

The Pharmaceutical Industry

Martin Donohoe, MD, FACP

The Pharmaceutical Industry Outline

- **Economics**
 - » drug costs
 - » drug development
- **Research**
- **Marketing**
- **Drug Regulation/The FDA**
- **Ethical, Legal and Policy Issues**



Home Care

- 80-90% of illnesses cared for outside formal health care system
- Family (women), friends, media
- Non prescription drug use = 2 x prescription drug use
- Non-prescription drug costs = 1/2 prescription drug costs

Self Medication

- **Inappropriate self (and child) medication**
 - **diarrhea**
 - **the common cold**
 - **other viral infections**

Self Medication

- **Enemas for diarrhea and fever**
- **Mix benadryl and alcohol for insomnia**
- **Educational brochures have variable effect on use of medical services, including OTC medication**

Inappropriate Self-medication: The Common Cold

- **Greater than 800 OTC medications available**
- **Not beneficial in children under 3 years old, except acetaminophen for very high fevers**
- **1/3 of children less than 3 years old treated**
- **2% received ASA
-risk of Reye's syndrome**

Inappropriate Self Medication: Diarrhea

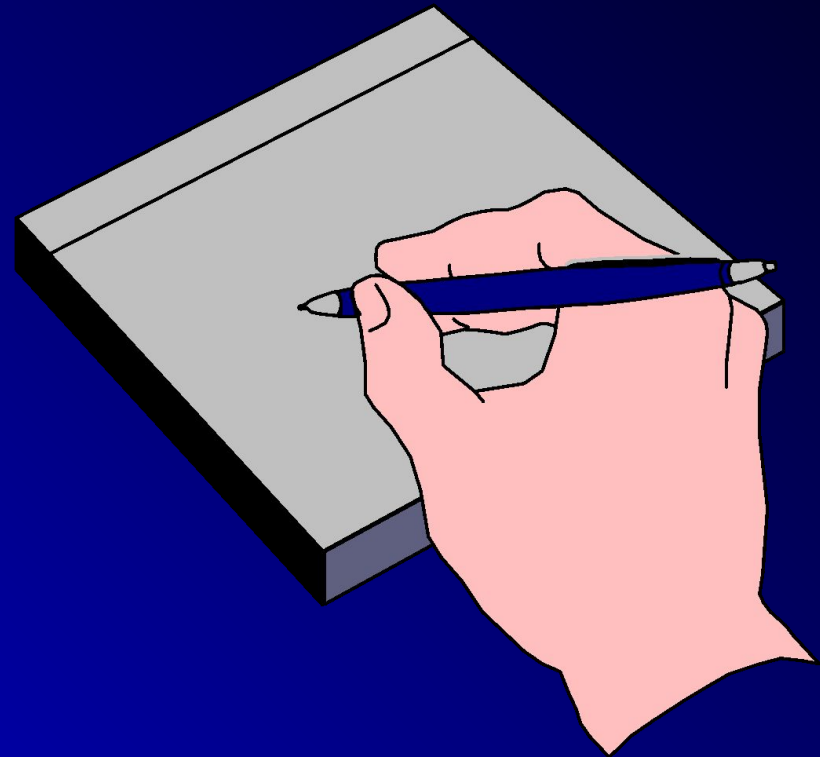
- **Greater than 100 OTC medications available**
- **15% of children less than 3 years old treated**

Inappropriate OTC Medication Use in Children

- Ineffective
- Potential for ADEs and ODs
- Profile of users' parents:
 - better educated
 - uninsured
- Provider visits reduce use
- Provider phone calls do not

Prescription Drugs

- **10,000
FDA-approved
drugs**
- **70% of all office
visits lead to
prescriptions**
- **1.5 - 2.0 billion
prescriptions/year**



Prescription Drugs

- **>10% of U.S. medical costs**
- **account for 44% of increase in health care costs in 1999**

U.S. Drug Use

- **81% have used at least one drug in the preceding week**
 - » **HTN and HA most common reasons**
- **50% took at least one prescription drug**
 - » **7% took 5 or more**
- **14% took herbal supplements (16% of prescription drug users)**

Prescription Drugs

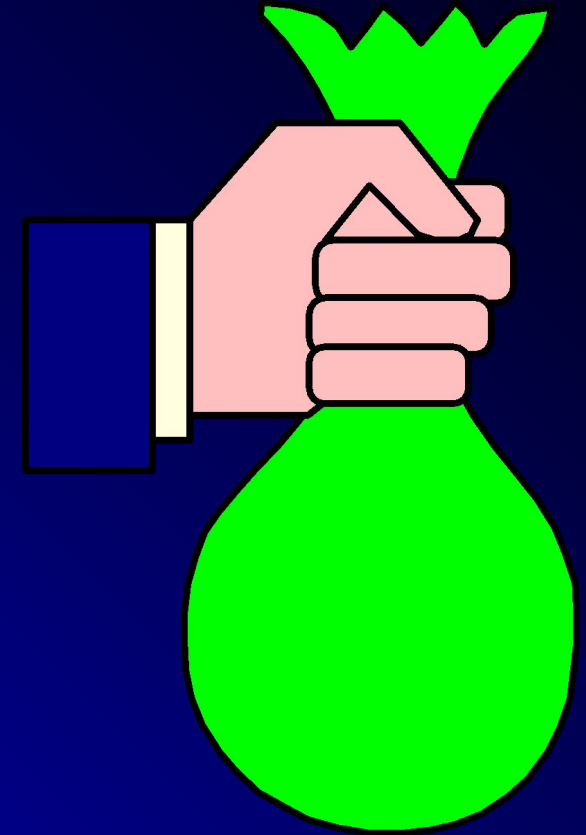
- **Over \$300/person/year, or \$22,500 over a 75-year lifetime**
- **Increased life expectancy from 55-75 from 1920 to present; decreased morbidity (HTN, DM, BPH, PUD, RA, Psychiatric D/Os)**
- **Cost effectiveness of drugs (cost/QALY < \$50,000 for 48-65% of medications)**

Economics of the Pharmaceutical Industry

- **Worldwide sales > \$145 billion/year**
- **US = Largest markets (40 % of worldwide sales)**
- **Sales for the 10 largest drug companies = \$28 billion in 2000, \$37 billion in 2001**
- **tax breaks - can deduct marketing and R & D expenses**

Economics

- **18.6% profit margin in 1999**
 - **16.4% in 2000 (\$24 billion)**
- **Largest of any industry**
 - **4 times greater than average return of all fortune 500 companies**
 - **8 out of 25 most profitable U.S. companies are pharmaceutical companies**



Economics of the Pharmaceutical Industry

- **Greater than 5000 companies worldwide**
 - less than 100 companies account for over 90% of worldwide market
- **Top 5 companies have market shares of 2.75 - 3.5%**

Mergers and Acquisitions

- Drug company mergers

- Pfizer-Warner-Lambert,
Upjohn-Pharmacia,
Glaxo-Wellcome-SmithKline Beecham, etc.

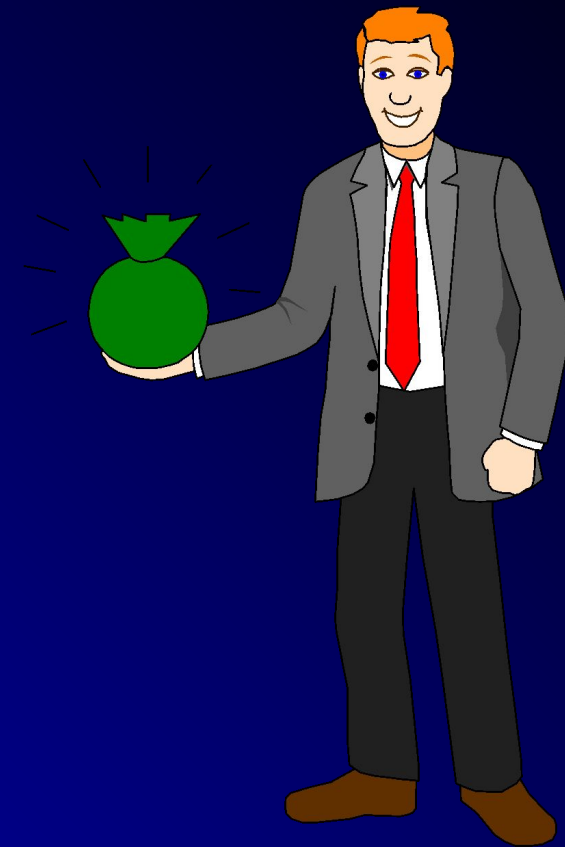
Pfizer acquired Pharmacia in 7/02 for \$60 billion to become the world's most powerful drug conglomerate

Mergers and Acquisitions

- Acquisition of generic divisions and PBM's
 - Merck-Medco
 - Glaxo-Wellcome-Smith-Kline Beecham-DPS
 - Lilly - PCS Health Systems
- Acquisitions of health care providers
 - Zeneca-Sallick Health Care

Economics

- Sales revenues tripled over last decade
- Prices increased 150% (verses 50% CPI)
- Spending up 17% from 2000 top 2001



Economics

- **Average CEO compensation = \$20 million (1998)**
- **Pharmaceutical Manufacturer's Association and Medical Device Manufacturer's Association are powerful lobbies**

Drug Industry Lobbying

- **\$38 million donated to Congressional campaigns in the 1990s**
- **\$84 million in 2000 election (2/3 to Republicans)**
- **GW Bush received \$456,000 during his 2000 election campaign**

Drug Industry Lobbying

- **623 lobbyists for 535 members of Congress**
 - » **Orrin Hatch (R-Utah) - \$169,000 in 2000 - #1**
 - » **John Ashcroft (prev. R-MO, now Atty. Gen'l) - \$50,000 in 2000**
- **Front groups - e.g., Citizens for Better Medicare (\$65 million ad campaign to defeat a Medicare prescription drug plan)**

Drug Costs

- **U.S. highest in the world**
 - 54% > Europe**
 - 34% to 80% > Canada (drug companies still among the most profitable in Canada)**
- **Cross border pharmacy visits increasingly common**
- **the fastest growing component of the \$1.3 trillion US health care bill**

Drug Costs

- **U.S. only large industrialized country not regulating drug prices AND the only major economic power that allows an inventor to patent a medicine (as opposed to the methods and processes used to produce it)**

Drug Pricing Policies and Regulations

- **Product Pricing Control**
 - » France, Italy, Spain
- **Reference Pricing**
 - » Germany, Netherlands
- **Profit Control**
 - » U.K.
- **No control**
 - » U.S.

