

MIT PRINCIPLES AND PRACTICE OF DRUG DEVELOPMENT

DRUG REGULATION AND REIMBURSEMENT

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PART I

DRUG REGULATION AND THE FDA

FDA and Pharmaceutical Companies are “Partners” in . . .

- FDA and pharmaceutical companies are “Partners” in:
 - Product Development
 - Manufacturing
 - Advertising and Promotion
- Some recent events have undermined the credibility of the FDA in executing its mandate – assuring the safety and effectiveness of marketed drugs.

1960's

- **Thalidomide Disaster**

- Already on the market in Europe – as tranquilizer.
- William Merrell Company submitted request to FDA examiner and no decision.
- Successive delays by FDA examiner and no decision.
- Recognition the drug responsible for Phocomelia (birth defect), highly prevalent in Europe.

1960' s *(continued)*

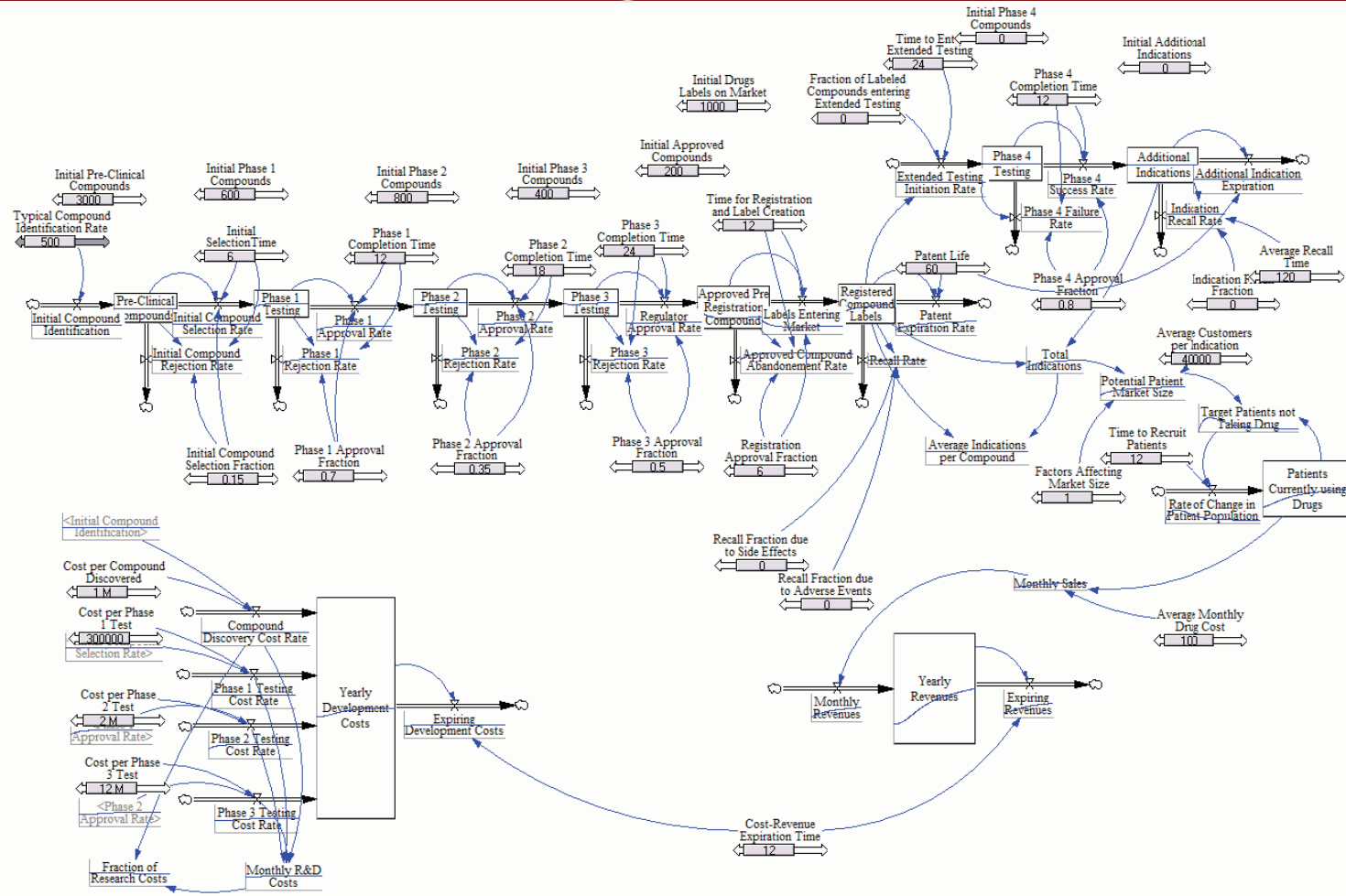
- 1962 Amendments to the Food Drug and Cosmetic Act
 - Required pre-market review (and approval), based on “SAFETY” and “EFFICACY/EFFECTIVENESS”.
 - EFFICACY vs. EFFECTIVENESS – which is the tougher standard?
 - Role of the “Clinical Trial”.
 - Adverse event reporting.
 - Manufacturer licensing and inspections.
- Impact of 1960' s Events: Prediction of “Drug Lag”

