

# FOOD AND DRUG LAW/EPSTEIN

## Contents

I. JURISDICTION .....	2
FDA Origins & Functions .....	2
Food & Drug Act of 1938: Gave three powers: .....	2
II. CONGRESSIONAL OVERSIGHT .....	4
Non-Delegation Doctrine .....	4
III. DOMAIN: Inside the Agency .....	6
DRUGS .....	6
New Drugs .....	7
DIETARY SUPPLEMENTS .....	8
MEDICAL DEVICES .....	9
ADULTERATION & MISBRANDING .....	10
IV. DRUG APPROVAL PROCESS .....	12
CLINICAL TRIALS .....	12
Pre-market Approval .....	12
PDUFA: Prescription Drug User Fee Act .....	13
Early Access .....	13
OFF-LABEL USE .....	14
GENERIC DRUGS .....	15
EXCLUSIVITY .....	16
V. POST-APPROVAL .....	17
POST-MARKET SURVEILLANCE .....	17
PREEMPTION .....	19
Concurrent Jurisdiction/Administrative Preemption .....	19
Statutory Preemption .....	19

## I. JURISDICTION

**Crowell v. Benson:** An agency receives deference when determining their own jurisdiction

### FDA Origins & Functions

1962: Amendments to strengthen and broaden existing laws (FDCA)

**Commerce Clause** – the jurisdiction of the FDA

Art. I § 8 (powers delegated to Congress): “the Congress shall have power to regulate Commerce with foreign nations, among the several states and with the Indian Tribes”

**Gibbons v. Ogden** (1824): The NY State Legislature granted Ogden\* exclusive navigation of the waters within the State. Gibbons, who was operating a competing service had been licensed by Congress. The Court found that federal licensing power preempted the state monopoly.

- However, the inspection of ships remained within the state police power

//If they hadn't left this up to the states, slavery could have been stopped by the federal gov't

**Brown v. Maryland** (1827) “**The original package doctrine**”: merchandise brought into the state in the original form or package in which it was imported was under federal jurisdiction. It had not “arrived” until they were delivered into the hands of the consignee and the package was broken.

**E.C. Knight** (1895): “the Sugar Trust Case” – the 1890 Sherman Antitrust Act attempted to curb concentrations to economic power – could the SAA suppress a monopoly in manufacturing, not merely its distribution. The Court held that it was not within the power of Congress to regulate.

**Champion v. Ames** (1903): Statute made it illegal to sell lottery tickets in interstate commerce (regardless of their legality within the state from whence they came). The Court upheld the conviction, and stated that it was within the **plenary** power of Congress to create the regulation.

- The dissent argued that this infringed on the states' police power

**1906: The Pure Food & Drug Act** //upheld by the Supreme Court

- Addressed issues of drug purity, passed in response to the *The Jungle*
- To prevent within the constitutional power...the manufacture/sale/transportation of goods/drugs that are so adulterated, or are poisonous, or are misbranded
  - Was limited to the District of Columbia *or* any territory
  - Could only seize products within the original, unbroken package

The typical police power of the state (that was curtailed by the Positive Commerce Clause): to regulate “health, safety, morals & general welfare”

**Hammer v. Dagenhart** (1918): Statute prohibited the shipment of goods that were made in a plant that used child labor, which the Court struck down as unconstitutional. Overruled in *Darby*.

- But how can the decision in *Champion* be squared with this decision?

Before the new act was written: there was an issue with a sulfonamide drug, which was very effective and was difficult to formulate. It used ethylene glycol (antifreeze) which caused many deaths

- The only part of the 1906 Act that it violated was that the “elixir” must contain alcohol
- This set the stage for expanding FDA authority

**Food & Drug Act of 1938:** Gave three powers:

1. On the record rulemaking: § 701(e) gives this power

§ 701(a) gives FDA authority to issue rules for “efficient enforcement of the Act”

2. Notice and comment rulemaking, also § 706 of the APA: expanded the preambles
  - a. The preambles of Acts are binding advisory opinions on the FDA
3. Interpretive rule

//before the FDA used seizure/enforcement actions which were not very effective:

- A. No predictability

B. Not efficient: the same company can keep shipping different batches of the *same* product  
 The regulation of drugs is dependent on the constitutional framework: the statute itself actually changes less than the underlying Constitutional Interpretation

1. With a liberal construction of FDA power there is tension between the Federal and State concurrent jurisdiction
2. There is a presumption in favor of expanded regulatory authority

Views of regulation	
<i>Ex post</i> : warranty – you know that whatever comes out is safe (regulate outputs)	<i>Ex ante</i> : You cannot have a regulation that <i>only</i> regulates inputs

- The FDA regulates more than just outputs: hiring practices, etc. Is this useful?

**Adulterated & Misbranded: US v. 40 Cases, More or Less** (2d Cir. 1961): The cans of oil sold were labeled “25 % olive oil” but actually contained little or no olive oil – therefore, the oil was adulterated ( § 402(b)(2)) and misbranded ( § 403(a))

- Can you regulate the vegetable oils mixed *entirely* in New York State? The Court held **yes**: it was originally carried across state lines and there should be a broad reading of the statute
- The remedy here was through the seizure system

//Prof. Epstein thinks that this was an incorrect interpretation

- There were the same issues with the Civil Rights Act (*Ollie’s BBQ*)

**Retkwa v. Orentreich** (N.Y.S. Sup. Ct. 1991): Defendant argued that the nonmedical grade silicone shipped from Dow Chemical was not an adulterated device when shipped interstate, and therefore, no contact with interstate commerce.

- Does not need to be adulterated when it leaves sender’s hand nor intent on sender’s part
- Sufficient if the device is held for sale **after** interstate commerce and *then* was adulterated
  - Different if physicians are using **approved** drugs for **unapproved uses** (rather than unapproved drugs for unapproved uses)

**1962 Kefauver-Harris Amendments**: Added clinical trials and PMA

- Before that, FDA had 60 days to challenge and 180 days to make decision re: new product
- Prompted by Thalidomide disaster

**1976 Medical Device Amendments**

§ 360k Preempted state requirements

**Dormant Commerce Clause**: limiting state power by national concerns, this doctrine comes up with Congress has been silent

- Original concern was about the race to the bottom from competition among the states
- But as seen in the *Washington Apple* case: there is really a **race to the top**

**Gibbons II**: Finds that there is no concurrent power with the Commerce Clause

**1937** (*Jones v. Laughlin; Wickard*) → **1938**: Allows the FDA to regulate everything: this is repudiation of the *E.C. Knight Case*

## II. CONGRESSIONAL OVERSIGHT

1. The FDA has a lot of fear of Congress
2. FDA has difficulty correcting its own judgments
3. There are issues with who ends up on advisory committees

### Non-Delegation Doctrine

*In favor of the broad interpretation:* **Hutt:** Congress chose to express the mandate in broad and general terms. Therefore, the Act should be regarded as a constitution – it establishes fundamental obj.