Decreasing Costs

- **Formularies**
- **Generics**
- **Volume discounts/mail order prescriptions**
- **Patient activism**
-e.g., AIDS/ACT UP
- **Crossing the border**
 - » **Illegal to import prescription drugs, but FDA usually turns a blind eye for 90 day supply or less**

Drugs: Who Pays?

- 55% out-of-pocket
- 25% private insurance
- 17% medicaid
- 3% Other (VA, Workman's Comp, IHS, etc..)

Drug Development: Who Pays?

- \$20 billion in 1999
- Pharmaceutical companies
 - » R & D budget increasing
 - » U.S. taxpayers
 - » NIH-funded research (total NIH budget = 20.3 billion in 2001)
 - » 1995 Reasonable Drug Pricing Clause removed

Drug Development Costs

- **1991 PHRMA study (flawed): up to \$800 million per drug**
- **Other estimate: \$300 – 600 million per new drug**
- **2000 Tufts/Public Citizen Reports: \$110 million**
 - » **55% of the research that led to the discovery and development of the top 5 selling drugs of 1995 paid for by the federal government**

Where Prescription Dollars Go

- **Research and development - 12%**
 - preclinical testing - 6%
 - clinical testing - 6%
- **Manufacturing and distribution - 24%**
- **Sales and marketing - 26%**
- **Administrative / miscellaneous expenses - 12%**
- **Taxes - 9%**
- **Net profit - 17%**

The Elderly and Prescription Drug Coverage

- **Elderly represent 12% of U.S. population, yet account for 33% of drug expenditures**
- **17% of the 37 million elderly Medicare patients are poor or near poor (incomes less than \$7,309 or \$9,316 respectively)**
- **The 64% of elderly Medicare enrollees with no coverage for outpatient drug costs are sicker and poorer than their counterparts with supplemental insurance.**

The Elderly and Prescription Drug Coverage

- **Average outpatient drug expenditure from \$59 - \$1,1153**
- **Drug expenditures increased 13% between 1994 - 1997; SS and SSI benefits increased by 1.3%**

Race, The Elderly and Prescription Drug Coverage

- **Older black Americans are more likely than whites to lack supplemental drug coverage**
 - » **30% vs. 10%**
- **Black Medicare enrollees are more likely than whites to not fill at least one prescription drug due to price in the past year**
 - » **1 in 6 vs. 1 in 15**

The Elderly and Prescription Drug Coverage

- **Consequences:**
 - » **The elderly, chronically ill without coverage are twice as likely to enter nursing homes**
 - » **Noncompliance, partial compliance**
 - » **Increased ER visits, preventable hospitalizations, disability, and costs**

The Elderly and Prescription Drug Coverage

- **Universal outpatient drug coverage cost-saving
-pharmaceutical industry strongly opposed**
- **Bush/Congressional prescription drug benefit proposals woefully inadequate**
- **States trying to decrease costs**
- **State Medicaid budgets in trouble, mostly due to rising drug costs**

The Elderly and Prescription Drug Coverage

- **2001 California Medicare Prescription Drug Discount Program**
- **75% compliance by pharmacies; only 45% before patient requested discount**
- **Compliance lower in poorer neighborhoods**
- **Important to consider the disabled 14% of Medicare enrollees (different drug use patterns)**

Expired Drugs

- Initial packaging date usually 2-3 yrs from the date of manufacture
- Pharmacists repackage – new expiration date usually 1 year
- Some OK
- Not OK:
 - » Epi-pen, ophthalmic agents, others controversial

Drug Reimbursement Systems

- **Copayments**
 - income variation
 - exempted groups
- **Cost-sharing**
- **Expenditure limits**
- **Positive and negative prescribing lists**
- **Therapeutic efficacy categories**

Pharmaceutical Benefits Managers

- 100-115 million patients affected
- Purpose
 - Improve prescribing practices
 - Control Costs
- Open vs closed formularies
- Report cards for MD's, but no good outcomes data

Pharmaceutical Benefits Manufacturers

- **Data**
 - may not decrease costs, due to increased OTC medications use, longer hospital stays, increased use of other drug categories
- **Most purchased by pharmaceutical companies**
 - conflict of interest
 - e.g., increased Merck prescriptions written after acquisition of Medco

Economics

- **320,000 Jobs**
(45% increase over last 10 years)
- **Increased employment / income**
(decreased for other U.S. manufacturing industries)

Generics

- **Increased market share**
 - 1983 = 15%
 - 1993 = 40%
 - 2000 = 42%
- **\$20 billion sales in 1999 (vs over \$90 billion for prescription drugs)**
- **Prices rose almost twice as rapidly as those of brand-name drugs in 2002**

Generics

- **Avg cost \$18 vs \$61 for comparable name-brand drug (1999)**
- **Doctors underestimate costs of name-brand drugs and overestimate costs of generics 90% of the time (Arch Fam Med 2000;160:2802)**

Generics

- **Drug Price Competition and Patent Term Restoration Act (1984)**
 - requires bioequivalence, rather than therapeutic equivalence
- **Pharmaceutical companies purchasing generic divisions (e.g., Merck - Medco)**
- **Large drug firms account for 70% of generic market**

Over-the-Counter Meds

- Price per prescription decreases, but insurance won't cover
- Antihistamines: Claritin, Zyrtec, Allegra
- H2 blockers

Over-the-Counter Meds

- OCPs
- Pharmacist-prescribed emergency contraception
 - » reduces number of unintended pregnancies
 - » cost saving

Generics - Litigation

- Under Hatch-Waxman Law of 1984, lawsuits brought by pharmaceutical companies against generic manufacturers, whether frivolous or not, can delay FDA approval of generic drug by 30 months
- 73% of cases won by brand name companies

Generics - Litigation

- **Dupont Pharmaceuticals vs Barr Laboratories:**
 - » **Coumadin/warfarin**
- **Novartis vs Sangstat**
 - » **Neoral/cyclosporine A**
- **Zenith Goldline Pharmaceuticals vs Abbott Labs**
 - » **terazosin/Hytrin; \$1 million/day**

Lobbying, Patent Extensions and Alternate Formulations

- **Lobbying and Congressional bills**
 - » **Schering Plough / Claritin - \$20 million lobbying campaign, big-name lobbyists (Howard Baker, Dennis Deconcini, Linda Daschle)**
 - » **Koop - Claritin, latex, Rezulin, polyvinyl chloride**
- **Alternate formulations**
 - » **Glucophage XR, Nexium, Sarafem, Prozac Weekly, Fosamax XR**

Lobbying

- **1998: agribusiness spent \$119.3 million lobbying Congress**
- **1998: environmental groups spent \$4.7 million on all issues combined**
- **Active lobbying (new laws, not enforce existing laws or fund existing programs)**
- **“Lobbying for lethargy” (maintain status quo)**

Lobbying

- **All industry = \$1.2 billion/yr (not including campaign contributions and soft money)**
- **All single issue ideological groups combined (e.g., pro-choice, anti-abortion, feminist and consumer organizations, senior citizens, etc.) = \$76.2 million**

Pharmaceutical Company Advertising

- \$15 billion/year in 2000
 - » over \$6 billion - advertising and marketing
 - » over \$7 billion - sales reps' salaries
 - » up to \$15,000/U.S. physician
 - » 50,000 salespersons: 1/10 prescribing physicians

Pharmaceutical Company Advertising – Drug Samples

- \$8 billion/year in samples (10-20% of office visits)
- Only ½ of samples go to patients
 - » Providers dispense samples at 10% - 20% of visits
- 60% of pharm reps self-medicate

Drug Samples

- **Prescription Drug Marketing Act of 1987 prohibits sales of samples**
 - » **Requires practitioner signatures**
 - » **Mandates record-keeping**
 - » **Specifies storage conditions**
- **JCAHO Standards**

Drug Samples

- **Pros/Cons**
- **Alternatives:**
 - » **Coupons**
 - » **Vouchers**
 - » **Medication Assistance Programs**

Truthfulness in Drug Ads

Wilkes et al.

Ann Int Med 1992;116:912-9

- **10 leading medical journals**
- **109 ads and all available references (82%)**
- **3 independent reviewers**

Truthfulness in Drug Ads: FDA Requirements

- True statements
 - effectiveness
 - contradictions
 - side effects
- Balance
- Instructions for use
- Approved uses only

Truthfulness in Drug Ads: Data

- 57% little of no educational value
- 40% not balanced
- 33% misleading headline
- 30% incorrectly called drug the “agent of choice”
- 44% could lead to improper prescribing

Truthfulness in Drug Ads

- **500 FDA violations from 1997-mid-2001**
 - includes 90 DTC ads
- **Increased FDA oversight and enforcement needed**

Untruthfulness in Drug Ads: Reasons

- **Advertisement income**
- **Business branch handles ads**
- **Oversight by journals would be prohibitively expensive**

Truthfulness in Drug Ads

- Higher percentage of ads misleading in Third World
 - » Most agents available OTC
- Doctors are influenced
 - » Prescribing patterns (e.g., Cipro, Calcium Channel Blockers)
 - » 1998: Trovan most promoted drug in US; sales most ever for an antibiotic in one year; use since limited by FDA due to liver toxicity

Doctors are Influenced

Formulary Requests

(JAMA 1994;271:684-9)

- **Met with drug rep – 3.4X more likely to request company's drug**
- **Accepted money to attend symposia – 7.9X**
- **Accepted money to speak at symposia – 3.9X**
- **Accepted money to perform company-sponsored research – 9.5X**

Dubious Advertising Tactics

- **Sponsored symposia and publications**
- **“Buying” ghost-written editorials**
- **Non-peer-reviewed papers in “throwaway” journals**
- **>100 for-profit medical communication companies**

Dubious Advertising Tactics

- **Disorders Made to Order:**
 - » **GAD, Social Anxiety Disorder, ADHD, etc.**
 - » **Sales of antipsychotics quadrupled from 1998-2002**
- **Time-Concepts, Inc. – links doctors with drug reps for a fee**

Direct to Consumer Advertising

- Began in 1980, briefly banned 1983-85
- Expenditures:
 - \$155 million—1985
 - \$356 million--1995
 - \$1 billion--1998
 - \$2.8 billion--2000

