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# Voluntary licensing practices in the pharmaceutical sector: An acceptable solution to improving access to affordable medicines?\*

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8 February 2007

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## Background

For the past eight years at least, civil society and health groups have consistently demanded that pharmaceutical companies should issue voluntary licenses (VLs) on patented medicines to generic manufacturers more readily. This is in order to bring more competition into the marketplace and make access to medicines more affordable.<sup>1</sup> The South African competition cases of 2002 resulted in a settlement and a handful of VLs being given by GlaxoSmithKline (GSK) and Boehringer Ingelheim (BI) (see Table 2 below) to generic companies in South Africa. The subsequent years also saw the beginning of a sharp reduction in the price of ARVs.<sup>2</sup> Since the period 2002, we have not seen pharmaceutical companies issuing a flurry of VLs as might have been expected.<sup>3</sup> This may be due to a number of factors – such as waiting to see how the patent regimes develop in countries like India, which is home to one of the largest generic pharmaceutical industries. Rather, originator companies have adopted other strategies in the face of continued public pressure by going into philanthropic over-drive, developing differential price mechanisms or donation programmes in developing countries.<sup>4</sup>

Of particular concern to the access to medicines debate and the ability of generic companies to play a continued role has been India's implementation of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) on 1 January 2005 and amendment of its patent law to protect pharmaceutical product patents. There has been considerable debate as to whether affordable generic medicines will now come to a stop should patents start being granted for many of the mailbox applications that

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\* This research was carried out on behalf of Oxfam GB.

<sup>1</sup> See for example, Dr Tido von Schoen-Angerer, MSF Thailand, 'How to win the medicine battle', *The Nation*, 1 December 1999

<http://www.accessmed.msf.org/prod/publications.asp?scntid=3082001039305&contenttype=PARA&> Statement by the World Health Organisation, 24 January 2003 see

<http://www.cptech.org/ip/health/aids/who01242003.html>, Oxfam's response to Pharmacia's non-exclusive licence for Delviridine, 24 January 2003

<http://www.cptech.org/ip/health/aids/oxfam01242003.html>

<sup>2</sup> See Medicines Sans Frontieres, *Untangling the web of price reductions – a pricing guide for the purchase of ARVs for developing countries* 9<sup>th</sup> Edition, (July 2006) <http://www.accessmed-msf.org/>

<sup>3</sup> A recent study by the Interfaith Center on Corporate Responsibility shows that on a five point scale of 1-5 (where 5 is the highest and 1 the lowest) the industry mean of fifteen of the major pharmaceutical companies providing access to antiretrovirals (ARVs) through licenses is 2.4. See K. Hartsough et al, *Benchmarking Aids, Evaluating Pharmaceutical Company Responses to the Public Health Crises in Emerging Markets*, 2006, pg 8

<sup>4</sup> Andrew Jack, 'The Drug Companies: A new mood of co-operation', *Financial Times*, 1 December 2006 <http://www.ft.com/cms/s/0bf3d478-7aed-11db-bf9b-0000779e2340.html>

have been waiting to be examined in India since 1995. In amending its Patents Act, India utilised some of the flexibilities available within TRIPS and inserted a number of provisions to protect its domestic industry and public health. These include more stringent patentability standards and the opportunity for any person to challenge a patent application before it is granted. The amendment also inserted a ‘grandfather’ clause which allows companies that have made a significant investment, were producing and marketing a pharmaceutical product prior to 1 January 2005, to be able to continue to do so provided a reasonable royalty is paid to the patentee. Indeed, the right to challenge patents before their grant has led to some successes with Novartis’s anti-cancer drug Gleevec being rejected and GSK’s application for Combivir (Lamivudine and Zidovudine) being withdrawn.<sup>5</sup> This has also led to some sections of civil society to encourage patent challenges before considering VLs as an option. Moreover, since India’s amendment of its Patent Act, there has been a renewed push to encourage other developing countries to utilise TRIPS flexibilities as a first measure towards ensuring IPRs do not unnecessarily block public health.<sup>6</sup>

However, despite implementing such safeguards, the threat of patents being granted remains.<sup>7</sup> Recent events such as the threat of the bird-flu pandemic and Gilead Science’s unusual step to offer non-exclusive VLs to eleven generic companies to manufacture and sell Tenofovir Disoproxil Fumarate (TDF) prior to a patent being issued in India has, yet again, raised the question – are VLs an acceptable option to ensuring access to medicines?<sup>8</sup>

The research set out here looks to provide answers to the above question by:

- 1) Defining a VL;
- 2) Mapping VLs that are currently in operation and whether they have helped to make medicines more accessible;
- 3) Looking at the pros and cons of VLs and generic industry views;
- 4) Suggesting best practices for VLs and conclusions.

The above research has been conducted through internet searches, interviews with generic companies, the researcher’s experience in reviewing various VLs, practices of the generics industry in India and the nature of IPRs there.

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<sup>5</sup> However, Novartis has now challenged the decision of the Chennai Patent Office that issued the decision as well as filing an action against the Indian Government arguing that a particular provision of the Patents Act is not compliant with TRIPS and the Indian Constitution.

