The Pharmaceutical Industry

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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 \times \text{ prescription drug use}
• Non-prescription drug costs = 1/2 \text{ 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-SmithKliineBeecham, 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% (versus 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

  - 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.

• 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

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, Metylphenidate, 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-inflammatories, 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 adenocarcinoma 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.


- 72% do not inform their physicians.
Efficacy of Herbal Products

• Gingko 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 psychosotic 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 or 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 15 years, 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 pescii*, 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.”

- $4 billion/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

• ¼ 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 (Saraflo) – 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

1. 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.

2. 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 its 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
  -temafloxocin, 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 Oraflex
  » 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

  » 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

• ¼ of scientific investigators have industry affiliations
• 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 -BLH; 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