Image removed due to copyright restrictions. The New Drug Development Process: Steps from Test Tube to New Drug Application Review.
See: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm053131.htm>

Some Differences in Regulation of Biologics

- Biologics License Application (BLA) instead of NDA.
- “Process Defines the Product”.
- No Analogous Pathway to Abbreviated New Drug Application (ANDA) for Biosimilars/ Biogenerics.

Drug Development is a Complex System



• *Diagram Courtesy of Nancy G. Leveson*



Image removed due to copyright restrictions. Drug discovery & development, new medicines timeline from PhRMA.
See: http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.

1970's

- Dalkon Shield Intrauterine Device (IUD) Disaster
- 1976 Medical Device Amendments
 - “Structure” of the Medical Device Industry.
 - “Sec. 510K – Substantial Equivalence.
 - Class I, II and III Medical Devices.
 - “Regulatory Patent”.
 - “510K ‘CREEP’ ”.

1980' s

- 1983 “ORPHAN” Drug Protection
 - Afforded market exclusivity for innovator when potential market for drug' s implication was less than 200,000 persons in U.S.
 - A basis for strategy on the part of biotech firms.

1980' s (continued)

- 1984 Patent Term Restoration and Generic Substitution Act (*Hatch-Waxman*)
 - Opportunities for patent term extension on the part of innovator.
 - One half day for each day between IND and NDA.
 - One day for each day during NDA review.
 - Maximum of 5 years, maximum period of market exclusivity – 14 years ·
 - Accelerated approval of generic drug applications, upon patent expiration.
 - Chemical equivalence.
 - Bioequivalence.
 - Six months market exclusivity for generic firm that succeeds in “breaking” the innovator’ s patent.

1990' s

- 1992 – Prescription Drug User Fee Act (PDUFA)
 - Increased resources to FDA for hiring more reviewers.
 - Required reports to Congress as to progress on increasingly stringent review time goals.
 - Allows FDA to collect fees from industry.
 - Fees applied to drug review process.

1990' s

- **1997** – Prescription Drug User Fee Act Reauthorization (PDUFA II) and Food and Drug Administration Modernization Act (FDAMA)
 - PDUFA reauthorized for 5 more years plus other streamlining measures.
 - Accelerate device review.
 - New rules for off-label drug use information dissemination.
 - Drugs in the investigational stage available to anyone in restricted circumstances.

1990' s *(continued)*

- FDA responded to challenge
 - Fast-track Approval process developed.
 - Adverse Event Reporting System (AERS) set up and Office of Post-Marketing Drug Risk Assessment (OPDRA) established under CDER.

PDUFA Credited with Decline in Approval Time

- Approvals > 2 years : 44% in 1993 to 6% in 1999.
- Approvals < 1 year : 20% in 1993 to 63% in 1999.
- Phase III development times decreased 4% while Phase I and Phase II development times increased 34% and 26%.

