

BIOE 301: Lecture 22

Role of the Food and Drug Administration

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Agenda

FDA's role in:

- Drugs
- Devices

What does it take to approve new technologies?

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Benefits of Dietary Supplements

- Vitamin C to prevent scurvy
 - Mid-18th century:
 - Scurvy killed more British sailors than war
- Folic acid to prevent neural tube defects
- Calcium to prevent osteoporosis
- Vitamin B₁₂ to prevent dementia
- Research in Alternative Medicine:
 - <http://nccam.nih.gov/>

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Impact of No Regulation

Sulfanilimide (1937)

- Antibiotic for streptococcal infections, used safely as a pill for years
- Most children can't swallow pills
- One company in Tennessee found they could dissolve drug in ethylene glycol (antifreeze)
- Tested for flavor, appearance, fragrance, NOT for toxicity



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Impact of No Regulation

137 children died

- Severe abdominal pain, nausea, vomiting, convulsions

1938

- Food, Drug, and Cosmetic Act
- Gave FDA authority it needed to regulate such products

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Misfortune, disaster, & tragedy

Lead to reforms in drug and
device regulation

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“Take Aways” from Last Class

- Strategies to speed up diffusion are important to disseminating new life saving technologies
- Historical precedents have set the tone for current regulation of drugs and dietary supplements
- It does not end here – more regulation is needed...

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Recent Events

- Toothpaste, other imports
<http://www.npr.org/templates/story/story.php?storyId=11744841>
- “The [FDA] has placed a hold on five types of farmed fish and seafood containing traces of antifungal and antibiotic drugs that are potentially harmful to humans...”
- “The popular Thomas and Friends Wooden Railway toys were voluntarily recalled in early June due to the presence of lead in some of the surface paints. The recall was particularly troubling for parents whose children have been playing – and chewing – on the toys for years.”

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Challenges of Health Technology Regulation in Developing Countries

Commerce becomes increasingly global

- Government of Panama manufactured cold medicines – imported what they thought was glycerin
 - Was actually diethylene glycol, falsely certified
 - Panamanian children began to die



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FDA

- Regulates products whose annual sales account for ¼ of consumer spending in US
- Responsible for ensuring SAFETY and EFFICACY of CHEMICAL, BIOLOGICAL agents and sophisticated medical DEVICES
- Safe:
 - Probable benefits to health for intended use outweigh any probable risk of harm
- Effective:
 - Device does what it is supposed to do in a reliable fashion

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History of Regulation

- 1906
 - First federal regulation of drugs
 - Pure Food and Drug Act
 - As a results of activism (Upton Sinclair and others...)
- 1938
 - Food, Drug and Cosmetic Act
 - As a result of Sulfanilimide tragedy

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History of Regulation

- 1962
 - Drug amendments to FD&C Act
- 1976
 - Medical Device Amendments to FD&C Act
- 1994
 - Dietary Supplement Health & Education Act
 - “...dietary ingredients used in dietary supplements are no longer subject to the premarket safety evaluations required of other new food ingredients or for new uses of old food ingredients...”
 - <http://vm.cfsan.fda.gov/~dms/dietsupp.html>

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1906

- Pure Food and Drug Act
 - Label could not contain any statement regarding therapeutic effect which is false and fraudulent
- FDA could act only after drugs were marketed
- Was not enough to show that product did not work
- Had to show that seller knew the claims it made were false

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1938

- Food, Drug and Cosmetic Act
 - New Drugs:
 - Could not be marketed without first notifying the FDA and allowing agency time to assess safety
 - Beginning of era in which it is illegal to market a new drug without FDA approval
 - Seller's belief regarding product's value was no longer relevant
 - Issue – does the product really work?

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1962

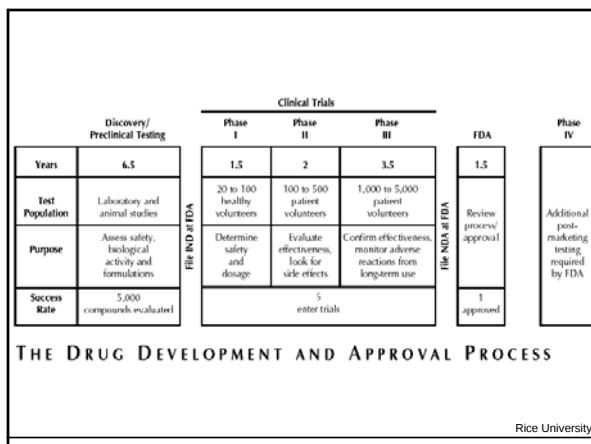
- Drug Amendments to FD&C Act:
 - FDA must review evidence of drug safety and effectiveness
 - Converted pre-market notification system into pre-market approval system
 - Evidence of safety and efficacy must come from well-controlled investigations by qualified experts
- FDA has the authority to prevent harm before it occurs