<sup>6</sup> For example, the Philippines is seeking to amend its Patent Act and insert a provision from the Indian Patent Act which prevents the patenting of new forms of known substances which do not show enhanced efficacy.

<sup>7</sup> Data obtained from the Mumbai Patent Office, indicated that patents have already been granted on new forms of known substances that may not meet the requirements of section 3d.

<sup>8</sup> Gregory Roumeliotis, Gilead rains manufacturing deals on India’s generic firms, *in-Pharma Technologist.com*, 26 September 2006 <http://www.in-pharmatechnologist.com/news/ng.asp?id=70811-gilead-roche-viread-saquinavir-hiv>.

## 1. Defining a Voluntary Licence

Typically, a VL is where a pharmaceutical company that holds patents on a product (patentee) offers on his own accord a licence to a third party (usually a generic producer) to produce, market and distribute the patented product. In exchange, the patentee will usually request a royalty on the net sales made by the licensee as well as impose other restrictions, such as geographical restrictions on where the licensee can sell the product, restrictions on what price the product may be sold at and any other terms or conditions it might insist on. This type of licensing is also referred to as ‘out-licensing’.

There is also what is known as ‘in-licensing’. A common model of in-licensing is where a pharmaceutical company may licence a compound at clinical or pre-clinical stage from a biotechnology company and develop the drug to market.<sup>9</sup> Ranbaxy has entered into a number of ‘in-licensing’ agreements, such as with The Debiopharm Group and Eurodrug Group.<sup>10</sup>

As well as in-licensing, other types of licenses granted by patent holders to generic companies could be marketing licenses (or distribution agreements), where a company may simply sell the branded version of the product.

For this research, we have focussed on the classic definition of voluntary licensing, which permits a third party to manufacture, market and distribute a patented product.

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<sup>9</sup> See D.P. Schaffer, *In-licensing as a business model*, Nature Biotechnology, Volume 20 and Lou and de Rond, ‘*The not invented here myth*’, Nature, Vol. 5, (June, 2006).

<sup>10</sup> See [http://www.ranbaxy.com/newsroom/pressrelease\\_det.asp?sno=304](http://www.ranbaxy.com/newsroom/pressrelease_det.asp?sno=304) and [http://www.ranbaxy.com/newsroom/pressrelease\\_det.asp?sno=275](http://www.ranbaxy.com/newsroom/pressrelease_det.asp?sno=275)

## 2. Mapping Current Voluntary Licensing Deals and Pricing

As shown in Tables 2, 3 and 4 below, between Africa and India, we have managed to identify 32 VLs that have been granted to generic companies. However, according to information provided via the pharmaceutical company websites, but which have not been specifically identified during research, that total could be 36. The pharmaceutical companies that have granted VLs and the treatment classification they relate can be broken down as shown in Table 1:

Pharmaceutical Company	No. of VLs Issued	Treatment Classification
GSK	7(8) <sup>11</sup>	ARV
BI	3(7) <sup>12</sup>	ARV
BMS	3	ARV
Gilead	12	ARV
MSD	2	ARV
Roche	4	ARV/avian flu
<b>Total VLs</b>	<b>31 (36)</b>	

**Table 1** – Total number of VLs issued

With the exception of Roche's VL to Hetero for Oseltamivir, all VLs we have identified relate to ARVs. According to general information available, the terms and conditions of the licenses appear standard in that they are non-exclusive and have geographical restrictions. Some of the licenses offer free technology transfer and assistance and are royalty free. Where a royalty is set in the VL and where such information has been made available, it appears that 5% is the norm.<sup>13</sup>

What is noticeable from the VLs on offer in relation to ARVs, is that with the exception of BMS's VL to Emcure for Atazanavir, none relate to 2<sup>nd</sup> line regimens.<sup>14</sup> Also, with the exception of Gilead's VL for TDF, the patent for which expires in 2017/18 (if granted in India) and the VL for Atazanavir, the VLs granted tend to

<sup>11</sup> According to GSK's website, they claim to have issued 8 VLs for the generic production of Lamivudine, Zidovudine and their combination Combivir®, see <http://www.gsk.com/media/archive.htm>

<sup>12</sup> According to BI's website, they claim to have issued 7 VLs for the generic production of Nevirapine (Viramune®), see <http://www.boehringer-ingelheim.com/corporate/asp/news/ndetail.asp?ID=4254>

<sup>13</sup> However, the royalty rate of 5% may only be the norm where VLs are issued as a result of public pressure e.g licenses resulting from the competition case and Gilead's licensing of TDF in India all request a 5% royalty.

