Threat to the future availability of affordable generics

India

ACCESS CAMPAIGN

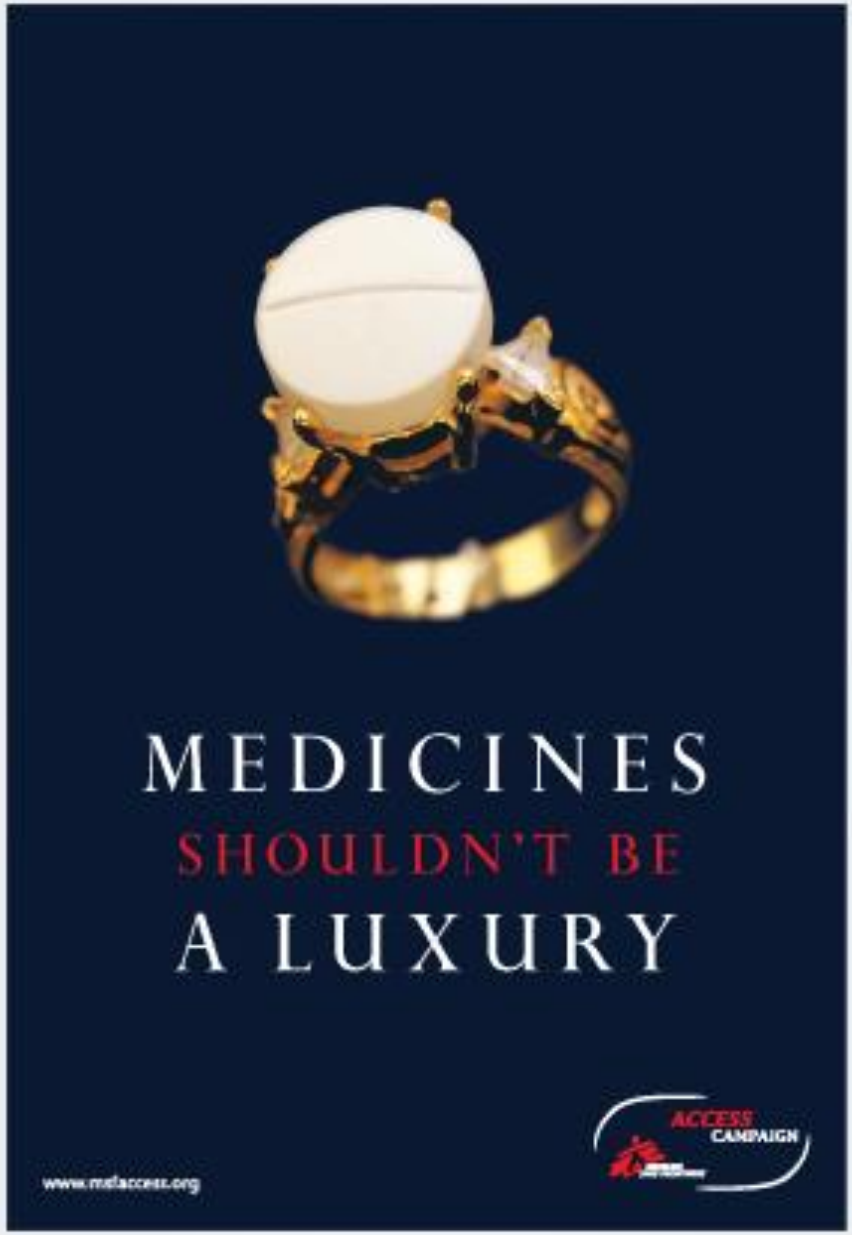
MEDECINS SANS FRONTIERES

- **Access Campaign** Founded in 1999 because MSF medical staff frustrated at not being able to diagnose and treat patients with appropriate and effective tools

- **Unaffordable:** Existing medicines, vaccines and diagnostics are priced out of reach -too expensive for individuals and government treatment programs.

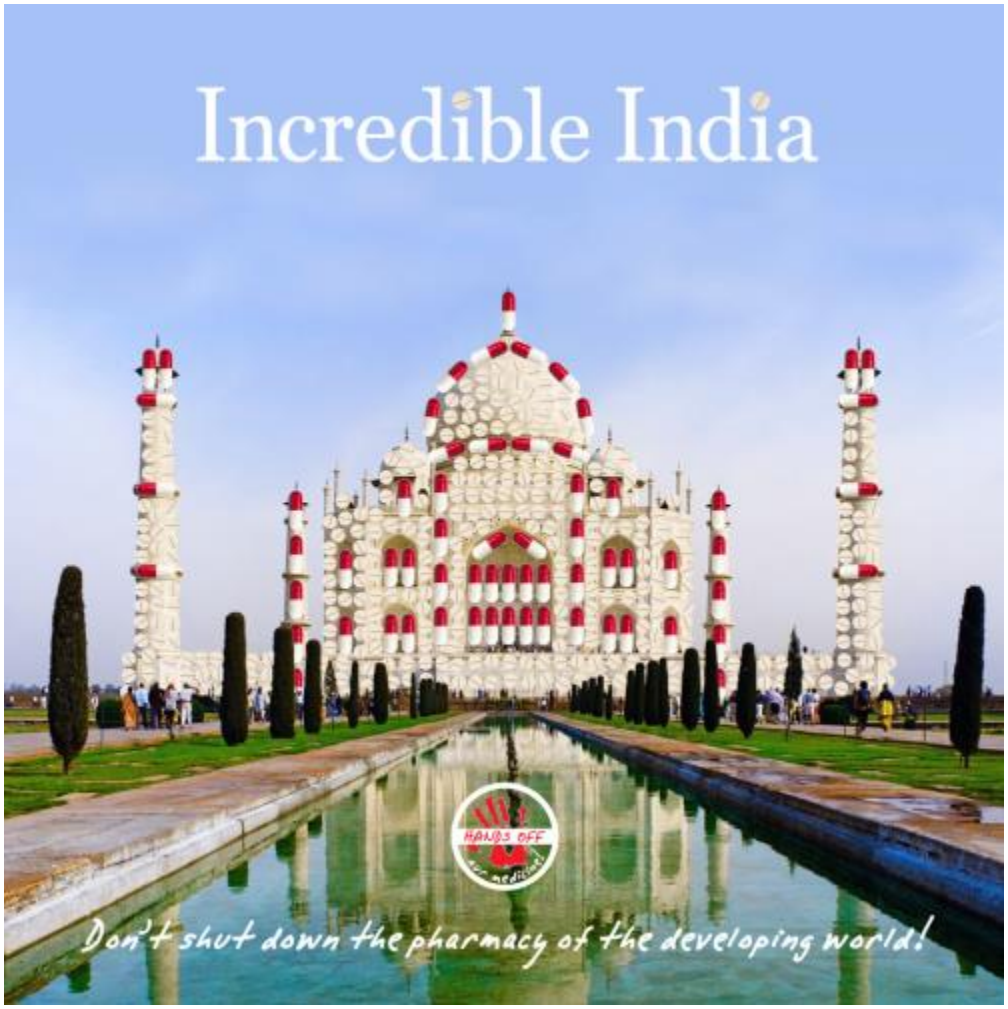
- **Unavailable:** Certain diseases 'neglected' few or no drugs or diagnostics exist or are being developed. (NTD, TB) Production of essential medicines and diagnostics that are needed but do not make profits are abandoned

- **Unsuitable:** Not adapted for needs of developing countries e.g heat stable, child formulations, diagnostic tools

