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

<table>
<thead>
<tr>
<th>Suspect</th>
<th>E-mail</th>
<th>phone</th>
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</thead>
<tbody>
<tr>
<td>Hazlet, Tom</td>
<td>thazlet</td>
<td>616-2732</td>
</tr>
<tr>
<td>Garrison, Lou</td>
<td>lgarrisn</td>
<td>221-5684</td>
</tr>
<tr>
<td>Kadiyala, Srikanth</td>
<td>harukim</td>
<td>543-9694</td>
</tr>
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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 and 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…>
Grade Table: Percent → NES

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<th>Percent</th>
<th>NES</th>
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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

<table>
<thead>
<tr>
<th>Perspective 1</th>
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<tbody>
<tr>
<td><strong>Fundamental Values</strong></td>
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<tr>
<td>Objective Technician</td>
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<tr>
<td>Client’s Advocate</td>
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<tr>
<td>Issue Advocate</td>
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</table>
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

- Legislative
- Administrative
- Judicial

Congress passes law; president signs
Agency "promulgates" regulation; "final rule" in FR
Agency may develop "guidelines"

comments from affected parties

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

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)
  - 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.gpoaccess.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

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

food

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

biologic

- 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

- … 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
To market to market 2

CBER & CDER [CVM]
- New Drug Application - NDA
  - Abbreviated NDA
  - Supplemental NDA
- Biologics License Application - BLA
  - Product LA & Establishment 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”

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

Table 3—Fee-Paying FAEs—5-Year Average

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>5-Year Average</th>
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<tbody>
<tr>
<td>Fee-paying FAEs</td>
<td>130.6</td>
<td>140.9</td>
<td>131.5</td>
<td>136.7</td>
<td>137.9</td>
<td>136.4</td>
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Table 4

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<thead>
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<th>Fee Category</th>
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<tr>
<td>APPLICATIONS</td>
<td>$1,770,000</td>
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<tr>
<td>Requiring clinical data</td>
<td></td>
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<tr>
<td>Not requiring clinical data</td>
<td>$580,000</td>
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<tr>
<td>Supplements requiring clinical data</td>
<td>$680,000</td>
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<tr>
<td>NDA AND IND/MTTS</td>
<td>$375,100</td>
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<tr>
<td>PRODUCTS</td>
<td>$645,000</td>
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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, jigglety jig.
To market, to market, to buy a fat hog,
Home again, home again, jigglety jog.
Summarize

- Regulatory process
- FDA rules, process