Source: Tufts Center for the Study of Drug Development

FDA Regulation of Advertising and Promotion

Division of Drug Marketing, Advertising and Communication (*DDMAC*)

- Doctor Detailing
- Print Advertising (*Professional Publications*)
- Direct to Consumer (*DTC*) Advertising

Off Label Drug Use: Background

Off-Label Drug Prescribing:

- Is legal.
- Is considered to provide an important pathway to clinical innovation.
- Can be a part of a manufacturer's "Strategy" to make a new drug successful in the marketplace.
- Cannot be a "Promoted" by manufacturer, but they can now distribute published "Peer Reviewed" articles.
- Is raising critical issues about the safety and costs of health care.

Off Label Drug Use: Results

- 2001 NDT1 reported 725 million “Drug Mentions”.
- Of these 150 million (21%) were for non-FDA approved uses.
- Among off-label uses, 73% lacked strong scientific support.
- Though, overall, 85% of recorded drug prescriptions were for EITHER FDA approved or otherwise scientifically supported uses.
- Off-label prescribing (*overall*) most common among:
 - *Cardiovascular Medicines 46%*
 - *Anti-asthmatics 42%*

Off Label Drug Use: Results *(continued)*

- Off-label prescribing without strong scientific support most common in:
 - *Psychotropic Drugs 96%*
 - *Allergy Medications 89%*
- Drug with largest proportion non-scientifically supported off-label use: Gabapentin – 66%
- Statistical analysis did not help us “explain” off label use.

The FDA's Bite

- Pre-market approval
- Injunction
- Seizure
- Fines
- Prosecution

FDA “Alphabet Soup”

Drug Discovery / Development / Production

| | |
|-----------|---|
| IND | Investigational New Drug |
| GCP | Good Clinical Practices |
| NDA | New Drug Application |
| ANDA | Abbreviated New Drug Application (<i>Generics</i>) |
| GMP | Good Manufacturing Practices |
| PLA / ELA | Product License Application / Establishment License Application |
| BLA | Biologics License Application |
| IDE | Investigational Device Exemption |
| 510K | Accelerated Premarket Approval of Devices |
| PMA | Premarket Approval (<i>Devices</i>) |

•SOME RECENT DEVELOPMENTS

- FDA “Guidance” on Use of Pharmacogenomic Data in Drug Development.
- Long Term Safety of Prescription Drugs – Controversy “Boils Over”.
- “Politicization” of Approval Decisions.

Post Market Drug Safety: The Vioxx Controversy

- Vioxx (Rofecoxib/Merck) is a CoX-2 inhibitor, non-steroidal anti-inflammatory drug (NSAID).
- Tremendous hope of reducing gastro-intestinal morbidity and mortality among patients with disorders causing inflammatory pain.
- Older NSAIDS: Aspirin, ibuprofen, naproxen all have GI bleeding as prominent adverse effect due to anti-platelet aggregation mechanism.

Post Market Drug Safety: The Vioxx Controversy *(continued)*

- Initial clinical trial indications: Acute pain, dysmenorrhea, osteoarthritis.
 - 5,000 + patients
 - Followed one year or longer
 - No cardiovascular “signals”
- Initial NDA approved May 1999.

Post Market Drug Safety: The Vioxx Controversy *(continued)*

- Two long-term clinical trials begun in 1999.
 - VIOXX GI OUTCOMES RESEARCH Trial (VIGOR) –
 - Comparator was Naproxen – for nine months.
 - APPROVE colon polyp prevention study.
 - This trial was placebo controlled and was to last for more than eighteen months.
- VIGOR found the risk of myocardial infarction was four times greater in the VIOXX group than the Naproxen group. Merck's interpretation was that Naproxen had a protective effect (via its antiplatelet activity) that was missing in VIOXX.

Post Market Drug Safety: The Vioxx Controversy *(continued)*

- APPROVE reported even more striking findings of CV risk – but risks not apparent until at least 18 months of therapy.
- Merck and FDA had been discussing labeling changes to Vioxx.
- Reports began to surface of a “Cover Up” on the part of Merck scientists and other officials.
- Merck voluntarily withdraws Vioxx from the market in 2004.

