

# **IPRs, Public Health and the Pharmaceutical Industry**

## **Issues in the Post-2005 TRIPS agenda**

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# **(Bio)Pharmaceuticals**

- **This sector brings the trade-offs and issues involved in patent theory to their extreme consequences**
- **An industry where patents are actually very important mechanisms of private appropriability**
- **A science-based, innovation-intensive industry**
- **A socially sensitive industry: health as a human right**
- **Undergoing deep and unforeseeable transformations**

# Pharma and Welfare Issues

- **Controversies about the welfare implications of patents have characterized this industry ever since its inception.**
- **But in the last thirty years or so, the establishment of strong tendency towards an extremely tight IP regime has made this debate even more heated.**
- **Pandemics make the problem even more “visible” and compelling.**

# Pushing the controversy to the extreme

## 1) Advent of biotech:

- progresses in molecular biology and their increasing relevance for industrial innovative activities have strained to the limit a patent system which was essentially conceived for technologies like mechanical engineering and chemistry.
- Stretching the notions of novelty and usefulness
- The development of the biotechnology industry itself is strictly dependent on a highly favourable IPR regime
- the transformations of the latter have been significantly influenced by the growth of the biopharmaceutical sector.

## 2) Bayh-Dole

- Commercialization of basic research

## (3) TRIPS Agreements ...

- Of which the pharmaceuticals industry is one the main supporters — has ignited raging controversies which go beyond domestic boundaries and reach the global level.



**PART 1**  
**IPR and the Pharma Industry**

# Main propositions

- **There are, indeed, profound trade-offs between the incentives to innovate and ensuring public access to medicines**
- **The effects of strengthening the patent regime depend (non linearly) on a wide variety of conditions in any given country:**
  - **institutions (price controls; health systems, in general; basic research..);**
  - **Capabilities and opportunities for innovation;**
  - **size of markets;**
  - **modes of competition;**
  - **the specific nature of patent laws themselves and court interpretations**

# Main propositions (2)

- **The IPR system governing pharmaceuticals has become increasingly dysfunctional — even in countries like the U.S.**
- **Excessively tight IPRs can have negative effects not only on prices, but also on the rates and directions of innovation**
- **Both economic theory and the evidence increasingly suggest that the strengthening of IPR regimes in developing countries is likely to impose upon them a series of negative consequences that most likely outweigh any potential benefits gained from the tighter regime.**

# Market structure

- **Pharmaceuticals has been traditionally dominated by a stable core of large, globalised innovative firms (USA, UK, Switzerland, Germany, Japan), but also:**
  - **Small domestic firms involved in adaptation, manufacturing, marketing**
  - **Biotech firms**
  - **Generics producers**
- **Small entry and turbulence (until biotech)**
- **Low demand price elasticity, high income elasticity**
- **Strong information asymmetries**
- **The third payer problem**

# The dynamics of competition

- **Schumpeterian competition:**
  - High profits after introduction of new drug
  - Imitation and me-too-drugs before patent expiration
  - Entry of generics after patent expiration
  - Branded “generics”
  
- **Low concentration (despite high R&D and marketing intensity, M&As):**
  - little cumulateness in innovation (random screening)
  - independent sub-markets

# The Golden Age

**The system seems to have been working reasonably well for many years**

- Innovative opportunities
- Welfare systems
- Moderate IPR regimes: The interpretation of novelty, The interpretation of usefulness, Scope and breadth

**High rates of innovation**

**The scope and efficacy of patent protection has varied significantly across countries.**

Many countries allowed only process patents did not offer protection for pharmaceutical products:

**Product patents:** France in 1960; Germany 1968; Japan 1976; Switzerland 1977; Italy and Sweden in 1978. In some cases, as in Japan and Italy (and possibly France) the absence of product patent protection induced firms to avoid product R&D and to concentrate instead on finding novel processes for making existing molecules. In other cases, primarily Germany and Switzerland, this negative effect didn't happen

# Trends :The Productivity Paradox

Between 1978 and 2003, research productivity, has been falling:

- R&D expenditures increased tenfold while patenting output increased only sevenfold (Nightingale and Martin 2004).
- New Chemical Entities approved by the FDA in the U.S. between 1983 and 2003. Some increase was displayed until the mid 1990s, followed by a sharp decline in the years since. In 2002, U.S. R&D expenditures in pharmaceuticals were 30 times greater than in the early 1980s, while roughly the same number of drugs were approved annually.
- High rates of attrition, longer times in Phase I, the Phase II bottleneck
- Depletion of opportunities, more difficult pathologies
- Increasing complexity, explosion of the research space
- Increasing costs of regulation (?)
- IPRs (?)