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Drug Approval Process

- Pre-clinical testing (cell, animal) occurs first
 - Assess toxicity
- Investigational New Drug (IND)
- Human clinical trials allowed with IND
 - Phase 1, 2, 3 clinical trials
- Manufacturer files NDA (New Drug Application) for permission to market new drug

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Phases of Clinical Trials

- Phase 1:
 - Goal: safety of compound
 - Low doses administered to small group of healthy volunteers
 - 20-100 volunteers
- Phase 2:
 - Goal: effectiveness of compound
 - 100-300 patients who suffer from condition
- Phase 3:
 - Final step before seeking FDA approval
 - Randomized clinical trial

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Post-Market Surveillance

- Phase 4:
 - Study longer term effects of drug exposure
 - Report adverse effects to FDA

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Not Many Drugs Make It

- For every 5,000-10,000 drugs that enter pre-clinical testing
- ONE makes it to market
- Cost of developing one new drug:
 - \$360 million-\$800 million

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Post-Marketing Surveillance

- Vioxx – withdrawn from market
- Celebrex – black box warning
- Bextra – sales suspended
- <http://www.fda.gov/medwatch/>
- <http://www.npr.org/templates/story/story.php?storyId=4500447>
- <http://www.npr.org/templates/story/story.php?storyId=5229443>
- <http://www.npr.org/templates/story/story.php?storyId=5336272>

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Regulation of Medical Devices

- FDA did not regulate devices before 1938
- 1938:
 - FDA could only challenge sale of products it believed were unsafe
 - Could only remove them from the market after patient injuries
- 1960s:
 - Rapid innovation in medical technology
 - Tried to regulate many as drugs: contact lenses, IUDs
 - Catastrophic failures of heart valves and pacemakers
- 1970s:
 - Broad recognition that different rules were needed to regulate devices

1976

- Device amendments to FD&C Act:
 - No single policy would work for all devices
 - Tongue depressor
 - Artificial heart
 - Three classes of devices would be used to regulate new technologies



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Three classes of devices...

- Class I:
 - Pose least risk to patient
 - Not life sustaining
 - GMP, proper record keeping required
 - 30% of devices
 - X-ray film, tongue depressors, stethoscopes
- Class II:
 - Not life sustaining, but must meet performance standards
 - Blood pressure monitors, Catheter guide wires
 - 60% of devices
- Class III:
 - Pose greatest risk to patient
 - For use in supporting or sustaining human life
 - 10% of devices
 - Stents, heart valves, LVADs
 - Require GMP, failure modes analysis, animal tests, human clinical studies under IDE

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Role of CDRH

- Ensure that products coming to market have more benefit than risk
- Ensure that products are labeled so that practitioners and patients know what to expect from their use
- Regulates 1,700 types of devices
- 23,000 registered manufacturers
- 1996: received 20,236 device related submissions

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Device Approval Process

- Device + intended use considered together
- Manufacturer submits request for marketing approval
- Advisory panel:
 - One consumer representative (non-voting)
 - One industry representative (non-voting)
 - Physicians and scientists
- FDA not required to follow recommendations of panel, although they usually do

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IDE

- Investigational Device Exemption
 - Enables experimental use of high risk device
 - Must have positive engineering and animal data
 - First give approval for feasibility studies with small number of patients
 - Then proceed to multi-center trials
 - Larger data sets frequently show results from small sample sets are not true

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Humanitarian Use Exemption

- Device designed to treat or diagnose condition that affects <4,000 patients/year
- Device would not otherwise be available without exemption
- No comparable device is available
- Patients will not be exposed to unreasonable or significant risk of injury or illness by device

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Medical Device Reporting

- System to detect device related problems in a timely manner
- Serious injuries or deaths that may have been caused by or related to a medical device must be reported to the manufacturer of the device within 10 days
- Must be reported to the FDA within 10 days

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Recently Approved Devices

New Device Approval

Binax Now® Malaria Test - K061542

This is a brief overview of information related to FDA's approval of an Evaluation of Automatic Class II Designation to market this device.