Direct to Consumer Advertising

- **US and New Zealand only countries to allow prime time TV advertising**
- **1989 - one drug achieved >10% public recognition**
- **1995 - 13 of the 17 most-heavily marketed**
- **2000 – Schering-Plough spent more to market Claritin than Coca-Cola Enterprises and Anheuser Busch spent to market their products**

Direct to Consumer Advertising: Use of Celebrities

- **Micky Mantle – Voltaren**
- **Bob Dole – Viagra**
- **Joan Lunden – Claritin**
- **“Newman” - Relenza**

Direct to Consumer Advertising

- Better educated/informed patients
- Discovery of unrecognized illnesses: diabetes, hypertension, hep C, ED, BPH
- More proactive patients
 - » >1/3 have sought more info, nearly 1/4 asked for drug by name (3/4 of prescribing doctors acceded to request)
 - » 2000: 8.5 million received a prescription after viewing ads and specifically requesting drug
 - » 50% thought ads received government approval

Direct to Consumer Advertising

- **Doctors more willing to prescribe requested agents**
- **Violations**
 - » **20 of the first 37 ads failed to comply with FDA regulations; 90 violations from 1997-2001**
 - » **FDA can request compliance, but cannot impose fines or other punishments**
 - » **FDA must act through the courts (although most companies comply with FDA requests)**

Direct to Consumer Advertising

- » Pfizer fined \$6 million for TV ads extolling benefits of Cipro over cheaper generic drugs (or no drugs) for childhood ear infections
- » In Spanish medical journals, nearly half of promotional drug ad statements not supported by cited reference
- » Bush administration has extended investigation period → more ineffective oversight

Direct to Consumer Advertising

- **Manufacturers must disclose all known and reasonably knowable risks, whereas physicians need disclose only material risks**
- **Increasing liability of pharmaceutical manufacturers for failure to warn patients of risks and adverse events associated with product use**
 - » e..g., NJ Supreme Court case, *Perez vs Wyeth Laboratories, Inc.*
 - failure to adequately warn consumers of Norplant risks

Direct to Consumer Advertising of Genetic Tests

- HER2 protein: breast cancer
- BRCA-1 and -2: breast and ovarian cancers
- Gaucher's Disease
- Newborn screening tests
- “Jewish genetic conditions”

Direct to Consumer Advertising of Genetic Tests

- **Overstate the value of genetic tests for clinical care**
- **May provide misinformation**
- **Exaggerate consumers' risks**
- **Exploit public's fears/worries**
- **Endorse a deterministic relationship between genes and disease**
- **Reinforce associations between diseases and ethnic groups**

Direct to Consumer Advertising of Genetic Tests

- **Inappropriate:**
 - » **Public has limited sophistication regarding genetics in general**
 - » **Lack of comprehensive premarket review of tests and oversight of advertisement content**
- **Existing FTC and FDA regulations for other types of health-related advertising should be applied to advertisements for genetic tests**

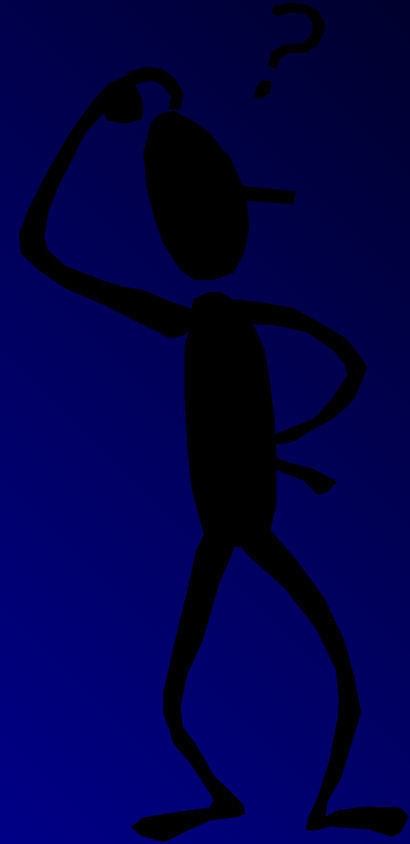
Gollust SE, et al. JAMA 2002;288:1762-1767.

Direct to Consumer Marketing of High-Tech Screening Tests

- E.g., Electron-beam CT / low-dose spiral CT for CAD
- Scientific and ethical issues
- Role of “luxury primary care clinics” / links with academia

Sources of Accurate and Reliable Drug Information

- The Medical Letter
- Peer-reviewed studies and reviews
- The FDA
- Large databases
 - The Cochrane Collaboration
- Textbooks
- Facts and Comparisons
- AHFS Drug Evaluations
- AMA Drug Evaluations
- Conn's Current Therapy
- Not PDR



Pharmaceutical Industry Research

- **Expensive**
 - » **\$150-500 million / new drug**
- **Patent protection = 20 years (was 17 until 1993)**
 - » **Pediatric exclusivity – additional 6 months if test for effects in children → additional \$600 million profits**
- **Average time from IND application to FDA approval = 10-11 years**

The Drug Approval Process

- **Discovery/Characterization**
- **Animal studies**
 - acute toxicity - LD50
 - Subacute toxicity
 - Chronic toxicity
 - Fertility and reproductive effects
 - Mutagenicity
- **IND Filed (20 approved for every 100 filed)**

The Drug Approval Process

- **Human Testing**
 - **Phase I: Pharmacological action, dose tolerance, toxicity, absorption, metabolism, elimination, bioavailability; 50-70 subjects**
 - **Phase II: Controlled trials in 100-200 diseased patients; dose-response curve**
 - **Phase III: Controlled trials in 800-1000 patients assess safety and efficacy; assess drug interactions, effects in elderly, and effects in liver and kidney disease**
- **NDA filed - approved**

FDA Classification of Therapeutic Potential

- **Before 1992:**
 - Type A - important therapeutic gain
 - Type B - modest therapeutic gain
 - Type C - little or no therapeutic gain
- **1992 Onward:**
 - P = priority review, therapeutic gain
 - S = standard review, substantially equivalent

Controlled Substances

- **Schedule I: No accepted medical use; high abuse potential**
-LSD, Heroin, ?Marijuana
- **Schedule II: High abuse/dependence potential**
- Meperidine, Methadone, Oxycodone, Amphetamine, Methylphenidate, Fentanyl, Cocaine

Controlled Substances

- **Schedule III: Lower abuse potential**
-Paregoric, Glutethimide, Pentobarbital
- **Schedule IV: Lower abuse potential**
-Diazepam, Midazolam, Dextropropoxyphene, Pentazocine
- **Schedule V: Low abuse potential**
- Buprenorphine, Propylhexedrine

Pharmaceutical Industry Research

- **IND phases 1, 2, and 3**
- **10,000 synthesized/tested compounds**
- **10 enter clinical trials**
- **1 FDA approved**

Issues in Drug Company Research

- 22% of new drugs developed over the last 2 decades truly innovative (i.e., not “me too” drugs)
- Unethical studies
 - » placebo controlled trials (e.g., anti-depressants, anti-psychotics, anti-emetics, anti-hypertensives, anti-inflammatory, etc...)
 - » Third World trials (AIDS/Africa; Surfaxtin (Discovery Labs with J&J/Brazil))

Seeding Trials

- **Sponsored by sales and marketing dept., rather than research division**
- **“Investigators” chosen not for their expertise, but because they prescribe competitor’s drug**
- **Study design poor**

Seeding Trials

- Up to 25% of patients enrolled in clinical trials
- Disproportionate amount paid for “investigator’s” work (writing a prescription)
- Physicians more favorable towards than patients

Issues in Drug Company Research

- **Species extinction/loss of biodiversity**
 - » **Taxol- Yew tree**
- **Indigenous peoples' rights over genetic resources and folk medicine knowledge**
 - U.N. Commission on Biodiversity
- **Patenting genes – right or wrong**

Issues in Drug Company Research

- **Novel therapeutic agents vs. copycat drugs**
- **Methodological Flaws**
 - » **Study design bias / invalid comparisons (young patients, inadequate dose of comparison drug)**
 - » **inadequate statistical power**
 - » **multiple exclusion criteria**



Issues in Drug Company Research

- **Methodological Flaws (cont.)**
 - » **economic analyses not performed**
 - » **therapeutic benefit claims more often supported by data than claims of less toxicity**
 - » **publication bias – tendency of corporate sponsors to publish only favorable results**

Issues in Drug Company Research

- 60% of industry-sponsored trials are contracted out to for-profit research firms, which in turn may contract with for-profit NIRBs for ethical review.
- Industry ethics consultants – watchdogs or showdogs
- Erosion of medical ethics

Issues in Drug Company Research Symposia

- Many are drug-company sponsored
- More likely to have a run-in period (eliminates non-compliers, adverse reactors)
- Favorable outcomes more likely
- Misleading titles
- Brand names
- Less peer review
- Promote unapproved uses

Non-Compliance

- Short term = 20%
Long term (CHF, DM, TB) = 40-60%
Long term (other studies):
 - 1/2-2/3 take > 80%
 - 1/3 take 40-80%
 - remainder < 40%
- Decreases with increased patient satisfaction
- No effect of age
- Illiteracy - 42 million Americans

Risks of Noncompliance

- Poorer health outcomes
-e.g., CAD/B-Blockers - MI
- Increases ER visits and hospitalizations
-10% of elderly hospitalizations

Monitoring Compliance

Direct Methods

- **Direct observation**
- **Pill counts**
- **Pharmacy records**
- **Serum/urine drug/marker levels**
- **Expected biologic effects**
- **Electronic medication dispensers**

Monitoring Compliance

Indirect Methods

- **Patient interview**
 - » **Asking patients**
 - » **Physician estimate**
- **50% Sensitivity**

Reasons for Noncompliance

- **Poor patient education**
- **Cost**
 - » **M.D. awareness poor**
 - » **Doctors more likely to under- than overestimate**
- **Dosing frequency**
- **Social barriers, public stigmatization**

Improving Compliance

- **Patient education**
- **Patient satisfaction**
- **Cost consciousness**
- **Eliminate copayments**

Improving Compliance

- **Decrease dosing frequency**
- **Tailor to specific patient activities**
- **Tid > q 8 hours**
- **Easy-to-use packaging/pill boxes/alarms**

