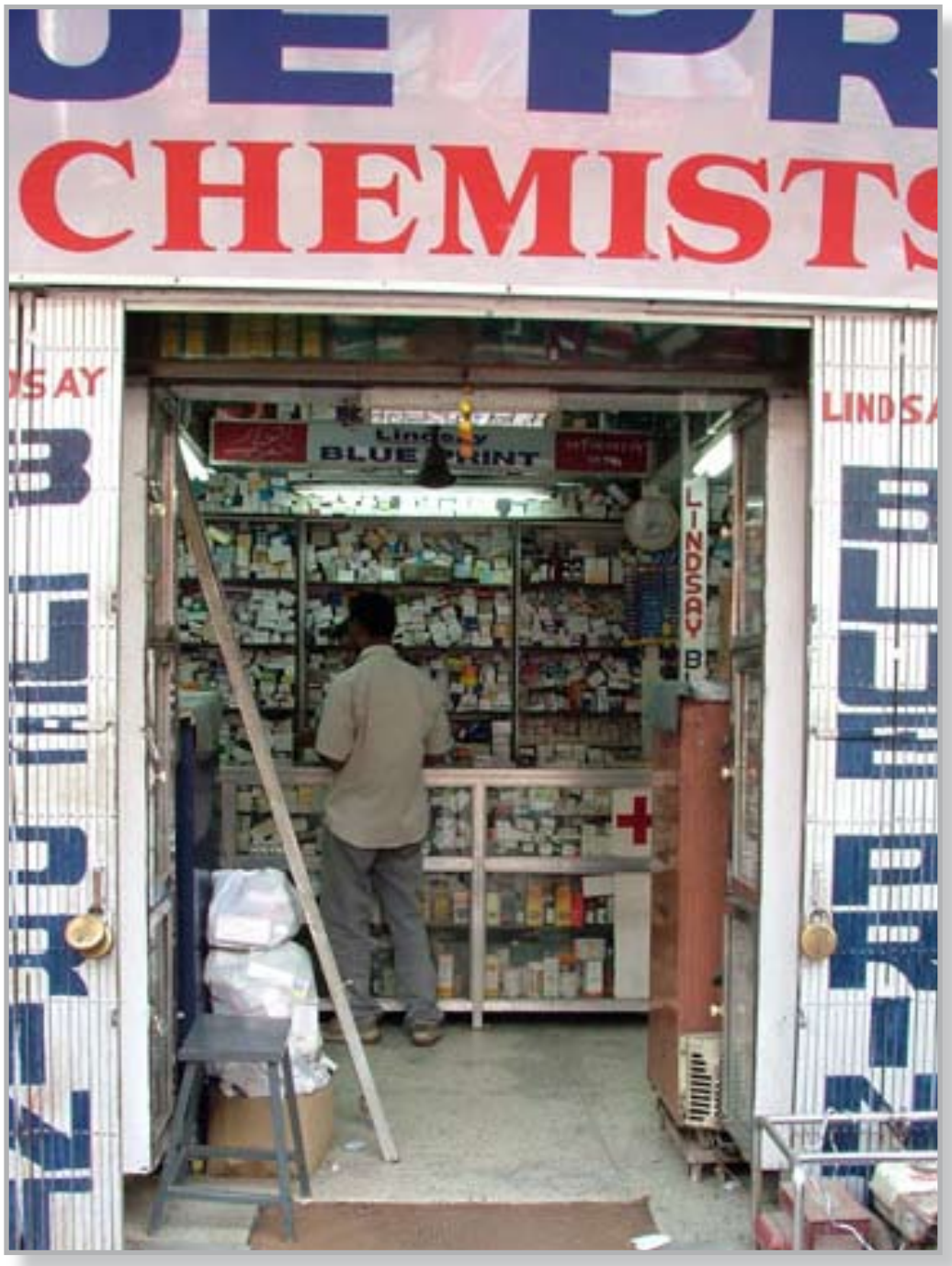

Indian Generics and Aids

A Fact Finding Mission in the "Pharmacy of the Poor"

Indische Generika und Aids

Eine Erkundungsreise in der „Apotheke der Armen"

Das Aktionsbündnis gegen AIDS

Das Aktionsbündnis gegen AIDS will mit seiner Kampagne das Schweigen über HIV/Aids brechen und setzt sich ein für eine Welt ohne Aids und Armut. Mit HIV/Aids zu leben, beeinträchtigt alle persönlichen Bereiche der Betroffenen. Weltweit bedroht die HIV/Aids-Epidemie Entwicklungschancen. Das Risiko, in noch größere Armut zu geraten, steigt durch die Krankheit. So fordert die HIV/Aids Epidemie weltweit ein gesellschaftliches Umdenken heraus.

„Jeder Mensch hat das Recht auf einen Lebensstandard, der seine und seiner Familie Gesundheit und Wohl gewährleistet, einschließlich Nahrung, Wohnung, ärztlicher Versorgung und notwendige soziale Leistungen (...)."

Artikel 25 der Allgemeinen Erklärung der Menschenrechte der Vereinten Nationen, 1948

Mit seinen Forderungen beruft sich das Aktionsbündnis gegen AIDS auf die HIV/Aids-Ziele der Vereinten Nationen vom Juni 2001 und wendet sich gezielt an die Bundesregierung und die Pharmaindustrie. Im Mittelpunkt der Forderungen steht der Einsatz für das Menschenrecht auf Leben und Gesundheit, die Bereitstellung zusätzlicher Mittel für die weltweite Aids-Prävention und -Behandlung durch die Bundesregierung, sowie die Reduktion der Kosten für die lebenswichtigen Medikamente durch die Pharmaindustrie. Mit bundesweiten Aktionen und im politischen Dialog erinnert das Aktionsbündnis gegen AIDS an die internationalen Vereinbarungen und Versprechen der Regierungen von UNMitgliedsländern und der G8. Es fordert deren Umsetzung, denn Politik, Pharmaindustrie und Öffentlichkeit müssen sich ihrer Verantwortung im weltweiten Kampf gegen HIV/Aids stellen. Das Leben von Millionen Menschen hängt davon ab, ob diese Versprechen eingelöst werden.