<sup>14</sup> It should be noted that Atazanavir needs to be used with Abbotts Ritonavir as booster. Abbott has yet to agree to voluntarily licence Ritonavir. At an International Treatment Preparedness Campaign meeting in London with Abbot on 13 July 2006, attended by Tahir Amin, Abbott insisted that it would not issue any VLs on its 2<sup>nd</sup> line drug heat stable Kaletra (Ritonavir/Lopinavir). Abbott is of the view that given the complex chemistry to make the drug, generic companies will not be able to match its allegedly not for profit price of US\$500-550. However, in an informal chat with Dr Hamied of Cipla, he mentioned that under the right market conditions and incentives, within a period of time he could possibly go lower than that price. This thought seems also to be echoed by Sandeep Juneja of Ranbaxy in the interview (see interview notes).

relate to base compounds which have very little patent life left, unless they form part of a patent coverage that includes the compound as a combination or an end formulation. For example, the patent for the base compound Zidovudine expired in 2006, while the patent for the base compound for Nevirapine expires 2009.<sup>15</sup>

### ***Pricing of generics under VLs against other generics***

According to MSF's 'Untangling the Web of Price Reductions'<sup>16</sup>, in developing countries, it is quite apparent that generics being offered by Indian companies that are not under a VL with the originator company are often cheaper than the originators product under differential pricing or a generic company offering the same product under a VL. For example:

Lamivudine - is offered by Aspen under a VL from GSK at \$69 per patient year (ppy) (which is the same price that GSK offers it) whereas, Cipla offers it at US\$51ppy and Aurobindo at US\$54 ppy.

Nevirapine - is sold by Aspen under a VL from BI at US\$97 ppy. Cipla offers it at US\$56 ppy, Aurobindo at US\$ 61 ppy and Ranbaxy at US\$61 ppy. BI sells the product for developing countries at US\$432 ppy.

TDF – Gilead's lowest price for least developed countries is US\$ 207 ppy.<sup>17</sup> Prior to the issuing of VLs to Indian generic companies, the only generic companies that were manufacturing and marketing the product were Cipla and Hetero. Cipla was selling the product at US\$973 and Hetero is now selling at US\$365.<sup>18</sup> Hetero has taken a VL. With the introduction of other 10 other companies with VLs (not including Hetero which was already producing), these prices are likely to reduce the price further. As a result, if Cipla continues to produce its generic version, depending on whether its patent opposition succeeds, it may reduce its price further to compete. (See also the case study for further facts).

It has to be noted here that Gilead's discounted price of US\$207 only applies to those countries eligible for Gilead's Access Program. Therefore, Cipla's original prices are cheaper than Gilead's for many of the Medium Human Development Countries not included in Gilead's Access Program. For example, El Salvador is not included in Gilead's program and is reportedly paying US\$1,700 ppy for TDF. As a result, it is possible that where Gilead does not have patent protection in Medium Human Development countries, Cipla may be in a position to compete. Also, Gilead has yet

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<sup>15</sup> See Medecins Sans Frontieres, *Drug patents under the spotlight – Sharing practical knowledge about pharmaceutical patents*, (May, 2003)

<sup>16</sup> *Supra.* n.2

<sup>17</sup> Middle-income countries, like Brazil, through negotiations and threats of issuing compulsory licenses, have managed to get Gilead to halve the original price to US\$1,380 ppy.

<sup>18</sup> Indeed Cipla has recently (1 December 2006) announced a reduction in its price for TDF to US\$195 for Low Human Development countries (e.g Angola, Burundi, Cameroon, Kenya, Lesotho, Nigeria, Tanzania) and US\$340 ppy for Medium Human Development countries (e.g Albania, Algeria, Brazil, China, Colombia, Egypt, India, Indonesia, Iran, Morocco and Venezuela). See 'Latest updates' to MSF's Untangling the Web of Price Reductions. *Supra.* n.2. This reduction is probably as a result of the VLs on TDF given to other generic producers in India in August and September and Gilead's discounted price for its Access Program. Prior to the VLs being issued only Cipla and Hetero were producing generic versions of TDF.

to register TDF for marketing in many of the countries eligible under its program and so its product will not be on the markets in these countries as yet – though it is not clear whether Cipla or Hetero already have marketing approval for TDF in such countries.

Examples where differential pricing of a product by the originator company for developing countries<sup>19</sup> is cheaper than generic production, whether manufactured under a VL or not, include:

Nelfinavir – Roche offers the product at US\$683 ppy. Hetero offers it at US\$986, Cipla at US\$1,337 ppy and Aurobindo at US\$1,379.

Ritonavir – Abbott offers the product at US\$83 ppy (for the capsule version). Hetero offers it at US\$190 ppy, Cipla at US\$313 ppy and Aurobindo at US\$336.

Lopinavir/Ritonavir – Abbott offers the product at US\$500 ppy. Cipla offers the product at US\$1,338 and Hetero at US\$1,898.

What is obvious from the above is that the more generic companies offering a product, the lower the prices fall. Gilead's issuing of VLs on TDF to several companies is likely to reduce prices further. Therefore, the commonly held belief that more market entrants make for a more competitive environment appears true.<sup>20</sup>

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<sup>19</sup> It should be noted that the definition given to developing countries by originator companies for the purpose of differential pricing may only relate to least developed countries and not include lower middle income countries.