# Trends : Biotech is no better

- **Although around 1/3 of new drugs originates from basic research conducted at universities, hospitals and biotech companies, the performance of the biotech segment is disappointing (Pisano 2006):**
  - **Operating profits**
  - **New drugs**
  - **transaction costs and market failures**

# Further changes in the industry

- **Regulation, product approval: (evidence-based medicine, multi-country trials...) before and after product approval;**
- **But also significant rationalization and time/cost cutting, especially for some categories of drugs (e.g. orphan drugs)**
- **Markets: diffusion of generics, appearance of new firms and countries as producers of generics**
- **Increasing marketing expenditures (prices of branded drugs increase after patent expiry, market segmentation); Direct to Consumer Advertising**
- **Cost containment policies**
- **Raising perceptions of health as a human right plus humanitarian catastrophes (HIV/AIDS)**

# Questions about the future of the industry

- **Is the Big Pharma, blockbuster model still viable?**
- **Is the current Biotech/Big Pharma model efficient?**
- **Underlying Issue : how to sustain R&D and innovation and confront the “productivity paradox” ?**

# The debate on IPRs in Pharma

- **Neverending debate on the effects of patents in pharma well before Trips (The Kefauver Commission (1962))**
- **Weak and inconclusive theoretical and empirical implications**
- **But still, despite the progress, empirical evidence remains flimsy: problems of measurement and sheer lack of adequate data**
  - **Data are extremely hard to get access to and when they do exist they are often available at prices and terms which are unaccessible to anybody except few specialized research groups.**
- **Not only patents: regulations restricting access to clinical trials data for generic producers**

# What do we know?

## Some empirical results

- **Studies on effects of lower prices on R&D (in the USA)**
  - Most of them suggest drastic reductions in R&D (e.g. Vernon)
- **Estimations of elasticity of innovation (as measured by patents) to IPR regime:**
  - **Arora, Cohen and Walsh:**
    - patent premium ranging from .50 to .90, but 1.75 to 2.25 for pharma:
    - %change in R&D wrt to 10% change in patent premium: 6% but 7.5% to 8.9 pharma;
    - Equivalent subsidy rate: 17% (22% pharma)
  - **Linn and Acemoglu (2004):** in pharmaceuticals a 1% increase in the size of the market for pharmaceutical products raises the number of new drugs by 4% to 6%, implying an elasticity of innovations to R&D ranging from .8 to .85

# Costs of patents

- **The average increase in price for pharmaceuticals due to patent protection is probably close to 400 percent, with the gap in many cases exceeding 1000 percent of the marginal cost (Baker and Chatani, 2002)**
- **Huge welfare losses: The size of the deadweight losses range between 0.1 and 0.5 percent of GDP, approximately equal to the amount that the industry currently claims that it is spending on pharmaceutical research in the United States.**
- **The deadweight loss may increase even more as costs of research increase (Baker, 2004)**

# Further costs

- **1) Higher profits, higher marketing expenditures, the efficiency of which is dubious, given information asymmetries and the third party payer**
- **2) Distortions in the directions of research:**
  - **useful research: discovery of patentable products.**
  - **less productive lines of research, duplicative drugs**
- **3) incentives are created through political interference to pursue less productive lines of research;**
- **4) incentives are created to obstruct the free flow of research findings**
- **5) Controversial evidence on the role and effects of “me too drugs”**

# Recent changes and the debate on tighter IPRs regimes

- **We have seen the effects of patents in general; what about further strengthening?**
  - **When patents are already strong, increasing patent protection further may actually depress the level of innovation)**
  - **The effects depend critically on existing technological capabilities, innovative opportunities and the stage of development of a country (incentives and competences)**
  - **These models similarly suggest that the relationship between patent length and innovation will display an “inverted U” shape.**
  - **Confirmed by studies by Lerner (2000) and Qian (2007)**
  - **Introduction of patent protection does not increase levels of innovative activity but may have stronger effects on changing the direction of innovative activity (Moser, 2005)**
  - **Non linear, non monotonic relationships**

**PART II.**  
**TRIPS and Acces to Care in DC's**  
**The post 2005 Issues**

# **The New Constraints Generated by the TRIPS**

## **The signing of the TRIPS (1994) meant**

- The extension at the world Level of patent protection provisions designed for the firms of the most developed countries (patenting of therapeutic molecules, 20 years length protection ...)

## **This “upward harmonization” of IP protection**

- Negated the differences in national capabilities to provide access to medicines, a provision that was at the basis of the former Treatise (WIPO, Paris Convention...)