Adverse Drug Events

- **Improper use by patients**
\$20 billion in direct costs
\$55 billion indirect costs
- **Prescribing/administrative errors**
3-6% of all medical admissions
1.4 medication errors/admission

Adverse Drug Events

(Harvard Medical Practice Study)

- **6.5 ADEs/100 admissions**
 - 1% fatal (est. 140,000 deaths/yr. in U.S.)**
 - 12% life-threatening**
 - 30% serious**
 - 57% insignificant**
- **28% preventable**
 - 42% life-threatening and serious reactions**

Adverse Drug Events

- **Error occurred at:**
 - Ordering - 56%
 - Administration - 34%
 - Transcription - 6%
 - Dispensing - 4%

Adverse Drug Events

- **Analgesics, sedatives, antipsychotics most commonly misused**
- **Pharmacoepidemiology/post-marketing surveillance**
 - » **Chloramphenicol - blood dyscrasias**
 - » **DES - clear cell adenoCA of cervix and vagina**

Adverse Drug Events: Reasons

- Drug knowledge dissemination
- Dose and identity checking
- Patient information availability
- Order transcription

Adverse Drug Events: Reasons

- Allergy missed / not noted
- Medication order tracking
- Interservice communication
- Change in hepatic or renal function

Adverse Drug Events

- 4th leading cause of death (?)
- Increased length of stay
- Increased risk of death
- Increased costs
\$2,262 - \$4,685 per inpatient event

Alternative Medicine

- **expenditures = \$27 billion out of pocket in 1997**
- **\$17.8 billion on supplements in 2001**
- **12% use herbs in one year (vs. 2.5% in 1990)**
 - » **\$5.1 billion in out-of-pocket payments**
- **46% of patients use an unconventional therapy**

Alternative Medicine

- **Between 1996 and 1998, 8% of normal-weight women and 28% of obese women used non-prescription weight loss products**
- **More CAM visits than PCP visits in 1997**
- **72% do not inform their physicians**

Efficacy of Herbal Products

- **Ginkgo biloba – possible minimal effects on dementia; likely unhelpful for intermittent claudication**
 - » Side effects: HA, N, D, skin rash, cerebral or extracerebral hemorrhage, seizures, Stevens-Johnson Syndrome
- **Hawthorne extracts – likely unhelpful for cardiovascular disease**
 - » Side effects: GI, palpitations, chest pain, circulatory disturbances and vertigo with high doses; may enhance positive inotropic effects of digoxin

Efficacy of Herbal Products

- **Saw palmetto – possible mild decrease in BPH symptoms, unknown effects on long-term outcomes, development of prostate CA**
 - » Side effects: mild, GI, similar to placebo
- **St. John's Wart – unlikely to help depression**
 - » Side effects: GI, dizziness, confusion, dry mouth, restlessness, HA, skin rash, sexual dysfunction, frequent urination, phototoxicity, mania psychositic relapses in schizophrenia patients, serotonin syndrome in users of SSRIs
- **Echinacea and Vitamin C – unlikely to prevent or modify common colds**

Risks Of Herbal And “Naturopathic” Remedies

- **Manufacturer may claim that the product affects the structure of function of the body, as long as there is no claim of effectiveness for the prevention or treatment of a specific disease, and provided there is a disclaimer informing the user that the FDA has not evaluated the agents**
- **Multiple violations / near violations**

Risks Of Herbal And “Naturopathic” Remedies

- **Products unregulated/untested**
- **Variable**
 - » **collection**
 - » **processing**
 - » **storage**
 - » **naming**
 - » **purity**

Risks Of Herbal And “Naturopathic” Remedies

- **Adulterants and contaminants include:**
 - » **Botanicals – e.g., digitalis, belladonna**
 - » **Microorganisms – Staph aureus, E coli, Salmonella, Shigella, Pseudomonas**
 - » **Microbial toxins – aflatoxins, bacterial endotoxins**
 - » **Pesticides**
 - » **Fumigation agents**
 - » **Toxic metals – lead, cadmium, mercury, arsenic**
 - » **Drugs – analgesics and antiinflammatories, corticosteroids, benzodiazepines, warfarin, fenfluramine, sildenafil**

Risks Of Herbal And “Naturopathic” Remedies

- Est. less than 1% of adverse reactions reported to FDA (vs. 10% est. for prescription drugs)
- 19,468 adverse events reports to poison control centers in 1998, vs. 500 to FDA
- Potential toxicities: cardiac, CNS, liver, kidney
- High risk users:
 - » Elderly, pregnant and nursing women, infants
 - » Poor overall health status
 - » Chronic users, prescription drug users

Risks of Herbal and “Naturopathic” Remedies

- Dietary supplements containing ephedrine, caffeine
 - » HTN, MI, CVA, psychosis, seizures
- Chapparal, germander, comfrey, skullcap, sassafras
 - » Hepatotoxic, carcinogenic
- Contaminated L-tryptophan
 - » Eosinophilia-Myalgia Syndrome

Risks of Herbal and “Naturopathic” Remedies

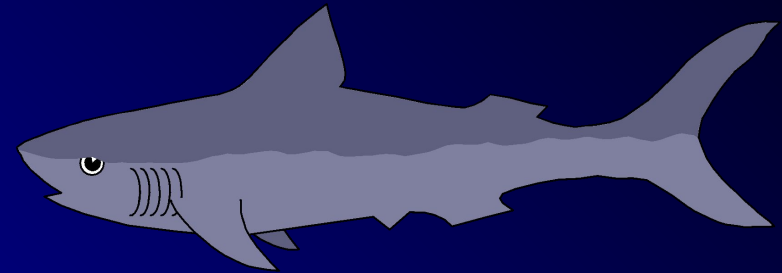
- **GE-L-tryptophan → EMS (1989): 5,000 in US affected, 37 deaths, 1500 permanently disabled**
- **Heart attacks, dysrhythmias, strokes and seizures from ephedra**
- **Bleeding from garlic, gingko, and ginseng**
- **hypoglycemia from ginseng**

Risks of Herbal and “Naturopathic” Remedies

- **potentiation of anesthetic effects by kava and valerian**
- **increased metabolism of many drugs by St. John’s wort**
- **↓CyA effectiveness secondary to St John’s Wort → transplant rejection**
- **1998: 32% of Asian patent medicines sold in the US contained undeclared pharmaceuticals or heavy metals**

Glucosamine/Chondroitin

- **Meta-analysis showed unlikely to be beneficial for RA and OA**
- **Major source = sharks**
- **Mass extinction; 70% of world's fisheries are fully exploited to overexploited; 75-85% reduction of US coastal shark species over last 10 yrs**
- **large “gray market” in shark products**



Pet Pharmaceuticals

- **\$3 billion market**
- **Clonicalm (clomipramine) for separation anxiety in dogs**
- **Anipryl (seligeline) for canine Cognitive Dysfunction Syndrome**
- **“Sea pet” shark cartilage treats for doggie arthritis**

Blurring the line between drugs and cosmetics

- **1999 spending on cosmetics:**
 - » **Hair care products: \$8 billion**
 - » **Skin care products: \$8 billion**
 - » **Makeup: \$6 billion (women devote an average of 19 minutes per day to their faces)**
 - » **Fragrance: \$6 billion**
 - » **Fingernail items: \$1 billion**

Botox

- **Botulinum toxin:**
 - » **Cause of botulism**
 - » **potential biowarfare/bioterror agent**
- **Medical Uses: blepharospasm, spasmodic torticollis, certain types of wrinkles**
- **Unlikely to work on sun- or smoking-induced wrinkles**

Botox

- **Manufacturer = Allergan**
- **1.6 million patients, \$309.5 million sales (\$100 million for cosmetic uses) in 2001**
- **Sales expected to top \$1 billion/year**
- **Upcoming \$39 million direct-to-consumer ad campaign**
- **\$80/dose + physician's fee (\$300 to \$1,000)**

Botox

- **Most users white, age 35-50**
- **12% are men**
- **In-home Botox parties; Botox scams**
- **Hollywood actors**
- **Potential future uses: migraines, back spasms, chronic pain, axillary hyperhidrosis**

Botox

- **Retreatments required q 3-4 months**
- **Side effects: masklike facies, slackness and drooling, rare allergic reactions**
- **Rivals = collagen injections (from cows, possible allergic responses), Perlane (“natural” collagen alternative from human tissue), Myobloc, face lift/eyelid surgery**

Under- and overuse of antibiotics

- **MDR TB in Russian prisons**
- **bronchitis and viral URIs in the US**
 - » **Recent decrease in use in children and adolescents, although still excessive**
- **Pet superstores and websites sell multiple antibiotics**

Factory Farms, Antibiotics and Anthrax:

Putting Profits Before Public Health

Martin Donohoe, MD, FACP

Outline

- **Factory Farming**
- **Agricultural Antibiotics**
- **Cipro and Anthrax**
- **Bayer**
- **Conclusions**

Factory Farming

- **Factory farms have replaced industrial factories as the # 1 polluters of American waterways**
- **1.4 billion tons animal waste generated/yr**
- **130 x human waste**

Factory Farming

- **Cattle manure 1.2 billion tons**
- **Pig manure 116 million tons**
- **Chicken droppings 14 million tons**

Factory Farm Waste

- Overall number of hog farms down from 600,000 to 157,000 over the last 15yrs, while # of factory hog farms up 75%
- 1 hog farm in NC generates as much sewage annually as all of Manhattan

Factory Farm Waste

- Most untreated
- Ferments in open pools
- Seeps into local water supply, estuaries
 - » Kills fish
 - » Causes human infections - e.g., Pfisteria piscii, Chesapeake Bay
- Creates unbearable stench
- Widely disseminated by floods/hurricanes

Agricultural Antibiotic Use

- **Agriculture accounts for 70% of U.S. antibiotic use**
 - » **Use up 50% over the last 15 years**
- **Almost 8 billion animals per year “treated” to “promote growth”**
 - » **Larger animals, fewer infections in herd**

Consequences of Agricultural Antibiotic Use

- **Campylobacter fluoroquinolone resistance**
- **VREF (poss. due to avoparcin use in chickens)**

Antibiotic Resistant Pathogens

- **CDC: “Antibiotic use in food animals is the dominant source of antibiotic resistance among food-borne pathogens.”**
- **\$4billion/yr to treat antibiotic-resistant infections in humans**

