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 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

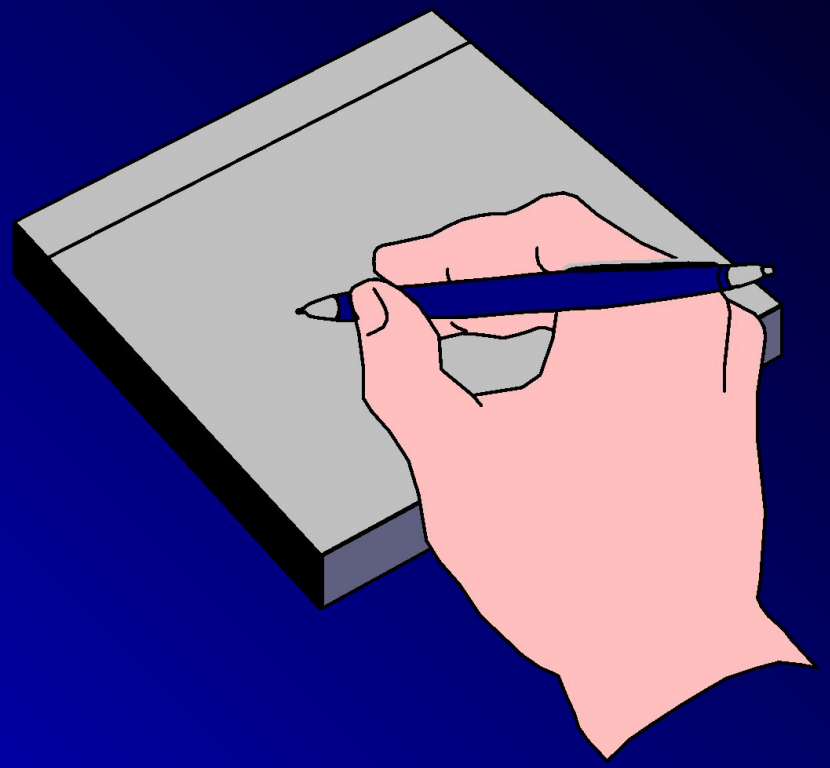
- Greater than 100 OTC medications available
- 15% of children less than 3 years old treated

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

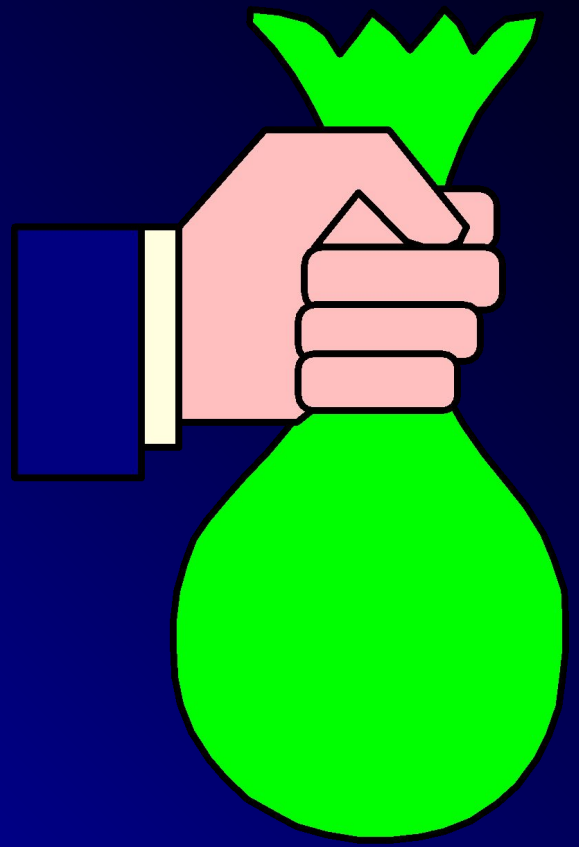
Economics

- 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-SmithKliine 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 then 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 compreheensive 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

