Innovation & Inequality:
New indicators from Pharma & Beyond
15-16 may 2010
Sant'Anna School of Advanced Studies, Pisa, Italy

The political construction of orphan drugs market: between innovation and access to care

Philippe Gorry, MD-PhD
Matthieu Montalban, PhD

Groupe de Recherche en Economie Théorique et appliquée – UMR CNRS 5113

Plan:

- 1. Background & problem
- 2. Theory
- 3. The political work & the construction of OD market
- 4. Conception of control
  - from blockbuster to nichebuster
- 5. The business models of OD market:
  - 4 examples
- 6. Conclusions

1 – Background (1):

- **Orphan disease: a burden**

  - Orphan diseases also know as rare diseases, they are usually genetic disease and there are 5000 to 7000
  - Appear early in life, frequently life-threatening or chronically debilitating with significant impact on quality of life with >30% mortality before adulthood
  - Low prevalence in the population but no single definition because no single cut-off
  - A public health problem: 6-8% of the population is affected by a rare disease
  - To be distinguished from neglected diseases which are endemic tropical diseases in low-income population without accurate or affordable treatment

1 – Background (2):

- **Orphan drug: a concept**

  - Definition: a pharmaceutical agent developed specifically to treat a orphan disease
  - the decade prior to 1983 saw fewer than 10 drugs come to market
  - lack of understanding of the pathophysiology mechanisms until 2000s post-genomic era
  - not be possible to test 1,000 patients in a phase III clinical trial
  - small & unprofitable market for pharmaceutical company
  - very expensive prices

1 – Background (3):

- **Orphan drug: a law & a new market**

  - January 1983: Orphan Drug Act in USA
  - **May 2000: Orphan medicinal products legislation in EU**
  - Under ODA & EU legislation, many orphan drugs have been developed: from January 1983 to June 2004, a total of 1,129 different orphan drug designations have been granted.
  - In 2003, the leading OD by worldwide sales revenue was Amgen's Erythropoietin (Epogen), with sales of $2.4bn

1 – Problem

- Does the OD act foster innovation and fulfill public health needs ?
- Does the OD act is the real cause of the OD increase on the market ?
- Does the OD act has stimulated the production of truly non-profitable drugs ?
- How pharmaceutical companies could make a large profit of drugs that have a small market ?
- OD market is a new strategic opportunity/BM for big pharma ?
- OD affordability and cost-effectiveness problems are compatible with the sustainability of health care systems?

2 – Theory (1):
« The myths of market », Neil Fligstein

- **Markets are social structures** characterized by extensive social relationships between firms, workers, suppliers, customers, and governments

- **Markets are political and cultural constructions,** embedded in institutions, produced by political compromises between firms, stakeholders and State

- **Firms and markets** need institutions that limit uncertainty and enable to act. Firms try to control markets, by avoiding direct competition on prices and by insuring a stable coalition with stakeholders in the organization

2 – Theory (2):
« The myths of market », Neil Fligstein

- **Markets need stable institutions to enable transactions:**
  - **Property rights**: *social relations that define who has claims on the profits of firms*
  - **Rules of exchanges**: *define who can transact with whom and the conditions under which transactions are carried out*"
  - **Governance structures** *are the rules (informal & laws) that define relations of competition & cooperation between firms, like antitrust laws or more informal practices that structures organizations like routines related to the way of arrange labour contracts or outsourcing*
  - **Conception of control:** are *common understandings that structures the perception of managers about how interprets the actions of competitors and a reflexion about how the market his structured; they reflect a common agreement about how a firm has to be organized, what strategies are pertinent in this specific field and about the hierarchy between firms on the market (that is to say that conception of control are symbolic violence). Conceptions of control become local culture of firm and industry*

3. *Political work & construction of OD market (1)*

- **Markets are political and cultural constructions**, embedded in institutions, produced by political compromises between firms, stakeholders and State **: the Orphan Drug Act in USA (1)**
  - Implemented as a result of the thalidomide scandal of the late 1950s. Why ?
  - Because, the Kefauver–Harris amendments of 1962 mandated that pharmaceuticals demonstrate their innocuity & therapeutic efficacy
  - After 1962 compliance with the increasingly stringent requirements of regulatory agencies & insurance against claims relating to product liability increased drug development costs.