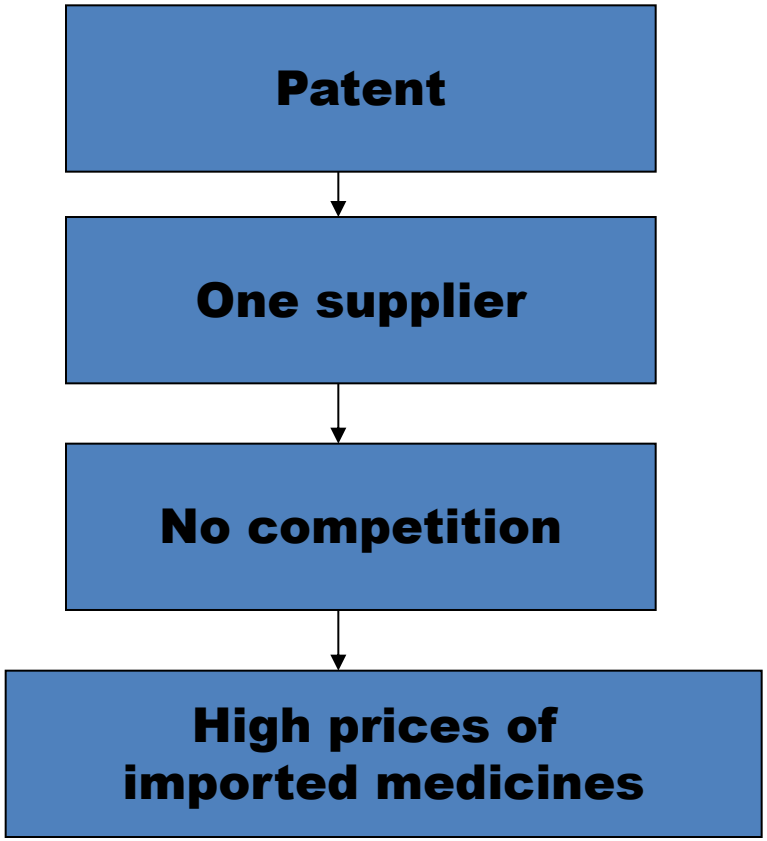


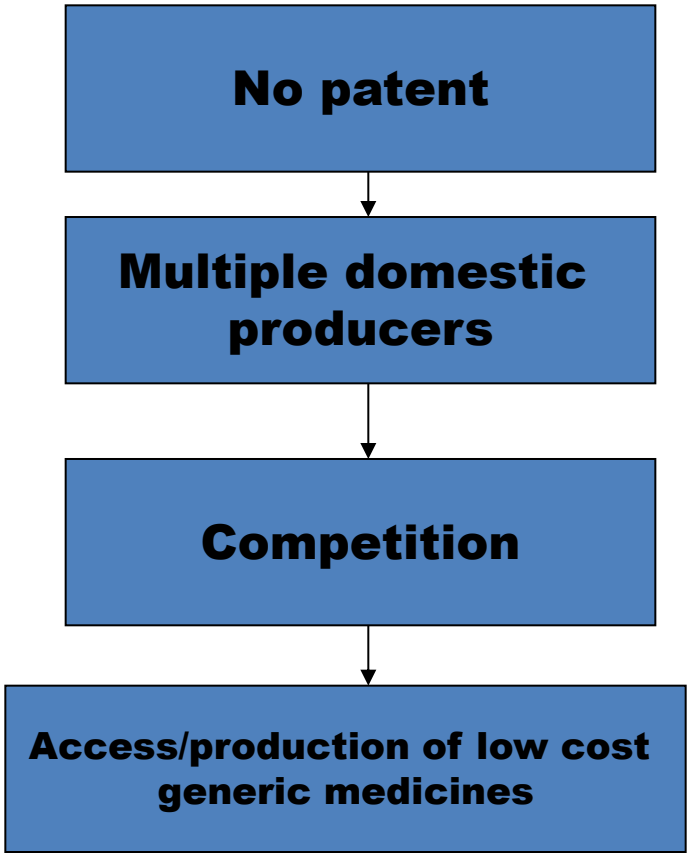
http://handsoff.msf.org

#HandsOffOurMeds



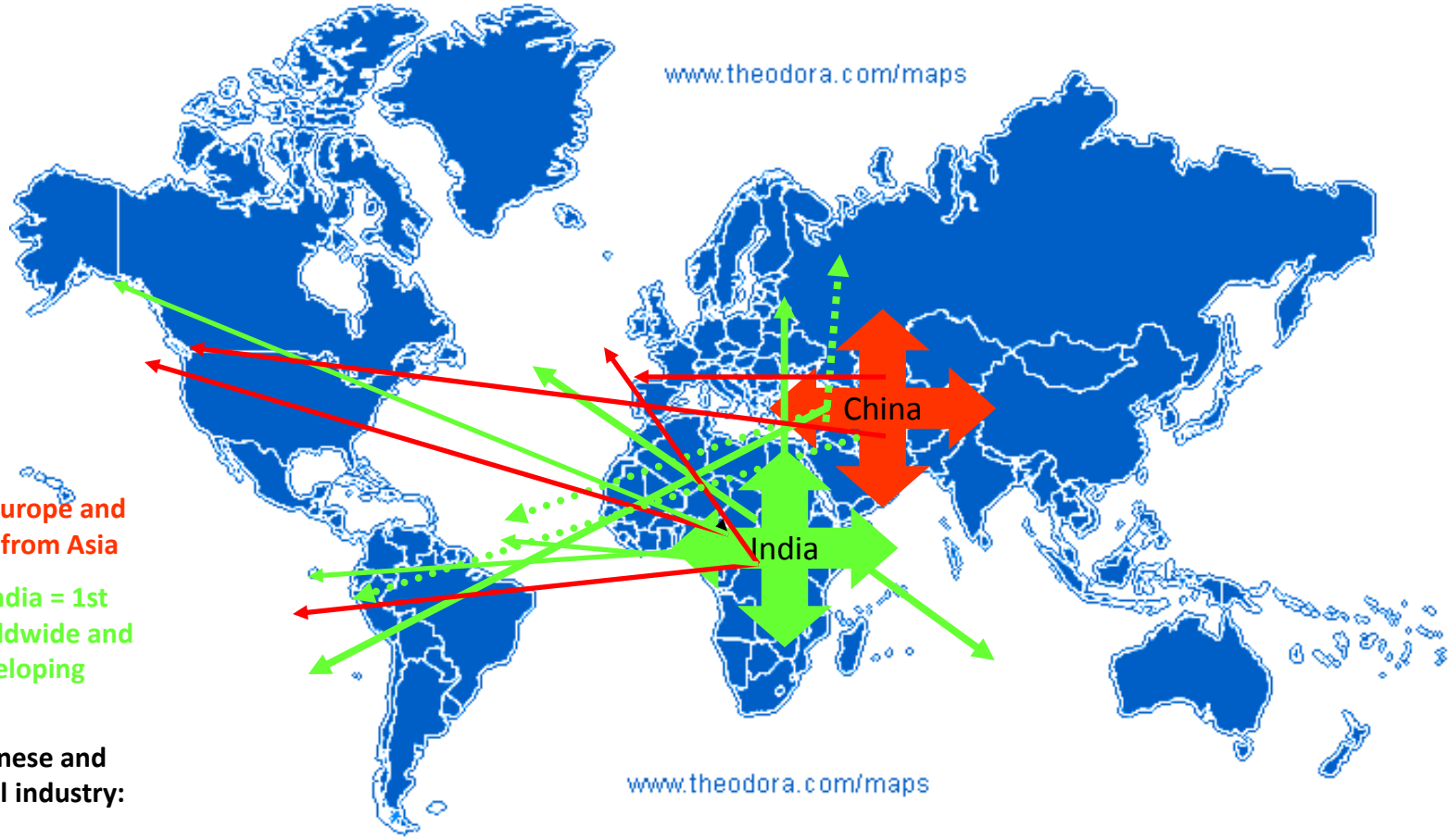
Local Patents linked to Local Prices





Production of drugs

TODAY



- Active Ingredients: Europe and USA: 80 to 90% come from Asia

- Finished Products: India = 1st generic producer worldwide and main exporter to Developing Countries (DC).

- Yearly growth of Chinese and Indian pharmaceutical industry: about 15 to 20%

- 56% of indian exports are made in D.C.