- If we interpreted it specifically, we would need to change the law when necessary
- The Congress in 1938 did not want the FDA to be bound to one way of doing things for many industries and wrote the statute broadly

Everything that is not expressly forbidden is permitted

*Against:* **Austern:** Argues that Hutt's paper should have been titled "How to rewrite an act of Congress without really trying"

- An agency should only enforce what Congress delegates to it
- *Schechter Poultry/J. Cardozo:* This is delegation running riot
- There should be more limitations of FDA power because there can be criminal sanctions

There are restrictions – GMPs are more than is permitted by delegation: You must have statutory authority

### Policy Issues: An Ideal System of Delegation

Whatever balance was struck, you should keep the same balance in the administrative agency

- But there is often drift within the agency: does this make them lawless?
- 1935: the Court struck down statutes under non-delegation, but since then, has been treated as a political matter rather than a judicial matter

### Good Manufacturing Practices

**Nat'l Association of Pharma Mfrs v. FDA** (2d Cir, 1981): In the amendments, there was a section that a drug was adulterated if its packaging/processing/holding fail to conform to current "good manufacturing practice". The court found that § 701(a) of the act and § 4 under the Administrative Procedure Act allowed rulemaking under this provision

- § 701(a) covered notice-and-comment rulemaking procedures: used guidance's rather than full rulemaking provisions to save time
- § 701(e) required a hearing as part of the binding regulatory procedure

**Can the FDA regulate good manufacturing practices?** Where do they get the power to regulate? § 701 says that there is "enforcement" – strictly speaking, GMPs are not enforcement

- But the Hutt view prevails: the FDA can displace custom

**US v. Bioclinical Systems** (D.Md. 1987): The FDA inspected the facility and found 29 violations of the GMPs, and brought an action to enjoin violations by Bioclinical

- The court found that the FDA had bypassed proper procedural requirements and had been imposing the SAL as a *de facto* requirement: you cannot enforce a draft guidance

The FDA had not gone through the proper process to enact the regulation:

- The process required was expensive
- And there was different custom followed in the industry without problems: what do you do when this happens?
  - You can use consumer testimony (not helpful)
  - Experts on safety: you would want to call people who *used to* work at the FDA

- Likely: the cost of the change on the industry is much more than the benefit
  - Typically, you are interested in balancing the marginal safety and the marginal cost

### Policy Issues

The judicial system is very deferential to the FDA. But the FDA lives in fear of Congress – Congress often criticizes the FDA for causing injuries, but not for failing to approve drugs

- See Frances Kelsey: who kept Thalidomide off the market
- But AIDS changed everything
  - Cancer is a similar dynamic: there is a first in line treatment that often fails and as treatments go on, they become more toxic

Before the B-S valve, most people used pig valves, which lasted for 10 years, 5% deaths/year.

- B-S valves have ~ 1% survival rate
- Epstein: did more people die from the breakages than from the removal from market? Likely not.
  - But if you make this kind of cost-benefit analysis you have the *Pinto* case (punitive)

**Bjork Shiley Valve:** this is a mechanical heart valve that is used to replace aortic or mitral valves

- Consists of a design that had a tendency to develop fractures that resulted in valve failure
  - There were also class actions from anxiety re: future valve breakage
- Taken off the market in 1986
  - FDA refused to let them on the market even after the valve was fixed

No heart valves are risk free (and it is difficult to test them)

1. The valves may collapse
2. There is a risk of insufficient blood getting through
3. Poisons from the valve may leech into the system

### Policy Issues

- Businesses don't like being subject to 50 different safety regulations (if there are different ones for each state) → this supports the creation of federal regulations
  - Uniform state law movement – e.g. creation of the U.C.C.
  - Federal floor + additional regulations by states? “Race to the top”?

#### Costs of Regulatory Framework:

1. Limits freedom of choice because citizens cannot obtain products not approved by the FDA
2. Impacts small businesses who cannot afford PMA – leading to *in-licensing*
3. No mechanism for public accountability: (i) no citizen participation and (ii) Court cannot compel drug approval
4. Deters manufacturers from seeking judicial remedies for fear of retaliation
  - a. There are no real judicial remedies: the FDA can always delay
  - b. Exposes company to seizure, threat of lost sales and protracted litigation
  - c. Concern of pending/new applications

**Unconstitutional Conditions Doctrine:** If you can approve or disapprove, you can affect how the deal ends up procedurally – once you have monopoly power, the situation transforms

- A regulation requires a nexus between the state interest and the condition
- Nature and extent of the condition are roughly proportional to the extent of the harm
  - FDA is like requiring resolution of all divorces in MA in exchange for driving

### III. DOMAIN: Inside the Agency

*Chevron*: (1) Has Congress spoken on the issue? (2) If not, is the agency action a permissible interpretation of the statute?

FDA Conflict of Interest regulations – these are guidances.

- You want to have the best experts within the FDA
  - The FDA, Merck, Lilly etc all want the same people
  - There aren't many "best" experts in the field
- We don't want *anyone* to use the second class experts
- You handle conflicts through disclosure/management

The extensive disclosure requirements with the FDA may end up causing the best people to avoid consulting with the FDA – can use waiver (§ 712(c)(2))

**What can the FDA regulate?** Can depend on how you make claims:

- The FDA looks at **objective intent**: what do the materials show
    - A manufacturer could determine classification of its product by choosing claims
    - But certain products have *only* a drug purpose: look at the active ingredient
    - Did not regulate Wonderbread (despite claims), but did try to regulate cosmetics
1. Drugs: typically covered under composition of matter patents
  2. Devices
  3. Combination Products: based on **primary mode of action** § 353(g); comparable products must be classified in similar ways, *Bracco Diagnostics*
  4. Dietary Supplements
  5. Food
  6. Cosmetics: have sustained FDA enforcement actions here when accompanied by **claims** that they affect the structure of function of the body

**Why can't you get FDA approval for marijuana?** Each product is a little bit different – processing is how you create uniformity

- There are too many chemicals inside and they don't have the ability to approve *all* of them
- Biologics: much more difficult to regulate

**Why are there more regulations for drugs than for food?** There are informational problems: (1) Does it work?; (2) Does it make you sick?

### DRUGS

§ 201(g)(1): the term "drug" means articles recognizes in the official US Pharmacopeia etc, (B) Articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals...

- A chemically inert substance can qualify depending on the claims: a bottle of water that is a cure for cancer (drug), as a sterilizing agent for tools (device), *Bradley v. United States*
- Intention can be **inferred from the totality of the circumstances surrounding the sale**

**Cholestin** (red yeast rice case): The dietary supplement had the same active ingredient as a drug

- The brand name reported them to the FDA (*Pharmanex v. Shalala*)

**Could the brand name have sued them?** While you probably do have standing – competitive harm, probably don't have a private cause of action for a statutory duty

(C) Articles, other than food, intended to affect the structure or any function of the body of man or other animals (targeted at weight loss drugs, *American Health Prods. v. Hayes*)

- *Squibb v. Bowen*: the structure of function definition is relatively narrow and not intended to encompass all articles that might have some remote physical effect on the body



**Bacto-Unidisk** (1969): Case arose in an *in rem* seizure proceeding against interstate shipments

- Argued that they were misbranded under § 502
- At the time, no premarket clearance requirements for devices, regulated **as a drug**

**Main question:** is the sensitivity disk (for use of antibiotics) a drug or a device? The court held that it was a drug because the definition of drug was intended to have broad coverage – because of the ambiguity, gives deference because of the mission to protect public health

- Because the disc helps select the correct drug: the FDA can regulate the discs as drugs

**Ova II** (D.N.J. 1975): This is a pregnancy test. Similarly, there was an *in rem* seizure action.

- Since pregnancy is not a disease, this is not for the “diagnosis of disease” – later amended to include “conditions” (pregnancy is a condition)
- The court found that the FDA could not regulate these pregnancy test

### New Drugs

What kind of evidence is needed for a New Drug Application?