## **Key consequence**

- The TRIPS have put an end to the right of developing countries to produce and/or import generics drugs, at low costs to satisfy the needs of the poor

# Pharmaceutical Patents Regime under the TRIPS

**2005 implies means the entry in a completely new world**

- End of the transitionnal period for DC's to comply with the TRIPS constraints
- Key event : the 2005 Amended Indian Patent Law

**However : existence of some "flexibilities" in the TRIPS treaty**

- Some Articles (Art 28 to 31) states the right to use « compulsory licenses », especially in case of « health emergency »
- Art 31f seems to prohibit the « imports » of generic drugs, even for the countries lacking of the technical capabilities required to produce the drugs locally  
... but : the working of these clauses were never clarified in a satisfactory manner...
- 2001 and the "Doha Declaration" opens some room for DC's and LDC's but the Declaration has never been enforced as an international law (see Genova 2002)

# Key features of the post 2005 period

- **As regards IP issues, the Post 2005 period is marked by a strong contradiction between**
  - **WHO´ s High Level Decision and Gleneagles´ statements recommending “universal access by 2010”**
  - **... At a time when a series of changes make this goal especially difficult to reach**
    - **End of the transitional period of the TRIPS agreement (signed in 1994)**
    - **Spread of TRIPS + agreements ...**
- **Hence ... the question addressed in this part of the presentation : are the TRIPS flexibilities “flexible enough” to secure access to care in DCs ?**

# Issues to be discussed

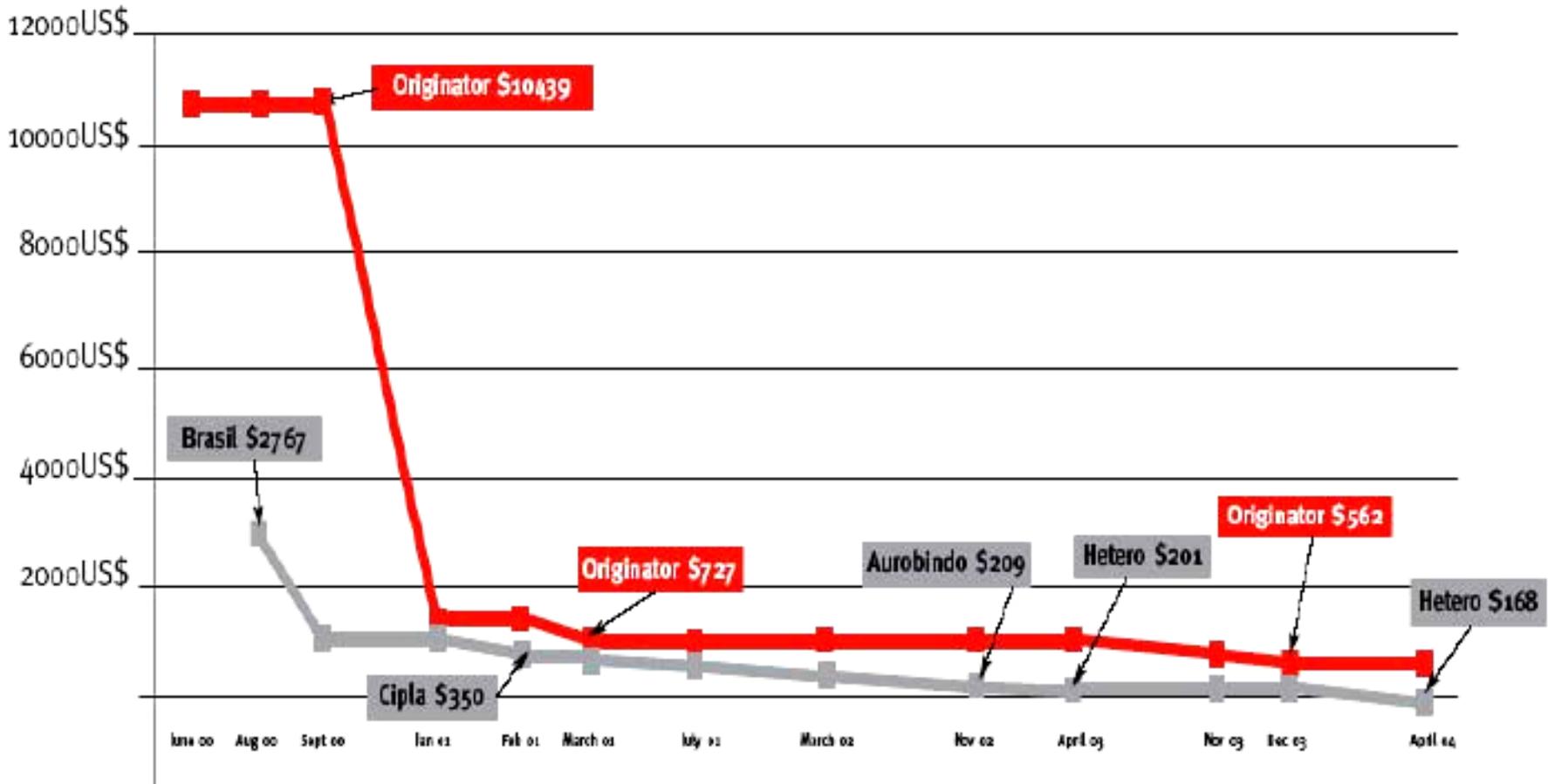
- **Looking to the past : the Pre-2005 period**
- **The post 2005 scene and the emergence of new IP issues**
- **Using TRIPS flexibilities : lessons from case studies**
- **Provisional conclusions**