<sup>20</sup> Other factors such as deals between Indian generic companies and the Clinton Foundation may also account for lower pricing.

## South Africa

Licensor	Licensee	Year	Product*	Terms and Conditions ***	Price US\$ (ppy)**
<b>GlaxoSmith Kline</b>	Aspen Pharmacare	2003/2004 (revised terms for VL)	Lamivudine (Retrovir®) Zidovudine (Epivir®) Lamivudine +Zidovudine (Combivir®)	Manufacture and market to public and private sectors of South African and Customs Union (SACU) and South African Development Community (SADC) countries; royalty of 5% on net sales (royalty not to exceed 5% when used in combination products); licence permits use in relation to combination products. <sup>21</sup>	\$69 (150mg Tablet Lamivudine)  \$158 (300mg tablets Zidovudine)  \$220 (Combivir®)
	Cipla-Medrpro	December 2004	As above	As above	N/A. <sup>22</sup>
	Feza Pharmaceuticals	August 2004	As above	As above	No product marketed to date. <sup>23</sup>
	Thembalami Pharmaceuticals	June 2004	As above	As above	Never marketed/company now dissolved. <sup>24</sup>
	Biotech Laboratories	December 2004	As above	As above	N/A
	Sonke Pharmaceuticals PTY Ltd	May 2006	As above	As above	N/A - no product marketed to date
<b>Boehringer-Ingelheim</b>	Aspen Phramacare	2003/2004	Nevirapine (Viramune®)	Manufacture and market to public and private sectors of SACU and SADC countries; royalty of 5% on net sales (royalty not to exceed 5% when used in combination products); licence permits use in relation to	\$97 (200mg tablets)

<sup>21</sup> However, the original VL issued by GSK to Aspen had a royalty rate of 30% (which was to be given back to selected NGOs) and only permitted sale to NGOs and the public sector. Following the competition case brought by civil society, a settlement agreement was reached and the terms were revised for Aspen and all other licensees. The same settlement terms were also agreed with Boehringer Ingelheim in relation to its product Nevirapine. See

<http://www.alp.org.za/modules.php?op=modload&name=News&file=article&sid=225>

<sup>22</sup> It is understood that due to the delay in GSK agreeing to a VL and the particular discrepancies with the South African Governments tendering process for ARVs, Cipla missed out on the opportunity to make a bid.

<sup>23</sup> See Avafia et al, *The ability of select sub-Saharan African countries to utilise TRIPs Flexibilities and Competition Law to ensure a sustainable supply of essential medicines: A study of producing and importing countries*, Tralac, page 14 (2006) and

<http://www.alp.org.za/modules.php?op=modload&name=News&file=article&sid=331>.

<sup>24</sup> Thembalami Pharmaceuticals (a joint venture between Ranbaxy and Adcock Ingram) has now dissolved as a company. Thembalami did not go to market with the products under licence as it was forced to withdraw from the tendering process for the government's ARV programme following the withdrawal of Ranbaxy's AZT, 3TC and Combivir® from the South African market in October 2004 (because of some inconsistencies with the WHO's pre-qualification requirements). See *supra* n.21

				combination products.	
	Biotech Laboratories	2003/2004	As above	As above	N/A
<b>Bristol Myers Squibb</b>	Aspen Phramacare	February 2006	Atazanavir (Reyataz®)	World Bank Tier 1 countries (Low income economies), including SACU and SADC countries; royalty free technology transfer; no price cap; agreement for perpetuity. <sup>25</sup>	N/A - no product marketed to date.
<b>Merck Sharpe Dhome</b>	Thembalami Pharmaceuticals	July 2004	Efaviranz (Sustiva®)	S. Africa and SADC countries, non-exclusive; supply to public and private sectors.	Never marketed/company now dissolved.
	Aspen Pharmacare	July 2005	Efaviranz (Sustiva®)	Non-exclusive; royalty free technology transfer.	N/A
<b>Gilead Sciences</b>	Aspen Pharmacare	April 2005	Tenofovir (Viread®) Tenofovir and Emtricitabine (Truvada)	Non-exclusive manufacture and distribution to Gilead's 'Access countries'; Gilead to supply API in specified countries; transfer of technology; Aspen to obtain regulatory approval in those countries in Africa where Gilead has not already registered; Aspen agrees sell at the price agrees under Gilead's Access Program. <sup>26</sup>	N/A – still awaiting marketing approval from the Medicines Control Council.
<b>Roche</b>	Aspen Pharmacare	September 2006	Saquinavir	Royalty free technology transfer; manufacture and supply in S.Africa, and any Sub-Saharan African country or countries defined as Least Developed defined by United Nations.	N/A

**Table 2 – Voluntary licenses in South Africa**

<sup>25</sup> See *Aspen and BMS conclude strategic deal*, (15 February 2006) at <http://www.aspenpharma.com/>

<sup>26</sup> See *Supra* n.2, page 42 and [http://www.gilead.com/wt/sec/pr\\_700521](http://www.gilead.com/wt/sec/pr_700521)