- OTC monographs: not marketed under NDA (Tylenol, etc)
- Safety & effectiveness: not a scientific judgment but a political judgment
  - In real like, these cannot have absolute meanings (*Ova II*)

Old drugs: drugs/devices that were introduced before May 28, 1976 (or are SE)

- Are there papers available from investigators competent in the field?

New drugs: any drug that is not GRASE (generally recognized as safe and effective): historically safe and effective, substantial evidence is not construed as it is elsewhere (*Universal Camera*)

- GRASE exception has been construed narrowly (§ 321(p)(1))
- Not designed to allow generic copies of previously approved drugs to enter market
- Claimant bears the burden of proving that drug is GRASE
  - Unless you have a old clinical trial running around, not useful

A new drug that is not properly approved: is adulterated or misbranded, *see Baxter Healthcare* (does new packaging make something a new drug?)

**50 Boxes** (1st Cir. 1990): the government has seized fifty boxes of a prescription drug Cafegot, which contains four ingredients: (a) two stop headaches; (b) the others stop side effects from the first ingredients. These ingredients had already been used in old drugs.

- The district court concluded that this was a new drug and “substantial evidence” has not been presented for its approval: the First Circuit affirmed.
- Evidence of “well-controlled” investigations: not really an exception at all

The fixed proportions here have several effects:

1. Limits medical judgments
  - a. The art of medicine is about choosing this correct dosage
  - b. But the FDA doesn’t take this into account
2. Standard formulation: likely helps most people and has easier use
3. Rigid: might be less responsive for others: but you already had the option of taking four different pills

## DIETARY SUPPLEMENTS

There is no premarket clearance for food – you can only regulate post-market

Concerns with Dietary Supplements: (1) Claims were not tested; (2) Serious adverse effects

“A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance..., (F) a concentrate...of any of the above” § 321(ff)(1)

**1994 DSHEA Act** provides that a dietary supplement is adulterated if it presents a “significant or unreasonable risk of illness or injury” under the conditions of use recommended in the label

Regulated them more stringently than food, but less stringently than drugs

- If you make *no* claims: like a food – *see, e.g.* Green Tea
- Concerns that don’t occur with naturally occurring substances:
  - Adulteration
  - High concentration (dosage): you must dosage limitations on dietary supplements

**Health claims** (§§ 321(g)(1)(D), 343(r)) – DSHEA provides a safe harbor, dietary supplements are deemed to be a food, *Whitaker*

1. Statements asserting a benefit related to a classical nutrient deficiency disease
2. Statements known as structure/function claims: describe the role of a nutrient or dietary ingredient intended to affect the structure/function and characterize a documented mechanism for which the nutrient acts to maintain such structure or function
3. Declarations of general well-being

Must contain an accompanying disclaimer “This product is not intended to diagnose...”

**Police Power:** to regulate health, safety, morals, & general welfare

**Whitaker v. Thompson** (D.C. Cir. 2004): Whitaker sought instruction that saw palmetto may improve voiding urgency associated with mild prostatic hyperplasia. The FDA denied the petition.

1. Health Claims: are those that pertain to the **prevention** of disease
2. Drug Claims: regarding the **treatment** of disease – thought this was a disease claim
  - a. Greater regulation is needed for the treatment of diseased populations

**Lane Labs** (D.N.J. 2004): Lane Labs sells products directly to consumers – “Benefin”

- A doctor who is on the Lane Labs payroll promotes these products: therefore, anything that he says can be imputed to Lane Labs
- Intended use: judged by the objective intent of the persons legally responsible for labeling

**Commercial Speech:** If it is connected to the company – only protected when (1) product is legal and (2) ad is true. If the guy is not connected to the company, much more protected.

- Here, there is a countervailing governmental right: health and safety (*Lochner*)
- Since the manufacturer (1) knows the most and (2) has the most bias, they have the most regulation. But promotions matter a great deal for drug companies (25-30% spending).

**Torts:** if you cannot do it with an employee, you cannot get an independent contractor to do it

**DSHEA:** § 342(f)(1)(A) “**significant**”: means high risk (no benefit analysis here) // threshold

- Risk significance doesn’t affect something like “safe and effective” – e.g. cancer drugs
- In *Nutraceutical*: Is there really “significant risk” at 9 mg?

“**unreasonable**”: this is a relative risk – government almost always prevails under this framework

**Nutraceutical v. Crawford** (D. Utah 2005): FDA made a final rule in 2004 that determined that EDS (ephedrine) is adulterated and not legally marketable in the United States; that the benefits of ephedrine do not improve long-term health and increases risks of heart attacks, etc.

- Plaintiffs brought Declaratory judgment action to say that this rule violates DSHEA



- The court agreed with plaintiffs: the requirement that EDS demonstrate a benefit – the FDA’s risk-benefit analysis places a burden on EDS manufacturer against Congressional intent (and the burden of proof is placed on the government to show adulteration)

**Nutraceutical v. Von Eschenbach** (10th Cir. 2006): Found that FDA correctly followed the congressional directive to analyze the risks and benefits of EDS

- The burden is on the agency to show that risks associated outweigh benefits and are therefore unreasonable (*after* marketing), does not undermine congressional intent

//Kuhlik: judges cannot really operate in this area without some degree of deference

## MEDICAL DEVICES

Two purposes:

1. To regulate products that actually prevent disease – “intended for use in the diagnosis of disease or other conditions...”
2. To regulate products that falsely claim to prevent disease

**§ 321(h)**: an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article:

1. Recognized in National Formulary/Pharmacopeia
2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals
3. Intended to affect the structure or any function of the body of man or other animals

### **Is it a drug or a device?**

What is the difference between drugs and devices? Drugs work via chemical reaction and devices work via a mechanical action – but does this distinction only matter *inside* the body?

**Alabama Tissue** (7th Cir. 1992): Heart valve processors filed a petition for review contesting the final rule by the FDA stating that replacement heart valve allografts are “devices”

- Generally: once you process something, it becomes “New” – you are no longer in the practice of medicine, you are within the FDA jurisdiction
- The FDA regulates the processing of blood: it doesn’t matter if it is “organic” [36]

The court held that the FDA was able to regulate the heart valve allografts as implants.