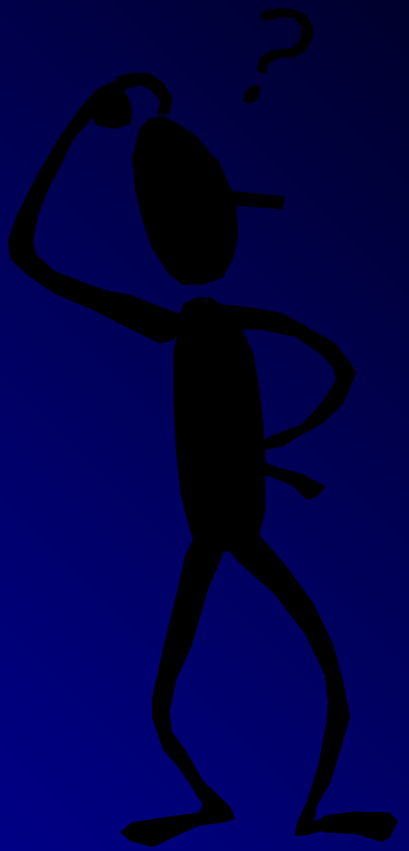
Gollust SE, et al. JAMA 2002;288:1762-1767.

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, Metlylphendate, 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 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

- 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 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

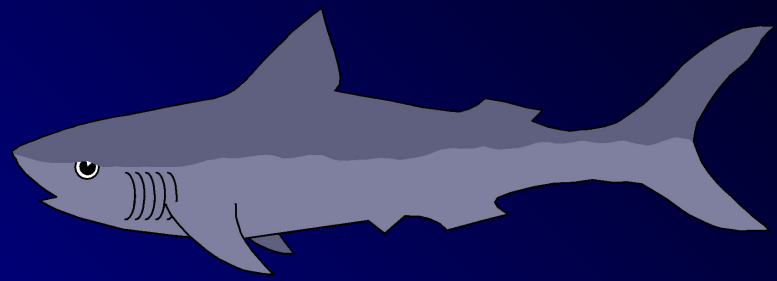
- GE-L-tryptophan → EMS (1989): 5,000 in US affected, 37 deaths, 1500 permanently disabled
- Heart attacks, dysrhythmias, strokes and seizures from ephedra
- Bleeding from garlic, gingko, and ginseng
- hypoglycemia from ginseng

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 annualy 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."
- $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

- 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 (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 bioequivalance, 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

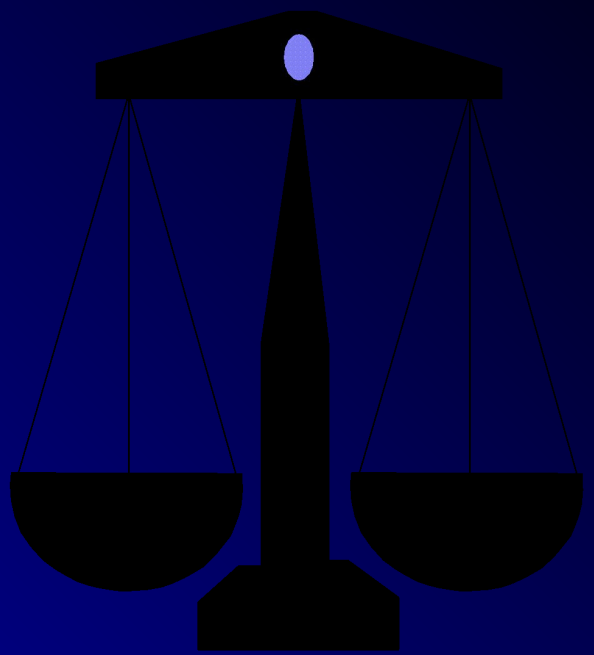
- 52 advisories involving 408,500 pacemakers and 114,645 ICDs from 1/90 - 12/00
- increasing rate between 1995 and 2000
- Over 1000 devices recalled each year
- 1.3 million device checks and analyses
- 36,187 device replacements
- $870 million