Das Aktionsbündnis gegen AIDS ist ein bundesweiter Zusammenschluss von über 100 Nichtregierungsorganisationen der Aids- und Entwicklungszusammenarbeit sowie über 280 Basisgruppen. Zur Koordination seiner Lobby- und Öffentlichkeitsarbeit wurde 2002 ein Kampagnenbüro beim Deutschen Institut für Ärztliche Mission (DIFÄM) in Tübingen eingerichtet und mit dem Aufbau eines bundesweiten Kampagnennetzwerkes begonnen. Das zivilgesellschaftliche Netzwerk finanziert sich ausschließlich über Mitgliedsbeiträge.

Indian Generics and Aids

Indische Generika und Aids

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Impressum

Hrsg.: Aktionsbündnis gegen AIDS
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Layout: Kai-Uwe Dosch (Titelfoto: www.pixelio.de)
Druck: printmedien-jacobsen@t-online.de

Neue Erkenntnisse zu Aidsmedikamenten aus Indien

In der ersten Märzwoche 2009 besuchte eine internationale Delegation[1] des Aktionsbündnisses Generikafirmen und Nichtregierungsorganisationen (NROs) in Indien, um die Situation der neueren Aidsmedikamente genauer zu erforschen. In den nächsten Jahren werden immer mehr Menschen aufgrund von Resistenzen neuere Aidsmedikamente benötigen. In den Gesprächen kristallisierten sich folgende Punkte heraus:

Nachhaltigkeit

Kann Indien die Produktion der neueren Aidsmedikamente ausbauen? Keine Frage – alle besuchten Firmen könnten mit sicheren Absatzmärkten ein Vielfaches der heutigen Menge produzieren. Viele der Firmen sprachen sich gegen Ausschreibungsverfahren aus, da in einigen Ländern die heimische Industrie stark favorisiert werde, wie dies wohl vor kurzem in Südafrika der Fall war. Die Firmen bevorzugen gemeinsame Lieferabkommen für den Medikamentenbedarf mehrerer stark von Aids betroffener Länder.

1 Delegierte aus dem Aktionsbündnis gegen AIDS (Kampagnenbüro, action medeor, Brot für die Welt, BUKO Pharma-Kampagne, medico international, MSF), zwei afrikanischen Partnerorganisationen von BfdW (TAC und EPN), einem indischen Partner von medico (LOCOST) sowie der englischen Stop AIDS Campaign

Auch wurden die inzwischen sehr stark gesunkenen Preise der ersten Therapielinie der Aidsmedikamente problematisiert. Auf diesem Niveau wären viele Generikafirmen gezwungen, bald aus manchen Produktionslinien auszusteigen, da sie keinerlei Profit mehr machten. Sollte sich diese Aussage bewahrheiten, hätten wir in Entwicklungsländern bald ein riesiges Versorgungs- und Finanzierungsproblem mit den Aidsmedikamenten der ersten Therapielinie. Und dies in einer Situation, in der knapp 70 % der HIV-Positiven, die diese Medikamente benötigen, immer noch keinen Zugang dazu haben.

Patentanträge

Auf die meisten neueren Aidsmedikamente haben die Originalhersteller Patentanträge in Indien gestellt. Laut indischen NROs kommt es jedoch einer Schatzsuche gleich, herausfinden zu wollen, für welche Substanz ein Patentantrag in Indien gestellt wurde. Biochemiker werden benötigt, um das jeweilige Präparat aufgrund der chemischen Substanz identifizieren zu können. Außerdem gibt es bisher noch kein zentralisiertes Antragsverfahren. Wer in Indien rechtzeitig Widerspruch gegen Patentanträge einlegen möchte, muss aufwendig recherchieren - die indische NRO Lawyers Collective hat dies in 15 Fällen getan. Laut indischem Patentgesetz (Section 3d) erhält eine leichte chemische Veränderung

Foto: AgA

Internationale Delegation des Aktionsbündnisses gegen AIDS und seiner Partner unter den Augen Mahatma Gandhis.

eines Medikaments kein neues Patent. So gehen viele indische Generikafirmen z.B. davon aus, dass die hitzestabile Form von Abbott's Kaletra® in Indien kein Patent erhalten wird. Oftmals werden jedoch trotzdem Patente vergeben. Die Indian Pharmaceutical Alliance, der Zusammenschluss indischer Generikahersteller, fordert das Aktionsbündnis deshalb auf, sich dafür einzusetzen, dass die Klausel 3d des indischen Patentrechts beachtet und fälschlicherweise genehmigte Patente rückgängig gemacht werden.

Die einzelnen indischen Generikafirmen reagieren unterschiedlich auf die Rechtsunsicherheit, die durch die Patentanträge vorliegt. Einige gehen davon aus, dass viele Patentanträge auf Aidsmedikamente der zweiten Therapielinie abgelehnt werden, da es sich oftmals um keine wirklich neuen Medikamente handelt. Viele Generikafirmen bemühen sich jedoch vorsorglich um freiwillige Lizenzen des Originalherstellers, um Rechtssicherheit zu haben. Dies ist beispielsweise bei Tenofovir Disoproxil Fumarate (TDF), einem wichtigen Medikament der ersten und zweiten Therapielinie, der Fall. Der Originalhersteller legt bei freiwilligen Lizenzen jedoch häufig fest, wohin exportiert werden darf, beansprucht Rechte auf alle Neuerungen der Generikafirmen für sich und erhebt eine Lizenzgebühr. Im Fall TDF steht das Medikament in Indien noch gar nicht unter Patentschutz, trotzdem müssen die Generikafirmen, die unter freiwilliger Lizenz produzieren, eine Gebühr an den Originalhersteller Gilead zahlen.

Für die ganz neuen Aidspräparate kommen die indischen Generikafirmen um Lizenzen nicht herum. Entweder sie müssen sich um freiwillige Lizenzen bemühen oder aber die indische Regierung muss eine Zwangslizenz verhängen. Das hat sie bisher jedoch noch nicht getan.