- But another court found procedural issues with this: and the FDA withdrew notice

**US v. Bowen** (9th Cir. 1999): Defendant repairs the Sterisafe hand sterilizer and manufactures the SteriDot High Purity Ampule, which is used with the Sterisafe. Defendant argues that these are not devices. The FDA concluded that this falls within “an instrument which is intended for use in the mitigation or prevention of disease in man”

- Inspection issue rather than effectiveness issue: here, the only thing that you need is that it is sterile: could use (1) *ex post* standards of inspection; (2) good manufacturing standards

**US v. Undetermined Number of Cases** (10th Cir. 1994): CRL tests containers for HIV antibodies

- CRL contends that the specimen containers do not qualify as devices
  - FDA contends that AIDS tests that do not use blood products or serum violate the Act, and the specimen containers themselves must obtain premarket approval
  - There must be a standard protocol: chain of control is very important
- Reusable bottles: can lead to false positive
- Diagnosis includes inconclusive diagnosis: incentives of accuracy

### **Classification within devices**

1. Class I: general controls, labeling requirements, good manufacturing practices: band-aids
2. Class II: 510(k) – substantially equivalent to previously approved drugs

- a. Reasonable assurance that it is safe and effective
- b. Heart valves?
- 3. Class III: PMA – “safe and effective”, many go through 510(k) (substantially equivalent)
  - If something has no safety risks and is not effective at all: most probably people will not buy

**General Exceptions:** (a) those products that are grandfathered in – you don’t want to take off all the devices from the market (but do you only grandfather in the ’76 version?) (b) Substantial Equivalence

**Lake v. FDA** (E.D. Pa. 1989): Lake invented a nose clip, and tried to get FDA approval to market the “Investigational New Drug” (IND) – FDA refused to approve it for colds/allergies and initially classified it as a Class III device (no effectiveness, no risk)

- The safety hazard is not from the device, but from the fact that you won’t get real treatment
  - Here, the FDA is really concerned with economic issues rather than therapeutic uses
- 1. Fraud claims
- 2. Consumer protection statutes

**Snoring Relief** (9th Cir. 2000): Sold a self-fitting, anti-snoring mouthpiece without prescription

- FDA found that it violated the FDCA without filing a PMA or 510(k)
  - Denied request to market SnorBan over the counter

Dangers: could block the passage or change mouth configurations

- Cannot use substantial equivalence analysis and then avoid any regulation *at all*
- No credible non-therapeutic uses: different from the dietary supplements cases where you can make health claims, like the *Squibb* case with the fungicide

**Contact Lens** (D.C. Cir. 1985): Hard contact (PMMA) lenses blocks air from your eyes and dries them out. You must use eyedrops/cannot sleep with them. Compare, RGP lenses which have the superior visual acuity from the hard lens, and the direct transmission of oxygen

- FDA wanted to regulate them as a Class III product
- CL petitioned FDA to reclassify them from Class III to Class II
  - Class II has a lower cost of entry, Class III companies don’t want generics to piggy-back on their PMA data

Court gave deference to the FDA decision to not reclassify the lens

**Ethicon** (D.D.C. 1991): Ethicon manufactures absorbable surgical sutures

- US Surgical Corporation petitioned FDA to reclassify the generic class of sutures to Class II (from Class III), the FDA agreed

Court gave deference to the FDA decision to reclassify the sutures.

### **ADULTERATION & MISBRANDING**

§ 501(a): a drug/device is adulterated if it consists in whole/part of any filthy, putrid, decomposed substance or may have been prepared in unsanitary conditions

§ 502: an item is misbranded if the labeling is false or misleading (if it doesn’t work, misbranded)

- If something is contaminated with bacteria – this is adulterated, if the product is also labeled as sterile, it is therefore also misbranded
- § 301(k) is the actual misbranding provision

**Acu-Dot** (N.D. Ohio, 1980): An acu-dot is a magnet attached to an adhesive patch and claims temporary relief of occasional minor aches. FDA claims that the item is “misbranded”. S

- Here, there *has* been a double-blind study showing that it works, and it is popular in Japan
- But Acu-Dot manufacturers suggested that it was a placebo effect:
  - Since the drug doesn’t actually work: it is misbranded and subject to seizure

**Evers** (5th Cir. 1981): Evers is owner and operator of the Ra-Mar Clinic which uses chelation therapy to treat clogged arteries. The government charged Dr. Evers with the misbranding of the chelating drug (Calcium EDTA)

- District court found that no misbranding could come from doctor's prescription of a lawful drug to his own patients: if Evers had owned a patent or owned the company – more like *Lane Labs* case, there would be no independence

1. Dr. Evers never held Calcium EDTA for sale after shipment in interstate commerce

§ 502(f)(1): in order to qualify for the prescription exception, must meet full disclosure requirements

§ 503(b)(2): also has many exceptions – the purpose of this scheme is to ensure that adequate information is provided to a licensed physician

- Evers' booklets do *not* contain sufficient information: but they are not for physicians – they are for patients who obtained the drug from him. District court is affirmed.

#### Policy Issues

1. A criminal prosecution is not the best way for the FDA to make new regulations – if the FDA wanted deference here, unlikely, because fairness issues are in favor of the defendant
2. Why not use a *seizure* action: probably because the US marshalls would come in with guns to seize the EDTA
3. Could use a civil injunction action

**Baxter Healthcare** (7th Cir. 1990): Baxter created freeze-dried form of drugs – most hospitals prepare their own drugs, but the Baxter program allows them to use larger scales

- The district court granted the FDA's preliminary injunction prohibiting Baxter from producing ready-to-use antibiotics products
- FDA claims that Baxter must apply for separate approval: Court upheld – only the medical establishments can do large scale compounding

//In 1997, as part of FDAMA, Congress codified the regulatory exemption by removing § 507

#### TOBACCO

**Brown & Williamson** (2000): FDA asserted jurisdiction (under Kessler) over tobacco products on the grounds that tobacco is a drug and cigarettes/smokeless tobacco are drug delivery devices: regulated them as a combination product

- The Court found that because Congress had already struck a balance, the FDA could not regulate. AND if the FDA had jurisdiction, would have required banning since beginning.
- This is clearly within the literal definition of “drugs” – tobacco has *no* therapeutic value
- Here Kessler read “structure and function” broadly

**The Tobacco Act of 2009:** § 321(rr)(1) “any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product”

1. Regulates Advertising
2. Cannot ban the drug (but can ban use/sales to minors)
3. Gave FDA authority to regulate tobacco products (even without therapeutic claims)

**Sottera** (D.C. 2010): This is a customs seizure case – saw the e-cigarettes at the border and thought that they were FDA regulated: FDA inspector came in and seized product: plenary power at border

- To get them back, Sottera had to sue the FDA
- Found that the Tobacco Act covers regulation of this product: not just the FDCA drug/device provisions: therefore, can regulate (1) advertising; (2) manufacture; (3) access
  - But cannot have the same kinds of restrictions that the FDA in *Brown*

**Garland Concurrence:** The FDA should not get *Chevron* deference for a litigation position

- The Tobacco Act means that Congress wanted them regulated under that Act, not FDCA

#### IV. DRUG APPROVAL PROCESS

**1962:** requirement that the FDA review an NDA within 6 months: this was never met

##### CLINICAL TRIALS

1. How much information do you need to gather? What risk are you willing to accept?
2. How can you correlate improved performance with extent of pre-market review?

