Introduction & Regulation & the ~~Pharmaceutical~~ Medical Products Industry

Methods in Pharmaceutical Policy Analysis
Pharm 532 Spring 2009
Hazlet, Garrison, Kadiyala

Agenda

- Course logistics
- Course objectives
- Grading
- Policy analysis perspective
- … break
- Regulatory Process, FD&C Act as example

Usual Suspects – all H375

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Logistics

- Reading
  - Weimer & Vining -- Policy Analysis (4e05)
  - Bardach -- A Practical Guide For Policy Analysis The Eightfold Path To More Effective Problem Solving (3e09)
  - Articles – class web site
    http://depts.washington.edu/pharm532
- Software -- Stata (student version)
  www.washington.edu/uware/stata/

Course Objectives

- Describe policy development models and use them to characterize health policy development involving ~~pharmaceuticals~~ medical products;
- Discuss the interaction of systematically collected information, scientific inquiry, community values and existing practice in the development of health policy;
- Become quickly conversant in a particular health policy area;
- Identify key interest groups, key policy makers and key information sources relevant to a specific topic area and a specific decision making context;
- Define a set of key policy issues in a given policy development context;

Objectives (2)

- Collect and summarize relevant information;
- Describe several analysis techniques used frequently in health policy analysis;
- State policy options in a form that will allow their assessment or analysis;
- Describe the most frequently used policy evaluation criteria and
  - articulate several measures which might be used to apply them to policy options;
  - articulate the strengths and weaknesses of policy analyses reviewed in class; and
  - Present results in a succinct, interesting and credible fashion, both orally and in writing
- Understand basic principles of economics as applied to health care and integrate these principles into policy analysis;
- Evaluate literature that uses health economic tools to assess impact of medical products policy on appropriate outcomes;
- Understand the economic context and consequence of medical product policy interventions.

Objectives (3)

- <pass the qualification examination on the first try…>

Grading

Activity	**Percent**	**Comments**
Project	50	**Presentation** on assigned date; **document** due 1700 10 June, via *CollectIt*
Midterm	30	Take home, due 1700, 01 May, via *CollectIt*
Homework	20	Four Causal Inference exercises Due date as assigned
Total	100	Fitted Numerical Equivalent Score

Grade Table: Percent → NES

from	to	you get	from	to	you get	from	to	you get	from	to	you get	from	to	you get
0.00	37.49	0.0	51.00	52.49	1.3	60.00	62.99	2.0	72.00	73.49	2.7	82.50	83.99	3.4
37.50	43.49	0.7	52.50	53.99	1.4	63.00	64.49	2.1	73.50	74.99	2.8	84.00	85.49	3.5
43.50	44.99	0.8	54.00	55.49	1.5	64.50	65.99	2.2	–	–	2.9	85.50	86.99	3.6
45.00	46.49	0.9	55.50	56.99	1.6	66.00	67.49	2.3	75.00	77.99	3.0	87.00	88.49	3.7
46.50	47.99	1.0	57.00	58.49	1.7	67.50	68.99	2.4	78.00	79.49	3.1	88.50	89.99	3.8
48.00	49.49	1.1	58.50	59.99	1.8	69.00	70.49	2.5	79.50	80.99	3.2	–	–	3.9
49.50	50.99	1.2	–	–	1.9	70.50	71.99	2.6	81.00	82.49	3.3	90.00	100.0	4.0

from UW Biostatistics

Project

- represents a policy change (or flaw) at a commercial or governmental level
- involves medical products (drugs, biologics, medical devices)
- tools from class, elsewhere
- select a journal where the evaluation might be published, and write for that journal
- midterm – to facilitate project and assess comprehension and progress
- presentation & paper (15-20 pages)
- group (not crowd) option, but independent demonstrations for midterm, final product

Academic Conduct

- See University Policy

http://depts.washington.edu/grading/issue1/conduct.htm

Classroom Safety

- Fire
- Earthquake

- Evacuate to [see map in classroom entrance]
- Keeping track … buddy system
- Persons with disabilities

Introduction to policy analysis

- How much Weimer & Vining do you “need”