# Looking to the Past : Procurement Policies in the Pre-2005 Period

- **1994-2005 : Transitional period allowing local production in developing countries**
- **Doha 2001, WTO August 2003 Decision...**
  - India and Thailand as the “Pharmacies of the south”
- **AAI policy of « preferential prices » for DC’s and LDC’s**
- **... In a context where very powerful financing mechanisms were installed**
  - GFATM, Pefpar, World Bank PAM,
  - **The combination of generic supply + AAI + branded ARVs at negotiated prices resulted in ... massive decreases in ARV prices (1st line)**

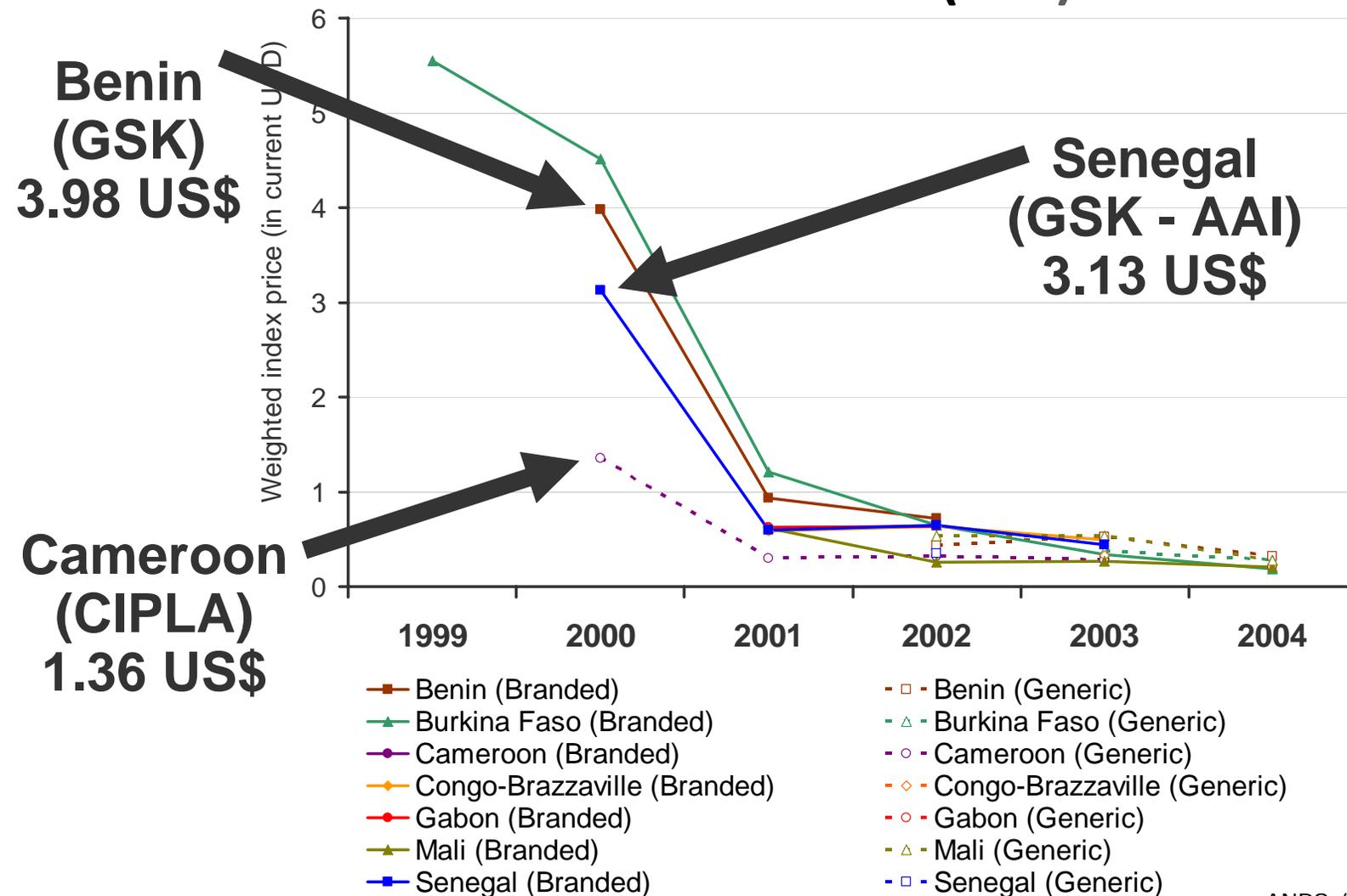
# Pre-2005 : A Spectacular decreases of prices The case of first Line Regimen (1/2)