There is a lot of (1) decentralized knowledge and (2) with clinical trials, you deal with everything before the application as nothing, although the FDA is slowly moving towards Bayesian statistics

- Before you approve a drug: what do you do?
  - You give a low dose of the drug – incremental increases, but there might be nonlinearities in the dose response curve
  - Then you might give them something else to deal with the side effects
- The delivery mechanisms for drugs are crucial: the information sharing between doctors update treatments
- But as a gatekeeper, there is no redundancy

**Investigational New Drug:** exception to interstate shipment of unapproved drugs

Phase I: introduction into human subjects (20-80 subjects) – looking for freak accidents

Phase II: controlled clinical trials for several hundred subjects

Phase III: controlled trials for several hundred-several thousand subjects

- Double-blind trial removes people who have known confounding factors:
  - Co-morbidities
  - Stage to which the disease has progressed
  - Less women than men: women get pregnant
- But a **positive** clinical trial doesn't tell you anything – a negative trial tells you a lot
  - Insurance company data is actually the most useful
- Durability is a good metric of safety/effectiveness: every drug that is on the market, when it is successful, expands in use (shark-fin)

**US v. Garfinkel** (8th Cir. 1994): Garfinkel was the principal investigator for an experimental drug, Anafranil. Under **§ 355(i)**, the recordkeeping obligations are put on the manufacturers/producers, rather than the PI

- Garfinkel was charged with violation of FDA regulations: the circuit court reversed the district court's order dismissing the two counts: the FDA interpretation does not conflict with Congressional intent

##### Pre-market Approval

**Edison Pharm** (D.C. Cir. 1979): Israel developed Cothyrobal, an injectable drug intended to treat hypercholesterolemia/hyperthyroidism. (Not GRASE either)

- The B12 in the drug was designed to reduce the toxicity of the active drug
- The Commissioner rejected the application because there were no double blind trials
  - But would it be ethical to require them? You should really compare this drug to levothyroxine (to see if it really reduces side effects)
  - But if that drug had too many adverse effects: what do you do?
- Should have used historical data, like with venom antidotes: Court deferred to the FDA

**Smithkline v. FDA** (Dexamyl) (D.C. Cir. 1978): A combination drug had Dexedrine (an appetite suppressant) and amobarbital (to limit side effects of Dexedrine)

- Commissioner refused to look at the data: (1) prior drug use – how to use normalized population and (2) classifications: anxiety

- Court upheld the summary judgment procedure because the applicant had failed to submit substantial evidence of efficacy

**Squibb** (D.C. Cir. 1989): In 1950s, Squibb received FDA approval for 4 oral combination drugs, each of which contained the antibiotic tetracycline and one of two anti-fungal agents

- The FDA found that candidal overgrowth is not a disease – withdrew approval (upheld)
  - Squibb could have made an argument for (1) mitigation or (2) prevention
- Unlike in *Brown & Williamson*, the FDA reads “structure and function” broadly here

### **PDUFA**: Prescription Drug User Fee Act

- Began in 1992, reauthorized every five years, \$1M for the full application (2008)
- Kessler was a very reform-minded commissioner and interested in money
- 1. Make the turnaround time for approvals shorter
  - a. You want to make sure that the money allocated for drug approvals is not diverted elsewhere: must guarantee that funds stay up
  - b. But it is difficult to lockdown the government from diversion of funds: would Congress simply decrease the appropriations to the FDA because of user fees?
  - c. But PDUFA did not affect the actual substantive approval criteria
- 2. The Act states that drug companies won’t pay user fees without commensurate Congressional appropriations
- 3. But there is still partial diversion: the fee also covers FDA enforcement actions

The FDA states that they will review 90% of applications within 10 months

- But more recently, there have been public hearings, which makes negotiation more difficult
- What about using drug approvals from Europe or Japan? Or splitting the burden?
- Once something is on the market: the FDA has no power – gatekeeper

### **What are the differences after PDUFA?**

- |                            |   |                     |
|----------------------------|---|---------------------|
| 1. Approval rate           | } | Has stayed the same |
| 2. Drug Recall             |   |                     |
| 3. Time: this has improved |   |                     |

### **Early Access**

**Early Access available:** if –

1. Intended to treat a serious or immediately life-threatening disease
2. No comparable or satisfactory alternative
3. The drug is being studied in a controlled clinical trial or clinical trials have been completed
4. The drug’s sponsor is actively pursuing market approval

The FDA can deny treatment from IND if:

1. The agency believes there is “no reasonable basis” to conclude effectiveness
2. Granting the request would expose the patient to an unreasonable amount of risk

**Abigail Alliance** (D.C. Cir. 2006): Alliance submitted a proposal for new regulations that make post-Phase I drugs available to terminally ill patients who were not admitted the clinical trials

- Came from a patient who was terminally ill with cancer and died

BUT: (1) can sabotage clinical trials (compound disorders) and (2) possible liability for companies

- But Physicians are more capable of giving individualized advice to patients than the trial results – can evaluate your risk factors (the FDA cannot do this)

**Tort of Intentional Interference with Advantageous Relationships** (schoolteacher shooting pupils scenario): The *prima facie* case is in favor of Abigail



- But the justifications make the interference legal: (1) you want enough people in the eventual clinical trials; (2) do you trust doctors enough and (3) do you want drug companies to be able to sell their drugs earlier

The panel found for Abigail Alliance: that the drugs must be made available earlier: fundamental right from *Cruzan* – right to refuse treatment → right to take medical treatment available

**Abigail Alliance II** (D.C. Cir. 2007) (en banc):

Concluded that there was a **no fundamental right** “deeply rooted in this Nation’s history” of access to experimental drugs for the terminally ill

- We have historically had experimental drugs
- The intentional interference tort doesn’t apply here – plus these drugs have immense risk
  - Because there is no fundamental right: the claim is subject only to rational basis scrutiny (*Lee Optical*) and the government does have a rational relation to a legitimate state interest
- If we recognize it here, to where does the right extend?

//Epstein thinks that we should have this for oncology drugs: here, there is a pressure from the family to live – not coercive as with *Glucksberg*, but *Kuhlik* points out that if manufacturers receive payment for the drugs, there are still coercion concerns

**Cruzan**: individuals have the right to refuse medical treatment, incompetent persons cannot

- Here, the pressure from the family is to take the treatment

**Glucksberg**: doctors who aid with assisted suicide are subject to prosecution: you don’t want elderly people coerced into suicide

- Here, unlike *Cruzan*, the pressure from the family is to die rather than live

### OFF-LABEL USE

An off-label use is use of drug/device in a manner not approved by the FDA

Medical practice exception does not apply to physician compounding of unapproved substances.