Classroom Decorum

- Fragrances
- Communication gizmos off
- Break between hours

- Class size lends itself to seminar format – lots of questions

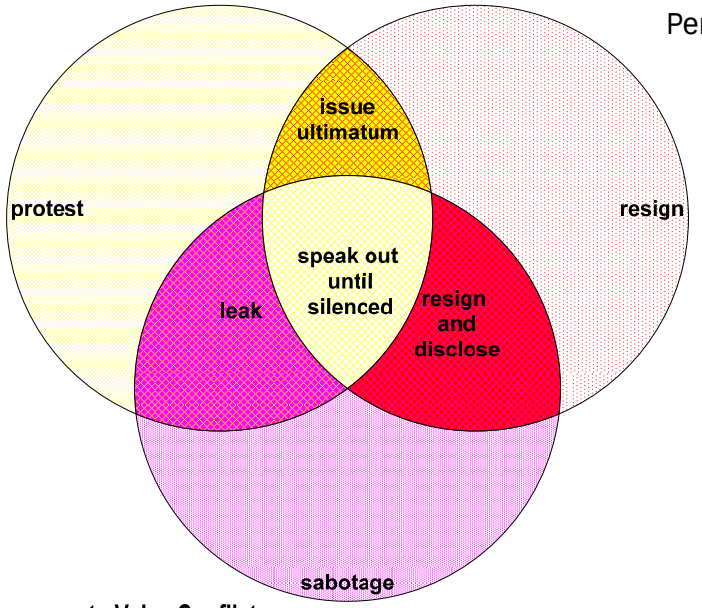
Policy Perspective

Three views on the appropriate role of the policy analyst

Weimer and Vining, Policy Analysis: Concepts & Practice, 4th Edition, Prentice Hall

Fundamental Values	Analytical integrity	Responsibilities to clients	Adherence to one's conception of good
Objective Technician	let analysis speak for itself; primary focus should be predicting consequences of alternate policies	clients are necessary evils; their political fortunes should be secondary considerations; keep distance from clients; select institutional clients whenever possible	relevant values should be identified but trade-offs among them should be left to clients; objective advice promotes good in the long run
Client's Advocate	analysis rarely produces definitive conclusions; take advantage of ambiguity to advance clients' positions	clients provide analysts with legitimacy; loyalty should be given in return for access to privileged information and political processes	select clients with compatible value systems; use long-term relationships to change clients' conceptions of good
Issue Advocate	analysis rarely produces definitive conclusions; emphasize ambiguity and exclude values when analysis does not support advocacy	clients provide an opportunity for advocacy; select them opportunistically; change clients to further personal policy agenda	analysis should be an instrument for progress toward one's conception of the good society

Perspective 2



Responses to Value Conflicts
from Weimer and Vining. Policy Analysis: Concepts and Practice, 4th Edition

Timeline

Policy Analysis in Perspective: Time constraints

Weimer & Vining. Policy Analysis: Concepts & Practice, 4th Edition, Prentice Hall

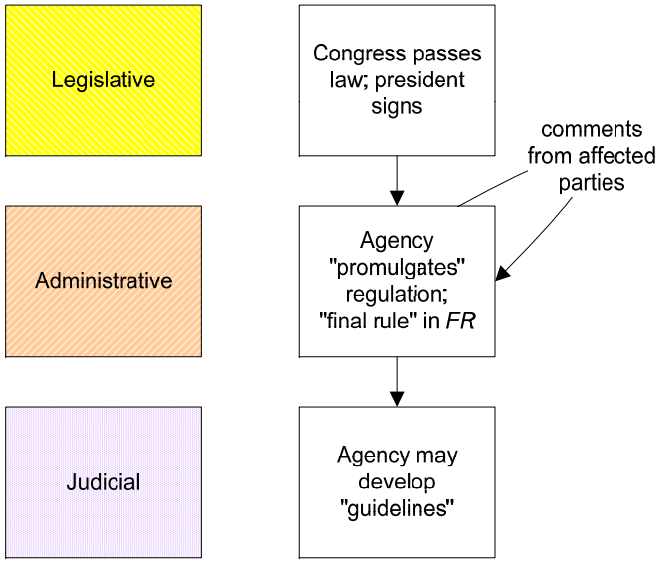
Academic Social Science Research	Policy Research	Classical Planning	Public Administration	Journalism	Policy Analysis
external time constrains rare	some deadline pressure; mitigated by issue recurrence	little time pressure because of distant time horizon	time pressure tied to routine decision making such as budget cycles	strong deadline pressure -- strike while issue is topical	strong deadline pressure -- completion of analysis usually tied to specific decision