May 2000-April 2004

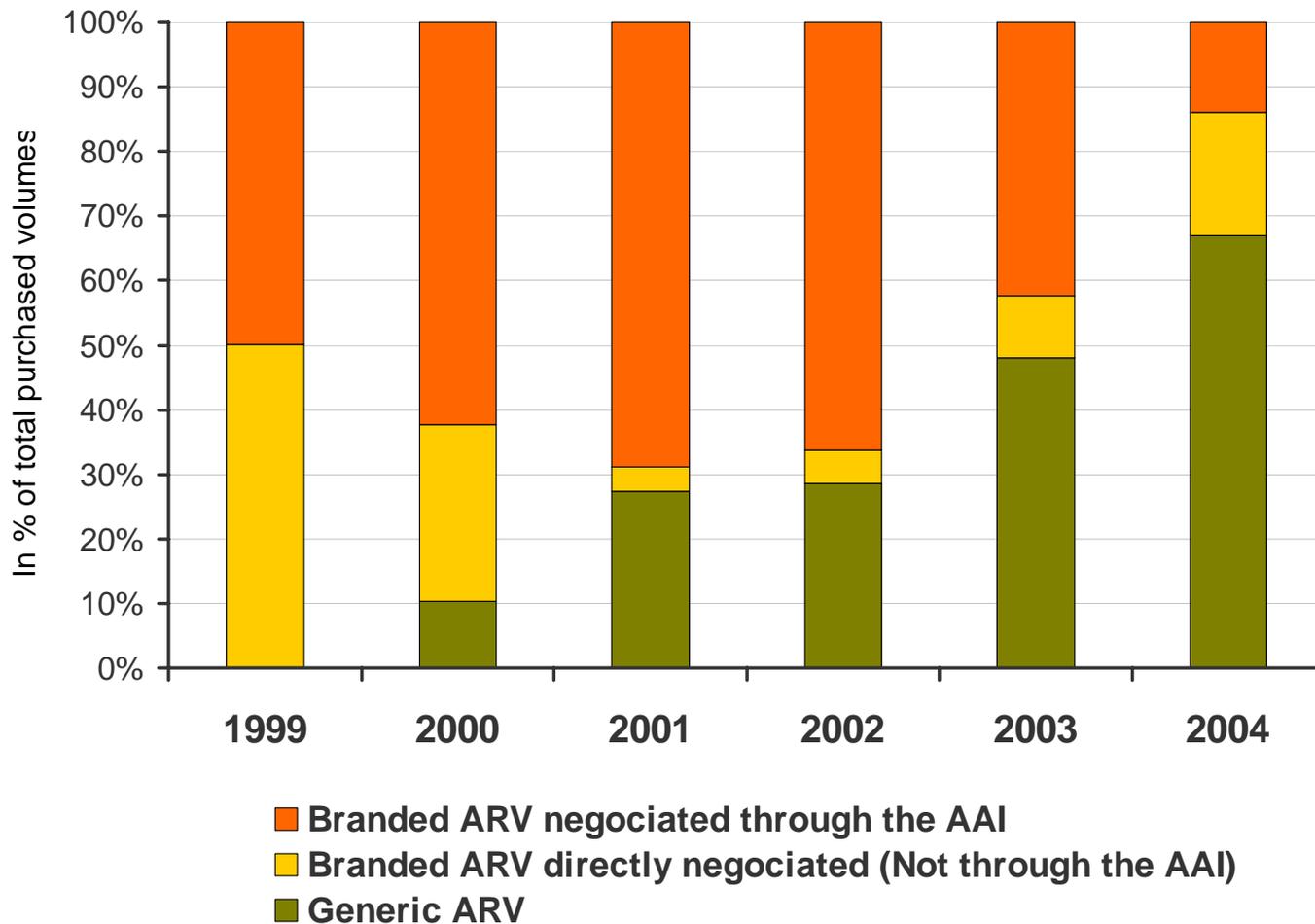


# Evolution of prices of ARV drugs in Africa

## Lamivudine (3TC)



# ARV procurement strategies in Sub-Saharan African countries



# Innovative treatments :

## The case of the FDC “Triomune”

Today : (estimated) half of all patients on ARVs in developing countries depend on Indian generic ARVs

- A major innovation : the first FDC on the market
- More generally : a large spectrum of generic ARVs available before 2005,
- Most of them being now pre-qualified by WHO
- India and Thailand as « pharmacies of the South »