- more than 50% of worldwide prescriptions are generics. Can be 80% - 90% in some DC

Active Ingredients

Finished Products

- **India as an alternative source to expensively priced pharmaceutical products**
- High Volume low price model
- Ability to induce competition in the market
- Indian companies able to meet stringent regulatory requirements including USFDA and WHO pre-qualification programme
- Key supplier of essential medicines to UN agencies and donors and India's national programmes (HIV, TB and malaria)
- The US and EU reaching the pain threshold on medicine prices with 100,000USD per year price tag for cancer medicines and 1000 USD a pill for Hepatitis C.
- US - 98% of PEPFAR's HIV drugs are generic, up from 15% in 2005 - Generics saved PEPFAR $380 million in 2010 alone

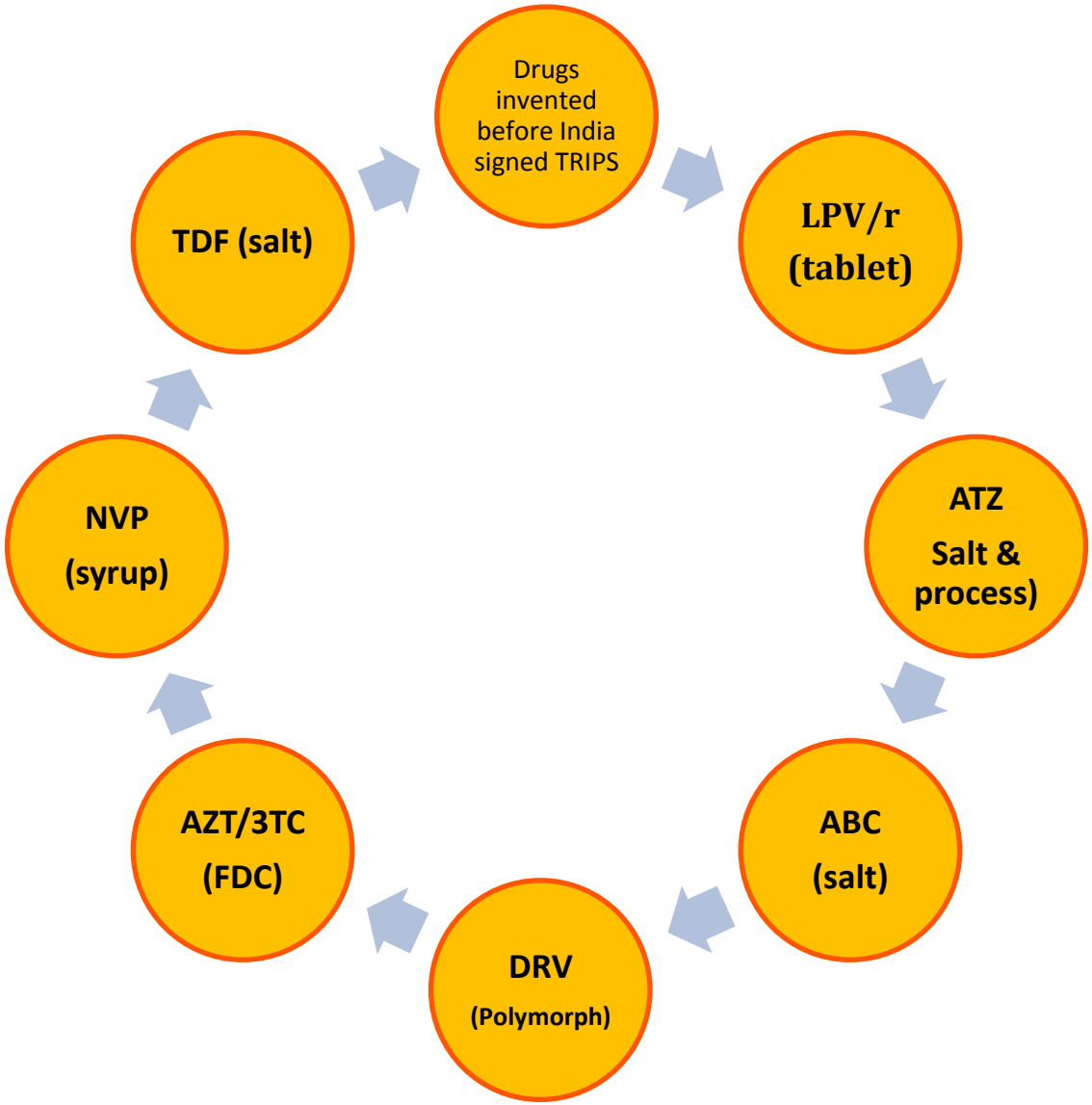
Key flexibilities that allow generics of new drugs (imp for Indian industry and public health)

- Patent oppositions with strict examination (e.g. darunavir for HIV, imatinib for cancer). Used by civil society and generic manufacturers
- Registration of generic versions of patented drugs (regulatory sys not originator centric or linked to the patent system).
- Judicial discretion on IP enforcement. Injunctions not granted if validity of patent granted questioned. E.g. BMS tries to block entacavir generics in 2010 but court refuses to grant injunctions as based on weak composition patent. Today the benefits of that decision will be felt when the WHO guidelines for Hepatitis B are implemented by developing countries.
- India has not signed a FTA with the EU or the US

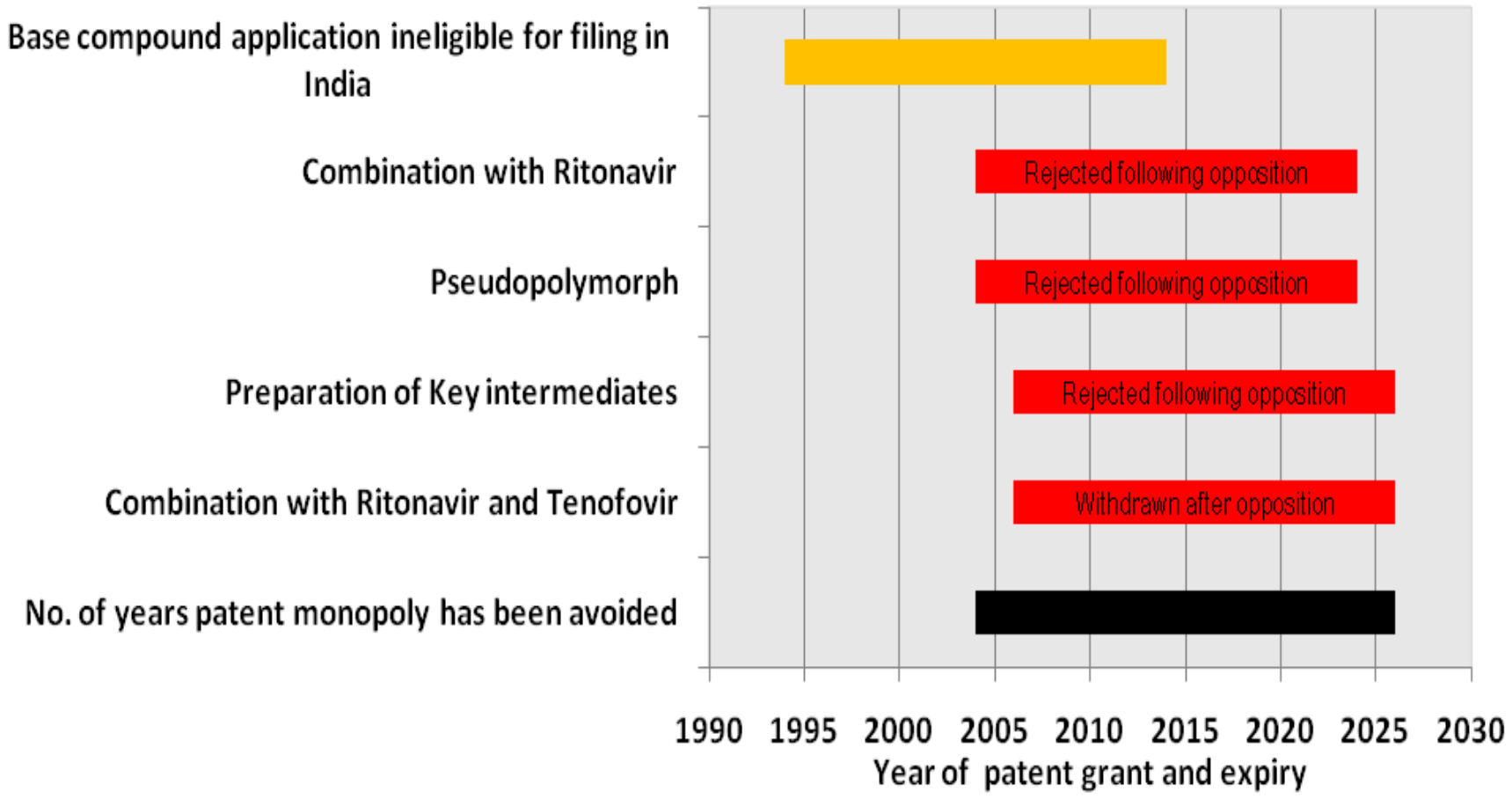
2005 - Patent applications on AIDS drugs in India

Not all patent applications are valid.

Many patent applications are for a new use Of an old drug, or simply for Derivatives of old Drugs or combinations of old drugs.