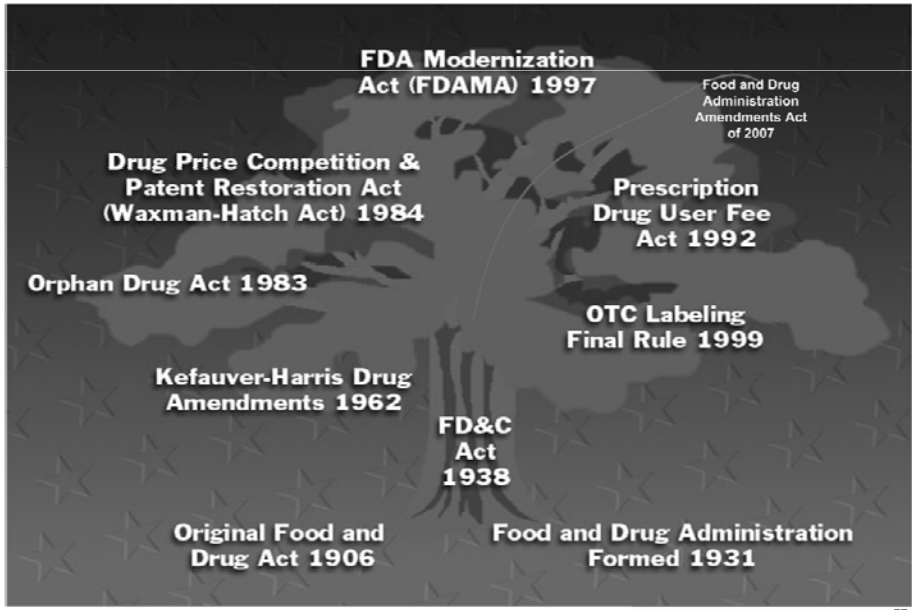
break

Regulatory Process, FDA History

- Regulatory Process
- History of FDA / PHS
- The Law
  - US Code
  - Regulations
  - Guidelines
- A drug by any other name
- "Other" Regulators
- International Issues
- To Market To Market …
- Preclinical
- IND / IDE
- NDA / BLA / ANDA / PMA / 510K
- Orphan / Pediatric
- Intellectual Property, Waxman-Hatch
- PUDFA2
- FDAMA - apocrypha
- Enforcement

Regulatory Process





An History of Disasters

- Biologics Control Act of 1902
- Food & Drugs Act 1906
  - Upton Sinclair, *The Jungle*
  - truthful label (strength & purity)
- Food, Drug & Cosmetic Act 1938
  - "elixir" of sulfanilamide
  - safety, IND, NDA, 60-day review

History (2)

- Durham-Humphrey Amendment 1951
  - collateral measures necessary for "safe" use
    - "Caution: Federal law prohibits …"
    - Rx to OTC switch
- Kefauver-Harris Amendment 1962
  - thalidomide; Bay of Pigs
  - effectiveness; 180 day NDA review
- Guidelines for Reproductive Studies 1966
  - public pressure

History (3)

- Orphan Drug Act 1983
  - rare diseases
  - tax break; patent protection
- ANDA 1984
  - bioequivalence for generic drugs
- Codification of IND Regulations 1987
- Expedited Approval, Serious & Life-Threatening Diseases (AIDS) 1994 [“Subpart E”]
  - Phase 4

History (4)