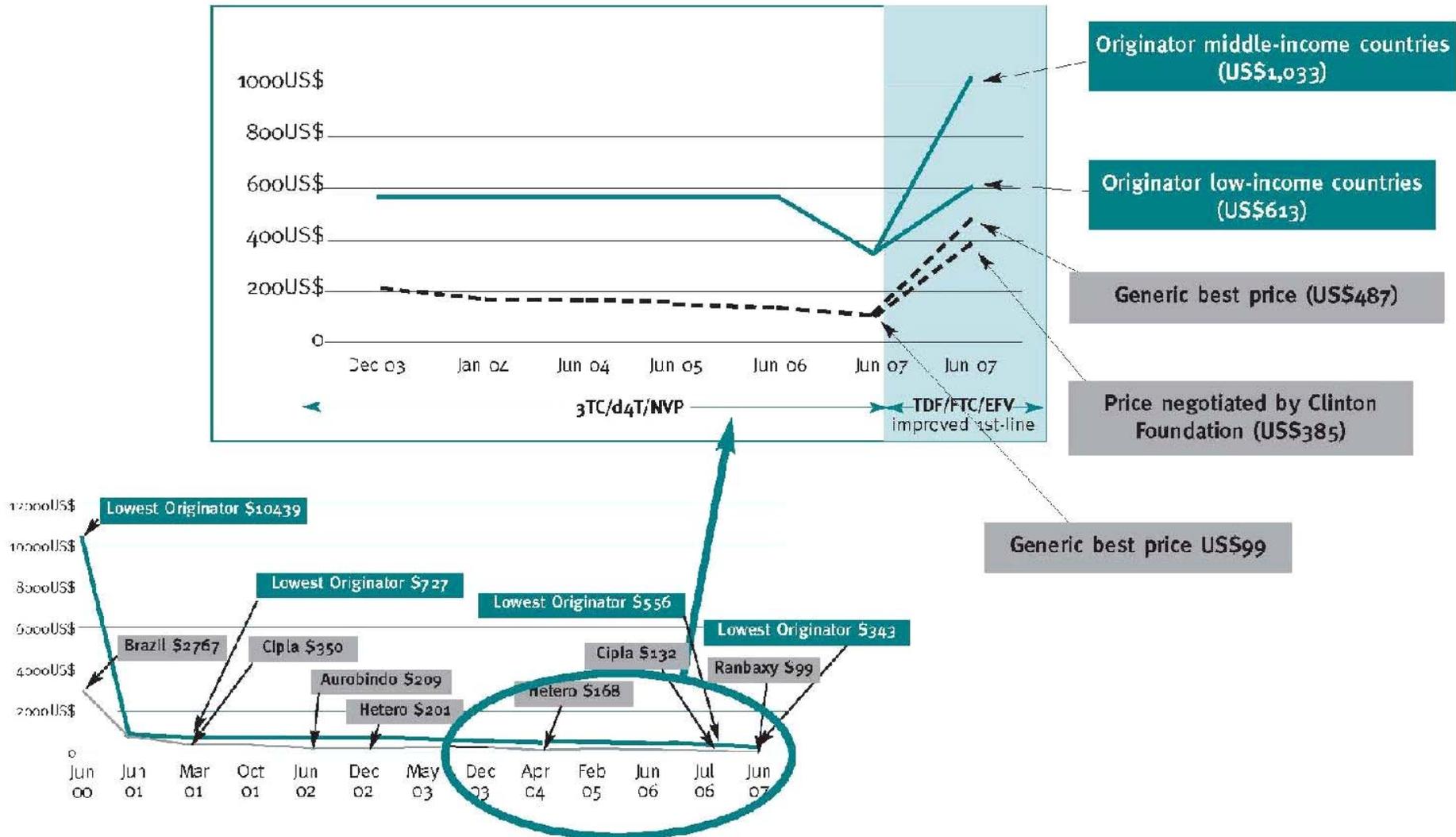
# The post 2005 scene

**Apart from the changes in the legal context ...**

- ❑ **Changes in the scale of population under ART...**
  - ❑ **Relevant increase in the number of patients under ART (3 millions in 2008)**
- ❑ **Along with changes in the therapeutic recommendations (WHO) with inclusion of new much more costly ARVs, most often protected by patents (TDF, LPV/r...)**
- ❑ **Rapid acceleration of people in need of 2nd and 3rd line treatments** within the national therapeutic programs
  - **yearly, 10 % of each cohort has to pass to 2sd line regimen**
- **New hindrances to the Sustainability of HIV/AIDS Programs in Southern Countries**

