submits Rx w/in 72 hours

Fed Reg of Long Term Care

- Trend toward long-term care in US
- LTCF – Long-Term Care Facilities
  - "nursing homes"
  - SNF – skilled nursing facility
  - ICF – intermediate nursing facility

Fed Reg of Long-Term Care

- Self-administration
  - For each LTCF resident a comprehensive care plan must be developed
    - Individual residents may self-administer meds if plan has determined this is safe
    - Plan must identify medication storage location
  - Unnecessary drugs
    - Excessive dose or duration
    - Inadequate monitoring
    - Inadequate indications
    - Adverse consequences

Fed Reg of Long-Term Care

- Fourteen day supply (DS) dispensing cycle
  - ACA mandates CMS to regulate on dispensing strategies for LTCF to reduce waste
  - Beginning Jan 2013, LTCF residents are dispensed no more than 14 DS at a time
    - exceptions
      - Antimicrobials
      - Agents required to be dispensed in original mfg package
      - Agents with packaging that improves compliance

Fed Reg of Long-Term Care

- LTCF must provide pharmaceutical services
  - Can be employed staff member or consultant contractor
    - Pharmacy services to be in a timely manner
  - Consultant pharmacist to keep pharmacy records on all LTCF patients
  - Drug Regimen Review for each LTCF resident at least once per month
    - Any irregularities reported to MD and DoN
    - Report must be acted upon

Federal Antitrust Laws

- Business competition in health care is vicious
  - Mfg, wholesalers, insurance plans, hospitals, pharmacies, prescribers
- Two federal laws help to ensure a "fairer" business environment
  - Sherman Antitrust Act
  - Robinson-Patman Act

Sherman Antitrust Act

- Passed in 1890
- Makes unlawful every contract, combination or conspiracy that restrains trade
  - Protects competition, not competitors
  - Thus, facilitates a competitive market, but does nothing for a business failing under intense competition
- Concerted activity
  - Must have agreement between 2 or more competitors to restrain trade
    - Each competitor could independently restrain and that is ok. Just not concerted.
- Market power
  - Investigations must analyze the market power of the alleged violator

Sherman Antitrust Act

- Mergers are closely analyzed under Sherman Act
  - Especially pharmaceutical companies and other health care entities that consolidation may lead to monopolistic powers
- Tying arrangements are also analyzed
  - Eg certain drugs are only shipped to pharmacy that can monitor blood pressure
    - This is a "tying" arrangement and was considered a restraint of trade

Robinson-Patman Act

- Passed in 1936
- Unlawful for sellers to discriminate price between multiple purchasers unless costs can be justified
  - "volume purchases"
- Common in pharmaceutical purchases were there is differential pricing
  - Manufacturers and wholesalers must have reasonable basis for the differentials

Omnibus Budget Recon. Act (OBRA) 1990

- Prior to this most federal laws were about pharmacy products and not about pharmacist services
- Primary goal of OBRA 90 was to save money and health care was a major expense
  - Depends on pharmacists to help save $
- Three major areas
  - Rebates
  - Demonstration Projects
  - DUR

OBRA 90

- Rebates
  - Requires mfgs to provide pharmaceuticals to state Medicaid programs at their "best price"
  - The mfg must pay a rebate back to Medicaid that compensates them for what they were billed by the pharmacy upon the dispensing of the medication
  - Medicaid pays the higher amount at point of care, but then is reimbursed by the mfg

OBRA 90

- Demonstration Projects
  - Goal: to determine through scientific means whether the outcomes of patient care improve and costs decrease when pharmacists are paid to provide DUR
  - Demonstration projects are accomplished in many different ways
    - Computerized records
    - Consultations

OBRA 90

- Drug Use Review
  - Focused on health care outcomes
  - Three parts
    - Retrospective DUR
    - Educational Programs
    - Prospective DUR
  - Big purpose is continuous quality improvement

OBRA 90

- Retrospective Review
  - Medicaid programs to have DUR board
    - Pharmacists and physicians
    - Reviews data collected by Medicaid claims databases
    - Looks for trends
    - If areas need improvement, then recommends educational programs

OBRA 90

- Educational Programs
  - Can be face-to-face (peer-to-peer) about certain professional habits
  - Can be in a group, symposium format
  - Goal is to improve the way the medications are being used

OBRA 90

- Prospective Review
  - Try to capture trends right at point of dispensing and initiate best practices to avoid future problems
  - Components
    - Screen prescription prior to dispensing
    - Patient counseling
    - Documentation of relevant information

OBRA 90

- Counseling standards
  - "offer to discuss" with each patient
    - Name & description of medication
    - Dosage, form, route, duration
    - Specific directions for use
    - Common severe side effects, interactions, contraindications and ways to prevent them,
    - Techniques for self-monitoring
    - Proper storage
    - Prescription refill information
    - Action in the event of a missed dose
  - Patients can "waive" counseling