Regulation of the Pharmaceutical Industry

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I. Introduction

Objectives of regulation of the pharmaceutical industry

- Regulation of safety, efficacy, quality, promotion
  - Benefits: better and more symmetric information about risks and benefits
  - Costs: adds to R&D costs and launch delay; effects on industry/market structure, competition

- Regulation of price, reimbursement, revenues etc.
  - social insurance programs seek to control moral hazard and limit market power created by patents
  - Issues:
    - appropriate criteria/structure for regulating prices
      - high fixed costs, low marginal costs
    - appropriate global sharing of R&D costs

II. Background and Brief History of Pharmaceutical Regulation

A: US

- 1938 Food, Drug and Cosmetics Act
  - Safety: Any firm seeking to market a new chemical entity (NCE) required to file a new drug application (NDA) to demonstrate that the drug was safe for use as suggested in proposed labeling
- 1962 Kefauver-Harris Amendments
  - Efficacy proof required, in randomized controlled trials
  - Safety: extended FDA regulation to cover clinical testing and manufacturing facilities
  - Removed the 180 day time limit within which FDA could reject an NDA
  - Promotion:
    - Restricts manufacturers' promotion to approved indications
    - Required that all promotional material include a summary of side-effects and contraindications
- 1984 Hatch-Waxman Act: Patent term restoration and competition
- 1992 PADUFA: user fees to hire more reviewers
- 1997 FDA Modernization Act: relaxed restrictions on DTC

B: EU

- UK and some other EU countries added efficacy requirements similar to US
- 1996 EMEA: centralized agency to review safety and efficacy
- Price and reimbursement regulated separately by each country

III. Effects of Safety/Efficacy Regulation

A. Costs of Regulation (summary of earlier review articles)

- Most empirical work to 1995 focused on effects of 1962 Kefauver Amendments
- Increased costs of drug development: larger, longer trials, more uncertainty
  - R&D cost per approved new chemical entity (NCE): $54m. in 1976 vs. $802m. in 2000 (current dollars)
- Longer time from patent to NDA or marketing approval
  - Increased since 1962, especially in US (Wardell, 1973; Wardell and Lasagna, 1975)
  - Decreased lags for more innovative drugs suggests management has some control (possibly at higher cost) (Meltzer and Dranove, 1994)
- Decline in number of new drugs launched 1960s-70s
  - Regulation or exhaustion of technological possibilities?
  - Reversed in 1980s-1990s
- Increased industry concentration in 1960s and 1970s
  - weak firms eliminated in US and UK, attributed to tough efficacy requirements; less true in countries (France, Japan) with weaker efficacy regulation (Thomas)
  - 1980s-90s Growth of biotech industry suggests no barriers to entry
  - More concentrated large pharma reflects M&A driven by patent expirations + gaps in pipeline, not regulatory costs

1980s-90s Regulatory Reforms Reduce Delay

- FDA priority review and fast track reduce review time
- PADUFA: user fees pay for additional reviewers
  - Accelerated approvals but with more post-launch safety problems (Olson)
  - More equal review times across firms (Olson)
- International harmonization: FDA, EMEA, Japan

High fixed R&D costs deter R&D for drugs with small potential market size

- Rare diseases
  - Orphan Drug Act: market exclusivity + more R&D credits
- LDC diseases
  - Need for push and pull subsidies for drugs with small/no market in high income countries e.g. malaria, TB etc.

B. Benefits of Safety/Efficacy Regulation

- Production and dissemination of safety and efficacy information is a public good
  - may be underprovided by the market
- Regulation should reduce risk that harmful or useless drugs are marketed
- Market/legal alternatives to regulation:
  - Reputation – evidence from generics markets suggests reputation works imperfectly

- Safety: Tort liability provide some incentives for safety, but
  - imperfect deterrent if courts err and/or firms judgment proof
  - more costly than regulation?
  - FDA compliance as a liability defense?
- Efficacy: physicians/consumers may acquire efficacy information over time but
  - Large RCTs superior to uncontrolled, observational data
  - learning by experience may entail a large welfare loss: waste and health risks
- Inconsistent standards for nutriceuticals