Technologietransfer in Länder mit niedrigem Einkommen, die erst 2016 den vollen Patentschutz gewähren müssen, wäre theoretisch eine Option für die indischen Firmen. Die meisten von uns besuchten Generikafirmen sahen dies jedoch als problematisch an. Die Rohstoffe, die für die Produktion der Medikamente benötigt werden, kommen fast ausschließlich aus Indien und China. Generikaproduzenten in anderen Ländern müssten deshalb weiterhin die Rohstoffe aus diesen beiden Ländern beziehen und hätten somit schon Fixkosten, die eine Preissenkung der Medikamente erschweren würden. Außerdem sind die neueren Medikamente komplizierter herzustellen und benötigen oft 17-18 chemische Verfahren – diese Technologie nach Afrika zu transferieren und die Fabriken international zertifizieren zu lassen, halten die indischen Hersteller für äußerst schwierig.

Rufschädigung

In der Vergangenheit wurden mehrere Ladungen generisch hergestellter Aidsmedikamente, die von Indien über Europa nach Afrika oder Lateinamerika transportiert wurden, beschlagnahmt. Weder in Indien noch im Importland stehen sie unter Patentschutz – ein Zeichen dafür, dass man das Wort „Fälschung" wohl bewusst falsch gebraucht. Die Medikamente entsprechen höchsten Qualitätsstandards, sind von WHO[2] und FDA[3] anerkannt und somit ganz klar keine Medikamentenfälschungen. Sie befinden sich in Europa lediglich im Transit. Dennoch werden sie von europäischen Behörden als ‚Fälschungen' angesehen. Wohin führt dieser irreführende Fälschungsbegriff?

Die Regierungen der Länder Uganda und Kenia sind dabei, Gesetze zu entwerfen, die Kopien eines Produkts, das irgendwo auf der Welt patentiert ist, automatisch als „Fälschung" (counterfeit) im eigenen Land ansehen und deshalb in ihren Ländern nicht zulassen wollen. Dies hätte verheerende Folgen für die zukünftige Versorgung mit preisgünstigen indischen Aidsmedikamenten in Afrika.

Das Aktionsbündnis gegen AIDS wird sich deshalb weiter dafür einsetzen, dass getestete, qualitativ hochwertige und preisgünstige Generika verschiedener Therapielinien hergestellt und in andere Länder exportiert werden können, so dass eine lebenslange Behandlung mit Aidsmedikamenten im öffentlichen Sektor in Ländern niederen und mittleren Einkommens realisiert werden kann.

Astrid Berner-Rodoreda, Brot für die Welt, Sprecherin im Aktionsbündnis gegen AIDS

2 World Health Organisation – die Zulassung der Medikamente durch die WHO ist z.B. für Global Fund Programme wichtig

3 Food and Drug Administration – diese US-amerikanischen Zulassungsbehörde ist für Lieferungen über das US-amerikanisch finanzierte PEPFAR-Programm wichtig

Introduction to Patents and AIDS in India

In March 2009, ten delegates of Action against AIDS Germany including three international guests visited India to meet four generic companies (Cipla, Hetero, Aurobindo and Matrix) that produce first and second line generic antiretroviral drugs (ARVs) and members of civil society groups (Lawyers Collective, Alternative Law Forum, MILANA, LOCOST, All India Drug Action Network).

This fact-finding mission had the following objectives regarding patents applications on ARVs in India as well as prices and reasons for prices for improved first line and second line ARVs in India and African countries:

- What are the effects of granting patents on second line ARVs on the production and marketing inside India and the exports to other (e.g. African) countries?
- What role does the Indian generic industry play for affordable ARV production?
- What role does the Indian civil society play for access to cheaper ARVs?

In this document, we provide articles that reflect opinions and positions of members and friends of Action against AIDS Germany.

Patents and profits

A patent is a set of exclusive rights granted by a state to an inventor for a limited period of time in exchange for the disclosure of an invention.[1] To be granted a patent the invention must be new, inventive, and industrially applicable. Therefore it is not enough for a patent being granted just to discover a substance or object (such as neem, a plant product used in agriculture) The patent grants the patentee monopoly over the production, use and sale of the invention for a given period of time. Therefore the patent excludes others from making, using, selling, offering for sale or importing the patented product. The patentee can thus exploit the patent to increase prices by limiting quantity. This monopoly is in fact the basic idea of granting any patent.

Any grant and enforcement of patent is governed by national laws and can be granted (or denied) by national authorities only within the authority of that country.

TRIPS and public health

While patents are valid only within the country of their issue, international treaties seek to harmonize patent laws. The World

1 http://en.wikipedia.org/wiki/Patent

Foto: AgA

Discussing patents at the Lawyers Collective HIV/AIDS Unit Bangalore.

Indian Patent Act of 1970	Indian Patent Amendment of 2005
No product patents on pharmaceuticals were allowed, only process patenting	Product patents are encouraged
The maximum time for patentability was seven years from the date of application and five years from the date when the patent is granted	Patents are granted for a minimum period of 20 years
Imported products were not patentable	No discrimination between local and imported products
The patent holder has to prove the patent infringement.	The filed generic company has to prove that no patent infringement took place.

Trade Organization (WTO) plays an important role in this process. The TRIPS Agreement (Trade Related Intellectual Property Rights) coerces all WTO member countries to manipulate their national laws to conform to the TRIPS agreement. In general this enforces a minimum period of 20 years for product patents. In regard to drugs such exclusivity rights can prevent affordable generics to enter the market and therefore lead to maintenance of high prices.[2] This means, that those most in need of basic essential medicines are unable to afford it. Survival becomes a commodity available only to the rich.

For striking a balance between TRIPS and the basic human right of access of essential medicines, TRIPS includes important safeguards to protect public health. These rights were reaffirmed by the Doha Declaration on the TRIPS Agreement and Public Health, which was adopted in November 2001 by the WTO Ministerial Conference. To assure better access to essential medicine it recognises: "We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health." Crucially, the Doha Declaration reaffirms the right of national authorities to grant Compulsory Licences (CL). CLs are non voluntary licences allowing a government to force the patent holder to grant use. In case of pharmaceuticals, governments can grant CLs on a second line ARV in case of a health crises such as HIV/AIDS, but also in case of many other reasons.[3] One remaining problem is that CLs are meant mainly for the domestic market, thus a solution is needed for countries without substantial manufacturing capacity to access compulsorily licensed drugs, like importing them. On 30 August 2003, a compromise was found to allow WTO members to issue compulsory licences to export generic versions of patented medicines to countries lacking manufacturing infrastructure. However this 'solution' works only on paper: Since 2003 only one small consignment of drugs was shipped from Canada to Rwanda. The requirements of the compromise are extremely unwieldy and since inception only four countries have implemented them into their national law; the burdensome drug-by-drug and country-by-country process discourages the use.[4]

2 D.H. Banta (2001): Worldwide interest in global access to drugs. The Journal of the American Medical Association, No. 285 (22), 2844-2846.