- In guidances, the FDA contends that there is improper labeling of medical products
- There are huge fines (~\$600 million) for off-label uses
  - These judgments are not contested because drug companies are repeat players

Most cases are brought by the **Department of Justice** – the FDA first works on the case and then refers it to the DOJ (typically, Boston/Philadelphia USAO)

**Washington Legal v. Kessler** (D.D.C. 1995): Physicians prepare materials in medical journals, articles and textbooks that discuss off-label uses (“enduring materials”)

- Using guidances is more useful for the FDA than using notice and comment because the latter is riskier for the FDA
- The Washington Legal Foundation has brought a citizen’s petition against the FDA
  - It is advantageous for the drug companies to have WLF bring the suit
  - Drug companies are repeat players with the FDA: they don’t want delays in approval

The court found that the sum of FDA’s guidances created a *de facto* policy, although most courts have dismissed similar actions for lack of ripeness/failure to exhaust administrative remedies

**Why doesn’t the FDA subject doctors who prescribe off-label uses to criminal prosecution?**

- The FDA cannot regulate the practice of medicine
- Can the drug company hand out materials prepared by others?

With regulation of existing approved products there is pushback: foreclosure is not a useful option

**Tort**: you have an obligation to warn even for an off-label use, but there is an implied representation that applies to that off-label use



**Femrite v. Abbott NW Hospital** (Minn Ct. App. 1997): Appellants underwent spinal fusion surgery, and they were implemented with an experimental device. They were not informed that it was an IDE nor part of the clinical trial, but the device had already been approved. The court held that you can have simultaneous off-label use and an investigational study.

- Alleged that the hospital allowing this type of surgery was medical malpractice
  - This would destroy all off-label use
- It does not matter whether you knew that it was unapproved if you knew all the risks
  - Courts are split over whether **informed consent** means you know experimental status (you do need this for clinical trials)

### GENERIC DRUGS

Pre-1962: public notice of efficacy, later generic drugs could refer to these findings

After 1962: the NDA was a private license to the innovator company (hard for generics)

- Therefore, generic drugs needed to do their own effectiveness studies
- Technically, they could do these during the patent term – but the research exemption was effectively eliminated

**Generix** (1983): A generic drug product using the same active ingredients still needs to get an NDA

**Hatch-Waxman** created a compromise:

1. Facilitated approval of generic drugs: allowed generic companies to get approval without doing its own studies
  - a. Set up a system called the Orange book: every approved drug with an appendix of every patent that claims that drug
  - b. The ANDA filed by the generic would seek one of two certifications:
    - ¶ III: we wait until the patent expires to seek approval
    - ¶ IV: we won't wait – the patent is either (1) invalid or (2) we don't infringe
      - This creates a Title 35 act of infringement (case or controversy)
      - If you sue within 45 days, you can get a 30 month stay of the approval: during which the patent case may be resolved
  - c. The first generic gets 180 days exclusivity, but brand names can make agreements with the generic companies

Typically, the generic will try to show equivalence for FDA purposes or (1) show invalidity or (2) say that because equivalence is different in patent law, say that it does not infringe

2. Extended patent term for innovator drugs
  - a. Title II: can get up to 5 years added (1/2 of the time required for the IND review)
  - b. One approval out of 10 pays for itself

**Serono** (D.C. Cir. 1998): Same as means clinical identity – bioavailability/bioequivalence

- If you are the innovator company and you change the structure of the active ingredients: you *will* need to run clinical trials: here, the generic was using a different isoform
  - But the generic does *not*: their ANDA can be approved
- Because of mandatory/permissive substitution laws: you want the generic to be as close as possible – pharmacists make more from generics
  - The pharmacy will substitute the generic without any kind of medical knowledge
- Hatch-Waxman does not allow new labels: § 355 allows new labels only for (a) formulation differences and (b) differences required to comply with FDA sulfite warning restriction
  - *BMS v. Shalala* (D.D.C. 1996) can approve a generic without all of the indications in the brand name label

**Zeneca** (4th Cir. 2000): In general, the FDA regulations require that the inactive ingredients in the generic are the same as the pioneer drug. Zeneca formulated propofol with EDTA to prevent microbial contamination (that was leading to high fevers)

- Gensia submitted an ANDA with propofol, but used sodium metabisulfite not EDTA
  - This required the creation of new labels for drug

The court still upheld the FDA judgment that the generic did not need to do new trials

Kuhlik: this is decided wrongly: (a) too much FDA deference – possibly because (b) this is a drug that is typically administered in a hospital

- No real post-market review for generics

### EXCLUSIVITY

- A kind of payment-in-kind system
- Doesn't apply to full NDA and paper NDAs, just ANDAs

Most drugs aren't studied on children: difficult to know if they will be safe/effective

### **Hatch-Waxman Exclusivity**

5 year data exclusivity: the FDA cannot approve a generic – applies when you get a new active moiety (a new active ingredient) – different salts of the same compound are the same active moiety

3 year data exclusivity: Applies for OTC switch – for a new label or a new indication and you were required to do clinical studies: 3 exclusivity

- But remember: suppose you got an approval for a once-a-day pill in lieu of two days: this you can't substitute the 2 a day generic. But suppose you get a new use – you could easily substitute the generic and get the new use off-label
  - The generic just can't use the new label – i.e. in *Mensing*

**Burroughs Wellcome** (E.D.N.C. 1986): Two different companies had an NDA approved

- Burroughs (the first to be approved) could not get exclusivity over the other company because they did not need Burroughs's data. **This is not absolute exclusivity.**
  - *Both* companies used a paper NDA – some previously published literature

**Mead Johnson** (D.C. Cir. 1988): There was a transitional period for Hatch-Waxman – some companies got ten years of approval.

- The FDA (before PDUFA) often gave preliminary approvals...but you must still do X
  - This is one such case: but the FDA's approval date is the one that sticks

**Purepac** (D.C. Cir. 1998): There is no need to have a "successful defense" to get the 180 day exclusivity provision – *Mora* removed that requirement

**Mylan** (D.D.C. 2000) *vacated* (D.C. Cir. 2002): Barr brought a ¶ IV on Imperial's drug

- Barr won in court, and there was a "pay-for-delay" settlement where Barr was paid to stay off the market
  - The other generics were prevented from entering by Barr's ¶ IV even though they had settled with Imperial and had amended to a ¶ III.
- This action found that Barr was no longer entitled to the 180 exclusivity: forfeiture if the generic does not enter the market at the earliest possible time

§ 1: **Division of markets: collusive settlement** – everyone knows that the patent is bad, and this is a patent extension via different means

§ 2: **Monopolization** – where you tie one product to another, more successful one

Orphan Drug Exclusivity: these are drugs with a very small market – you can get full market exclusivity for seven years (even if someone else has an NDA)

- Specifically targeted at the biotech system
- Issues: creates race to approval in a parallel development system (now the FDA fudges the approval dates)
- Active moieties: you do not want to deprive patients of superior drugs (there is a provision)
- However, this system has led to very expensive orphan drugs, not least because they are very difficult to make
  - But if you don't have the system, you don't get *any* drugs