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

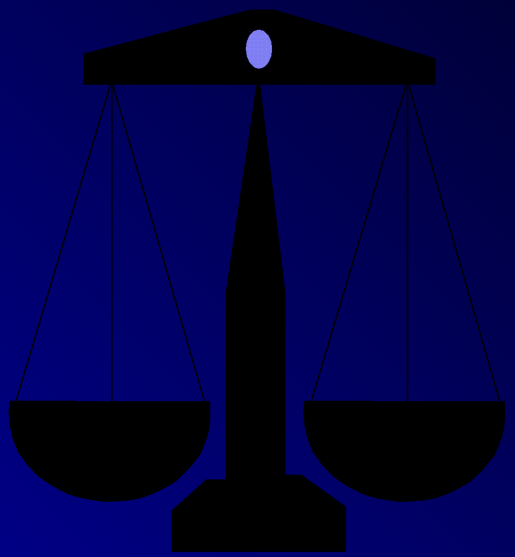
Criminal activities

- 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



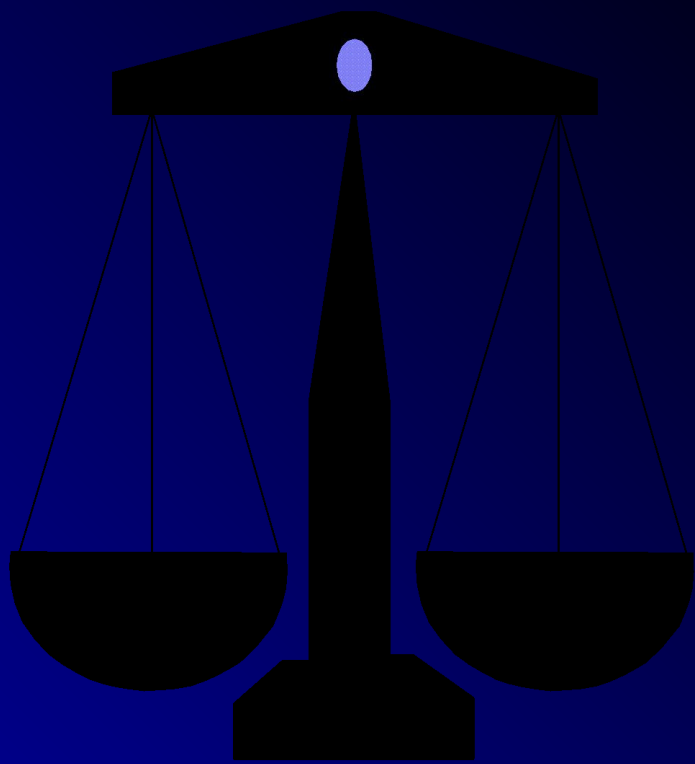
Criminal activities

- 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 o 125 different drugs in factories that failed to comply with good manufacturing practices