  => In order to maximize returns, the pharmaceutical industry focused on large disease populations

3. *Political work & construction of OD market (2)*

- **Orphan Drug Act in USA** (2)
  - By 1962, 26 drugs have been approved for rare disease indications
  - By 1983, only 10 more new drugs have been marketed

  (House of Representatives Subcommittee Report, 1982)

Case: *In 1956 penicillamine was introduced for the treatment of Wilson's disease.' with old-fashioned toxicity testing, by 2 firms, 10 years later when J. M. Walshe wanted to introduce Trien, as an alternative for a few patients intolerant of penicillamine, no manufacturer would provide it.*

  - In 1981 the US Pharmaceutical Manufacturers' Association set up a Commission on Drugs for Rare Diseases and the following year the generics industry formed a parallel body
  - In 1982 an "informal coalition" (later known as NORD) of support groups and families called together to advocate legislation supporting development of OD
  - 1983 , President Ronald Reagan signed the ODA into law

3. Political work & construction of OD market (3)

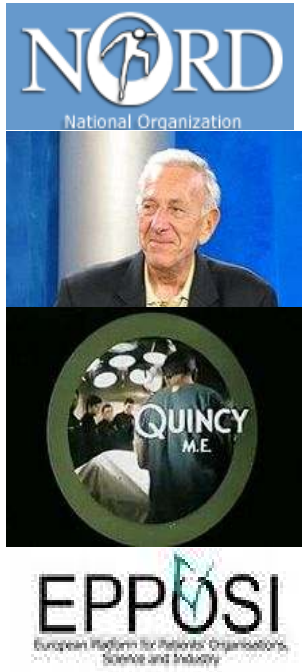
- **Orphan Drug Act in USA** (3)
  - Under the law, companies that develop a drug for a disorder affecting fewer than 200,000 people in the United States
  - The ODA created a number of incentives for the pharmaceutical industry which include:
    - 7 year market exclusivity for orphan drugs;
    - tax credits totaling half of development costs
    - research and development grants;
    - fast-track development and approval;
    - access to Investigational New Drug Program and preapproval;
    - waived drug application fees
  - 1993: NIH Office of Rare Disease was set up
  - Rare Disease Act (2002) : disorder affecting fewer than 200,000 people in US or about 1 in 1,500 people

3. Political work & construction of OD market (4)

- **Orphan Drug legislation in EU** (1)
  - 1991/1992: In Europe (Directive 91/507/EEC, July 19th. 1991), as in France (from year 1992, articles L.601–2 and R.5142–22 of the 'Code de la Santé Publique') the principle of OD has been acknowledged.
  - 1995: Report on rare disease written by A. Wolf (INSERM) has been sent INSERM's parent bodies, including the health and research ministries at a time when France is starting its 6-month EU presidency
  - 1995: French health minister presented a memorandum to the European Council of Ministers of Health on June 2
  - In 1996 august, the European Commission released a draft paper on the proposal for a EP and Council Regulation on OD
  - 2000, May: Orphan medicinal products legislation in EU
    - Life-threatening & debilitating diseases with low prevalence <1/2000
    - EU's definition is broader than that of the USA, in that it also covers some tropical diseases
  - In 2009, 577 molecules had received orphan designation and 57 had received marketing authorization in Europe

3 - Political work & construction of OD market (5)

- **Markets are social structures** characterized by extensive social relationships between firms, workers, suppliers, customers, and governments
  - Patients – governments relationship:
    - National Organization for Rare Disorders, founded in 1983
    - Episodes of the TV series *Quincy, M.E. for helping the ODA pass in the USA: "Seldom Silent, Never Heard" (1981) and "Give Me Your Weak" (1982).*
    - The show's star, Jack Klugman, even testified on Capitol Hill in favor of the bill
  - Patients – firms relationship:
    - European Platform for Patients' Organization, Science & Industry (EPPOSI, founded in 1994)
  - Firms-governments relationship:
    - EuropaBio Task Force on Rare Diseases & Orphan Medicinal Products