**Baker Norton** (D.D.C. 2001): Baker developed Paxene and BMS developed Taxol, and Taxol was approved first. Baker could not get approval until after the exclusivity period for Taxol had ended

- The definition for drugs (during the approval process) is narrow – when you change the colors, the shape of the pill etc, you have to get approval
- But for the exclusivity, it is a broad definition: or it would not mean anything – you could change the pill shape and get around the exclusivity provision: Court upheld

**Pediatric Exclusivity:** Here, you get 6 month market/data exclusivity (not a patent extension)

**Nat'l Pharm. Alliance** (D.D.C. 1999): Court upheld the draft pediatric list of approved drugs that might produce health benefits: the FDA can grant additional exclusivity for drug product lines

## V. POST-APPROVAL POST-MARKET SURVEILLANCE

1. Detect previously unknown adverse reactions
  - a. If you studied the drug in 10000 patients, you are not likely to catch a 1/10000 event
2. Evaluate in greater detail known risks
3. Uncover adverse reactions from interactions
4. Uncover adverse reactions from particular sections of the population

Lowest level: adverse event reporting (AER)

- The main way that they find out is from physician reporting
  - Estimated that < 10% of adverse events are reported
  - Once these are reported: minimized from changes in labeling
- **Seldane:** however, doctors rarely change their practices – (1) don't read the warnings; (2) have more than one doctor; (3) patients fill out intake forms
- The FDA does *not* have mandatory drug recall authority
- Labels are categorized by severity

**Vioxx:** sometimes the drug company will take something off the market without FDA pressure

- 16000 people die each year from stomach bleeds
- “Vigor”: study that compares Vioxx with naproxen (Aleve, Midol)
  - Allows the label: “causes fewer stomach bleeds”
  - But more Vioxx users had heart problems, but naproxen may well *reduce* the rate of heart attacks
- “Approve” study compared Vioxx to a placebo: showed that cardiac risk definitely increased

2004: Merck took Vioxx off the market

**Henley** (2d Cir. 1996): FDA regulates the labeling of oral contraceptives on package inserts. Henley requested that the FDA amend the warning label requirements – cited thirteen studies that established links between long term use and breast cancer

- Under the APA § 706(2)(A): a district court may set aside agency findings only if they are “arbitrary, capricious or an abuse of discretion”

The court upheld the FDA's decision: this is not an abuse of discretion and the FDA's determination best reflects the current scientific information regarding the risks/benefits

**Label Requirements:** FDA plans to change this and add "highlights" section, § 501(f)(1)

1. Clinical pharmacology
2. Indications and Usage: prescriptions are exempt from these requirements (**Evers**), but if the using party is not a physician, then it is misbranded (**Rayford**)
3. Contraindications (where the risk > benefits)
4. Warnings: risks that are more serious than adverse reactions (but risks ≤ benefits), includes black-box warnings (most serious)
5. Precautions: animal studies, pregnancy (category X where risks > benefits)
6. Adverse reactions (rare) – "reasonable association with use"

### Tort Liability

**Custom is not always a defense to Tort liability:** entire industries can lag behind in manufacturing requirements, *see TJ Hooper*: Blood industry (American Red Cross) – scrutiny after HIV. The FDA ended up putting the entire industry under injunctions/consent decrees.

### **Product Liability Considerations:**

<b>Upstream:</b> uniform warnings for all patients	Websites for the patients to understand	<b>Downstream:</b> Physician's Desk Reference etc.
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*Henningsen v. Bloomfield Motors* (1960): Cannot disclaim products liability

Epstein: should take out regulation and have a voluntary market like surgery

Kuhlik: Would be very difficult to have a market like surgery – different incentives/smaller market

- Typically, you would not have manufacturing defects: the batch is recalled
  - Traynor concurrence in *Escola*
- Design defects: unlikely – although *see* Rest. 2d of Products: § 402(a)
  - Misuse of the product?
- Mostly warning defect cases:
  1. Adequacy of the warning
  2. Must show that the product is the causal agent AND
  3. A new warning would have changed behavior (effect of the heeding presumption)

**Nelson** (W.D. Mo. 2000): Nelson lost his eyesight when taking Cordarone (prescription heart medication) and sued the defendants. Defendants moved for summary judgment.

- Adverse Event Reports are *not* admissible: there is no causation requirement
  - Doctor's identities are kept confidential: you want to be able to collect information without fear of tort liability (plaintiffs' bar)
  - Even if they are probative, would likely be prejudicial
  - Includes things like: while patient was taking Zocor, was hit by a truck
  - Even if they were admissible: **not enough to get to jury** (B-C range)
- Institutional framework trumps state discovery rules (*see Tarasoff*)

**Laerdal** (D. Or. 1994): A manufacturer of a medical device who received information about death/serious injury must submit report within 5 days and a written report within 15 days

- Laerdal did not submit the report about the defibrillator because the FDA investigator concluded that the information regarding the death was "indefinite"
- Even if you check the device later and it works: this is insufficient: FDA wants more info

Was this because of a bad battery in the defibrillator? Did the EMT check the battery?

**Doctrine of Private Necessity:** Forsham v. Califano: Plaintiffs are physicians who orally administer phenformin. The Sec’y of HEW suspended the NDA for phenformin under “Imminent Hazard” doctrine. The court upheld the Secretary’s decision.

- No subsequent case invoked imminent hazard authority
- The only person who can use is the Secretary: this is not delegable authority
- Post-market surveillance serves as a background for (a) enforcement and for (b) withdrawal

### PREEMPTION

#### **Concurrent Jurisdiction/Administrative Preemption**

**State Regulation:** Rayford (Tex. Ct. App. 2000): Rayford is a qualified sonographer, who purchased an ultrasound machine from GE and went into business as “Baby Images”

- Non-diagnostic use of the product is largely the same as the diagnostic use
- There would very little difference in the use of the product under doctor supervision
  - Seems like this is being used as a an anti-competitive mechanism
- Typically: use is defined by the manufacturer and not the user
- Not adulterated, but *was* misbranded
- FDA was aware of the nonmedical use and didn’t do anything: but this was not any kind of clear action (similar to *Wyeth* type situation)

A.P.A. v. Weinberger (D.D.C. 1976): FDA action prohibited all licensed pharmacies from dispensing methadone – regulating the dispensation of a drug

- The court determined that Congress created two complementary institutions: the FDA – which new drugs can enter the flow of commerce
- The DEA (Justice Department) has control over permissible distribution of a cleared drug
  - Here, the FDA overstepped the boundaries of its authority

Here, the issues are similar as with dietary supplements – “safety” includes possibility of misuse

**Proposition 65** (1986): regulation passed in California that required a warning on all substances that cause cancer or birth defects – “no person in the course of doing business shall knowingly and intentionally expose any individual to a chemical known to cause reproductive toxicity...”