- 1992 Prescription Drug User Fee Act
- 1994 Dietary Supplement Health And Education Act
- 1997 Food And Drug Administration Modernization Act
- 2000 Washington Legal Foundation [65 *FR* 14286]
- 2002 PDUFA3; phase 4 for new approvals; more streamlining (risk management)
- Recent legal challenges
  - Shalala v. Western States; commercial vs. free speech
  - 21CFR201.57(b)(9) Pediatric use
  - “critical path”
  - Drug Safety Board (FDA, NIH, VA)
- 2008 PDUFA IV
- 2008 FDAAA

html/opacom/backgrounders/miles.html

Pediatric Rule

- FDA's Pediatric Rule was challenged in court. On October 17, 2002, the U.S. District Court for the District of Columbia ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials.

The Law: code → regulations ← courts →

- 21 USC 301 (the “Act”); 42 USC 201 (Public Health Service Act)
- http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm
  - thou shalt not
    - adulterate
    - misbrand
  - penalties – administrative, civil and criminal
- 21 CFR 1-1299…
  - proposed rule (NOPR) in *Federal Register;* comments
  - final rule in *FR* with effective date; importance of preamble
  - www.accessdata.fda.gov/scripts/oc/ohrms/index.cfm
  - www.gpoacces.gov -- browse feature for *FR*

The Law [2]

- Guidelines
- www.fda.gov/cder/guidance

FDA Centers

- CDER – Centers for Drug Evaluation & Research
- CBER – Biologics
- CVM – Veterinary
- CFSAN – Food Safety & Applied Nutrition
- CDRH – Medical Devices and Radiological Health
- National Center for Toxicological Research

CDER

what makes a "drug" a "drug"?

- 4 things
  - recognized in an "official compendium"
  - *intended* for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, **and**
  - intended to affect the structure or function of the body of man or other animals, but not food
  - Components (defined 21CFR10.3)

  - RX vs. OTC; brand (NDA) vs. generic (ANDA)

CDRH

medical device

- Same as "drug", except
  - "… does not achieve any of its principal intended purposes through chemical action … and is not dependent upon being metabolized …."
- PMA, 510(k), "clearance"

cosmetic

CFSAN

- Intended to be [shake & bake] for cleaning, beautifying, promoting attractiveness, altering appearance
- components
- not soap
- man or any other beast?

food

CFSAN

- … used for food or drink for man or other animals
- GRAS
- chewing gum
- components
- cf. dietary supplements
  - Proxmire Amendment
  - DSHEA

biologic

CBER

- Parallel evolution -- Public Health Service
- any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man
- "licensed" at the pleasure of the HHS Secretary
- "biotechnology derived therapeutic", "well-characterized biologic" → CDER
- big administrative differences; some similarities
- Combination products
- "cats marching …" again, and again

- BLA, "follow-on biologic"

Veterinary Medicine

CVM

- … and any other beast
- … beasts for eating
- … as companions (or whatever)
- "Green Book"

Other "Regulators"

- FDA's authority is over interstate commerce
- 10th Amendment restrictions on preemption
  - *The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved for the States respectively, or to the people.*
- Gonzales v. Oregon, 2005

Other Regulators [2]

- …governing capacity to introduce into commerce
  - DOC
  - EPA
  - FTC
  - HCFA → CMS
  - CPSC
- … governing payment
  - diverse federal / state agencies
  - fiscal intermediaries