Alternatives to Agricultural Antibiotic Use

- **Decrease overcrowding**
- **Better diet/sanitation/living conditions**
- **Control heat stress**
- **Vaccination**
- **Increased use of bacterial cultures and specific antibiotic treatment in animals when indicated**

Alternatives to Agricultural Antibiotic Use: Vegetarianism

- ↓ water/grain needs
- ↓ animal fecal waste
- ↓ rendering/mad cow disease
- ↓ rBGH (→ ↑IGF-1 in milk)
- Health benefits
- Meatpacking = most dangerous job in US

Alternatives to Agricultural Antibiotic Use: Vegetarianism

**European Union bans antibiotics
as growth promoters in animal
feed (1/06)**

Food-Borne Illness

- **1/4 of US population affected per year**
- **Each day 200,000 sickened, 900 hospitalized, 14 die**
- **↑d in part due to ↑ing centralization of meat supply**
 - » e.g., E. coli OH157

Campylobacter

- **Most common food-borne infection in US**
- **2.5 million case of diarrhea and 100 deaths per year**

Campylobacter Resistance to Fluoroquinolones Increasing

- **13% in 1998, 18% in 1999**
- **Fluoroquinolone use up 40% over same period**
- **Continues to increase**
- **FDA proposed ban on fluoroquinolone use in poultry**
 - » **Supported by APHA, PSR and others**

Fluoroquinolones

- **Animal Use**
 - » **Sarafloxacin (Saraflox) – Abbott Labs – voluntarily withdrawn from market**
 - » **Enrofloxacin (Baytril) – Bayer– FDA withdraws approval (7/05)**
- **Human Use**
 - » **Ciprofloxacin (Cipro) - Bayer**

Anthrax

- **Cipro – patent expires 2004**
- **Doxycycline – generic**
- **Penicillin - generic**
- **Huge potential profits**
 - » **280 million Americans, others**
 - » **20-25% increase in Cipro sales one month after 2001 anthrax mailings, per the nation's largest PBM**

Cipro

- **Best selling antibiotic in the world for the last 8 years**
- **Eleventh most prescribed drug in the US**
- **20th in US sales**
- **1999 gross sales = \$1.04 billion**

Bayer and Cipro

- **1997 onward – Bayer pays Barr Pharmaceuticals and two other competitors \$200 million not to manufacture generic ciprofloxacin, despite a federal judge’s 1995 decision allowing it to do so**
- **2002 – Bayer granted six months additional patent on Cipro, under pediatric extension bill, in exchange for conducting safety and efficacy tests on children**

Cost of Cipro

- Drugstore = \$4.50/pill
- US government = \$0.95/pill for anthrax stockpile (twice what is paid under other government-sponsored public health programs)

Cost of Cipro

- **US government has the authority, under existing law, to license generic production of ciprofloxacin by other companies for as little as \$0.20/pill in the event of a public health emergency**
- **It has failed to do so**
- **Canada did override Bayer's patent and ordered 1 million tablets from a Canadian manufacturer**

Why?

- **Weakening of case at WTO meetings that the massive suffering consequent to 25 million AIDS cases in Sub-Saharan Africa did not constitute enough of a public health emergency to permit those countries to obtain and produce cheaper generic versions of largely unavailable AIDS drugs**
- Africa accounts for 1% of world drug sales**

Other Consequences

- **Opens door to other situations involving parallel importing and compulsory licensing**
- **Threatens pharmaceutical industry's massive profits**
 - » **the most profitable industry in the US**
- **Weakens pharmaceutical industry's grip on legislators**
 - » **\$80 million dollars spent on lobbying in 2000 election**
 - Revolving door between legislators, lobbyists, executives and government officials**

Bayer

- **Based in Leverkusen, Germany**
- **120,000 employees worldwide**
- **Annual sales = \$28 billion**
- **US = largest market**

Bayer

- **Pharmaceuticals**
- **Third largest manufacturer of herbicides in the world**
- **Dominates insecticide market**

Bayer

- **Number one biotech company in Europe (after 2001 purchase of Aventis CropScience)**
- **Controls over half of genetically-modified crop varieties up for approval for commercial use**
- **Risks of GMOs**

History of Bayer

- **WW I: invented modern chemical warfare; developed “School for Chemical Warfare”**
- **WW II: part of IG Farben conglomerate, which exploited slave labor at Auschwitz, conducted unethical human subject experiments**

History of Bayer

- **Early 1990s – admitted knowingly selling HIV-tainted blood clotting products which infected up to 50% of hemophiliacs in some developed countries**
 - » **US Class action suits settled for \$100,000 per claimant**
 - » **European taxpayers left to foot most of bill**

History of Bayer

- **1995 onward - failed to follow promise to withdraw its most toxic pesticides from the market**
- **Failed to educate farmers in developing nations re pesticide health risks**
- **2 to 10 million poisonings / 200,000 deaths per year due to pesticides (WHO)**

History of Bayer

- **1998 –pays Scottish adult volunteers \$750 to swallow doses of the insecticide Guthion to “prove product’s safety”**
 - » **Suing the FDA to lift moratorium on human-derived data**
- **2000 – cited by FDA and FTC for misleading claims regarding aspirin and heart attacks/strokes**

History of Bayer

- **2000 – fined by OSHA for workplace safety violations related to MDA (carcinogen) exposures**
- **2000 – fined by Commerce Dept. for violations of export laws**

History of Bayer

- **2001 – FDA-reported violations in quality control contribute to worldwide clotting factor shortage for hemophiliacs**
- **2002 - Baycol (cholesterol lowering drug) withdrawn from market**

Bayer's Corporate Agenda

- **Bluewash: signatory to UN's Global Compact**
- **Greenwash: "crop protection" (pesticides)**
- **Promotion of anti-environmental health agenda:
"Wise Use," "Responsible Care" movements**

Bayer's Corporate Agenda

- **Corporate Front Groups: “Global Crop Protection Federation”**
- **Harrassment / SLAPP suits against watchdog groups**
 - » e.g., **Coalition Against Bayer Dangers**

Bayer's Corporate Agenda

- **Lobbying / Campaign donations / Influence peddling:**
 - » **Member of numerous lobbying groups attacking “trade barriers” (i.e., environmental health and safety laws)**
 - » **\$600,000 over last five years to US politicians**
 - » **\$120,000 to GW Bush's election campaign**

Bayer

- **Fortune Magazine (2001):** one of the “most admired companies” in the United States
- **Multinational Monitor (2001):** one of the 10 worst corporations of the year

Conclusions

- **Triumph of corporate profits and influence-peddling over urgent public health needs**
- **Stronger regulation needed over:**
 - » **Agricultural antibiotic use**
 - » **Drug pricing**
- **Stiffer penalties for corporate malfeasance necessary (fines and jail time)**
- **Important role of medical/public health organizations and the media**

Frankenfoods (aka “Brave New Foods”)

- **Genetically-engineered seeds are now being used to plant 25% of America’s corn crop, 30% of it’s soybeans, and 50% of canola**
- **At least 60% of convenience foods now sold in the U.S. contain genetically-altered ingredients**
- **No labeling required**
- **FDA and EPA: Genetically-altered foods “have not been shown to be unsafe.”**
- **1998 *Nature* study - transgenic traits 20x more likely to “flow” to other plants by cross-pollination**

Frankenfoods

- *Bacillus thuringiensis* corn - resistant to the corn-boring bug, but pollen from corn lands on milkweed, which monarch butterfly larvae and caterpillars eat → death.
- Beans and grains with more protein
- caffeine-less coffee beans
- strawberries packed with more natural sugars
- red grass, mauve carnations
- Companies - Shell, Monsanto, Mitsubishi, Sandoz, Aventis, Pharmacia, Hoechst

Frankenfoods

- **FDA being sued for allowing genetically-engineered foods on the market without adequate safety review**
 - » **FDA reviewer worked for Monsanto before and after his FDA tenure**
- **Majority of Americans unaware GM foods already widely marketed**
- **Japan - labeling common; India - bans testing of altered crops; British Medical Association has called for a ban on testing and production**

Excessive Paper Packaging in Pharmaceutical Samples

- Paper packaging 39% of US garbage; only 42% recycled; landfill space decreasing
- Deforestation
- One of each IM clinic drug samples:
 - » paper packaging 65% of overall package weight
 - » pill volume/paper product box volume = 0.0132
- Sample packages large, waste paper, take up excessive space

The History of U.S. Drug Regulation

- **1785: Massachusetts - first food adulteration law**
- **1848: Drug Importation Act – prohibits importation of unsafe or adulterated drugs**
- **1902: Biologics Control Act – gives government regulatory power over antitoxin and vaccine development**

The History of Drug Regulation

- **1906: Pure Food and Drug Law (The Jungle)**
- **1912: Shirley Amendment**
-makes false advertising illegal
- **1914: Harrison Narcotic Act**
-criminalizes distribution and possession of certain psychoactive drugs (1960s - LSD, 1980s - Ecstasy)

The History of U.S. Drug Regulation

- **1927: Caustic Poison Act**
 - warning labels, antidote information required
- **1938: Food, Drug and Cosmetic Act**
 - establishes FDA
 - Drug safety required pre-marketing
 - diethylene glycol in Elixir of Sulfonamide

The History of U.S. Drug Regulation

- **Early 1940's**
 - animal testing required before human testing
- **1951: Durham-Humphrey Amendment**
 - differentiates prescription from non-prescription drugs
- **1958: Food Additives Amendment**
 - requires premarketing safety (not benefit)
 - Olestra, folate
 - Delaney Clause

The History of U.S. Drug Regulation

- **1962: Kefauver-Harris Amendment**
 - response to thalidomide crisis
 - requires pre-marketing effectiveness
- **1974: Proxmire Amendment:**
 - “nutritional supplements are not drugs”

The History of Drug Regulation

- **1976: Medical Device Amendment**
- **1977: Pregnant and (potentially pregnant) women excluded from drug trials
-overturned in 1993**
- **1977: Saccharin Labeling Act**

The History of U.S. Drug Regulation

- **1981: Drug Ad Regulations passed**
- **1982: Tamper-Resistant Packaging Regulations**
 - Tylenol/Cyanide
- **1983: Orphan Drug Act**
 - 5000 diseases affecting < 200,000 Americans
 - Financial incentives (increased patent protection, 50% tax breaks, research funding)
 - 700 drugs