3 WTO Ministerial Conference (Fourth Session, Doha, 9-14 November 2001):

DECLARATION ON THE TRIPS AGREEMENT AND PUBLIC HEALTH

§5(b) Each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.

§5(c) Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

4 MSF Press Release (12 December 2005): WTO sacrifices access to medicines before Hong Kong ministerial meeting.

Indian Patent Law

"Transition countries" like India had to amend their national law in 2005 to conform to the TRIPS agreement whereas "least developed countries (LDCs)" still have time until 2016. India did not allow product patents on pharmaceuticals from 1970 until 2004 and therefore the most important generic industry developed to provide cheap generics for the global south. This role is now under threat as with the beginning of 2005 India had to change its patent law[5]:

- However, the Patents (Amendment) Bill of 2005 allows the use of the TRIPS flexibilities to the largest possible extent[6]: Compulsory licence for the use within India and for export of medicines to countries which have insufficient or no manufacturing capacity is part of the amendment. Interesting to note is that both possibilities were never used until now.

- Section 3 (d) excludes inventions from discovery, which are only of a new form of a known substance without any additional therapeutic value. This is meant to prevent "evergreen-

5 Jean O. Lanjouw: The Introduction of Pharmaceutical Product Patents in India. „Heartless Exploitation of the Poor and Suffering?", NBER Working Paper, No. 6366, Yale University and the NBER, 47-48

6 The Patents (Amendment) Bill 2005 passed by Indian Parliament, http://www.indianembassy.org/press_release/2005/Mar/12.htm

Foto: Andrea Czekanski/AgA

Astrid Berner-Rodoreda, Beate Ramme-Fülle, and Christiane Fischer planting a tree of hope against AIDS in India.

ing" of patents.

- It is possible for civil society groups and generic industry to file a post or pre-grant opposition against a patent application. A hearing is compulsory.

These possibilities are widely used by groups such as the Lawyers Collective[7] or generic companies such as Cipla to fight patents being granted on essential medicines. A good example is the second line ARV, the heat stable form of Lopinavir/Ritonavir, where Abbott has applied for a patent.[8]

In other cases, such as the patent application of Boehringer Ingelheim on the paediatric suspension of Nevirapine[9] the Positive Women's Network filed a pre-grant opposition and won the case. As Nevirapine is a "a new form of a known substance" it is not patentable under Sec 3(d) of Indian Patent Law... Thus generic production of Nevirapine will be continued to be produced. To summarize on what has been written: Indian Patent Law, although allowing product patents and therefore limiting the scope of generic production, allows for the possibility to counter evergreening.

As it is by now, once a patent would be granted on drugs such as second line ARVs, the situation, whether affordable generic production can continue, remains unclear. There are several possibilities:

- The generic company will depend on voluntary licences (VL) from Big Pharma to continue production. This would be likely to happen in case of Gilead, which granted a VL to Indian generic companies for Tenofovir. However also a VL would increase the price as the generic firms need to pay a royalty to Gilead. Gilead would therefore be in the position to dictate the conditions for the VL.

- The Indian government could issue a compulsory licence (CL) for local needs and for export. Whether the Indian government is willing to go this step, remains unclear.

- The generic production could be stopped, as only branded products would be on the market, the price would be likely to increase, this would be likely to happen in case of the heat stable Lopinavir/Ritonavir, as Abbott has the policy not to grant VLs.

Treatment of HIV Patients

HIV slowly destroys the immune system of the body, the so-called CD4 immune cells. If the number of these cells decreases below a certain threshold, the patient needs to start and continue treatment for the rest of his/her life. A cocktail of at least three ARVs from different drug classes has to be swallowed. If the patient does not take his/her drugs regularly and/or the drug supply is not constant, resistances develop and the patient has to be switched to second line treatment. Even under the conditions of strict adherence at some point in time resistances will develop and second line treatment needs to be started. In poor countries standard drug regimes are used, which make it simpler to assure continuous drug supply. The World Health Organisation (WHO) recommends the most affordable and qualitative best combinations with less side effects. The old recommendation by WHO were of Stavudine, Aciclovir or Lamivudince and Nevirapine or Evaviranz. In the new recommendation Tenofovir replaces Stavudine due to a more favourable toxicity profile and less adverse side effects. However the price increase, even using Indian generics, is huge. While the old regime is available for 87 US$ per patient per year the best price for the Tenofovir based regime is 349 US$ per patient per year. In case the patient needs to be switched to second line treatment the price for Lopinavir/Ritonavir alone is 447 US$ per patient per year.[10] In the case patents are granted, the expected price increase would further threaten access to these drugs for the poor in the global south.

In conclusion, to guarantee access to affordable generics for the global south we as Action against AIDS demand that the pharmaceutical companies Abbott, Bristol-Myers Squibb and Gilead withdraw their applications in India for patents on new, essential AIDS medicines, as patents can be deadly and the human right to life needs to be prioritised before pharmaceutical profit.

Christiane Fischer, BUKO Pharma-Kampagne, Action against AIDS, Germany

7 http://www.lawyerscollective.org

8 Abbott Patent 339/MUM/2006, Filing date: 26.8.2004

9 Patent number 2485/DEL/1998, case decided on 31.8.2007 by the Patent office

10 MSF, Untangeling the Web of Price Reductions, Geneva, July 2008

Indian Generic Industry and ARVs

Assessment by Indian Generic Firms and Civil Society

For many years the Indian generic industry flourished and made it possible for Sub-Saharan Africa to have access to affordable ARV drugs of the first generation. This was mainly due to the Indian Patent Law of 1970 which enforced process but no product patents on medicines[1].

According to an observational study carried out between January 2004 and March 2006 on 2,162 orders of AIDS drugs for Sub-Saharan Africa reported to the Global Price Reporting Mechanism at the World Health Organization, generic companies supplied 63 % of the drugs, at prices that were on average about a third of the prices charged by brand companies. 85 % of the generic drugs came from India.[2]

India has been the world's pharmacy for the poor with regard to first line ARVs – will this be the case for second line ARVs as well? What are the factors that impede production of generic second line and newer ARVs? In our talks with Cipla, Hetero, Matrix and Aurobindo as well as in our talks with the Lawyers Collective and the Alternative Law Forum we explored the barriers to large-scale production of newer ARVs.