3. Political work & construction of OD market (7)

- **OD markets need stable institutions to enable transactions**
  - **Property rights:**
    - **the OD market exclusivity (but the efficiency of this incentive remains to be demonstrate since its overlapped by the 20 years patents rights)**
  - **Rules of exchange: the same rules than drugs + others rules:**
    - **tax credits, R&D grants; waived drug application fees**
    - **The approved designation build the market not the drug by itself**
  - **Governance structure**
    - **OD act**
    - **FDA Office of Orphan Products Development (OOPD) , OD Board in the Dpt. of Health & Human Services**
    - **Fast-track development and approval**
    - **FDA & EMEA agreed to utilize a common application process in 2007**

3. Political construction of OD market: timeline

Year	Science	Market	Regulation
1950	Thalidomide		
1962			Kefauver–Harris amendments
1973	Recombinant technology		
1976		Genentech	
1979	Monoclonal antiblodies		
1980			Bay Dohle Act
		Patent for gene cloning	
1981		Genzyme	Diamond v. Chakrabarty case
1982		Humulin	SBIR Act
1983	PCR		US Orphan Drug Act
1984			Mathias-Waxman Drug Price Competition Act
1987	CF gene cloning		
1989		EPO	
1990	Gene therapy treatment		
			EMEA
1995			INSERM Report
1996			EC proposal in font of EP
1998		Herceptin	
2000			EU Orphan medicinal legislation
2001		Fabrazyme	

4. *Conception of control?* :
from blockbuster to nichebuster

- During the 90s, the dominant **model of control** of the industry was « blockbuster » conception of control:
  - **Using patents and refocusing on ethical drugs and mass markets**
  - **Capturing US market**
  - **Intense marketing**
  - **M&A**
- As a consequence, Big Pharma was not interested in rare diseases, allowing small firms to focus on OD & develop specific BMs
- But growing difficulties for Big Pharma:
  - **Pressures of States and insurers to limit reimbursement and prices**
  - **Declining of R&D productivity & drug pipeline drying up**
  - **Competition with generics firms**
  - **Safety problems (side effects etc…)**

=> End of 'blockbuster' **model of control**, so need to find a new on: 'personalised medecine & nichebusters'

=> OD are now interesting for Big Pharma

5. The business models of OD market:

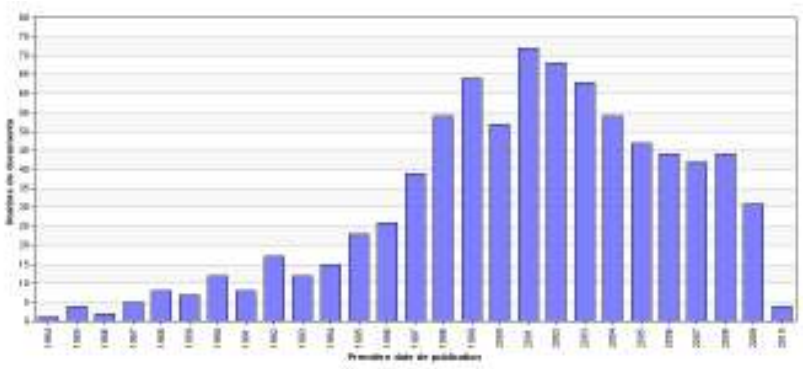
4 firms – 4 BMs

	Genzyme	Swedish Orphan	Novartis	Pfizer
Main source of profits	OD	OD	Blockbusters + OD	Blockbusters
Product-policy	OD + diversification in biosurgery, transplant, R&D services, diagnosis etc…	OD	Focus on blockbuster & diseases with no treatment + generic drugs+using OD and finding new designations	Focus on blockbuster+ OTC + OD as a secundary objective
Organization	Vertical integration from research to marketing, highly RD intensive. NEBM	Focus on phase III, production & distribution. Acquisition of existing molecules. Strong networking with patients	Vertically integrated but important networking & outsourcing research to biotechs; « Proof of concept »	OEBM, vertically integrated with more and more outsourcing
Financing & governance	SV, stock options, acquisition/diversification, issuance of stocks for financing, no dividend	Hold by a VC firm Stock options	Shareholder value, high SVD, stock option for management, acquisitions	Shareholder value, high SVD, stock option for management, M&A

5. The business models of OD market:
GENZYME (1)

- ***A first mover, typical of a "orphan-led" business model***

  - Founded in 1981by H. Blair, 12000 employees, 4.6 bn$ revenues
  - A high tech company with 818 patents with tight relations with academic research (26% of Genzyme patents coassignees are universities)