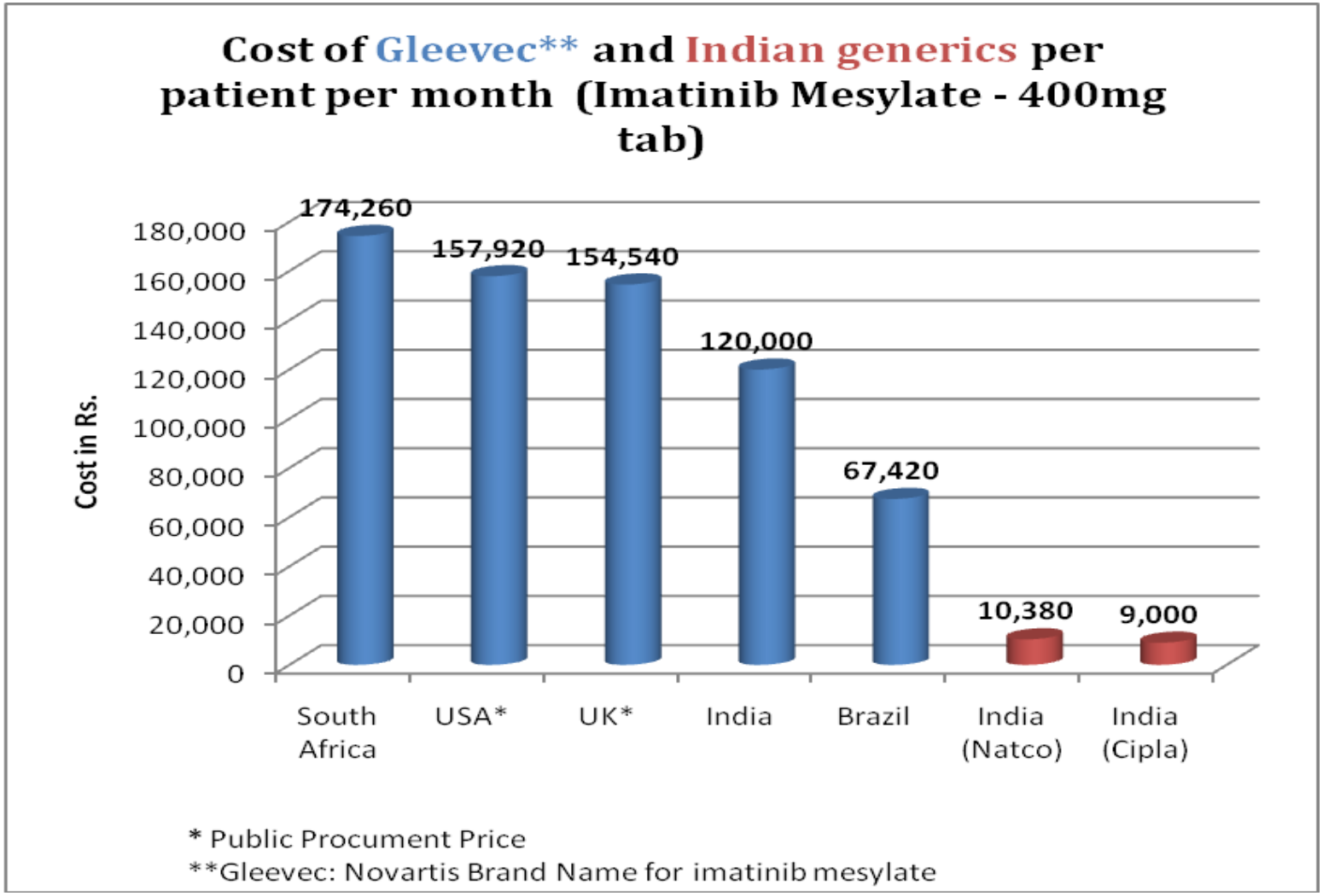


Darunavir Patent Applications in India

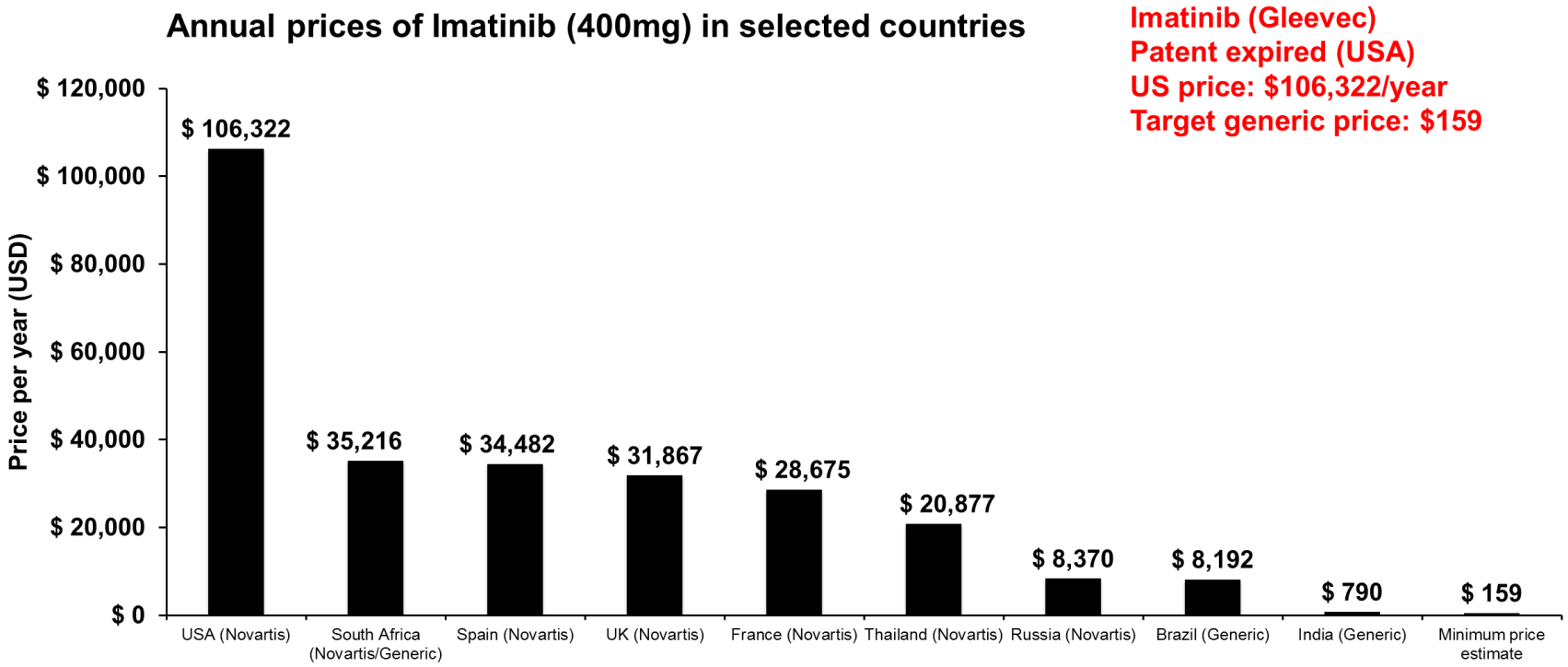


Novartis patent application on life saving cancer drug – CPAA files opposition in 2005

Glivec's patent 1993 application on the base compound was not eligible for an Indian filing because India joined the WTO only in 1995.


Cost of Gleevec** and Indian generics per patient per month (Imatinib Mesylate - 400mg tab)
Cost in Rs.
180,000
160,000
140,000
120,000
100,000
80,000
60,000
40,000
20,000
0
174,260
157,920
154,540
120,000
67,420
10,380
9,000
South Africa
USA*
UK*
India
Brazil
India (Natco)
India (Cipla)
* Public Procument Price
**Gleevec: Novartis Brand Name for imatinib mesylate

Presented at 18th ECCO - 40th ESMO European Cancer Congress, 27th September 2015, Vienna, Austria [abstract number: 1203]



- Mass production of generic antiretrovirals has saved millions of lives for people with HIV/AIDS. There is the potential to repeat this medical success story for the treatment of cancer, DR TB and other diseases.

Will India continue to produce generic drugs?

- This will depend on the interpretation & implementation of safeguards in the Patent Act and the Drugs & Cosmetic Act

- If India agrees to US demands on data exclusivity and patent linkage, then these measures will completely block, what remains of generic competition.