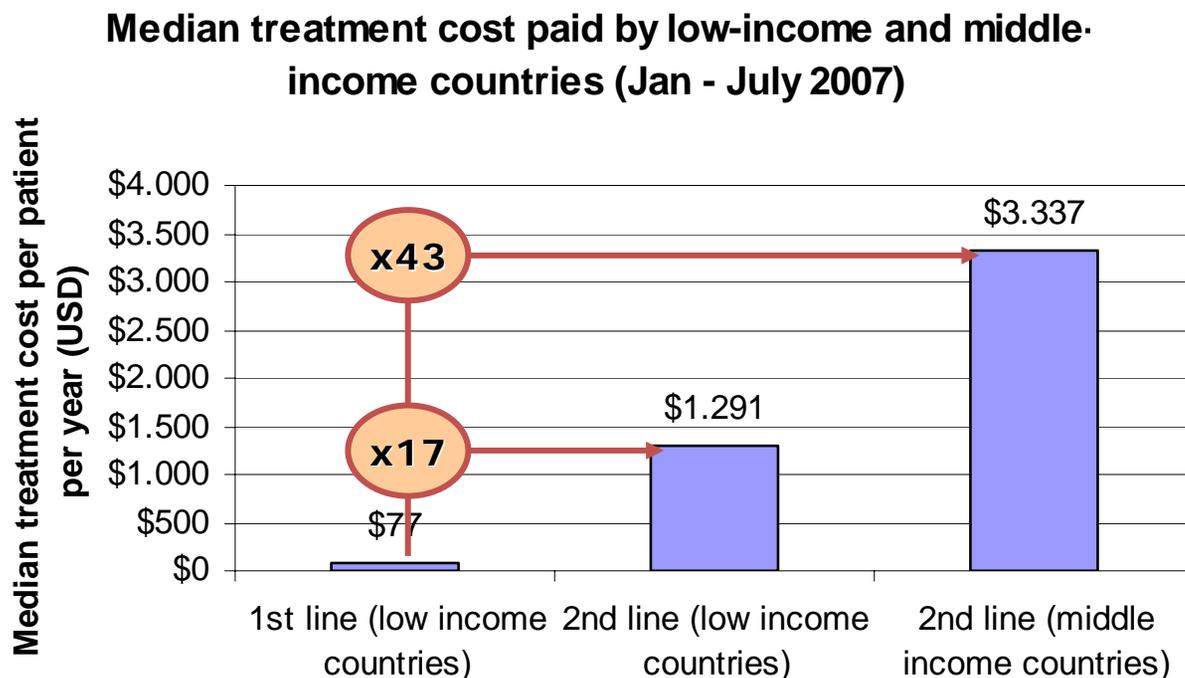
# Impacts of the new legal framework on access to HAART

## (1/2) The case of 1st line regimen's prices



# Impacts of the new legal framework on access to HAART

## (2/2) The budget surge for 2sd line treatment



Median price paid in 2007 by developing countries for the most commonly used second-line antiretroviral treatment (abacavir + didanosine + lopinavir/r), compared with first-line regimen (lamivudine + stavudine + nevirapine)

# Using TRIPS flexibilities : lessons from case studies

## Understanding TRIPS Flexibilities

- “Bolar Exception” for scientific use
- Parallel Imports
- Pre-Grant Oppositions
- Compulsory Licenses → different alternatives provided by article 31 of the TRIPS agreement, including : Governmental Use, National Emergency, Public Interest ...

# Pre-grant opposition and Compulsory License what is it about ?

## □ Pre(& post)-grant opposition

*“documents and information intended to assist the examination may be filed by (any) interested persons between publication of the application and completion of the examination”* Brazil’s legislation, article 30 of Law 9279/96

## □ Issuing of Compulsory License

*“ limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner” (article 30).*

## **The case studies in a nutshell (1/2)**

- **3 key drugs : EFV, TDF, LPV/r**
- **3 major countries**
  - **India : 1st world provider of generics**
  - **Brazil : largest HIV programme in the South**
  - **Thailand : major producer of generics with large national programme of access to care**
- **2 types of flexibilities**
  - **Pre-grant opposition (TNF)**
  - **Compulsory licenses (EFV, LPV/r)**

# **The case studies in a nutshell**

## **(2/2) Post-2005 uses of TRIPS Flexibilities**

- **Pre Grant opposition**

- **Thailand's Pre-Grant opposition to AZT+3TC patent application (2006)**
- **India's Pre-Grant opposition to Tenofovir's patent application (2006)**
- **Brazil's Pre-Grant opposition to Tenofovir's (2007)**