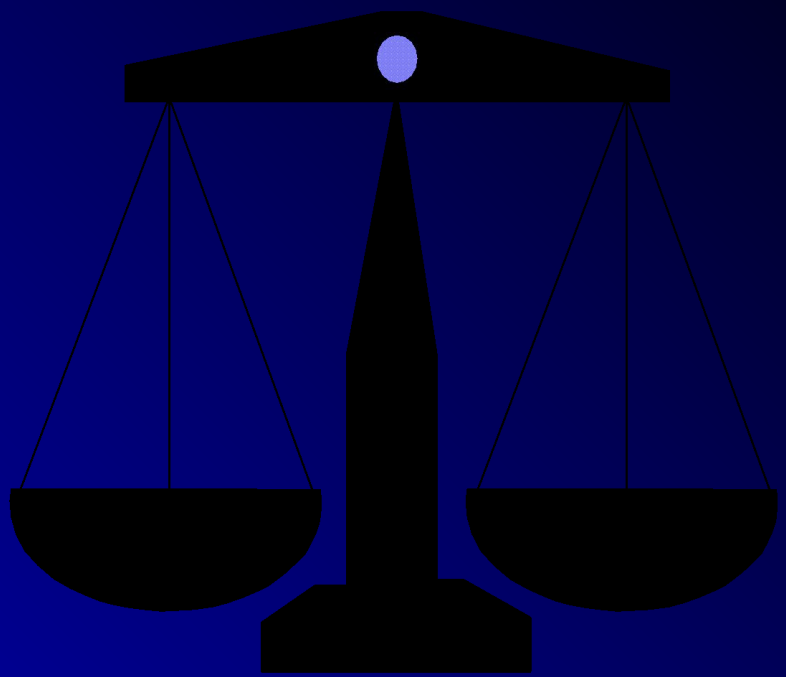
Criminal activities

- 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



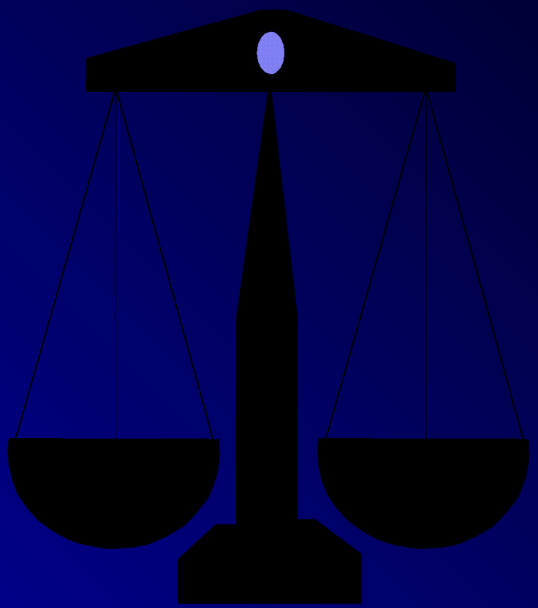
Criminal activities

- 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



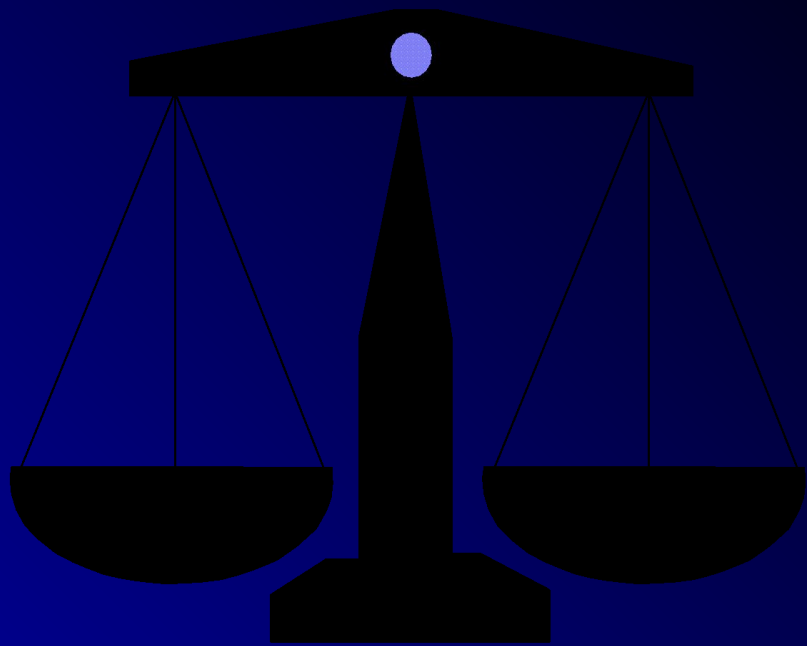
Investigations / Possible Criminal Activities

- 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

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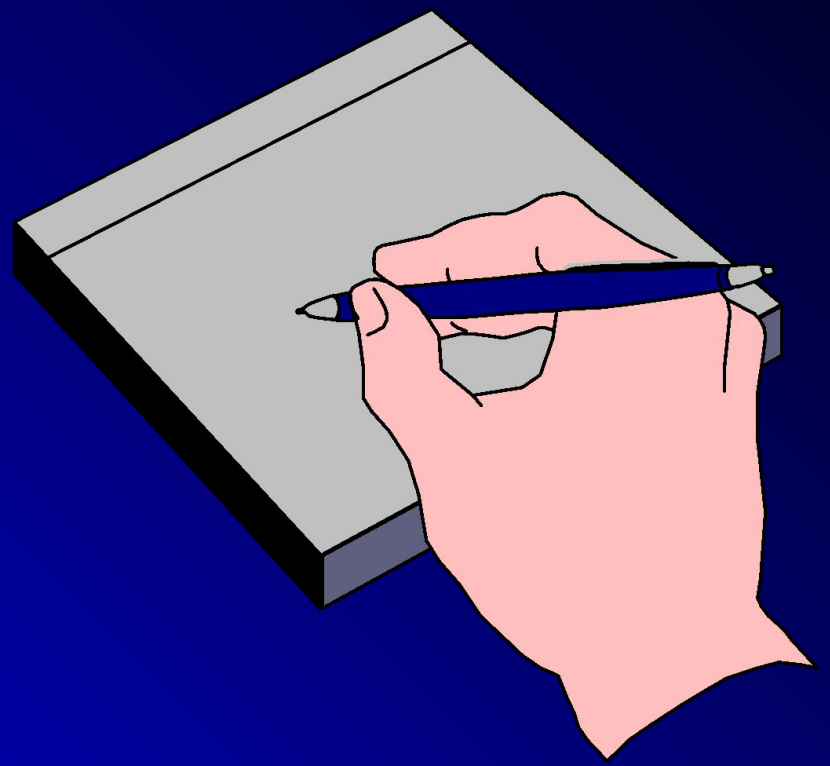

Physician Prescribing Habits

- 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

- 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 then 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

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