- signs FTAs with TRIPS Plus IP text (EU India FTA or RCEP)

Hepatitis C
Rapid developments
2013/2014/2015

- A revolution with oral treatments for HCV – Direct Acting Antivirals (DAAs)
- WHO HIV department welcomes the viral hepatitis program
- **First DAA (oral drug) registered EMA & USFDA in Dec 2013**
- Developed countries reach the "pain threshold" for the cost of new drugs.
- Debate on prohibitive costs. Sovaldi : 84 000 USD for 12 weeks in USA, 56000 euros in France
- MSF starts treating HCV in HIV+ and now expanding to mono-infected
- First WHO HCV guidelines released in April 2014
- Essential Medicines List - opens its mandate to viral hepatitis
- Patent opposition and rejection in India for Sofosbuvir (January 2014)
- First sofosbuvir generic – Hopetavir (Bangladesh)
- **Indian generics follow – Hepcvir, Hepcinat, Sofovir (approximately 500$ for 12 weeks)**


SOVALDI...
SO EXPENSIVE
GILEAD'S SOFOSBUVIR
APPROVED BY THE EMA AND FDA
$84,000
BUT ACCESSIBLE FOR HOW MANY?
SOVALDI...
SO EXPENSIVE
GILEAD
TO WAIT

Andrew Hill, Department of Pharmacology and Therapeutics, Liverpool University, UK

- Following a methodology already employed to estimate the scope for reductions in the prices of antiretroviral drugs
- researchers calculated the cost of the raw materials required
- along with the costs of synthesis, formulation and packaging, and factored in a small profit margin as is customary for generic drugs.
- Calculated antivirals for treatment of hepatitis B and C
- DR TB drugs
- **Cancer drugs - Tyrosine Kinase Inhibitors (TKIs)**

Analysis to estimate minimum cost of DAAs and associated diagnostic monitoring

- Large scale generic production in process (e.g. India)
- If demand is high (5 million treated per year) the cost of DAAs could be reduced to
  - USD 152 for 12 wk course of sofosbivur + ribavirin
  - **USD 122 for 12 wk course of sofosbuvir + daclatasvir**
- Elimination of HCV is becoming possible

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

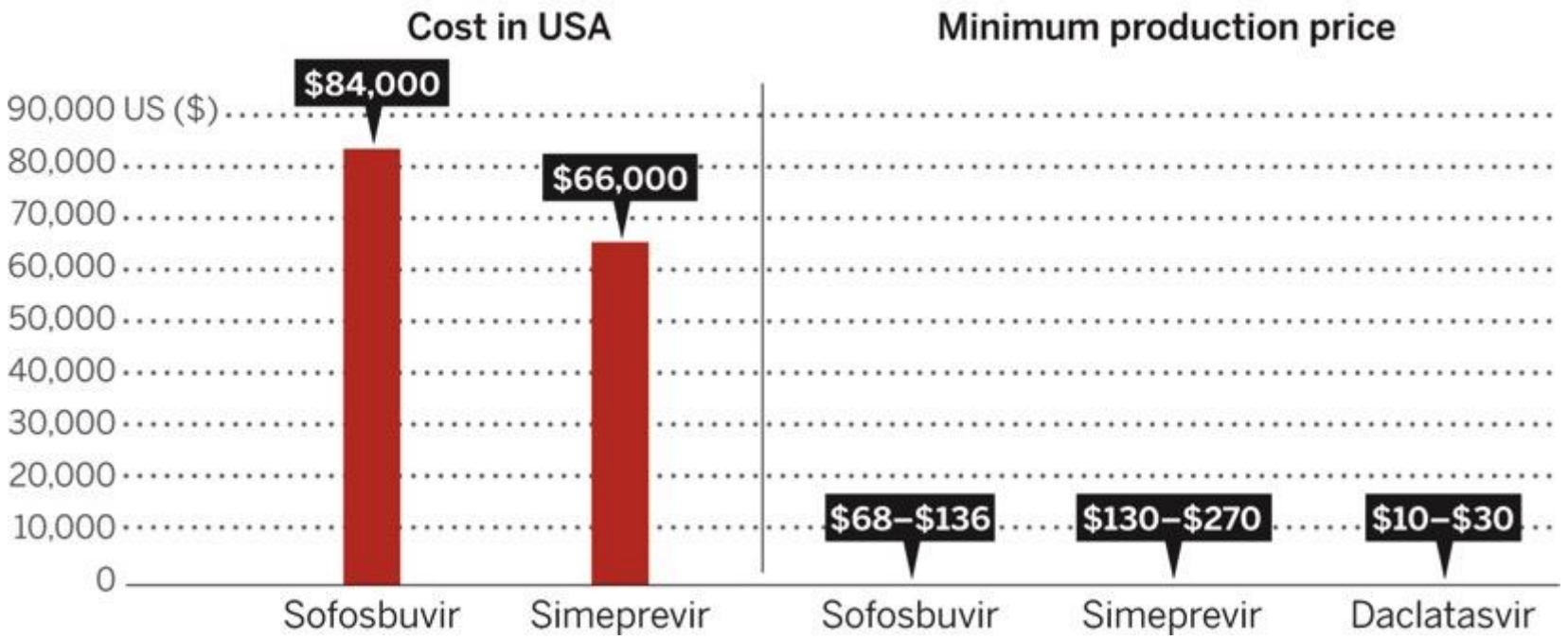
Minimum Target Prices for Production of Direct-Acting Antivirals and Associated Diagnostics to Combat Hepatitis C Virus

Nikolien van de Ven,[1] Joe Fortunak,[2] Bryony Simmons,[1] Nathan Ford,[3] Graham S. Cooke,[1] Saye Khoo,[4] and Andrew Hill[4]

Combinations of direct-acting antivirals (DAAs) can cure hepatitis C virus (HCV) in the majority of treatment-naïve patients. Mass treatment programs to cure HCV in developing countries are only feasible if the costs of treatment and laboratory diagnostics are very low. This analysis aimed to estimate minimum costs of DAA treatment and associated diagnostic monitoring. Clinical trials of HCV DAAs were reviewed to identify combinations with consistently high rates of sustained virological response across hepatitis C genotypes. For each DAA, molecular structures, doses, treatment duration, and components of retrosynthesis were used to estimate costs of large-scale, generic production. Manufacturing costs per gram of DAA were based upon treating at least 5 million patients per year and a 40% margin for formulation. Costs of diagnostic support were estimated based on published minimum prices of genotyping, HCV antigen tests plus full blood count/clinical chemistry tests. Predicted minimum costs for 12-week courses of combination DAAs with the most consistent efficacy results were: US$122 per person for sofosbuvir+daclatasvir; US$152 for sofosbuvir+ribavirin; US$192 for sofosbuvir+ledipasvir; and US$115 for MK-8742+MK-5172. Diagnostic testing costs were estimated at US$90 for genotyping US$34 for two HCV antigen tests and US$22 for two full blood count/clinical chemistry tests. *Conclusions:* Minimum costs of treatment and diagnostics to cure hepatitis C virus infection were estimated at US$171-360 per person without genotyping or US$261-450 per person with genotyping. These cost estimates assume that existing large-scale treatment programs can be established. (HEPATOLOGY 2014;00:000-000)

Costs of new drugs for hepatitis C per person, 12-week course

New generation drugs for HCV



Andrew Hill, and Graham Cooke Science 2014;345:141-142

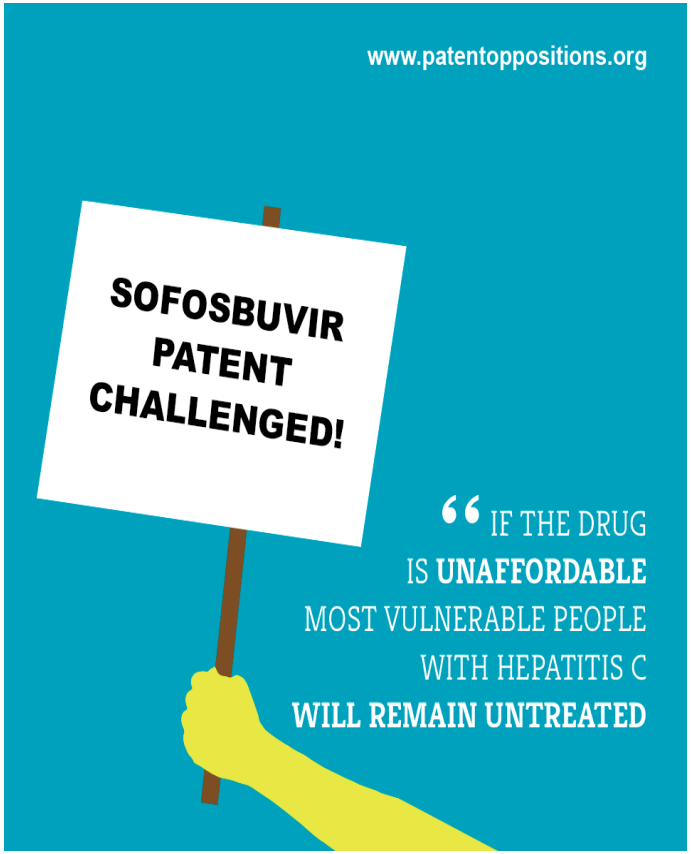
Published by AAAS

#Challenge (Patents)