Complex production procedures

Cipla, Hetero and Matrix unanimously declared that the cost of the newer ARVs largely depends on the cost of the raw material and the chemical processes necessary to manufacture the drug. The production of the API (active pharmaceutical ingredient) is one of the major factors which influences pricing. Whilst a product like first line Nevirapine only takes 4-5 chemical processes, the second line ARV Lopinavir/Ritonavir takes 17 to 18 chemical steps to manufacture. All three companies agreed that 90 % of the costs of second line ARVs are due to complex production procedures. However, according to Matrix, costs can be reduced by optimizing these procedures. They felt that a 10-20 % reduction might be possible.

1 For further information on the Indian patent law, see "Introduction to Patents and AIDS in India" on p. 5 and "Indian Patent Law and ARVs" on p. 12.

2 PLoS ONE. 2007; 2(3): e278 - published online 2007 March 14. doi: 10.1371/journal.pone.0000278.

Volume and Tendering

The generic firms put volume (large-scale production) at about 10 % of the cost. Thus, whilst assurance of having a large market for the product would certainly bring down the price, the production process in their opinion was much more significant for pricing a drug.

All of the generic companies we talked to were of the opinion that the present tendering system needs to be reformed for various reasons:

- It gives the contract to the lowest bidder. If a company wants to get rid off surplus stock, it can go below production costs which will make it impossible for others to compete.
- Some countries (South Africa was given as an example) seem to protect their own market in favouring bids from their own national companies. These bids, according to some generic firms, were up to 30 % higher than those from India and they still won the tender. Some Indian firms decided not to take part in the tender, as they knew they would not have a chance in competing against the domestic South African firms.
- It is a short-term contract – sometimes only for a few months which gives no security to the firms with regard to the investments they need to make for producing the newer ARVs.

Alternatives which were discussed were a meeting with high-burden countries to find out what their needs are over the next few years and to work out with generic firms what price and volume they can offer, i.e. a pooled procurement system similar to the Clinton Foundation negotiations.

Patents

From the discussion we held with the generic firms and civil society organisations, it became clear that for the newer and especially the very new drugs – those for which patent applications have recently been lodged in India - we increasingly face a huge problem with patents.

Drug Name	Volume (patient year equivalents)	Percentage Total Volume	Percentage Brand	Percentage Generic	Avg. Brand Price	Avg. Generic Price
First Line ARVs	522,517	96 %	35 %	65 %	277	114
Second Line ARVs	18,984	4 %	93 %	7 %	591	601
Total	541,501	100 %	37 %	63 %	304	116

N = 2,162 orders

Volumes calculated on the basis of WHO daily dosing guidelines to generate patient year equivalents.

Average prices in US$ per patient per year and calculated on the basis of total US$ paid for drugs/total drugs in category.

Foto: Andrea Czekanski/AgA

Quality check of the Indian generics firm Cipla.

Latest ARVs

For the newer drugs (mostly third line ARVs) which were patented elsewhere in the world after 2005, the amendment to the Indian Patent Act fully applies, that is to say they will in all likelihood be granted product patents. For these drugs, most generic firms in India prefer to apply for voluntary licences from the originator company. Some generic firms also hope for the Indian Government to issue a compulsory licence in cases where a voluntary licence may not be granted. However, up to now, the Indian Government has not made use of these TRIPS flexibilities. Thus, lower prices for these drugs in developing countries will only be possible under voluntary or compulsory licensing.

The option of establishing a patent pool as planned by UNITAID was something most generic firms have not heard of and that they had misgivings about on the grounds that it was still unclear who would put their patents in and what patents would be put into the pool (all process patents or only the end product patent), what countries the patent pool covered, who could draw on it, if all patents put in the pool had the same conditions, etc. Most thought it was an unworkable model.

The only other option for producing the latest ARVs – transferring production to least developed countries which have until 2016 to become fully TRIPS compatible – was not seen as a viable option by most generic firms. Cipla was one of the very few Indian generic companies interested in the issue and might even consider opening an API plant in Africa to make prices more competitive. The other firms regarded capacity in Africa as too limited to try and produce the substantially more complex chemical substances for newer ARVs and to get the production sites pre-qualified by WHO.

Second line ARVs

For most of the second line ARVs, the patent applications went into the so-called mail box, i.e. the applications were lodged between 1995 and 2005. Here we have to look at the applications almost on a case-by-case basis to see if the ingredients of these drugs were known and patented in the past so that the new version might only be a minor modification either in form or in combining various known chemical substances – i.e. cases in which clause 3 (d) or (e) of the Indian Patent Act would apply.

One of the first challenges which civil society and the generic firms face is to identify the originator firm and the product for which the patent is applied for as the publishing of the data is often quite cryptic and put in bio-chemical terms. Whilst pre-grant opposition has been a successful instrument in not getting patents granted which fall under section 3 (d) and (e), there is no guarantee that the patent is refused.

All of the firms visited seemed confident that they would be able to continue producing LPV/r– currently one of the most important second line ARVs. Cipla, Hetero, Matrix and Aurobindo have produced LPV/r as a generic product. Matrix is so far the only generic firm to have received WHO approval for its generic version of LPV/r in February 2009.[3] It is also the only firm which is confident of selling LPV/r in the near future below the price set by the originator company, i.e. US$ 500/pp/pa. Both Aurobindo and Matrix received tentative FDA approval in March 2009.[4] Most firms think, it is unlikely that a patent on LPV/r will be granted under the Indian Patent Act. Even if it were granted, most firms seemed confident that the Indian Government would issue a compulsory licence (CL) so that they could continue producing the generic version of LPV/r. Their confidence is based on the roll-out of LPV/r as a second line drug in India in 2008[5] – India therefore has an interest in having access to the drug at an affordable price for its own domestic market. So far, however, India has not issued a CL. One would have to see, if the Indian Government would