IV. Patents

- Given high cost of R&D, patents are essential to induce investment
  - Static efficiency loss if patents lead to suboptimal consumption, due to P > MC
    - mitigated by insurance in industrialized countries: consumers pay only modest co-payment at point of service
  - TRIPS requirements for patents for all WTO members by 2015 => concern that drugs will become even less affordable in LDCs

- Market segmentation and differential pricing can in theory make drugs more affordable in LDCs
  - R&D as a global joint cost => Ramsey pricing is optimal
  - Unregulated price discrimination may result in roughly appropriate (Ramsey) differentials but
    - Are price levels appropriate?
    - Incentives for free riding by large purchasers/in regulated markets (see below)
  - In practice, market segmentation and ability to price-discriminate is undermined by parallel trade and cross-national price referencing
    - Differential pricing within LDCs also needed

- Patents may lead to wasteful, rent-seeking R&D: racing or inter- and intra-firm spillovers (Henderson and Cockburn)
- Do substitutable 'me-too' products reflect excessive product differentiation and lead to higher prices or does competition between similar products stimulate price competition, hence benefit consumers

V. Regulation of Prices, Insurance Reimbursement, Profits etc.

A. **Pharmaceutical industry is structurally competitive**: low concentration overall, no barriers to entry into R&D
   - Higher concentration in some therapeutic categories
   - But contestable: entry targets larger markets (Acemogliu and Lyn); market size and success probabilities are negatively correlated (Danzon, Nicholson and Pereira)

- Rational drug design facilitates imitative compound development

B. Demand is relatively inelastic due to

- Patients have imperfect information on efficacy =>
- Physician prescription required, but physicians may lack price information and/or be imperfect agents
- Insurance/third party payment: 70% in US, over 80% in most industrialized countries with universal drug coverage

C. Third party payers seek to limit prices they pay => price regulation in countries with social/national insurance schemes

- Moral hazard => optimal insurance contracts include some controls
- Ideal pharmaceutical insurance contract balances moral hazard control vs. risk reduction + incentives for R&D

D. Forms of price and reimbursement regulation

- Direct price regulation (Italy, France, Canada)
  - Criteria: prices of similar products in same country (internal referencing); foreign price of same product (external referencing)
- Reference price reimbursement (Germany, Netherlands, New Zealand)
  - Limits reimbursement, not price
  - RP = max. reimbursement for all products in a group, based on generic or therapeutic substitutes
- Profit controls: rate of return on capital (UK)
- Drug budgets/revenue limits: by company (France); by physicians (Germany)
- Cost-effectiveness requirements (UK, Australia)

E. Evidence of Effects of Regulation

- Cross-national differentials in prices
  - Brands vs. generics
- Price regulation undermines generic competition
- Price regulation negatively associated with launch of new drugs (fewer drugs launched, longer delays)
- Distortions in location of production
- Location of R&D: tax-inducements, incubators, funding of basic research etc.
- Vaccines

F. Industry Profitability and ROI

- R&D and promotion are expensed, but are more appropriately treated as intangible investments with a multi-year payout
- Adjusted rates of return on book value of capital are lower than unadjusted
- Discounted cash flow for revenues over lifetime for a cohort of drugs (Grabowski and Vernon, 1990, 2003; OTA, 1994) show IRR similar to cost of capital or at most small excess returns

VI. Promotion and Advertising

- Anticompetitive: promotional expenditures lead to increased market power and higher prices (Walker, 1971)
- Beneficial: promotion provides information to physicians and consumers on availability and effects of products; facilitates entry; may encourage compliance
    - Rent-seeking versus information production (Hurwitz and Caves (1988)
- Direct to consumer advertising (DTC)
    - 1997 FDA relaxed requirements in US under First Amendment claims; FDA is required by law to consider risk/benefit trade-off, not costs;
    - DTC still banned in other countries, which do consider cost implications
    - Mixed evidence of effects of DTC in US: expanding market vs. stealing shares; inappropriate physician visits and drug use

VII. **Regulation of Generics: US**

- ANDA process for approval of bioequivalent generics
- Pharmacists authorized to substitute generic for brand unless physician writes "brand required"
- Pharmacist incentives to substitute cheap generics
- Generic companies compete on price
- Contrast regimes where generics are not certified as bioequivalent; pharmacist can only substitute if physician prescribes generically; pharmacist is paid a percent of the price => branded generics, small shares, relatively high prices.

VIII. Conclusions