- Finding the patent application (MSF and WHO landscape)
- Covering all evergreening and process patent claims
- Without strict patent examination – by patent office - no negotiation power Filing patent oppositions in India to promote generic production of API/formulation

- **Bangladesh** no IP barriers – generic production of DAAs has now been established
- **Egypt** – rejection of sofosbuvir patent has led to local production and supply. Pharco applying for WHO prequalification
- **India** – Patent oppositions on SOF lift chilling affect and attract multiple producers. Healthy competition emerging. Daclatasvir in the pipeline
- Promote free generic competition: patent oppositions/ invalidations, and use of all TRIPS flexibilities. ➔Goal: diagnostic –cure package< $500 per cure.

SOFOSBUVIR – applications should be examined



- **Pre-grant examination**
- *Patent on sofosbuvir has already been rejected by Egypt, which did not consider the medicine scientifically innovative.*
- *The controller general's decision holds that "there are a number of earlier compound structures that are very close to what Gilead is trying to get a patent for.“*

Important Recent Events

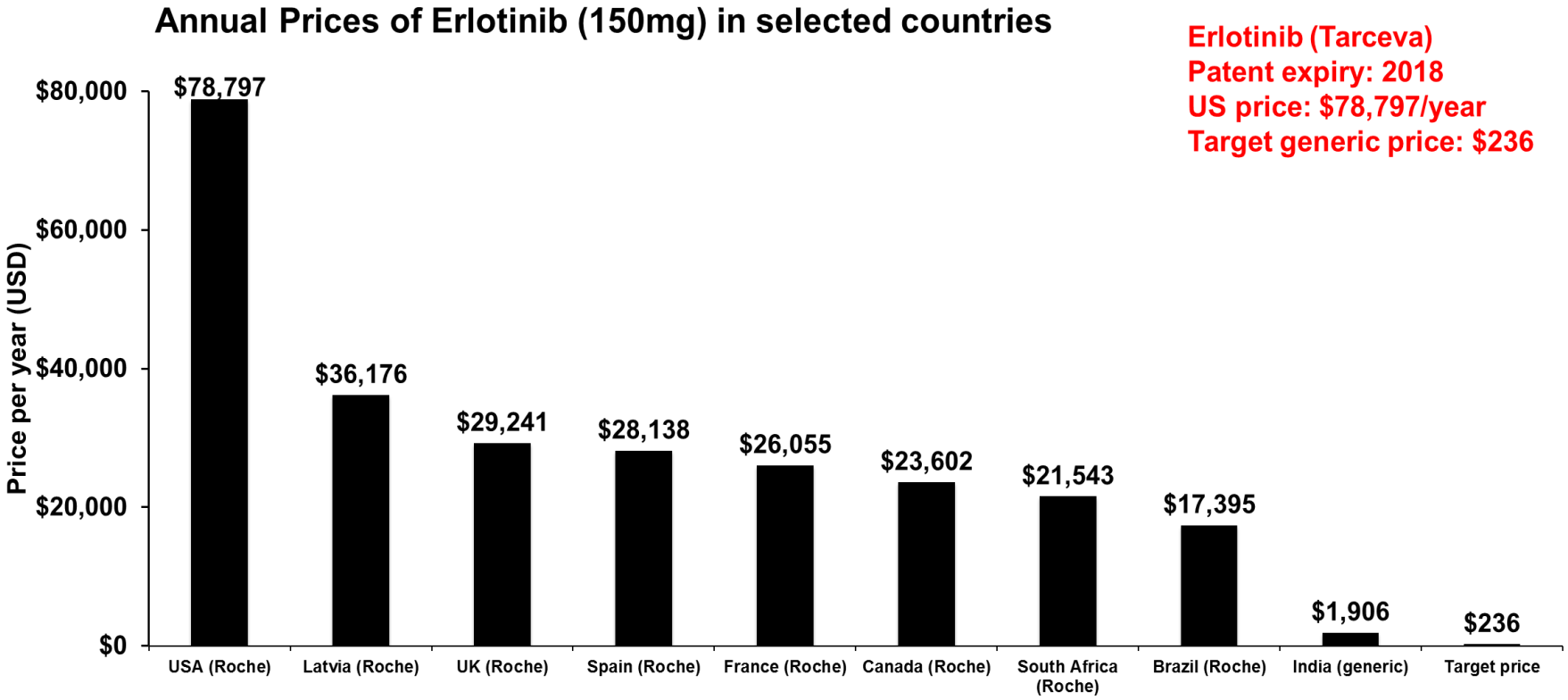
Gilead issued licenses for Sofosbuvir (SOF) and Ledipasvir
and SOF/GS5816
BMS plans voluntary licensing for Daclatasvir

- Elements of the Gilead license
  - to Indian generic producers (they select)
  - 7% Royalty rate of generic price
  - Right to manufacture and sell drug separately, as two-drug combination or in combination with other drugs
  - Control API supply – block exports to countries producing formulations
  - Generic licensees can supply outside 101 countries **if** compulsory license issued
- License Excludes:

high-burden not included:

- **Thailand**
- **Malaysia**
- **Ukraine**
- **Brazil**

Erolotinib – for lung cancer and pancreatic cancer

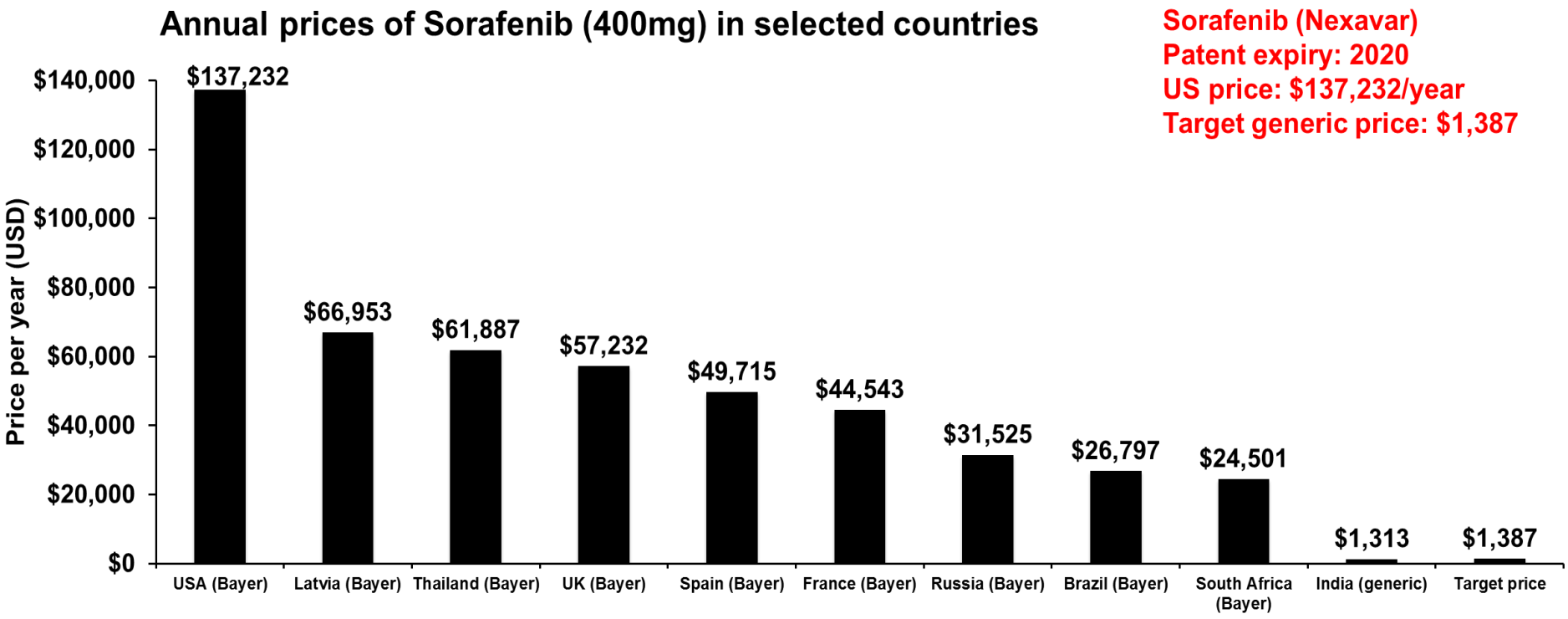


Erlotinib (Tarceva)
Patent expiry: 2018
US price: $78,797/year
Target generic price: $236