3 http://mylan.mediaroom.com/index.php?s=43&item=411

4 http://www.medicalnewstoday.com/articles/142456.php and http://www.prdomain.com/companies/A/AurobindoPharma/newsreleases/200931268993.htm

5 http://www.globalhealthreporting.org/article.asp?DR_ID=56291

use the flexibilities of the TRIPS agreement. At this stage it seems more likely that the patent application for the tablet form of LPV/r will not be granted based on sections 3(d) of the Indian Patent Act. Abbott has so far not issued a single voluntary licence to a generic firm for producing LPV/r and has not expressed any intentions of doing so in the near future. It has recently sued Mylan for planning to sell the tablet form of LPV/r at low cost prices before the patent has expired in 2021.[6]

The Indian Pharmaceutical Association and Cipla believe that out of the more than 7500 patent applications in the mailbox, 5000 are frivolous meaning that no patent should be granted. Whilst Cipla is confident that the exemptions in the Indian Patent Act will block frivolous patents, other generic firms would rather play it 'safe' and apply for voluntary licences even before the patent is granted. The conditions of these voluntary licences and their long-term implications need to be studied in detail to predict the effect on pricing of second line and other newer ARVs in developing countries.

The American originator firm Gilead has issued voluntary licences to 11 generic firms for the production of TDF, a substance used in improved first as well as second line ARV regimens. Matrix, Hetero and Aurobindo produce TDF under this voluntary licence. Matrix got tentative FDA approval for TDF in November 2007; Aurobindo got tentative FDA approval for TDF in February 2009. Matrix sells TDF for 144 US$/pp/pa and expects further reductions through pooled procurement with Clinton Foundation. Cipla was the only generic firm visited which challenged Gilead's patent application on TDF[7] and is confident that TDF will not be granted a patent. Cipla was therefore not interested in applying for a voluntary licence from Gilead, as they see a number of problems with this contract others have signed:

- There is only a patent application for TDF for which pre-grant opposition has been filed – so why should a royalty fee of 5 % be paid whilst there is no patent on the drug in India?
- If the patent application gets rejected in India, the firms who have signed the contract with Gilead may not get out of that contract which, according to Cipla, was made under British law.
- There are grant-back licences to Gilead for all improvements on methods and modifications relating to the API or the finished product.
- Export to certain middle-income countries of the finished product or the API is not possible.

In addition, the following issues are seen as detrimental by international experts to ensuring access to TDF at affordable prices worldwide:

- Gilead seeks to impose royalties on all product sales for TDF from the licensed suppliers of APIs, including sales where patents do not exist, as the licence covers over 90 countries.
- Gilead seeks to cut off the supply of generic APIs of TDF outside of the licensed territories.
- The partitioning of the generic TDF API market between approved and non-approved sellers and licensed and non-licensed territories will lead to less competition and less efficient economies of scale in the market for generic TDF APIs.[8]

Even if the patent on TDF should get granted, Cipla is prepared to fight it out in court. The other firms see the advantage of being able to export TDF without any legal hassle. However, the long

6 http://archives.chicagotribune.com/2009/mar/17/business/chi-tue-brf1-abbott-mar17

7 http://www.medicalnewstoday.com/articles/43409.php

8 see James Love, Knowledge Ecology International, http://www.keionline.org/misc-docs/ftcgilead12feb07.pdf

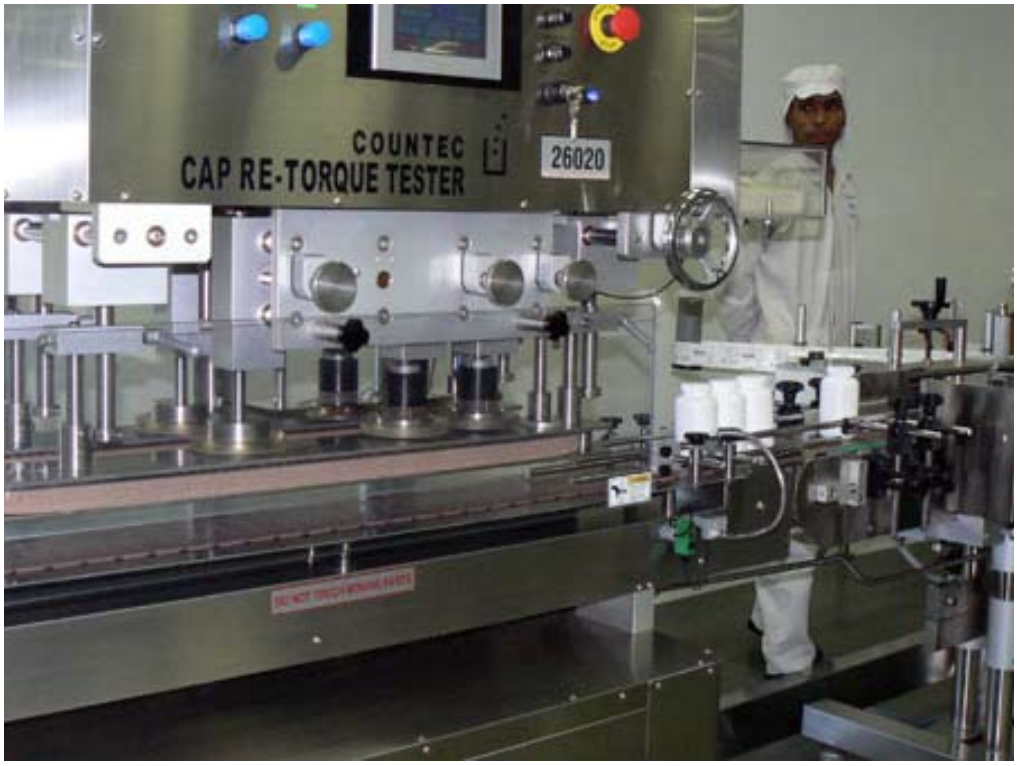

Foto: Andrea Czekanski/AgA

Aids drug production of the Indian generics firm Cipla.

Foto: Beate Ramme-Fülle/AgA

Dr. Yusuf K. Hamied, CEO Cipla, signing a petition of Action against AIDS.

term implications of the voluntary licences may well mean that middle income countries pay much higher prices than they would need to and that the price for APIs is high in countries which do not have patents on TDF as well as the non-licensed territories.