The History of U.S. Drug Regulation

- **ODA: More than 40 drugs developed, including 28 new molecular entities**
 - Ceredase, rHGH, r-EPO
 - Controversies
 - 1991 Modification (patent lapses after \$200 million in cumulative sales)
- **1984: Drug Price Competition and Patent Restoration Act**
 - generic bioequivalence, rather than therapeutic equivalence, now required for approval

The History of U.S. Drug Regulation

- **1994: Dietary Supplement Health and Education Act**
 - supplements excluded from purity, composition, effectiveness and safety review
 - supported by Orrin Hatch (R-Utah), recipient of \$169,000 from pharm ind in 2000, more than any other Senator)
 - Office of Dietary Supplements established at NIH

The FDA: Current Issues

- **Nicotine/Cigarette regulation**
- **Policies re transgenic foods**
- **Guidelines on industry-sponsored events, texts and reprints, gifts, speakers fees**
- **Codes of conduct, renunciation of human rights abuses (e.g., use of pharmaceuticals in lethal injections)**

The FDA: Current Issues

- **Waiver of informed consent during wartime**
 - Pyridostigmine
 - Botulinum-toxoid vaccine
- **Regulation of drug promotion on the Internet**
 - links between websites
 - international issues
 - chatrooms and newsgroups
- **Funding/existence uncertain**
 - S.B. 830

The FDA Modernization and Accountability Act of 1997 (SB-830)

- **Cuts from 2 to 1 the number of trials required to show efficacy and safety for new drugs and devices**
- **Allows manufacturers to make unproved claims regarding the costs and health care consequences of their products to bulk purchasers**
- **Allows device manufacturers to choose their own safety/efficacy reviewer, with whom they can negotiate payment terms directly**
- **Removes mandatory post-marketing surveillance of implantable medical devices**

US Drug Regulation

- **2002: The Best Pharmaceuticals Act for Children**
 - » **Extends patent protection when companies promise to conduct additional studies in children**
 - » **No oversight mechanism**

Ethical issues re drug research in children

FDA Oversight

- **2100 scientists in 40 labs in Washington, D.C. and around the U.S.**
- **1100 investigators and inspectors**
 - » **Monitor and inspect 95,000 FDA-regulated businesses**
 - » **Visit >15,000 facilities per year**
 - » **Collect 80,000 domestic and imported product samples for label checks**

FDA Oversight

- **3000 products per year found to be unfit for consumers and withdrawn from marketplace**
- **30,000 import shipments per year declined at port of entry because the goods appear to be unacceptable for use in the United States**

FDA Oversight

- U.S. outpaces Germany and Japan (and equals the UK) in rate of approving new drugs
- Avg. time to approval 14 mos (2000) vs 34 mos (1993)
- Regulation success stories
 - thalidomide



FDA Oversight

- **“Me too” drugs vs. “new molecular entities”**
 - » FDA approved 341 NMEs from 1991-2001
- **User fees speed review and approval**
 - » >\$300,000/drug
- **Over half of FDA scientific experts conducting drug application review have financial conflicts of interest because of industry ties.**

FDA Oversight

- **17 FDA-initiated market withdrawals, 1970-1995**
-temafloxacin, flosequinan, Redux, Rezulin, etc.
- **9 withdrawals over last 6 years**
 - » Lotronex (off/on), Rezulin, Duract, Policor, Trovan, Raxar, Baycol, etc.

FDA Oversight: Recalls and Safety Alerts

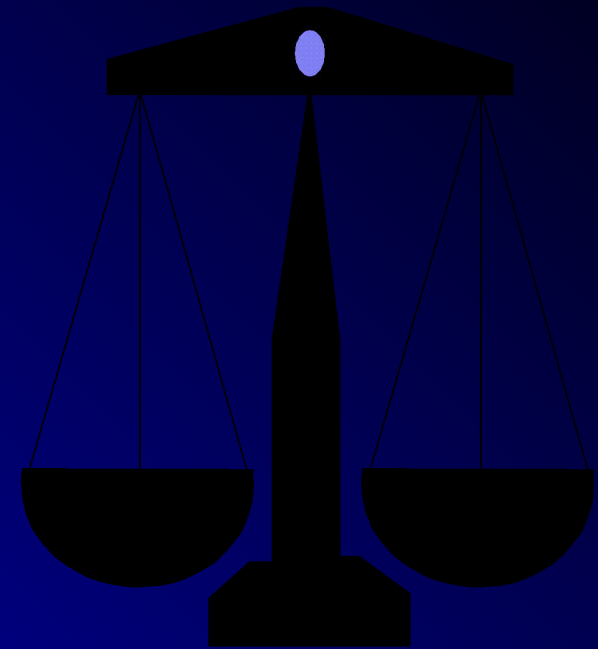
- **52 advisories involving 408,500 pacemakers and 114,645 ICDs from 1/90 - 12/00**
- **increasing rate between 1995 and 2000**
- **Over 1000 devices recalled each year**
- **1.3 million device checks and analyses**
- **36,187 device replacements**
- **\$870 million**

FDA Oversight

- **Ad review and phase 4 studies (post-marketing surveillance) underfunded (\$17 million annually for safety review = amount Americans spend on prescription drugs in 90 minutes)**
 - » **completion rates of phase 4 commitments <10%**
- **more than half the experts hired to advise the FDA on drug safety have industry ties**
- **At 55% of FDA meetings between 1/98 and 6/00, at least half the members had a financial stake in the proceedings**

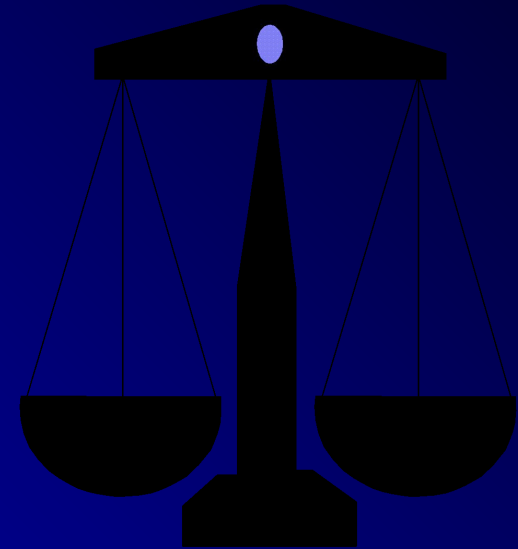
Criminal activities

- **FTC investigating**
 - » **Astra-Zeneca for blocking generic competition for Prilosec;**
 - » **Bristol-Meyers Squibb for illegally preventing competitors from selling generic versions of Taxol**
 - » **Mylan laboratories for illegally tying up chemical feed-stocks used to make generic lorazepam**
 - » **Hoechst for preventing Cardizem CD from going generic**



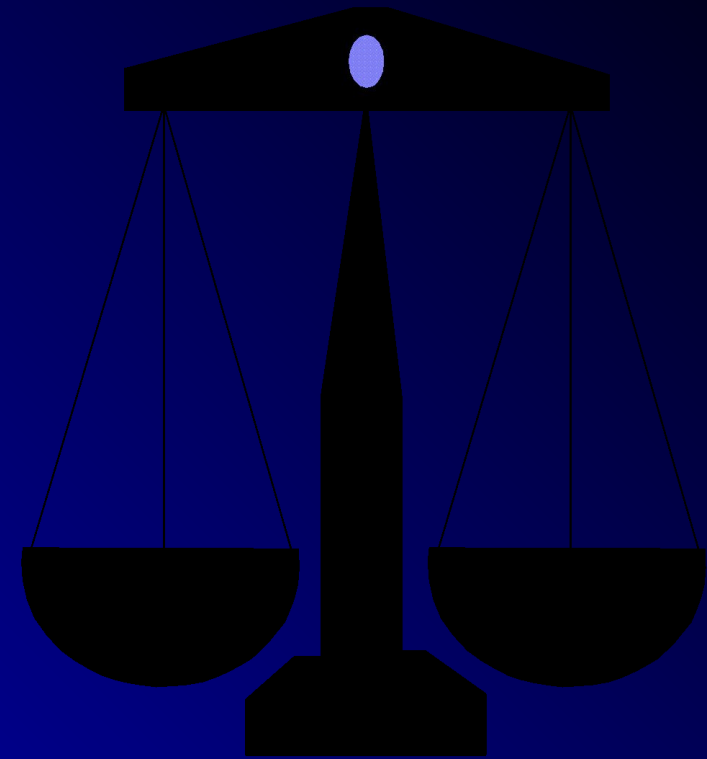
Criminal activities

- Schering-Plough charged with paying \$90 million to 2 competitors to postpone introduction of generic versions of K-Dur
- Pfizer to pay \$49 million for Medicaid fraud re Lipitor charges
- Schering-Plough to pay \$500 million in connection with production of 125 different drugs in factories that failed to comply with good manufacturing practices



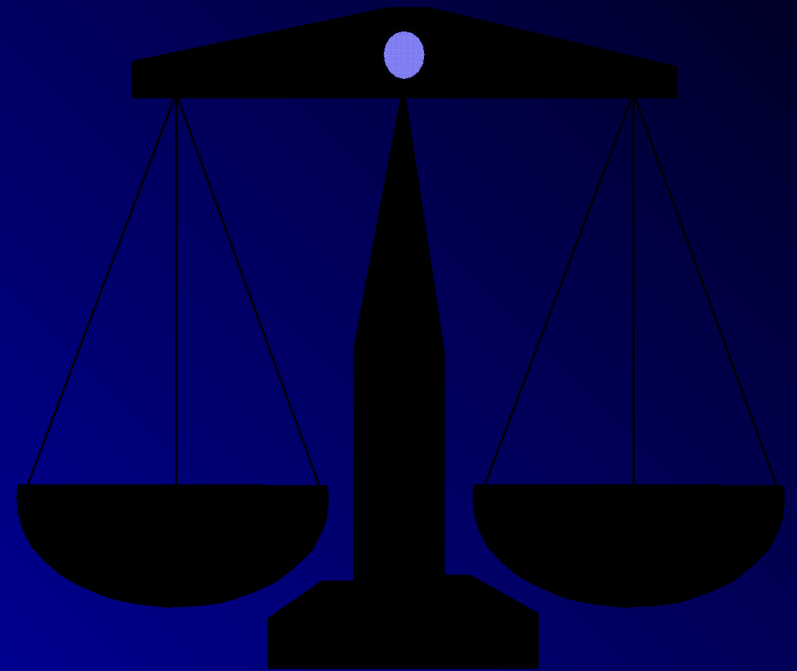
Criminal activities

- **Lilly pleaded guilty to criminal charges for withholding information from the FDA about deaths and life-threatening drug reactions due to Orflex**
 - » 49 deaths + 1,000 serious injuries
 - » \$45,000 fine
- **SmithKline/Selacryn**
 - » 36 deaths; 500 cases of liver and kidney damage
 - » \$34,000 fine