The Delhi High court applied the test of whether patients would suffer irreparable hardship if a generic drug was blocked from the market and the court would in effect be stifling Article 21 (The Right to Life) of the Constitution of India (I.A 642/2008 IN CS (OS) 89/2008, Delhi High Court, Order dated March 19, 2008

Presented at 18th ECCO - 40th ESMO European Cancer Congress, 27th September 2015, Vienna, Austria [abstract number: 1203]

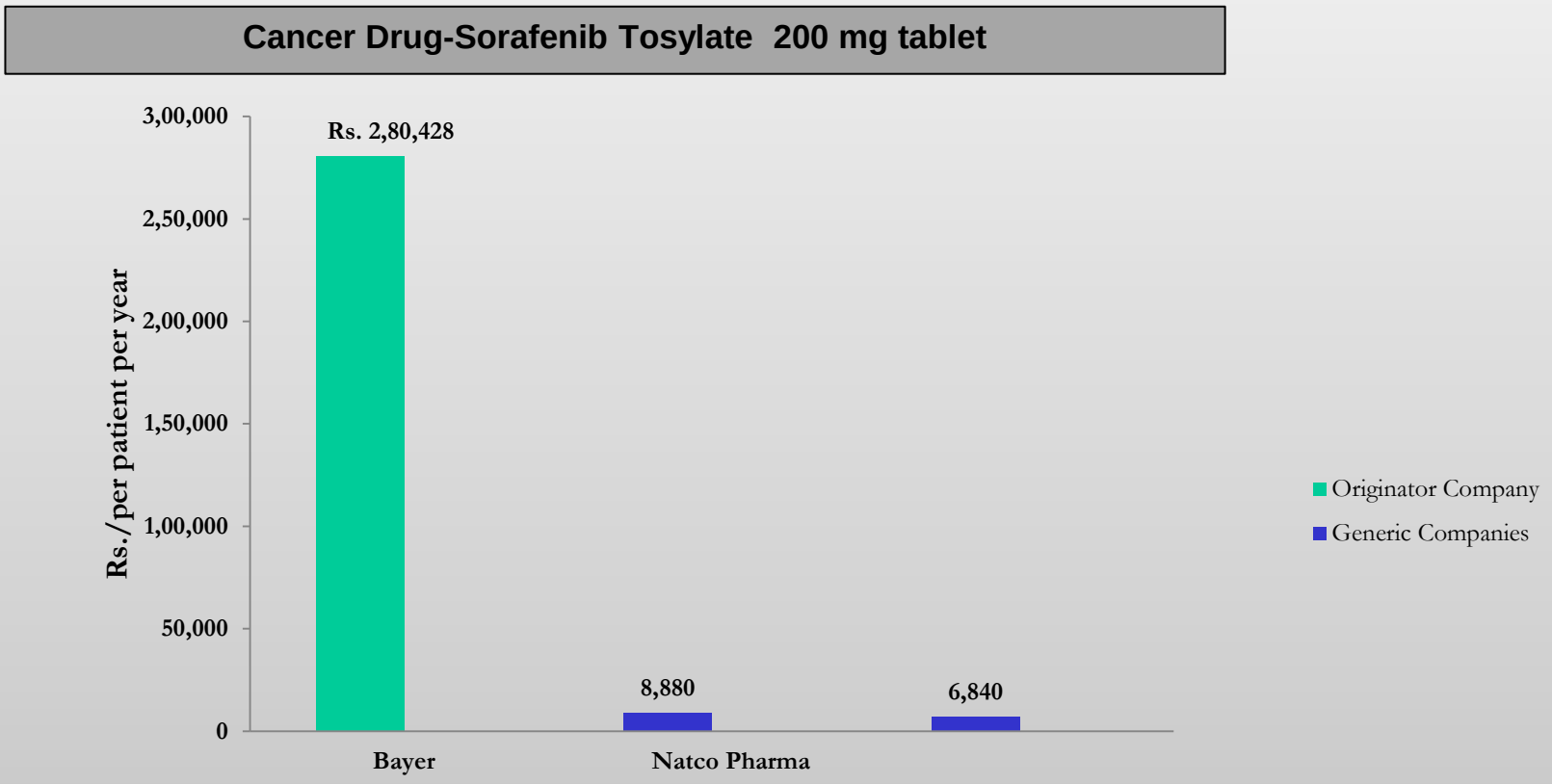
Sorafenib – for treatment of renal and liver cancer



Sorafenib (Nexavar)
Patent expiry: 2020
US price: $137,232/year
Target generic price: $1,387

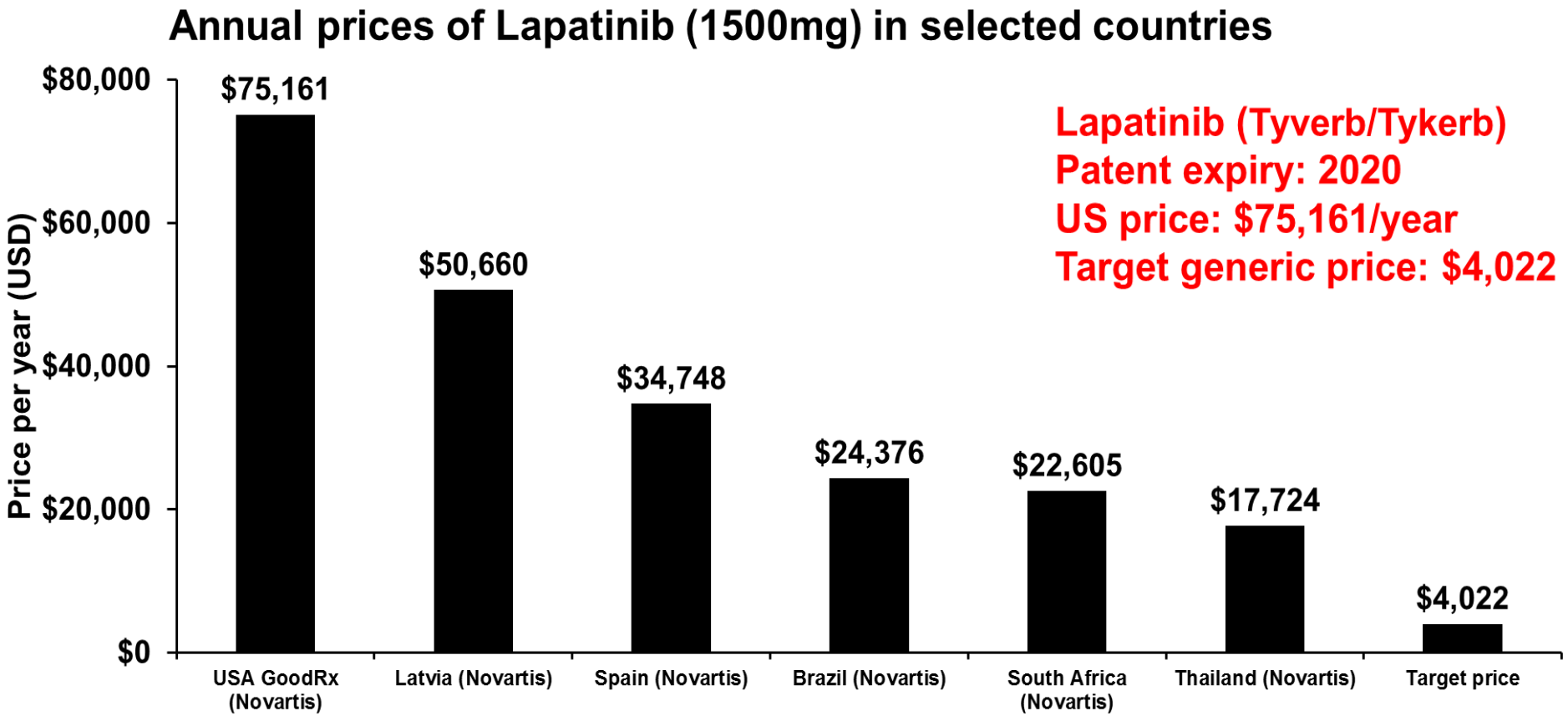
Presented at 18th ECCO - 40th ESMO European Cancer Congress, 27th September 2015, Vienna, Austria [abstract number: 1203]