Non-enforcement of patents in India for these drugs would certainly make the long-term availability and pricing more secure. However, we also need to look at the production processes and the costs involved in buying the machinery to produce the newer ARVs. In order for generic firms to invest in producing newer drugs, they need to be certain of having a market and of being able to sell the product cheaper than the originator firm but with enough of a profit margin to sustain production. Pooled procurement might be the way forward here. For middle income countries the import of cheaper drugs may only be possible by issuing a compulsory license. Thus, the full flexibilities of the TRIPS agreement need to be upheld in India and elsewhere.

India and China are the countries which produce the APIs for ARVs and any attempt to restrict access to APIs in other countries as is allegedly taking place in connection with the Gilead voluntary licensing should be scrutinized and publicly criticized.

Conventional first line ARVs

What about the older ARVs? Here a number of Indian generic firms felt that rock bottom had been reached with regard to pricing and that many generic firms would pull out of producing first line regimens, if prices were further pushed. For civil society it is difficult to know exactly what the production costs of generic firms are. One can assume that the machinery has long been paid off and so the actual production costs are rather low. However, if no profit margin is made anymore or generic firms are pushed to offer prices below production, the sustainability of providing first line ARVs in developing countries would be severely threatened. Keeping in mind that at present 97 % of people receiving ARVs in developing countries are on first line and that this constitutes only 31 % of those in need of ARVs,[9] first line needs to be around for the long-term and to come at affordable prices. Remedies that were suggested by generic firms in India were to have fixed prices for certain ARVs and ARV regimens. These suggestions should be discussed with Clinton Foundation, PEPFAR, Global Fund and other major ARV purchasing/distributing agencies.

Counterfeit Issue - Defaming the Indian Generic Industry?

In recent months a number of shipments of ARVs from India to Latin America and Africa were seized in Europe because they were regarded as "counterfeits". These drugs were under patent in Europe. Under the EC directive 1383/2003 they were regarded as violating European patents, even though they were not meant for any European country but were merely in transit at European airports. The term "counterfeit" is a total misnomer, as the drugs had been pre-qualified by the WHO or FDA and therefore been declared safe and of high quality; neither were they shipped under a false name. They also did not violate patents as the drugs were not patented in India or the importing country. So why call them "counterfeits"? Is it to discredit the Indian generic industry? No doubt, sub-standard drugs exist and some may well be produced in India. Yet, any drug tested and declared safe by the WHO and FDA is not a counterfeit drug. Attempts to ruin the reputation of high-standard generic firms in India have already succeeded to some extent. Both Kenya and Uganda are working on anti-counterfeit bills which label any copy of a product that enjoys patent protection anywhere in the world as "counterfeit".[10] This would bring to an end all generic imports of ARVs and have tragic consequences for the scale-up of ARV treatment and will therefore need to be opposed.

Summary

Whilst production processes and volume play an important part in pricing and need to be addressed in terms of finding alternatives to the present tendering processes, patent issues will be the main obstacle for producing and marketing the newer ARVs. Civil society needs to remind governments to uphold the full TRIPS flexibilities (including compulsory licences), to support pre- and post-grant opposition to patenting ARVs whose substances are already known and see to it that free trade agreements do not exacerbate the patent situation in developing countries. Also, the impact of voluntary licences needs to be critically assessed in cases, where the originator firm has too many strings attached. Civil society needs to fight against attempts by originator companies, individual states and the EU to mislabel high-quality products as "counterfeits" – instead the "counterfeiting of patents" in terms of ever-greening substances needs to be exposed.

Astrid Berner-Rodoreda, HIV Advisor, Bread for the World, Action against AIDS, Germany

9 http://www.who.int/hiv/pub/towards_universal_access_report_2008.pdf

10 http://www.eac.int/customs/component/content/article/56/56.html and http://www.essentialdrugs.org/edrug/archive/200904/msg00014.php

Indian Patent Law and ARVs

Background of Indian Patent Law

Until the early 1970s, India primarily imported most drugs and prices of drugs in India were amongst the highest in the world. Recognising that this was due to the product patent protection available to pharmaceuticals, India changed its patent regime. In 1970, India enacted a new patent law. The Patents Act, 1970, which came into force in 1972, sought to remedy the problem by only recognising process patents in relation to drugs and agro-chemicals. This change, coupled with other regulatory changes, enabled the growth of a robust Indian pharmaceutical industry (generic companies). The consequent competition resulted in the lowering of prices of medicines in India. By 1988-9, India became a net exporter of drugs[1].

In 1995, India became a signatory to the WTO. This required India to comply with the minimum mandatory requirements set out in the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). By 2005, it was to introduce a TRIPS-compliant product patent regime for pharmaceuticals. Thus, in 2005, India amended its patent law to provide for product patent protection for pharmaceuticals. In light of this, concerns have arisen over the ability of Indian pharmaceutical companies to continue to provide less expensive, generic medicines to patients in India and other developing countries.

1 Sudip Chaudhuri: The WTO and India's Pharmaceuticals Industry, 46

Post 2005 Impact on ARVs

Atazanavir, Lopinavir (PIs) and Tenofovir (NRTI) are antiretroviral drugs used as second line ARVs, as recommended by World Health Organization. Atazanavir and Lopinavir are part of the second line regimen, which was recently initiated in the 2008 ARV roll out programme in India. To our knowledge, none of these drugs are patented in India and generic versions of these drugs are available. However, foreign multinational pharmaceutical companies have filed patent applications in respect of all these drugs in India.

Atazanavir

Generic Atazanavir is marketed as Atazor®[2] (100, 150, 200 and 300 mg) and Atavir® by Indian companies such Emcure, Cipla and Aurodindo in India. Generic active pharmaceutical ingredi-

2 http://www.emcure.co.in/products.html

Foto: Andrea Czekanski/AgA

Lopinavir/Ritonavir is marketed as Lopimune® by Cipla.

ents (APIs) are also available. The main advantage of this drug is once-a-day dosing, tolerability and favorable effects on lipid levels.

Patent Status

So far, we have traced two applications relating to Atazanavir in the Indian patent official journal.

1. Patent Application No. 805/MAS/1999 bearing title "HETEROCYCLIC AZAHEXANE DERIVATIVES" filed by Novartis AG.

We filed a pre-grant opposition against this patent application. As Novartis AG did not reply to the examination report issued by the Patent Office within the stipulated time, the patent application has been deemed to be abandoned by the patent office in August 2007.