Product Name: Binax Now® Malaria Test
Manufacturer: Binax, Inc. - a subsidiary of Immunos Medical Innovations, Inc.
Address: 10 Seaboard Road, Suite 170, Seabrook, NJ 08074
Approval Date: Jan 13, 2007 (Approved Evaluation of Automatic Class II Designation)
Approval Letter: <http://www.fda.gov/cdrh/cdrhfiles/k061542.pdf>

New Humanitarian Device Approval

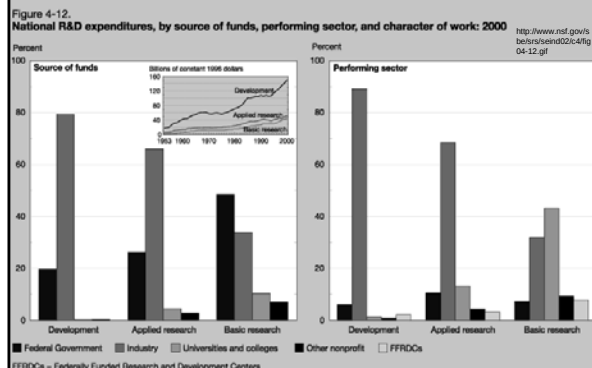
MESOMARK™ - H060004

FDA approved this device under the [Humanitarian Device Exemption \(HDE\) program](#). See the links below to the Summary of Safety and Potential Benefits (SSPB) and other sites for more complete information on this product, its indications for use, and the basis for FDA's approval.

<http://www.accessdata.fda.gov/scripts/cdrh/cdrhfiles/cfTopic/MDA/mda-list.cfm?list=1>



Who Funds R&D? Who Does R&D?

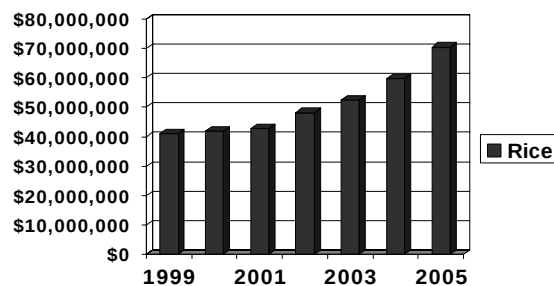


Types of Universities

- Carnegie Classification
 - Taxonomy of colleges and universities
 - Doctorate-Granting Institutions
 - Research Universities /Very High Research Activity ← Rice
 - Research Universities/ High Research Activity
 - Doctoral/Research Universities
 - Master's Colleges & Universities
 - Baccalaureate Colleges
 - <http://www.carnegieclassification-preview.org/index.aspx>

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Total Research Expenditures @ Rice



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R&D Funding for Biomedical Research

- Federal government:
 - Funds ~ 36% of all medical research in US
- Mostly funded through NIH:
 - Current NIH budget: \$28 billion/year
 - NIH budget doubled from 1998-2003
 - This year: 0% increase
 - Focus is on basic research

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US Senate Report – May, 2000

- 21 drugs introduced between 1965 and 1992:
 - Considered by experts to have had highest therapeutic impact on society
 - Public funding of research was instrumental in development of 15 of the 21 drugs (71%)
 - Three-captopril (Capoten), fluoxetine (Prozac), and acyclovir (Zovirax)-had more than \$1 billion in sales in 1994 and 1995
 - Others, including AZT, acyclovir, fluconazole (Diflucan), foscarnet (Foscavir), and ketoconazole (Nizoral), had NIH funding and research to help in clinical trials

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NIH

- National Cancer Institute
- National Eye Institute
- National Heart, Lung, and Blood Institute
- National Human Genome Research Institute
- National Institute on Aging
- National Institute on Alcohol Abuse and Alcoholism
- National Institute of Allergy and Infectious Diseases
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Biomedical Imaging and Bioengineering
- National Institute of Child Health and Human Development
- National Institute on Deafness and Other Communication Disorders
- National Institute of Dental and Craniofacial Research
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institute on Drug Abuse
- National Institute of Environmental Health Sciences
- National Institute of General Medical Sciences
- National Institute of Neurological Disorders and Stroke
- National Institute of Nursing Research
- National Library of Medicine

The Funding Process

- NIH → Issues request for proposals
- Investigator → Writes a proposal
 - Hypothesis
 - Background & Significance
 - Preliminary Results
 - Research Design and Methods
 - Protection of Animals and Human Subjects
- Peer-Review
 - Score
 - Comments
- Institutional Review
- Funding Decision

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Scores

- 1/3 Unscored
- 2/3 Scored
 - 100 best
 - 500 worst
 - Typically need score of 100-170 to be funded
 - Approximately 10-15% of submitted proposals are funded
- Summary sheet

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“Take Aways”

- What were two major laws that were enacted to give the FDA more regulatory responsibilities?
- What were three amendments made to the Food, Drug, and Cosmetic Act that have impacted the way drugs, technology, and supplements are regulated?
- Know the different phases of clinical trials and why they are significant...
- What are the different classes of devices?
- What sort of controversy surrounds Vioxx?

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