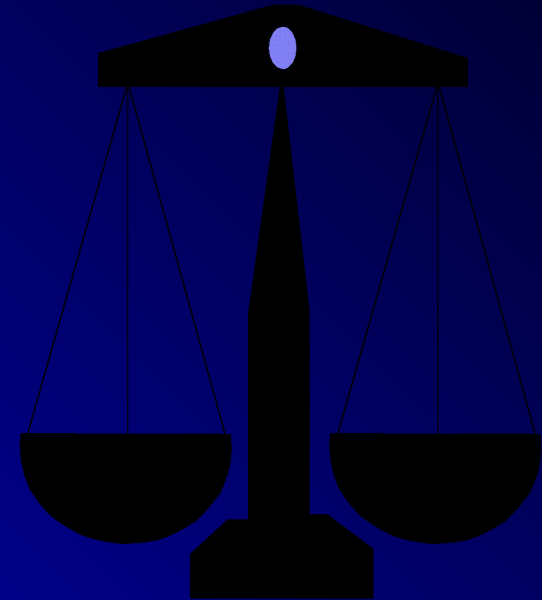
Criminal activities

- Wholesale price manipulation
 - » Bayer AG, Abbott Labs, SmithKline Beecham, Glaxo Wellcome, and Bristol-Myers Squibb under investigation by HCFA for overcharging Medicare and Medicaid at least \$1 billion/year
- Vitamin price fixing
 - » Guilty pleas and fines: Hoffman LaRoche, BASF AG, Aventis SA, Takeda, Eisai, and Daichi



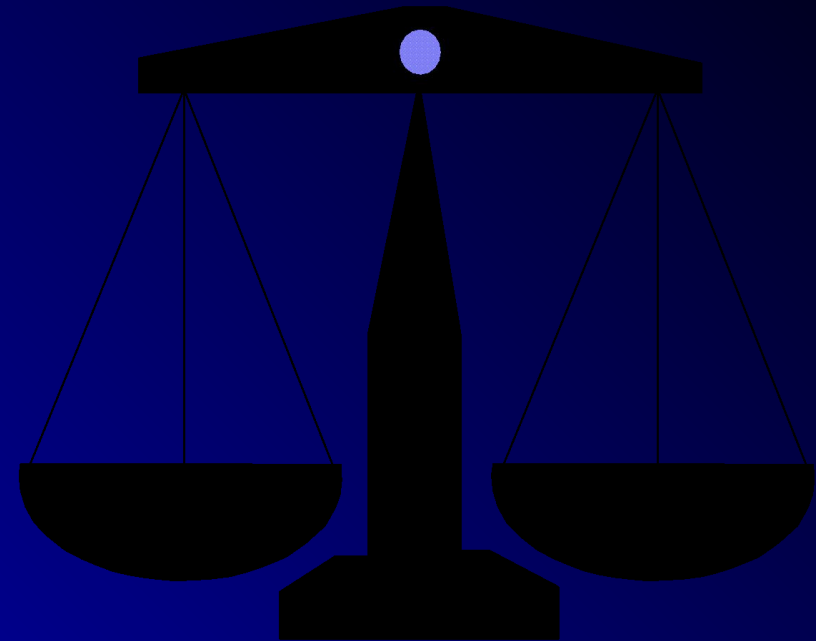
Investigations / Possible Criminal Activities

- **Justice Department investigating:**
 - » **Metabolife for falsification of ephedra safety data**
 - » **Merck and Co. and Briston-Myers Squibb for sales and accounting practices**
 - » **Johnson and Johnson for alleged manufacturing improprieties in Puerto Rico**
 - » **Warner-Lambert for hiding dangers of Rezulin**



Investigations / Possible Criminal Activities

- **?Criminal charges?**
 - » **Albuterol-less inhalers from Schering Plough**
 - » **sloppy manufacturing; delayed recall**
- **NEJM Editor Drazen cited by FDA in 1999 for making “false and misleading” statements about levalbuterol**



Drug Companies Behaving Badly: The 10 Worst Corporations of 2002

***Multinational Monitor**

- **Wyeth**

- » Revealed that Ayerst (subsidiary) had funded Dr Robert Wilson's 1966 book "Feminine Forever"
- » Labeling menopause as a disease, promoting HRT as "cure" for maintenance of beauty

- **Schering Plough:**

- » Justice Dept. investigation for price-fixing
- » Federal investigation of Medicaid fraud
- » \$500 million fine for repeated failures to fix manufacturing plant problems in NJ and Puerto Rico

Third World “Donations” (Dumping) of Pharmaceuticals

- **Genuine gifts**
- **Dubious “gifts” -- reasons:**
 - clear out stocks of nearly-expired drugs/poor sellers
 - tax write-offs (up to 2x production costs)

Third World “Donations” (Dumping) of Pharmaceuticals

- **Egregious Examples:**
 - Expired Ceclor to Central Africa
 - Garlic pills and TUMS to Rwanda
 - 50% of donations to Bosnia expired or medically worthless
- **Recommendations:**
 - WHO list of essential drugs
 - Expired date at least 1 year away

Anti-AIDS Drugs and Africa

- **36 million infected with HIV; 2/3 in sub-Saharan Africa (1.3% of global pharmaceutical market)**
 - » Only 1/1000 S. African AIDS patients getting anti-HIV drugs
- **PHRMA lawsuit vs South Africa (supported by US govt)**
 - » parallel importing
 - » compulsory licensing
 - » dropped after activist campaign
 - » US donation to UN AIDS Relief Fund = \$200 million

The FDA: The Future

- Trade name review prior to marketing approval
 - Losec/Lasix
- Mandated patient package inserts
- Criminal sanctions for repeat advertising regulations violators
- Simplify oversight
 - problems with benzodiazepine triplicate forms
- International clinical trials registry

The Internet and Pharmaceuticals

- **New website created q 3 seconds**
- **1/4 of websites have health information**
- **Unethical sales (e.g., Viagra)**
 - » **AMA and FDA oppose on-line prescribing; states passing laws to prohibit**

The Internet and Pharmaceuticals

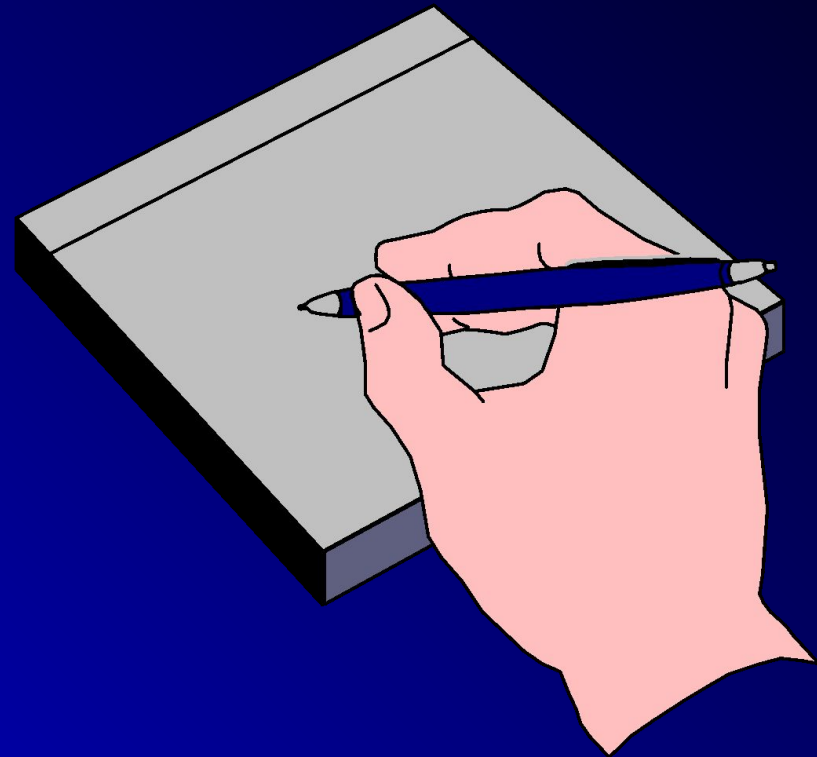
- **Free software / Physician profiling**
 - » **“ePocrates”**
- **Internet pharmacies**
 - » **\$1.9 billion sales (1999); expected to reach \$20-25 billion by 2005**
 - » **privacy concerns**

Physician Prescribing Habits

- **Influences**
 - texts, journals, colleagues, marketing and advertising
 - ego bias
 - how benefits presented
 - average vs stratified life expectancy gains
 - NNT
 - Cost effectiveness
 - how side effects presented
 - # affected vs # withdrawing from study

Physician Prescribing Habits

- Influences
 - texts, journals, colleagues, marketing, and advertising
 - ego bias
 - how benefits presented
 - average vs stratified life expectancy gains
 - NNT
 - Cost effectiveness
 - how side effects presented
 - # affected vs # withdrawing from study



Physician Prescribing Habits

- **Up to 85% of residents prescribe to non-patients**
- **50% of residents self-prescribe**
 - » **early 1990s - benzos**
 - » **2000 - SSRIS for depression, antihistamines for sleep**

Pharmaceuticals Sales Reps' Techniques

- Appeal to authority
- Appeal to popularity
- The “red herring”
- Appeal to pity (Dryden - “Pity melts the mind”)

Pharmaceuticals Sales Reps' Techniques

- Appeal to curiosity
- Free food/gifts
- Testimonials
- Relationship building/face time

Pharmaceutical Sales Reps' Techniques

- **Active learning -- reinforcement plus change**
- **Favorable but inaccurate statements**
- **Negative comments re competitors' products**
- **Reprints not conforming to FDA regulations**

Relating to Pharmaceutical Reps

- Awareness of sales tactics
- Question them, ask for references
- Level of presence
 - open vs locked-out (it would cost < \$100,000/yr to feed 30 residents lunch each weekday)
 - benefits/harms

Academia and Industry

- **US R&D (2000):**
 - » **industry - \$55-60 billion**
 - » **federal government - \$25 billion**
 - » **private foundations - \$8-10 billion**
- **Industry funds 8-40% of university research (a 7-fold increase since 1970)**

Academia and Industry

- **1991: 80% of industry sponsored clinical trials performed in non-profit academic medical centers**
 - » **70¢ of every pharmaceutical industry research dollar**
- **2001: 40% (60% in CROs)**
 - » **34¢**

CROs and SMOs

- **Contract Research Organizations (CROs):**
provide central oversight and management of clinical trials
- **Site Management Organizations (SMOs):**
organize physicians' offices into trial networks and oversee the rapid recruitment of patients

Academia and Industry

- **3-fold increase in the number of physicians conducting “research” in the last decade**
- **“Investigators” can make from \$500 to \$6000 per enrolled subject**
 - » **Active recruiters can make from \$500,000 to \$1 million per year**

Unfunded Studies

- **23% in 1 month**
-53% of these were case series
- **29% involved unaccounted-for direct clinical costs**
-?passed on to patients or 3rd party payers?