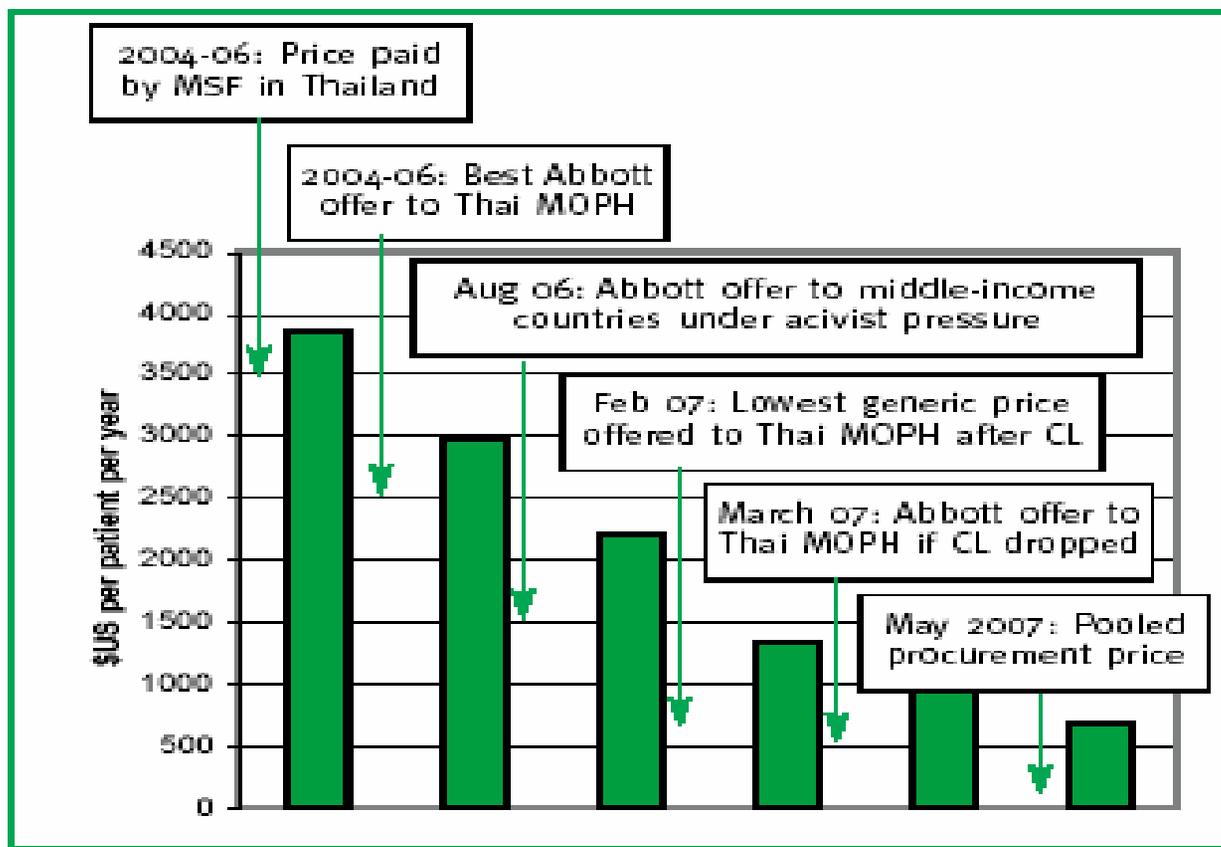
- **Compulsory License**

- **Thailand issues a CL on Efavirenz (2006)**
- **Thailand issues a CL on Lopinavir/r (2007)**
- **Brazil's Compulsory License of Efavirenz (2007)**

# Positive Outcomes

- **Pre-grant on TDF (India, 2006, Brazil 2007)**
  - Offers at lower prices from patent owners (the quality of the patent was known as poor)
  - ... Surprisingly : US PTO in a recent move has negated some of the claims first granted
  - India (and Brazil) have refused to grant a patent to the drug
- **Compulsory licences**
  - EFV
    - Many successive offers at lower prices by patent owners in different countries
    - Since feb 2007, already (in generic form) available in Thailand
    - Since March 2009, ditributed in Brazil
  - LPV/r still in process in Thailand

# Positive Outcomes of the use of IP flexibilities : the case of EFV



# But serious limits too ....

- **Complex mechanisms...**
- **Implemented always under high political pressure...**
  - **The case of Brazil 2006 (LPV/r)**
  - **India 2006 and 2007**
  - **Thailand**
- **Subject to oppositions and litigations by patent owners**
- **Mechanisms not available for countries lacking of technological capabilities...**
- **Few uses, to date :**
  - **3 countries, 3 drugs only ! ...**
  - **(even if used successfully in some “minor” countries)**
- **Total impact on costs remains very modest**

# **Questions arising from the case study on the use of TRIPS flexibilities**

- **Should the future of 3 millions people under ART (to morrow much more !...) be dependant of battle fought on judicial grounds ?**
- **Need of innovative mechanisms guaranteeing the procurement of drugs, especially the new most innovative and efficient ones (2sd line, and switch to new 1st ones...)**
- **More then ever creativity is required to put in practice the Doha Statement**
  - **“the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health”**

# General Conclusion(s)

- **Preserve open science**
- **Excessive tightness of the IPR regime even in the North**
- **A real issue for global R&D and –perhaps - and its productivity**
- **Opportunities in the light of the restructuring of the pharma industry**
- **There are methods for softening the problem**
- **expanding local markets through the construction of better health systems**
- **Are size of the market and patent protection substitutable? Incentives and volumes of R&D expenditure**