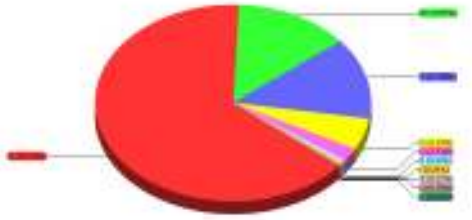
  - 10 OD designations for 10 different products in EU with 4 OD authorized (1st in 2001, last 2006) targeting genetic diseases (only 1 anticancer drug)
  - Example: Fabrazyme for Fabry disease (450 patients /France)

5. The business models of OD market:
GENZYME

- ***A first mover, typical of a "orphan-led" business model***

– 50% Revenues with OD: 1.2 billion for Cerezyme, 678 millions for Sevelamer & 494 million from Fabrazyme

– a diversified company in biosurgery, cardiometabolic, fine chemical, renal & hematology products & services, R&D services, diagnostics, …



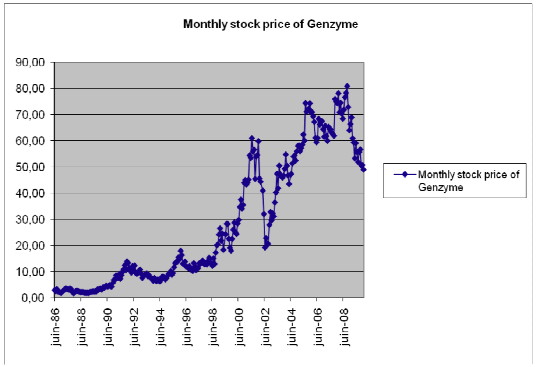
– growth by merging (54 operations; 1/3 firms sharing IP Genzyme portfolio)

– R&D investment 22-24%

– on NASDAQ since 1986:

– no dividend distribution but shares repurchasing

– ROE 3.44% between 1994-2008



=> OD regulation helps Genzyme BM to support biotech innovation & public health expectation

5. The business models of OD market:
SWEDISH ORPHAN

- ***A specific SMEs orphan-led business model***

  - dedicated to rare diseases with 91 employees and 82 million of euros revenues in 2008.
  - 2 products free of IP protection, 3 designations (2 approved in EU for 2 genetic diseases) with more than 40 drugs in its portfolio
  - BM build on licencing-in drugs (patent portfolio: 4 co-owned patents), & networks of patients, physicians and hospital as intangible assets
  - Develops OD that have passed preclinical phases & phase I invented by others (firms or academics)
  - Generated 42,5% of ROE in average
  - In 2004, SOI was acquired by Growth Capital and Skandia Investment, two private equity funds, and SOI has been acquired by Biovitrum AB in 2010.

=> OD regulation helped SOI to put on the market drugs unprotected by patents & demonstrate economic sustainblity of the BM at the same time

5. The business models of OD market: *NOVARTIS*

- ***A Big Pharma investing more and more in biotech & ODs***

  - formed in 1996 by the merger of 2 Swiss companies, Sandoz and Ciba-Geigy; agribusiness & Consumer Health were progressively sold or divested,
  - focused on biotechnologies with an equity investment in (and after an acquisition of) Chiron (with a portfolio of 12 OD designations) for $5.1 Billion
  - OD portfolio: 9 products (only rare cancer) with 20 designations and 3 authorizations, in EU since 2001
  - main OD is Gleevec/Glivec, Novartis' 2nd-biggest blockbuster with t $3.9 billion of revenues

⇒ **OD regulation were bypassed by Novartis to get OD designation for drugs with large markets by "salamy slicing" strategy**