Academia and Industry

- **Majority of authors of Clinical Practice Guidelines have industry ties**
- **Authors of NEJM reviews and editorials can accept up to \$10,000/year in speaking and consulting fees from each company about whose products they are writing**

Academia and Industry

- **Increasing exclusive university - corporate agreements**
 - » **MIT – 5 yr, \$15 million deal with Merck and Co. for patent rights to joint discoveries**
 - » **DFCI – Novartis**
 - » **Many other examples**

Academia, Industry and Medical Research

- **1999-2001: Federal authorities restricted or shut down human subject research at 9 universities**
- **E.g., Jesse Geisinger case at U Penn:**
 - » **Gene therapy experiment**
 - » **Not disclosed to patient:**
 - » **University had equity stake in the company sponsoring the study**
 - » **Reports of serious adverse events and deaths in monkeys**

Academia - Industry Collaboration

- $\frac{1}{4}$ of scientific investigators have industry affiliations
- $\frac{2}{3}$ of academic institutions hold equity in start-ups that sponsor research at the same institutions
- Up to 80% of science and engineering faculty perform outside consultations
- Academic entrepreneurs, patents
-e.g., Herbert Boyer, U.C.S.F., Genentech

Collaboration Difficulties

- **Complicated university beaureacracies/regulations - 50%**
- **Disputes over intellectual property - 34%**
- **Changes in academic research focus - 33%**
- **Conflict of interest - 30%**
- **Misconduct/poor science - 12%**

Collaboration Difficulties

- Impaired sharing of knowledge, materials
- Difficulty in repeating/verifying important research
- Driven by usual academic competitive jealousies, fears of contract violations and subsequent litigation, and desire to protect financial interests and keep stock prices high

Educational Concerns Regarding Industry Funded Research

- **Diversion of faculty away from teaching, towards more remunerative consultations**
- **Faculty change research direction**
- **Fellows/post-docs diverted to industry-related topics**
- **Publication delays affect career development**

Concerns Re Research in the U.S.

- Inverse relationship between growth in NIH awards during the past decade and managed care penetration
- Decreasing funding for patient-oriented research
- Low enrollment causing delays in evaluating cancer medications (< 5% of patients participate in clinical trials)
- Insurance coverage of clinical trials decreasing

Withholding of Data

- Only 12% of university conflict of interest policies specify limits on permissible delays in publication
- Reasons for withholding of data:
 - Competition
 - Recognition/protect scientific lead
 - Patent application
 - Intellectual property disputes
- Results of withholding of data:
 - Unnecessary duplication
 - Slows development and testing of new drugs

Withholding of Data: Examples

- Chamberlin family - obstetrical forceps
- UCSF Synthroid study (Boots/Knoll Pharmaceuticals)
- JAMA Celebrex (Pharmacia) study: fewer ulcers than ibuprofen at 6 months, but no difference at one year (only 6 month data submitted and published)
- comparisons with genetic code
- implications for health services research, public health

Industry/Special Interest Groups and Researchers

- **CDC gun violence studies - NRA**
- **Breast Implants - Congress, Women's Groups**
- **Lead exposure studies - (Needleman) - lead industry**

Industry/Special Interest Groups and Researchers

- **Spinal fusion - North American Spine Society, pedicle screw manufacturers**
- **Multiple Chemical Sensitivity Syndrome - patient advocacy groups, attorneys, immunodiagnostic testing labs**
- **Pharmaceutical company / tobacco company financial ties, conflicts of interest**

Harassment of Researchers

- **Betty Dong/UCSF (Synthroid) - Boots/Knoll Pharmaceuticals**
- **Nancy Oliveri/University of Toronto (deferipone) - Apotex**
- **UCSF (Remimmune) - Immune Response Corporation**

Harassment of Researchers

- **David Healy/University of Toronto (Prozac) - Eli Lilly**
- **Anne Holbrook/McMaster U/ PUD-GERD panel (Prilosec) - Astra Zeneca**
- **David Kern/Brown U (“flock workers’ lung) – Microfibres**
- **Tobacco companies – multiple lawsuits against universities**

The Pharmaceutical Industry and Medical Ethics

- **Funding of conferences, Centers of Ethics, individual investigators**
 - » E.g., \$1 million gift from SmithKline Beecham to Stanford University Center for Biomedical Ethics
- **Rapid growth of for-profit non-institutional review boards (NIRBs)**
- **Using patents to inhibit other companies' research**
 - » The Tragedy of the Anti-Commons

The Pharmaceutical Industry and Medical Ethics

- **Ethics consultants serving on corporate boards**
 - » E.g., Harold Shapiro continued to draw annual director's salary from Dow Chemical while serving as Chair of NBAC
- **Most bioethics journals do not require conflict of interest disclosures**
- **Loss of appearance of independence; damage to credibility**
- **Pharmaceutical industry involvement in research and production of chemical warfare agents and drugs used to facilitate executions**

Recommendations for Industry-Sponsored Research

- **Written agreements with university, not researcher**
- **Alternatives selected based on clinical relevance**
- **Stepwise project results not provided to sponsor until study is funded and open publication guaranteed**

Recommendations for Industry-Sponsored Research

- Full disclosure of conflicts of interest
- No gag clauses regarding publication
- Investigator not to act as consultant during study
- Database of clinical trials

Industry/Special Interest Groups and Researchers/Societies

- **Pork barrel research funding - Congress**
 - » c.f., legislating medical practice - e.g.,
drive-through deliveries
- **APHA: Colgate-Palmolive; AHA:
Genentech; AMA - Sunbeam (dissolved)**

AMA Guidelines Re Gifts to Physicians from Industry

- **Minimal value gifts O.K.**
-pens, notepads, modest meals, textbooks
- **Film, videos, CDs; “Dinner to Go” (Merck); “Look for a Book” GlaxoSmithKline PLC); Palm Pilots (Dupont)**
- **No cash gifts**

AMA Guidelines Re Gifts to Physicians from Industry

- **No gifts with strings attached**
- **CME sponsorship money to conference sponsor, not participating physicians**
- **Meeting expenses for trainees funneled through institution**

AMA Guidelines Re Gifts to Physicians from Industry

- **AMA \$1 million “educational” campaign:**
 - **\$325,000 from AMA**
 - **9 drug companies to contribute the rest**
- **Vermont law now requires physicians to disclose all gifts over \$25**

Patients' Attitudes Toward Pharmaceutical Company Gifts *(Gibbons et al.)*

- 200 patients, 270 physicians
- 1/2 of patients aware
- 1/4 believe their doctor(s) accepted gifts
- 1/3 felt costs passed along to patients
- Patients felt gifts less appropriate than did physicians
- Physicians and patients disagree on appropriateness of seeding trial payments (La Puma, et al.)

Guidelines for Speakers at Industry-Sponsored Events

- Educational, not promotional
- Based on scientific data and clinical experience
- Full disclosure of relationship with company and honoraria
- Travel expenses not lavish
- Few mechanisms for surveillance/guideline enforcement



Trends to Watch For

- **Drug companies buying health providers**
-Zeneca Group/Salick Health Care
- **Drug companies purchasing Pharmaceutical Benefits Managers and Disease Management Groups**

Trends to Watch For

- **Medical school / drug company alliances**
 - » **Novartis - UC Berkeley; Pharmacia - Wash U. in St Louis; Ribazyme - Univ. of CO; Pfizer -BIH; Novartis -DFCI; Shiseido - MGH**
- **CME - Medical Education and Communication Companies**
 - » **paid mainly by drug companies; provide “educational” materials gratis**
 - » **1/2 of the \$1.1 billion spent on CME in 1999**

Human Experimentation: US and Abroad

- 90% of health research dollars are spent on the health problems of 10% of the world's population
 - research on major diseases of the developing world underfunded, not profitable
- Third World experimentation with inappropriate placebo-controls: AIDS drugs/Africa; Sulfazyme/Brazil
- Stop-gap source of care / meds for poor

Human Experimentation: US and Abroad

- Human Experimentation Companies
- For-Profit IRBs
- Private-practice-based “investigators”

Enhancing Cooperation Between Physicians and the Pharmaceutical Industry

- **Improving compliance**
- **Decreasing adverse events**
- **Promotion and funding of basic science and clinical research**

Conclusions

- **Pharmaceuticals and Biotechnology Industries**
 - Tremendous contributions to health
 - Motivation = “alleviate suffering”
 - Primary responsibility = “make money for shareholders”
- **Awareness of worrisome trends in the business of drugs, research and health care**
- **Advocate locally and nationally for solutions**

Useful Phone Numbers

- **FDA and Regulated Products Info**
1-800-222-0185
- **Medwatch/Adverse Events Reporting**
1-800-332-1088
- **Advertising/Promotion/Marketing Concerns**
1-800-238-7332
- **Prescription Drug Indigent Programs**
1-800-PMA-INFO
- **Medications Assistance Program (OHSU)**
x4-1457

Contact Information

Public Health and Social Justice
Website

<http://www.phsj.org>

martindonohoe@phsj.org