Politicization of Drug Approval Decisions

- RU-486 (Mifepristone)
 - “Abortion” pill that can be taken during the first few weeks of pregnancy.
 - In use in Europe since 1988.
 - First approved by FDA in 2000.

- Plan B
 - An “After the Fact” contraceptive pill.
 - Reduces probability of pregnancy from unprotected intercourse from 8% to 1%.
 - First approved by FDA in 1999.
 - Application to switch from Rx to OTC was voted favorably by FDA advisory group, but then disapproved by FDA in 2004.

FDA Modernization Act (FDAMA)

- Signed into law by President Bush on September 27, 2007.
- “Most Sweeping” reform of FDA in years.
- FDA gets new authority to track after market side effects of drug and to take actions if signs emerge that medicines are unsafe.
- Reauthorizes FDA to collect “User Fees” from drug and device firms for review of their applications for premarket approval of new products.

FDA Modernization Act *(continued)*

- Creates an “FDA” foundation and makes FDA more of a “Granting” agency.
- Limits some of drug firms’ protection from product liability.
- Dropped from legislation in final negotiations: Provisions to accelerate biogenerics.
- Turmoil continues!

PART II

INSURANCE REIMBURSEMENT FOR PHARMACEUTICALS

Role of Medicines in Clinical Practice

“If all of the medicines in the world were thrown into the sea, it would be all the better for mankind and all the worse for the fishes.”

Oliver Wendell Holmes, M.D.
(father of the Supreme Court Justice 1842)

(frequently quoted by Dr. Robert H. Rubin)

Role of Medicines in Clinical Practice

- Antibiotics revolutionize battlefield medicine.
- Post World War II: Continued development of antibiotics to treat acute infections.
- 1950's Focus on medicines taken for other acute, short-term needs (*pain, anxiety . . .*).
- Drug prices considered “high” relative to prices of other goods and services, but this attracted little attention as they were used mainly for short periods of time.

Drugs and Health Insurance

(before 1965)

- Prior to 1965, people who had health insurance obtained their coverage through their employment.
- Health care costs accounted for a small percentage of GDP.
- Drug costs were a small part of health care costs.
- If/when drugs were covered by employer-based health insurance, the impact was rarely visible as an issue.

Drugs and Health Insurance (1965)

- **Medicare Enacted – Coverage for the Elderly and Disabled**
 - Federal program
 - Administered regionally
 - Part A – Inpatient hospitalization coverage
 - Part B – Doctor visit coverage
 - Drug coverage (*essentially*) not part of this

- **Medicaid Enacted – Coverage for Indigent Populations**
 - Federal mandate; partnership with states
 - States make the rules and administer programs
 - Wide variability across states
 - Drug coverage added over time

Drugs and Health Insurance

(~ 1970's to Present)

- Drugs take on increasing importance in clinical practice
- Drugs effectiveness in management of chronic disorders
(*hypertension, congestive heart failure, diabetes, mental disorders, gastrointestinal disorders . . .*)
- Drugs effective in management of some “Orphan” diseases
(*Gaucher's disease, rheumatoid arthritis, multiple sclerosis . . .*)
- People taking medicines for chronic disorders take them “every day for the rest of their lives”
- Drug prices increase (*much*) faster than the overall rate of inflation
- Drugs assume increasing proportion of health care costs (*growing from ~ 8 to ~ 15%*)

Senior Citizens “Left Out”

- Employer – based health insurance plans and Medicaid (*coverage for indigent*) could change with the times
- Medicare did not cover drugs, except in limited circumstances
- Commonly, seniors suffer from multiple chronic disorders (*at the same time*), each one appropriately managed by medicines
- Without insurance coverage, costs borne by individuals can rapidly become large
- Seniors go without prescribed medicines
- Seniors seek lower prices and buy drugs from Canada, Mexico where prices are much lower

“Tension” between Drug Innovation and Prices

- Drug companies say that the prices they charge are needed to continue the stream of innovative products
- Drug prices are higher in the U.S. than in any of the other major markets
- European countries and Japan impose a mix of Government price controls on drugs
 - “Reference Prices” for newly launched drugs
 - Restricted formularies
 - Limits of promotion costs
 - Limits of companies’ profits
 - Expectations of economic development (*jobs*)
 - Sanctions on doctors for “inappropriate” prescribing