5. The business models of OD market:
PFIZER

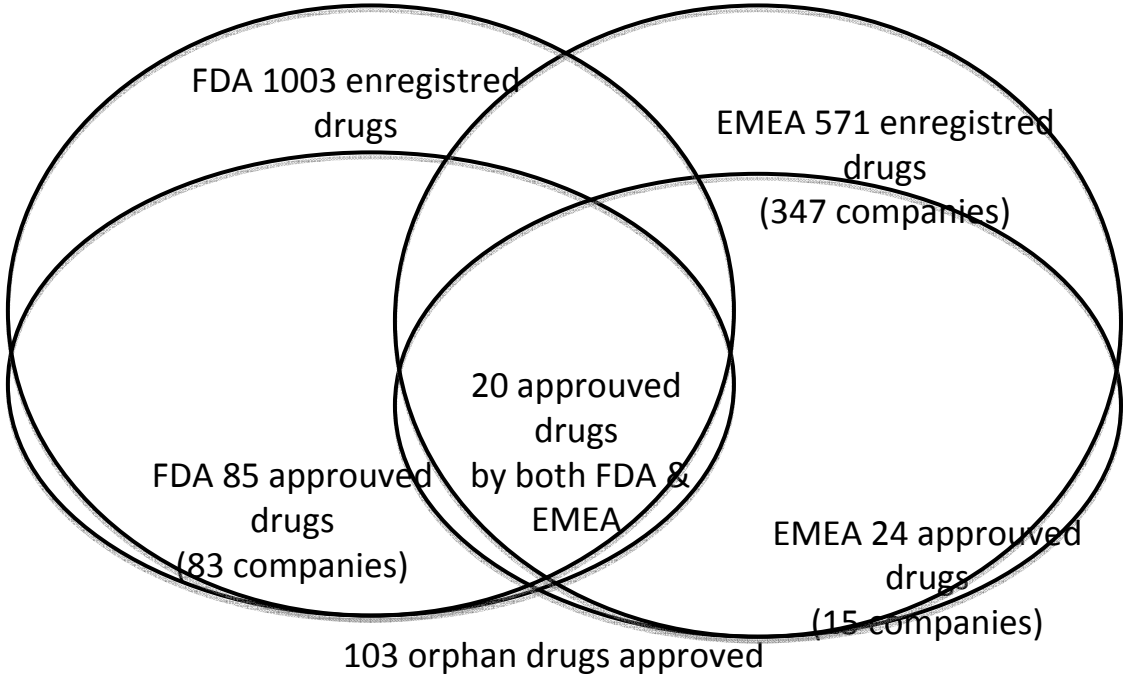
- ***The typical blockbuster-led BM trying to change its BM***

  - 9 blockbuster in 2009, focusing on large markets like HTA, cholesterol, arthritis pain, erectile dysfunction
  - 4 in-house developed OD (for 4 designations & 4 authorizations in EU)& 3 others acquired through fusion with Wyeth Inc.
  - Among them, Onsenal (celecoxib) and the Revatio (sildenafil citrate) are in fact preexisting molecule of 2 others blockbusters: Celebrex (for pain and arthritis) and Viagra (for erectile dysfunction)
  - These drugs generated around $1.9billion, ie 4.2% of the total pharmaceutical sales

=> OD regulation served Pfizer to circumvent IP dead-end & generic competition on its blockbuster portfolio.

6. Conclusion (1)

Does the OD act foster innovation and fulfill public health needs ?



Does the OD act has stimulated the production of truly non-profitable drugs ?

Example: Cerezyme 200 000$/patient/year

From 8/8/2000 to 12/06/2009

6. Conclusion (2)

- **Innovation**
  - 30%/70% biotech/chemicals ODs,
  - Highly patentable products vs recycling of IP unprotected drugs
- **Public health**
  - Fulfill patients needs (new drugs available in EU for 23 genetic diseases among 48 rare conditions granted)
  - Problem of sustainability (ex: Fabry disease 200 K$/patient/year)
- **Industry dynamic**
  - Big pharma are the player (45% of authorized new drugs by FDA AND EU)
  - Direct (new BM) or indirect (merger) control of the market
  - "Cyclic" conception of control (before 1962, between 1962-1983, after 1983 and nowadays)
- **Policies**
  - Distortion of the market is linked to the definition of rule (designation approval vs drugs approval -> "salamy slicing" strategy)
  - OD market as a paradigme for future EU personalized medicine policies

- **NB: OD act in Eu was a chance to promote news drugs for neglected disease which haven't been undertook by pharma companies.**

6. Conclusion (3)

How to conceal the cost of innovation and the sustainability of public health system ?

At the present time, political agenda are focusing
on reinforcing innovation policies to sustain economy,
therefore public stakeholders invest in high risk activity
while the benefits are captured by the firms.

This a dilemma for public health future
unless advance in post-genomic medicine
cut down the risk and the cost of R&D & clinical trials.