*Africa*

<b>Licensor</b>	<b>Licensee</b>	<b>Year</b>	<b>Product*</b>	<b>Terms and Conditions***</b>	<b>Price US\$ (ppy)**</b>
<b>GlaxoSmithKline</b>	Cosmos Limited	September 2004	Lamivudine (Retrovir®) Zidovudine (Epivir®) Lamivudine and Zidovudine (Combivir®)	Manufacture and distribution in Kenya, Uganda, Tanzania., Burundi and Rwanda.	N/A
<b>Boehringer-Ingelheim</b>	Cosmos Limited	October 2004	Nevirapine (Viramune®)	Manufacture and sale in Burundi, Kenya, Rwanda, Tanzania and Uganda.	N/A
	Memphis	November 2004	Nevirapine (Viramune®)	Egypt and neighbouring countries.	N/A
<b>Roche</b>	Cosmos Limited	September 2006	Stavudine	Free technology transfer; manufacture and supply in Kenya and any Sub-Saharan African countries or countries defined as Least Developed defined by United Nations.	N/A
	Universal Corporation Limited	September 2006	Saquinavir	Free technology transfer; manufacture and supply in Kenya and any Sub-Saharan African countries or countries defined as Least Developed defined by United Nations.	N/A

**Table 3 – Voluntary licenses in Africa**

## India

Licensor	Licensee	Date	Product*	Terms and Conditions ***	Price US\$ **
Gilead Sciences	Alkem Laboratories	September 2006	Tenofovir (Viread®)	See case study	N/A
	Aurobindo Pharma	September 2006	As above	See case study	N/A
	FDC	September 2006	As above	See case study	N/A
	JB Chemicals & Pharmaceuticals	September 2006	As above	See case study	N/A
	Matrix Laboratories	September 2006	As above	See case study	N/A
	Medchem International	September 2006	As above	See case study	N/A
	Ranbaxy Laboratories	September 2006	As above	See case study	N/A
	Shasun Chemicals and Drugs	September 2006	As above	See case study	N/A
	Emcure Pharmaceuticals	August 2006	As above	See case study	N/A
	Hetero Drugs	August 2006	As above	See case study	\$365 (TDF 300mg) ppy
	Strides Acrolab	August 2006	As above	See case study	N/A
Roche	Hetero Drugs	May 2006	Oseltamivir (Tamiflu®)	Production for government stockpiling in India and developing countries in Africa; respecting IPRs for Tamiflu worldwide. <sup>27</sup>	\$15-20 (for one course of 10 tablets)
Bristol Myers Squibb	Emcure Pharmaceuticals	Feb/March 2006	Atazanavir (Reyataz®)	Royalty free, technology transfer; manufacture and sale in India and Africa	Approximately \$88 p/mth. <sup>28</sup>
	Aurobindo	March 2006	Didanosine (Videx®) Stavudine (Zerit®)	Manufacture and sale in S.Africa and 49 other countries.	N/A

**Table 4 – Voluntary licenses in India**

\* 1<sup>st</sup> Line ARVs - Lamivudine, Zidovudine, Lamivudine + Zidovudine (Combivir®), Nevirpine, Stavudine and TDF.

<sup>27</sup> It should be noted that to date the patent for Oseltamivir (Tamiflu) has not been granted in India.

<sup>28</sup> P.T Jyothi Datta, *Gilead in pact with 3 Indian cos for AIDS drug*, Business Line, The Hindu, 16 August 2006 at <http://www.thehindubusinessline.com/2006/08/16/stories/2006081603630100.htm>

2<sup>nd</sup> Line ARVs – Atazanvir, Didanosine, Saquinavir. TDF, TDF+ Emtracitibine.<sup>29</sup>

\*\* All prices are taken from MSF's 'Untangling the Web of Price Reductions'.<sup>30</sup> With the exception of Hetero, licensees have yet to release the price of TDF under the VL. According to discussions with some of the licensees and based on our research on the internet, the licensees are either awaiting marketing approval and/or working with the technology transfer provided in the licence in order to develop their production mechanisms and/or whether to utilise the technology transfer. For example Shasun expects to be marketing within twelve months of entering the licence. See *Supra N. 8*. See also interview notes (Question 1) with Ranbaxy, who expect to be marketing their version of TDF within the first half of 2007.

\*\*\*It should be noted that the apart from VL Agreement issued by Gilead which has been reviewed by the authors, the terms and conditions for the other VLs discussed are based on what has been reported in the press.

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<sup>29</sup> It should be noted that TDF is considered both a 1<sup>st</sup> line and 2<sup>nd</sup> line ARV. Indeed, when used in combinations, some 1<sup>st</sup> line ARVs (e.g Zidovudine) can form part of 2<sup>nd</sup> line ARV regimens. Also, whether a drug is classified as 1<sup>st</sup> line or 2<sup>nd</sup> line can depend on individual country classification. For more detailed discussion see World Health Organisation, *Antiretroviral Therapy for HIV Infection in Adults or Adolescents – Recommendations for a Public Health Approach* (2006, Revision).