- FDAMA: states cannot impose additional warning (preemption) **except** Prop 65
- Prop 65 was enforced either by the state OR by private action
  - Included nicotine as a chemical known to cause reproductive toxicity

Dowhal (Cal 2004): FDA granted permission to nicotine patches with warning “Nicotine can increase your baby’s heart rate: seek advice of a health professional”

- Dowhal alleged that defendants violated Prop 65 because they didn’t follow warning
- FDA did not let them change the warning to “harm your baby” language: too strong

This is an example of **conflict** preemption: the state law is preempted

Dental Amalgam (9th Cir. 1996): the MDA (unlike the drug law) has an express preemption provision – what is the scope of that preemption?

- Anytime that there is a federal requirement for a device, there is preemption
- Because the FDA did not require any regulation (no PMA) the state regulation is **not** preempted

#### Statutory Preemption

Comes from the Supremacy Clause to (1) achieve uniformity and (2) not allow one state to legislate for all others (race to the top)

## Policy Issues: Other methods for safe harbor

- A. Contract Liability
  - a. But you can't have unconscionable contracts
- B. Fund (like the vaccines)
- C. Defense of Federal Compliance (Regulatory Compliance Defense)
- D. Tort Reform (Class Action law in 1966, failure to warn requirements)
- E. Preemption
  - 1. Congress can **expressly** preempt state law
  - 2. **Implied Preemption:**
    - a. When state law actually **conflicts** with federal law
    - b. When state law **frustrates** the purposes of a comprehensive federal law

- The DEA establishes a schedule of narcotics
  - But see: Thalidomid, Accutane: in cases where the DEA is not pushing back against FDA, they are more able to control distribution – DEA usually beats FDA
- **Oxycontin:** Purdue Pharms was prosecuted by United States because too much of the drug was diverted (and they had told doctors that their drug was less likely to be diverted)
  - **Park Doctrine:** can hold CEOs responsible for the crimes of their underlings, even if they had no specific knowledge of their actions
- Administrative preemption only works against state regulations, not **torts**

**Riegel v. Medtronic** (2008): The Balloon Catheter is a Class III device that was approved in 1994 and its label underwent supplemental approval in 1995/96. → **express preemption**

- The doctor inflated it to 10 atm (above the burst pressure label) and it burst the artery
- Plaintiff brought suit that the catheter was negligently designed

§ 360k bars common-law claims challenging the safety and effectiveness of a medical device given pre-market approval by the FDA

- In *Lohr*, the Court found that common-law claims do constitute requirements and are therefore preempted: *Lohr* – 510(k) pathway is not a specific requirement for safety
- The specific labels from the PMA process means that the this device receives preemption

**Ginsburg** dissent: Believed that the MDA was to preempt state statutes, not tort claims

**Wyeth v. Levine** (2009): Physician directly injected the drug Phenergan into patient's vein via IV-push method (rather than IV-drip method) and gangrene developed, arm was amputated

- Plaintiff brought suit because the label was defective
  - The Vermont jury found that the petitioner had failed to provide adequate warning
- The Court held that the FDA approvals did not provide a complete defense to Levine's tort claims: here, the approval was a general approval, rather than the specific approval in *Riegel*

When Congress has legislated in a field that States have traditionally occupied: we assumed that the state's powers are not suspended (and no express preemption clause, like in *Riegel*)

- This is a pretty crazy case: clear negligence by the doctor – intervening cause
  - Sometimes the physician colludes with the plaintiff to say they followed warnings

**Brusewitz** (2011): Because of tort-suits against vaccine manufacturers that were leading to short supplies in the vaccine market (very compelling plaintiffs) as well as inconsistent vaccinations by parents, Congress created a no-fault vaccine compensation scheme. → **express preemption**

"No vaccine manufacturer shall be liable in a civil action for damages for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings."



1. If you fall into several cases: you need not show causation and you can recover
    - a. The special master has the burden to rebut causation (5% of cases)
  2. If you fall outside, you have the burden of showing causation (5% of cases)
- Here, the plaintiff did not recover from the special master/no-fault scheme. Therefore, they sued in state court. It was held that the no-fault scheme preempted her design-defect claim.

- Rest. §402A comment *k*: there is an exception to strict liability for unavoidably dangerous things: specifically addresses pharmaceutical drugs and vaccines

**Breyer:** the FDA should be regulating this – this is what we want and they support preemption

**Sotomayor (dissent):** thinks that this should be regulated by the states – how can we have innovation without tort suits: but torts are a compensation system

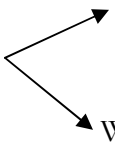
- Simple, unregulated products might be addressed properly by the tort system, but innovation and design of complex products cannot

**Colaccico** (3d Cir. 2008): Do SSRIs cause suicide?

- There is no express preemption for drugs (*Wyeth* – ergo, a presumption against preemption) as there is for medical devices (*Riegel*) and for vaccines (*Brusewitz*)
- Here, unlike in *Wyeth*, the FDA had actually considered the stronger warning for SSRIs and had rejected it: therefore – preempted

**Generics:** **Mensing** (8th Cir. 2009), *cert granted*: Mensing’s doctor prescribed Reglan and the pharmacist filled prescription with generic bioequivalent. Patient developed tardive dyskinesia

- Court dismissed claims against brand name because she hadn’t taken their products //not a market-share liability case as with *Sindell* (DES) – we know which products she took
- Retained claims against the generics: manufacturer could have changed the label and Hatch-Waxman does not preempt against generics
- Could have also written a letter to the doctor: generic companies are not really equipped for patient testing

Policy Issues: Informed Consent	
<b>What about patterns of user error?</b>	
	<p>Warning to Physicians: likely more specific and descriptive</p> <ul style="list-style-type: none"> <li>• Some people think that all information should come through the doctor: doctor can tailor the identifications for the patient</li> </ul> <p>Warnings to Patients: but what about the internet</p>
<p>More specific warnings are not necessarily more useful: less information can be more valuable</p> <ul style="list-style-type: none"> <li>• Some doctors may not like informed consent: you might scare the patient (and they won’t take necessary medicine) – on the other hand, you want patient autonomy</li> </ul>	
Preemption	
<p>Why might some FDA officials oppose preemption? It takes some pressure off the FDA to always get it right. Remember: you cannot have claims against the FDA (<i>see Berkowitz</i>)</p> <ul style="list-style-type: none"> <li>• Routine bench-scientists like preemption</li> </ul> <p><b>Kessler &amp; Vladeck:</b> they are concerned that the FDA is underfunded and often gets it wrong – therefore, the tort system works as a good supplement</p> <p><b>Sharkey:</b> puts more reliance on the FDA, but is still concerned about error</p> <ul style="list-style-type: none"> <li>• Wants a “searching review of the administrative record”</li> </ul> <p>Kuhlik: technically this makes sense, but actually creates perverse incentives – the record is rarely very clear, and the FDA and the manufacturers speak the same language</p> <p><b>Epstein:</b> There are two errors – not letting drugs in and letting too many in -- should have blanket</p>	

preemption

- The CBE idea suggested by Kessler and in *Mensing* is crazy: you really have to discuss with the FDA before changing the label
- Opponents of preemption are concerned about data not shared with the FDA: but this would be the object of a fraud action (Park Doctrine)

Currently: there is not that much deference to the FDA