However, Novartis AG has filed a divisional application No. 310/CHE/2007 bearing title "HETEROCYCLIC AZAHEXANE DERIVATIVES".

2. Patent Application No. 6425/DELNP/2006 bearing title "PROCESS FOR PREPARING ATAZANAVIR BISULFATE AND NOVEL FORMS" filed by Bristol-Myers Squibb.

Lopinavir/Ritonavir (Kaletra®)

Kaletra® is available as soft gel capsules in India. Generic versions are marketed as Lopimune®, Ritocom®, Ritomax-L® and V-Letra® by generic companies such as Cipla, Hetero, Alkem (Cytomed) and Ranbaxy respectively[3].

The new heat stable Kaletra® is considered as a better option when compared to soft gel capsules due to its non refrigeration aspect. Recently, Mylan received approval by World Health Organization under prequalification program, for the heat stable form of Kaletra® (Aluvia®)[4]. Matrix is the Indian subsidiary of Mylan. In light of this, it would need to be seen if the generic version of Aluvia® will be made available in India.

Patent Status

There are nearly 15 patent applications filed by Abbott for both individual drugs (Ritonavir and Lopinavir) or as combination (Kaletra®) drugs in India. Of these, civil society groups have filed pre-grant oppositions to four patent applications—one application relates to Ritonavir, one relates to Lopinavir, one relates to soft gel Kaletra® and one relates to heat stable Kaletra®.

The patent application relating to soft gel Kaletra® is deemed to be abandoned, as Abbott did not respond to the examination report issued by the Indian patent office. The other three applications are still under examination.

To our knowledge, no patent has been granted with respect to these applications. However, we need to peruse all of the applications closely to identify if the claims in these applications could potentially block generic versions. Patenting of even one of the individual drugs, either Lopinavir or Ritonavir, could have an adverse impact on the availability of all fixed dose combinations of Kaletra®.

Foto: Beate Ramme-Fülle/AgA

Ramya Sheshadri, Lawyers Collective, signing a petition of Action against AIDS.

TDF (Tenofovir Disproxil Fumarate)

TDF is an important first line and second line drug which is widely used. Generic versions are marketed as Tenvir[5], Tofovir[6], by generic companies such as Cipla and Alkem (Cytomed). Even other generic companies like Ranbaxy, Hetero and Matrix are manufacturing TDF[7].

Gilead, the originator company, has entered into voluntary license with several generic companies in India, even when there is no patent on the drug.

Patent Status

We have been able to identify five applications pertaining to TDF. The civil society group has filed pregrant opposition's against three applications. Presently two oppositions are pending in the patent office.

To our knowledge, no patent has been granted with respect to these applications. As mentioned earlier we have to monitor the applications and scrutinize if the claims in these applications could potentially block generic versions.

Impact of Product Patents in India

If these key drugs are patented in India the impact will be disastrous as it would stall the production of generic drugs. It can have

3 Indian Drug Reference (No. 3, 2008, updated till 31 May 2008)

4 http://www.msnbc.msn.com/id/29386313/

5 http://www.cipla.com/admin.php?mode=cat&action=disp&parentid=2&catid=9

6 http://www.alkemlabs.com/product/product.php?cid=Mw

7 MSF (2008): Untangling the Web of ARV Prices

an impact on the Indian government second line ARV programme initiated in 2008, as Kaletra® and TDF are the key drugs of the second line ARV roll put programme. It will also freeze the import of drugs to developing and least developing countries.

When drugs are patented, the patentee can exclude other generic companies from manufacturing, consequently due to monopoly and absence of competition drugs will be exorbitantly priced.

Under these circumstances the options available for the Indian civil society and patient groups is to file a pre-grant opposition against these key drugs. However if the patent is granted we need to lobby with the government to issue compulsory license and file of post-grant opposition.

Patent Linkage: Bayer Case

Another cause of concern have been the attempts of pharmaceutical companies to introduce TRIPS-plus provisions, including patent linkages, in India. Patent Linkage is a system aiming at preventing the registration and authorisation of generic versions of a patented drug for marketing until the expiry of the patent. This would considerably delay the entry of generic drugs into the market.

Previously, certain groups have advocated with the Indian government to introduce the patent linkage system. In early 2008, the media reported Dr. Surinder Singh, the Drug Controller General of India (DCGI) as stating that the DCGI was planning to introduce patent linkage system and was in the process of obtaining data on drugs which have been granted patents from the patent office.[8] The Indian Pharmaceutical Alliance and civil society groups raised objections to the proposal and also questioned the lack of consultation with affected stakeholders. In light of this, the DCGI decided against introducing the patent linkage system until the issue was discussed and debated.[9]

In the meantime, Bayer filed a writ petition in Delhi High Court against the Union of India, the DCGI and Cipla, seeking an order that the DCGI should consider the patent status of its drug Sorefenib Tosylate before granting marketing approval to Cipla. The court thereby directed the DCGI to not grant marketing approval to Cipla until the final order was passed[10] in the matter.

Concerned about the consequences of this litigation Cancer Patients Aid Association (CPAA), represented by Lawyers Collective HIV/AIDS Unit, filed an intervention application in the matter. In January 2009 the hearing was held, CPAA argued that patent linkage raised a grave public health concern and would have implications on the public at large. CPAA pointed out that Bayer was attempting to introduce a policy change, which is otherwise the prerogative of the Legislature, through the court. It further argued that the patent and drug regulatory systems are two independent systems under Indian law and it is not permissible to link them.

The matter was posted for further hearing on February 2009; the Counsel of Bayer has concluded his arguments and the other parties in the case will be heard in the upcoming hearings[11].

Ramya Sheshadri, Lawyers Collective HIV/AIDS Unit, Bangalore, India

8 http://www.business-standard.com/india/storypage.php?autono=321993

9 http://www.livemint.com/Articles/2008/07/08004318/Plan-linking-generics-to-paten.html

10 http://www.livemint.com/Articles/PrintArticle.aspx?artid=F9EDBBA0-E0CE-11DD-AB25-000B5DABF636

11 http://www.ip-watch.org/weblog/2009/02/25/drug-patent-linkage-is-subject-of-court-case-dispute-in-india/