<sup>30</sup> *Supra* n.2

### 3) The Pros and Cons of VLs and Generic Industry Views

There are a number of factors to consider when assessing the pros and cons of VLs – the key factors are highlighted below.<sup>31</sup> Also, based on our interviews with generic industry in India, there are differing views on the commercial incentives, benefits and negative aspects of VLs.

#### *Pros of VLs*

- Can help to speed up access to products. As all generic companies in developing countries are now operating under product patent regimes, entering into a VL may make it more commercially viable to invest in producing products rather than await the outcome of pre-grant oppositions or other legal actions. However, in the case of TDF and Tamiflu, despite the threat of patents, Cipla still proceeded to manufacture and export TDF at least. Also companies like Cipla, Ranbaxy, Hetero and Matrix had already developed their own technology prior to entering a VL. In the current environment of patent oppositions, while successful oppositions may prove more beneficial overall, the delay in patent offices issuing decisions and the likelihood of appeals may only drag matters out. This may ultimately impact patients who have to wait for patent offices, courts and lawyers to decide on a patent before a generic company may decide to manufacture and export.<sup>32</sup>
- Through transfer of technology, VLs may help to speed up access on products which generic companies may have difficulty producing (e.g 2<sup>nd</sup> line ARV regimens) and marketing in a commercially viable manner. Also transferring technology may help domestic companies which are less technologically advanced i.e. in sub-Saharan Africa, play catch-up, develop their own R&D and potentially help local economies.<sup>33</sup>
- Can help to improve manufacturing methods as generic companies may develop cheaper ways over proprietor's technology, thereby reducing the price further.

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<sup>31</sup> See also D. Dionisio, *Profit Rules and the Right to Appropriate Antiretroviral Treatments: Suitability of Incentive-Bound WHO-Mediated Voluntary Licenses for Equitable Long-Term Solutions*, World Health Organisation, [www.who.int/entity/public\\_hearing\\_phi/submission/13Nov06DanieleDionisio.pdf](http://www.who.int/entity/public_hearing_phi/submission/13Nov06DanieleDionisio.pdf) and Friedman et al, *Out-licensing: a practical approach for improvement of access to medicines in poor countries*, The Lancet, Vol 361, (25 January, 2003)

<sup>32</sup> However, in some cases the Indian patent offices are issuing decisions within six months, which is still a shorter period or the same as what it appears to take a generic manufacturer under a VL to put its product on the market.

<sup>33</sup> In reality this is likely to be more difficult in the current environment of free and bilateral trade agreements.

- Can speed up access where the licensor allows the licensee to rely on its pharmaceutical data or the ability to use such data for the purposes of marketing approval in export countries where data exclusivity provisions apply. This also has the effect of the licensee avoiding having to do clinical trials and submitting its own data, which would otherwise impact the overall price.
- May help to meet demand in under-served markets by having other manufacturers ‘look after’ markets which are less profitable for originator companies.
- If VLs are non-exclusive, they can encourage greater competition amongst license holders, which can result in further reduction of prices.

### *Cons of VLs*

- Offering VLs on products, which have yet to be granted a patent, can be a tactic to deter opposition by generic companies or ‘settle’ oppositions.<sup>34</sup> Such strategy only serves to undermine the due process of pre-grant opposition procedure and undermine safeguards in patent laws designed to prevent non-meritorious patents being granted.
- VLs rarely appear to be offered ‘voluntarily’ by originator companies, but usually only after public pressure, legal action or epidemic/pandemic scenarios. For example, the licenses issued in S.Africa followed the competition court case. The Tamiflu licence to Hetero was as a result of public and media pressure that Roche would not have the capacity to meet demand if there was a pandemic.<sup>35</sup> The offer of TDF VLs were presented a week after opposition in India by patient groups and continuous campaigning by MSF and other health groups.<sup>36</sup> According to our findings, VLs have not been issued for diseases that do not get the same public attention as HIV/AIDS.
- VLs without suitable technology transfer may only delay entry to market by a generic company. In the case of the TDF VLs, the consistent complaint has been that the royalty free technology transfer given by Gilead does not add to much more than what is already disclosed in the patent specification.

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<sup>34</sup> See Case study for TDF. In a telephone conversation between the author and one of the business managers at Shasun Chemical and Drugs, it was said the VLs from Gilead were more a ‘patent settlement’ rather than a VL.

<sup>35</sup> See Basheer and Amin, *Taming of the Flu: Working Through the Tamiflu Patents in India*, Journal of Intellectual Property Rights, Vol 2, pg. 113, (March, 2006) Available at [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=889868](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=889868)

<sup>36</sup> In a meeting with Gilead, Gilead insist that they had been talking to a number of Indian companies about the possibility of VLs well before the opposition was filed and the VL announcement. This may be the case considering many of the generics had proceeded to invest and develop their own versions – see interview notes with Ranbaxy which suggest that they would seek to develop generic product if there is a prospect of a VL.