“Tension” between Drug Innovation and Prices

(continued)

- In 2000:
 - 29 of 75 top selling medicines originated in U.S. firms
 - 0 of 75 originated in Japanese companies (*second largest market*)
 - 10 of 75 originated in U.K. firms – fewest price controls and among highest prices in Europe

Medicare Part D – Drug Coverage

- Enacted in 2003, after years of contentious debate
- Took effect in 2006
- Market-based system of competing insurance plans offering drug coverage
- Government prohibited from negotiating lower drug prices, based on volume of purchases
- Idea was to improve access of senior citizens to needed medicines, while, at the same time, keeping drug companies' profits high
- Estimated costs to Government \$400 billion over ten years – almost certainly a low estimate

Medicare Part D – Drug Coverage

(continued)

- Direct Government subsidies to corporate retirees' health insurance plans
- New plans offered by private insurers
 - Addendums to existing plans providing drug coverage
 - New HMO – type plans offering drug coverage
 - Free standing drug coverage plans

Medicare Part D – Drug Coverage

(continued)

- Mechanics
 - Patient pays monthly premium (*~ \$35 for free standing drug plan*)
 - Patient pays \$250 deductible
 - Patient pays 25% of prices up to initial coverage limit of \$2,250
 - No coverage between \$2,250 and \$3,600 (*“dough nut hole”*)
 - After patient pays \$5,100 (*monthly premiums + deductible + co-payment + out-of-pocket*), Medicare pays 95%)
- Hybrid of “First Dollar” and “Catastrophic” coverage

Medicare Part D – Drug Coverage

(continued)

- Private insurers permitted under the legislation to offer plans with “Equivalent” benefits
- Private plans would compete on amount of monthly premiums, which specific drugs they offered, as long as they meet minimum standards on mix of drugs in their formularies
- Individual plans would negotiate “preferred” prices for offering one competing (*Blockbuster*) drug instead of another (*e.g., Crestor instead of Lipitor as “First Choice” for lipid control*)

Medicare Part D – Drug Coverage

(continued)

Most plan offer “tiers” of coverage:

- ~ \$10 or a month’s supply of a generic
- ~ \$25 for a “Preferred” brand drug
- ~ \$40 for a “Non-preferred” brand drug
- As much as 50% of acquisition price for some expensive drugs

Medicare Part D – Drug Coverage

(continued)

Seniors Have Decisions To Make:

- Healthy seniors choose whether to participate?
- Stay in retiree health plan vs. opt for Medicare Part D. plan?
- Choose a Medicare HMO or a free standing drug plan?
- Select particular plan on the basis of a monthly premium, deductibles and co-pays and whether it covers the specific drugs they need?

Medicare Part D – Drug Coverage

(continued)

Unanswered Questions

- How many seniors are better off with Medicare drug coverage than they were before it existed?
- How much does it actually cost the Government?
- As share of drug costs in overall health costs continues to increase (*as most expect*), will the Government seek to limit its contribution through controls on prices?
- If Government price controls are eventually implemented on drugs, how will that impact future pharmaceutical innovation?

Filling the Doughnut Hole

- Gradually phasing down the amount beneficiaries pay for generic drugs starting in 2011;
- Implementing a requirement in 2011 that drug manufacturers offer a 50% discount on brand-name drugs filled in the donut hole;
- Phasing down cost-sharing for brand name drugs starting in 2013;
- and reducing out-of-pocket amount needed to reach catastrophe coverage from 2014-2019.

Pharma and the 2010 Affordable Care Act (ACA)

- Negotiations prior to passage of legislation resulted in “compromise” with pharmaceutical industry - \$80 billion in foregone price increases over a ten year period.
- ACA addressed one of the major flaws in the 2003 Medicare Part D Prescription Drug Benefit – eliminated the “Doughnut Hole”.
- ACA rolled back a major aspect of the 2003 Act that had created large subsidies to employers, in order to prevent employees and retirees from dropping employer-based drug coverage.

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