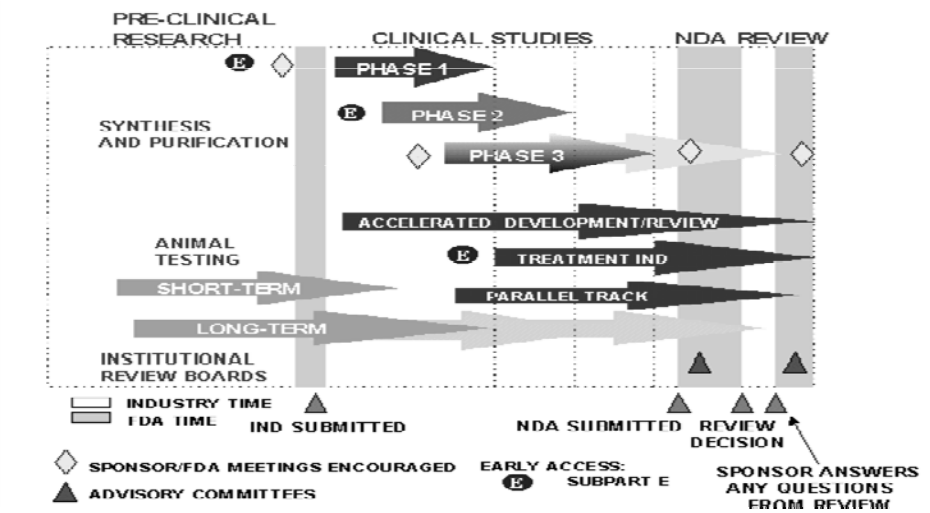
International Issues

- GATT Paraguay, Doha Rounds; WTO
- Import & export; "parallel trade"
- International Commission on Harmonisation
  - Common Technical Document
- Standards organizations: UL, CA, CE, ISO, USP
- Drugs of Abuse
- Counterfeit
- Price

To market to market (to buy a fat pig)

- intent
  - experiment [human subject protection]
  - therapy [safe & effective under conditions of intended use ≠ fraud]
  - what the practitioner does with the stuff …
- Investigational New Drug [exemption] - IND
- Investigational Device Exemption - IDE

PHASE I	PHASE II	PHASE III
20-100 Patients	Up to several hundred patients	Several hundred to several thousand patients
Testing mainly for safety	Testing for some short-term safety but mainly for effectiveness	Safety, dosage, effectiveness



http://www.fda.gov/cder/handbook/index.htm

To market to market 2

CBER & CDER [CVM]

- New Drug Application - NDA
  - $A_{bbreviated}$NDA
  - $S_{upplemental}$NDA
- Biologics License Application - BLA
  - P_{roduct}LA & $E_{stablishment}$LA

CDRH

- Premarketing Approval – PMA (some Class II and all Class III)
- 510(k) – substantial equivalence to a predicate device
- "clearance"

To market to market 3

Incentives to Industry

- Waxman-Hatch '84 [aka Drug Price Competition and Patent Term Restoration Act][1,2]
  - generics [ANDAs]
  - up to 5 years patent term extension in exchange for regulatory delay
- Orphan Drug Act
- Pediatric
- "Follow-on biologicals"

1. Engelberg AB. Special patent provisions for pharmaceuticals: have they outlived their usefulness? *J.L & Tech*. 1999;39:389.
2. Guidance for Industry 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act http://www.fda.gov/cder/guidance/2576fnl.pdf

To market to market 5

Prescription Drug User Fee Act 1,2,3 & now 4

TABLE 3.—FEE-PAYING FAEs—5-YEAR AVERAGE

Fiscal Year	2003	2004	2005	2006	2007	5-Year Average
Fee-paying FAEs	119.5	145.1	121.5	136.7	127.2	130

TABLE 4.

Fee Category	Fee Rates for FY 2008
APPLICATIONS	
Requiring clinical data	$1,178,000
Not requiring clinical data	$589,000
Supplements requiring clinical data	$589,000
ESTABLISHMENTS	$392,700
PRODUCTS	$65,030

http://www.fda.gov/OHRMS/DOCKETS/98fr/07-5052.pdf

PDUFA Warts

- other parts of FDA's budget
- Generic industry; device industry; others
- faster approval ↔ public safety
- availability of drug information

Enforcement

- debarment (clinical investigators)
- clinical hold (INDs)
- refuse to file (NDAs, etc.)
- foot dragging
- "disgorgement"
- FDA Form 483 Inspectional Observations; Warning Letters
- Seizures
- Injunctions
- Prosecution

- Administrative, civil, criminal

Home again home again …

To market, to market, to buy a fat pig,
Home again, home again, jiggety jig.
To market, to market, to buy a fat hog,
Home again, home again, jiggety jog.

Summarize

- Regulatory process
- FDA rules, process