According to a source in the industry, the technology transfer from Gilead was very basic and did not include proprietary data. As a result he said they would still have to do their own lab work. The source also mentioned that Hetero dismissed the technology transfer as not being of any use.<sup>37</sup> As a result licensees that have not already developed their product may have to spend more time in the laboratory thus delaying entry. Some of the licensees also mentioned that their own technology is as good, if not better than the technology transfer given by Gilead.

- Licensors are able to put geographical restrictions on the licensed territories and also use their own modelling for defining low income and middle income countries. For example, licensors may classify India as a lower-middle income country whereas according to the World Bank, it is listed as a low-income country.<sup>38</sup> Gilead for example recognises India as a low-middle income country. Licensees are not likely to be permitted to sell in developed countries.
- Vendors may also segment markets by only allowing licensees to sell to the public sector or governments. In developing countries, the margins for profit usually lie in the private sector. Also, in developing countries most purchases for medicines tend to be made privately due to lack of public health systems. This can be a disincentive for generics to enter into Vendors.
- Licensors can control the API market by only permitting licensees to purchase from certain suppliers. This has the effect of preventing licensees seeking out cheaper API in order to drive prices down further. For example, in the TDF Vendor, Gilead has excluded licensees from sourcing API from China, which could potentially reduce the price. Licensees are only permitted to purchase API from Gilead licensed suppliers.
- Vendors may request licensees to license back, on a royalty free basis, any developments or improvement on the product. This may deter licensees from entering a Vendor due to lack of incentives. This was a particular clause in the TDF licence.
- Exclusive licenses may suit a generic entrant's commercial incentives. However, exclusive licenses do not enhance competition and bring prices down. The usual rule of thumb is that there should be at least five licensees in order to ensure adequate competition, although this can also be a disincentive. Gilead's offer to eleven licensees can only help competition and drive prices further down, even if only five or six companies eventually market.
- Although a royalty rate of 5% is reasonable in licensing terms, this cost is usually borne in the eventual price of the generic product. As a result the cost is passed down to the patient.

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<sup>37</sup> The exact description given by the source was that Hetero felt that the technology transfer 'might as well be thrown into the sea,'

<sup>38</sup> See

<http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20420458~menuPK:64133156~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html>

- VLS may deter Governments from issuing compulsory licences (CL) or even making use of Government Use provisions. This is particularly so in current free trade environment and pressures being put on developing countries. Also, whereas the terms of a VL will be determined by the originator company, a CL is usually left to the patent office to define the conditions. As a result the terms and conditions may be less restrictive and more public health friendly.
- The granting of VLS does not necessarily mean that the licensee will bring the generic version to market, thereby ensuring competition and lower prices. As can be seen from Table 2, many of the licensees of GSK's Combivir did not eventually go to market for various reasons. In the case of the VLS issued by Gilead, where the licensee has not already developed its own technology to produce the product in question and where the technology transfer package is not considered the best way to obtain the highest yield, there is every possibility that the licensee may find it too costly to bring the product to market at a competitive price. As a result, only three to four of the licensees may eventually go to market, which means that the price of the product may not fall as much as if all the licensees went to market.

### ***Generic Industry Views***

In our interviews with Indian generic companies that have been involved in or have entered into VLs, the opinions on and reasons for entering VLs can be varied.

Cipla is firmly of the belief that where an originator company does not have a patent yet, then there is no reason to enter into a VL. If the prospects of successfully opposing a patent are high, then Cipla is likely to opt for that route first. Overall, Cipla is currently developing its strategy on VLs, but currently sees them as overly restrictive and still monopolistic or as managed competition.

Ranbaxy is also one to consider the patent rights first. However, they are also keen to respect IPRs and have the assurance of not being sued. Ranbaxy's business model appears more geared to entering into VLs in order to develop what it calls its 'product basket'. This seems to be a common feature with many of the Indian companies. With respect to geographical restrictions, although there has been much discussion about Brazil and China not being included in the TDF VL licensing territories, Ranbaxy is not overly concerned by this. According to Ranbaxy, this is because Brazil and China do not purchase from them.

In other interviews with generic companies, the decision to enter into a VL has been driven by commercial reasons. Shasun entered into the VL because it wants to enter into the ARV market. The fact that Gilead's licensing terms appeared reasonable and that they are seen as one of the 'better' companies helped their decision. Also, Shasun has applied for a number of process patents on TDF and this was also a relevant factor in their taking a licence, supposedly to help develop these patents with Gilead.



#### 4) Best Practice Guidelines for VLs and Conclusions

In light of the pros and cons discussed above, VLs are not the preferred answer to help improve competition to solve access to medicine issues in developing countries. Ultimately, developing countries should be allowed to adopt TRIPS flexibilities within their patent laws without pressure from developed countries. By requiring stricter standards of patentability, many of the current drugs on which VLs are being sought or have been granted e.g TDF and Combivir (Lamivudine and Zidovudine) would not even be in issue. Generic companies would be able to produce these without restriction. In connection with creating stronger patent systems, VLs should not be allowed to undermine the due process of pre-grant oppositions, as in the case of the TDF VL.