Compulsory license issued when generic company applies



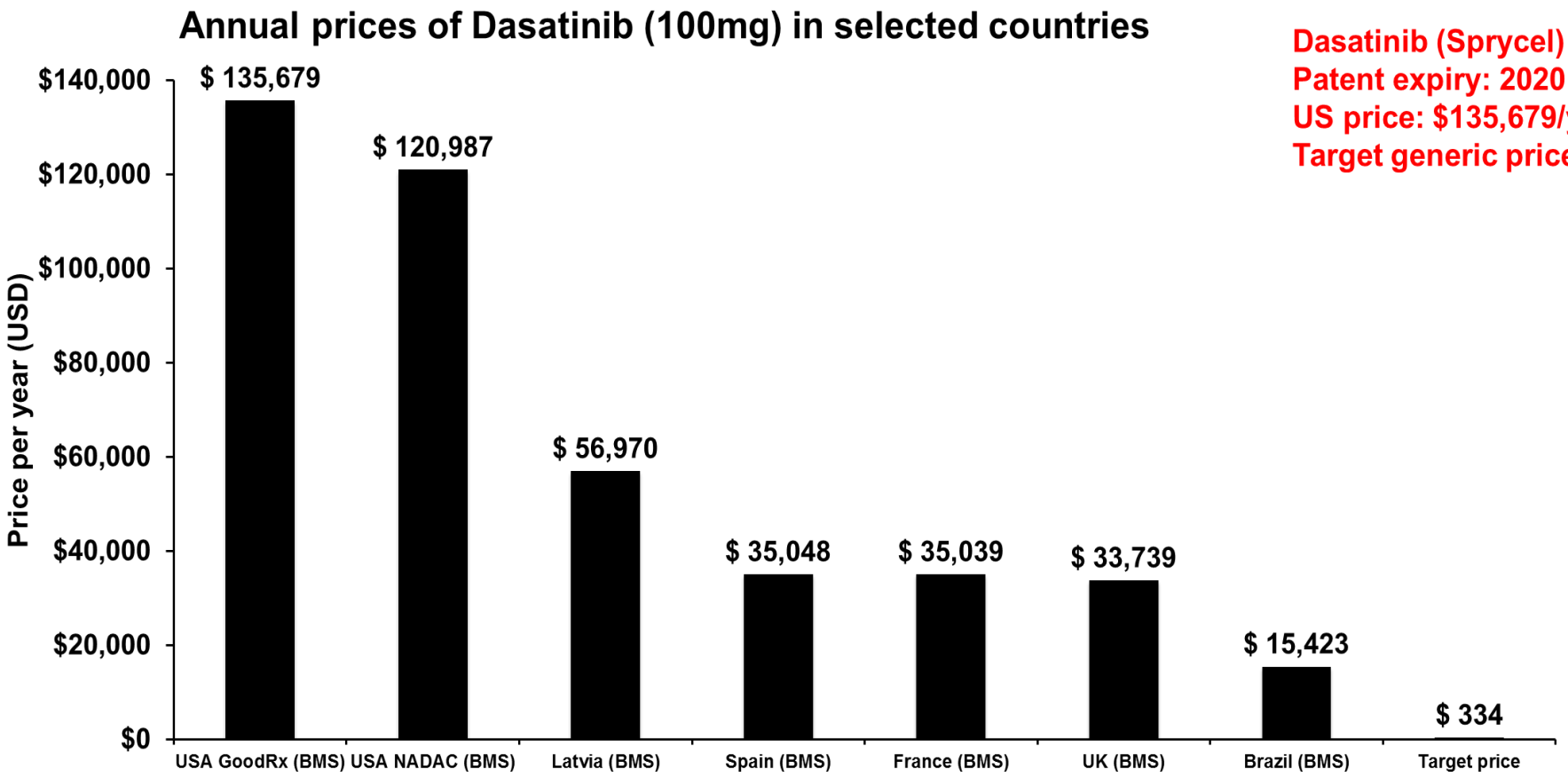
*** The graph highlights the generic price of the cancer drug sorafenib tosylate. The drug is patented in India and Bayer's price is unaffordable. Natco has applied for a compulsory license to the Indian patent office in July 2011 and has committed to substantially reduce the prices by 97%(31 times) for cancer patients in India who need the drug if the compulsory license to produce the generic version is granted to the company by the Indian patent office.**

Lapatinib – for treatment of breast cancer



Presented at 18th ECCO - 40th ESMO European Cancer Congress, 27th September 2015, Vienna, Austria [abstract number: 1203]

Dasatinib – for treatment of leukaemia



Dasatinib (Sprycel)
Patent expiry: 2020
US price: $135,679/year
Target generic price: $334

Presented at 18th ECCO - 40th ESMO European Cancer Congress, 27th September 2015, Vienna, Austria [abstract number: 1203]

CL case on dasatinib (denied), Injunctions against generic manufacturers

Price for Dasatinib (50 mg tablet) per month

	BMS (Sprycel)	Natco (Dasanat)
2010	1,87,505	
2011	1,65,680	
2012	1,65,680	9000
2013	discounted price 70,000	Taken off the market

Public enterprises providing treatment with Dasatinib:
Indian Railways; CGHS, Bhopal Memorial Hospital & Research Centre, Kidwai; Memorial Institute of Oncology, Bangalore; Army Hospital Research and Referral (R&R) in New Delhi; The Malabar Cancer Centre, Kerala; Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow; Government of Andhra Pradesh; V.M.C.C. and Safdarjung hospital; ChandiMandi, Chandigarh (under the Command Group of Hospitals belonging to the Defense);

Newest MDR-TB drug prices could fall by up to 95% through generic production

Agent	Patent expires	Current lowest price per month	Target price achievable per month
Bedaquiline	2023 ++	$136	$8.80-$16.40
Delaminid	2023 ++	$3108	$3.50-$8.60

Otsuka, which holds multiple Indian patents (IN250365, IN253642, IN268015) By granting the salt form (9790/DELNP/2009) of the drug (an obvious form of the drug), the patent office has already extended the monopoly from 2023 to 2026, an additional three years.
Another application on its use in combination with other drugs (1255/KOLNP/2008), has been also granted.
Working statement – conducting market research

Challenges - domestic

- *Increasing levels of patent grants by patent office on intermediates and API that will block exports and domestic production*
- *Delhi High Court - IP enforcement becoming stringent, even covering API manufacturers. Ex parte injunctions undermining bolar and other safeguards in patent law.*
- *Task force for IP enforcement, IP courts ((IP policy)*
- *Domestic Biosimilar producers being sued when they launch their medicine.*
- *Domestic registration by CDCSO increasingly becoming linked to registration dossier from originator company. Local delays mean international delays.*
- *patent linkage implementation under consideration by the MoH. Likely to affect generic development of new drugs and vaccines ahead of patent expiry or during patent dispute.*
- *All key bureaucrats in key positions influencing IP policies and patent issues are changing (MoH, DIPP, Dept of Commerce, Ministry of Science & Tech)*
- *Innovation debate completely linked to IP. New IP policy will soon be in place*

Dept of pharmaceuticals
Tiered pricing/negotiations
Several shortcomings

- Inferior to competition for achieving affordable prices
- Arbitrary and not logical
- Leaves a disproportionate amount of control in the hand of the patentee
- Not co-related to cost of production
- Does not lead to price reduction over time
- Will be used by patentees to undermine CLs for generic competition

Challenges – international

Bilateral US pressure

IP enforcement – EU trademark regulations even after amendments could end up capturing legitimate generics in the custom net

US led Transpacific agreement (TPPA) will block Indian exports of medicines to the region and beyond. Critical period – if negotiations fail to culminate in the coming month, the US goes into elections and the TPP will be significantly delayed.
RCEP?


MILLIONS OF PEOPLE
RELY ON AFFORDABLE MEDICINES
FROM INDIA TO STAY ALIVE.
Incredible India
Prime Minister Modi,
STAND STRONG AGAINST U.S. PRESSURE TO CHANGE YOUR LAWS!
Don't shut down the pharmacy of the developing world!