However, if regulated more strictly in order to ensure competition in the market place, they can play a role in promoting speedier and more affordable access to medicines. We set out below some suggested best practice guidelines for ensuring that VLs do not become an empty gesture and another marketing tool for originator companies under the guise of corporate social responsibility:<sup>39</sup>

- VLs should not be used to undermine legitimate pre-grant opposition /observations processes. Where oppositions are in process, originator companies should allow such procedures to be completed before VLs are discussed.
- VLs should not be issued only when there is continuous public pressure, an epidemic or threat of pandemic. The lack of VLs on medicines for diseases other than HIV/AIDS is problematic. For example, HIV/AIDS patients, due to their weak immune systems, are more prone to opportunistic infections (OIs) such as hepatitis and cytomegalovirus infections. Indeed, OIs are often the cause of many deaths amongst people living with HIV/AIDS.<sup>40</sup> Therefore, while access to ARVs may prolong the lives of HIV/AIDS patients, there is also the equal need for affordable treatments for OIs. For example Roche's drug Pegasys® for treating Hepatitis C reportedly costs in India around US\$5,000 for a six month course.<sup>41</sup> Originator companies should be seen to offer generic companies VLs for other treatments also.

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<sup>39</sup> See also B. Baker, *Arthritic Flexibilities for Accessing Medicines: Analysis of WTO Action Regarding Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health*, *Indiana International & Comparative Law Review*, 613-715, (2004).

<sup>40</sup> For example, cryptococcal meningitis has been known to affect up to 20-25% of people living with HIV/AIDS in Thailand, see Carmen Perez, *Price Differences of Fluconazole, Consequences and Conclusions*, *Medecins Sans Frontieres*, (November 1999) at <http://www.haiweb.org/campaign/novseminar/perez.html>. For further explanation and examples of opportunistic infections (OIs) see <http://www.aegis.com/topics/oi/>.

<sup>41</sup> Pegasys® was the first pharmaceutical product patent to be granted in India See P.T Jyotti Datta, *Roche gets product patent on Hepatitis C*, *Business Line*, *The Hindu*, (3 March 2006) <http://www.thehindubusinessline.com/2006/03/03/stories/2006030302040200.htm>.

- Any technology transfer should be of a nature that does not require the licensee to go back to the lab and incur further costs that may delay marketing. All technology transfer should be royalty free.
- Geographical restrictions should only be limited to developed countries and not lower or upper middle income countries where large populations are in need of access to medicines. Therefore, countries like Brazil, China and Argentina should not be carved out for the originator, but should be open to generic competition also.
- VLs should be permitted for both public and private sectors. This not only acts as an incentive for generic manufacturers but also helps to account for the lack of public health systems in developing countries where medicines are often purchased privately.
- Originators should not place restrictions on generic companies when it comes to sourcing API. Licensees should be permitted to seek out API from non licensed suppliers, provided such API meets standard good manufacturing practices.
- Licensees should not be required to grant back any technology improving the originators technology on a royalty free basis. In order to provide incentives for R&D to generic companies with respect to further reducing manufacturing costs, generic companies should be allowed to receive a royalty.
- VLs should be non-exclusive and should be handed to at least five to eight generic manufacturers at a time in order to truly ensure competition.
- VLs should not include any price controls or limitation on product output.
- For the purpose of registering and marketing approval, the originator company should permit the licensee to rely on proprietary data so as to avoid delay and further cost of clinical trials.
- The duration of VLs should be that of the patent term, after which the parties should not be bound, including with respect to any technology transfer.
- The royalty rate should be 4-5%. However, in the case of a VL being granted based on a patent that is due to expire within five years, originator companies should request a nominal royalty, such as 0.5%-1.5%. Similarly where the VL is based on the combination of two known compounds, then the royalty rate should be in the region of say 1-2%.

The basis of these royalty rates is that they should reflect the length of time that remains on a patent and how many years the product has been on the market. For example, if a patent on a product is in its last five years, this will mean that the originator will usually have had at least 5 years of a monopoly position and would have likely recouped its research investment, particularly where the original molecule was discovered by a university or other public

research/funding, as is often the case.<sup>42</sup> VLs on patented base compounds that are nearing the end of their protection period and/or have been developed into new combinations or formulas should attract a low royalty rate. As it is arguable that combination /incremental patents are not the height of innovation<sup>43</sup>, and indeed it is questionable whether they should be patented, if patents are to be granted for such products then any royalty rates should reflect the level of inventiveness and investment.

- Originator and generic companies should be made to disclose the terms and conditions of VLs issued so as to ensure best practices.

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<sup>42</sup> The commonly held view in the pharmaceutical industry is that it takes between 8-12 years to bring a product to market. As a result it is argued that the actual patent protection in order to recoup investment is only 8-12 years.

<sup>43</sup> See United States Government Accountability Office Report, *New Drug Development: Science, Business, Regulatory and IP Issues Cited as Hampering Drug Development Efforts* (November 2006), pages 33-34 at <http://www.gao.gov/new.items/d0749.pdf>