

Overcoming the Patent Barrier: Ways to Increase Production and Access to Medicines Within the Patent System

Green Chemistry and Production of Essential Medicines
in Developing Countries

Abuja, 18 March 2008

Tahir Amin

Director and Intellectual Property Solicitor
tahirmamin@gmail.com



INITIATIVE FOR MEDICINES ACCESS & KNOWLEDGE

www.i-mak.org

“Over 10.5 million lives a year could be saved by 2015 by scaling up access to existing interventions for infectious diseases.”

World Health Organisation



Barriers to Increasing Production and Access to Medicines in Developing Countries

- Low income
- Lack of health care systems
- Poor infrastructure for distribution
- Lack of human capital development
- Lack of technology transfer and know-how
- Lack of investment
- Inefficient regulatory bodies
- High tariffs/custom duties/sale taxes



Barriers to Increasing Production and Access to Medicines in Developing Countries

Patents?



What is a Patent?

- A legal/scientific document (patent specification) that sets out an invention and the boundaries of protection (claims) sought (i.e a property deed/title to a piece of intellectual property which others may not trespass on without the owners consent)
- Patent right typically lasts for 20 years for one invention (in some countries can be increased to slightly more than 20 years)
- Patent rights are national rights. There is no such thing as a global patent right



What is a Patent?

Invention claimed must be:

- Novel (new) i.e not described in an earlier patent or publication/orally, or in the public domain otherwise
- Have an inventive step i.e compared to what was known in the field, the invention claimed was not obvious to a skilled person in that art
- Has industrial application i.e is capable of being manufactured and having utility
- Patent specification must sufficiently describe how to make the invention and the best mode of doing so known to the applicant at the time



What is a Patent?

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
6 May 2005 (06.05.2005)

PCT

(10) International Publication Number
WO 2005/039551 A2

(51) [Go To Previous Page](#) Classification: **A61K 31/00**

(21) International Application Number:
PCT/US2004/027401

(22) International Filing Date: 23 August 2004 (23.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/650,178 28 August 2003 (28.08.2003) US

(71) Applicant (for all designated States except US): **ABBOTT LABORATORIES** [US/US]; Dept. 377 Bldg AP6A-1, 100 Abbott Park Road, Abbott Park, IL 60064-6008 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ROSENBERG, Jörg** [DE/DE]; Bruchstrasse 29, 67158 Ellerstadt (DE). **REINHOLD, Ulrich** [DE/DE]; Hilgardstrasse 18, 67346 Speyer (DE). **LIEPOLD, Bernd** [DE/DE]; U1, 8; Mannheim, 68161 Mannheim (DE). **DERNDL, Gunther** [DE/DE]; Am Dörrling 7, 67273 Herxheim (DE). **BREITENBACH, Jörg** [DE/DE]; Hans Sachs Ring 95a, 68199 Mannheim (DE). **ALANI, Laman** [US/US]; 4612 Merchant Square, Lansdale, PA 19446 (US). **GHOSH, Soumojeet** [IN/US]; 48826 Central Park Drive, Canton, MI 48188 (US).

(74) Agents: **FUZAIL, Kalim, S.** et al.; Dept. 377 Bldg AP6A-1, 100 Abbott Park Road, Abbott Park, IL 60064-6008 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of



What is a Patent?

WO 2005/039551

(54) Title: SOLID PHARMACEUTICAL DOSAGE FORM

(57) Abstract: A solid pharmaceutical dosage form providing improved oral bioavailability is disclosed for inhibitors of HIV protease. In particular, the dosage form comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a T_g of at least about 50 °C. Preferably, the pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.



What is a Patent?

There have been attempts to improve the bioavailability provided by solid dosage forms by forming solid solutions of the drug. The term "solid solution" defines a system in a solid state wherein the drug is molecularly dispersed throughout a matrix such that the system is chemically and physically uniform or homogenous throughout. Solid solutions are preferred physical systems because the components therein readily form liquid solutions when contacted with a liquid medium such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of the components from a crystalline or microcrystalline solid phase. If, however, the drug absorption in the gastrointestinal tract is slow the drug released from the solid solution may result in a high supersaturation and precipitate in the aqueous fluids of the gastrointestinal tract.

There is a continuing need for the development of improved oral solid dosage forms for HIV protease inhibitors which have suitable oral bioavailability and stability and which do not necessitate high vehicle volumes.

The present invention provides a solid pharmaceutical dosage form comprising a solid dispersion of at least one HIV protease inhibitor in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant. In one embodiment, the pharmaceutically acceptable water-soluble polymer has a glass transition temperature (T_g) of at least about 50 °C.

The term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed evenly throughout the other component or components. For example, the active ingredient or combination of active ingredients is dispersed in a matrix comprised of the pharmaceutically acceptable water-soluble polymer(s) and pharmaceutically acceptable surfactant(s). The term



What is a Patent?

WO 2005/039551

PCT/US2004/027401

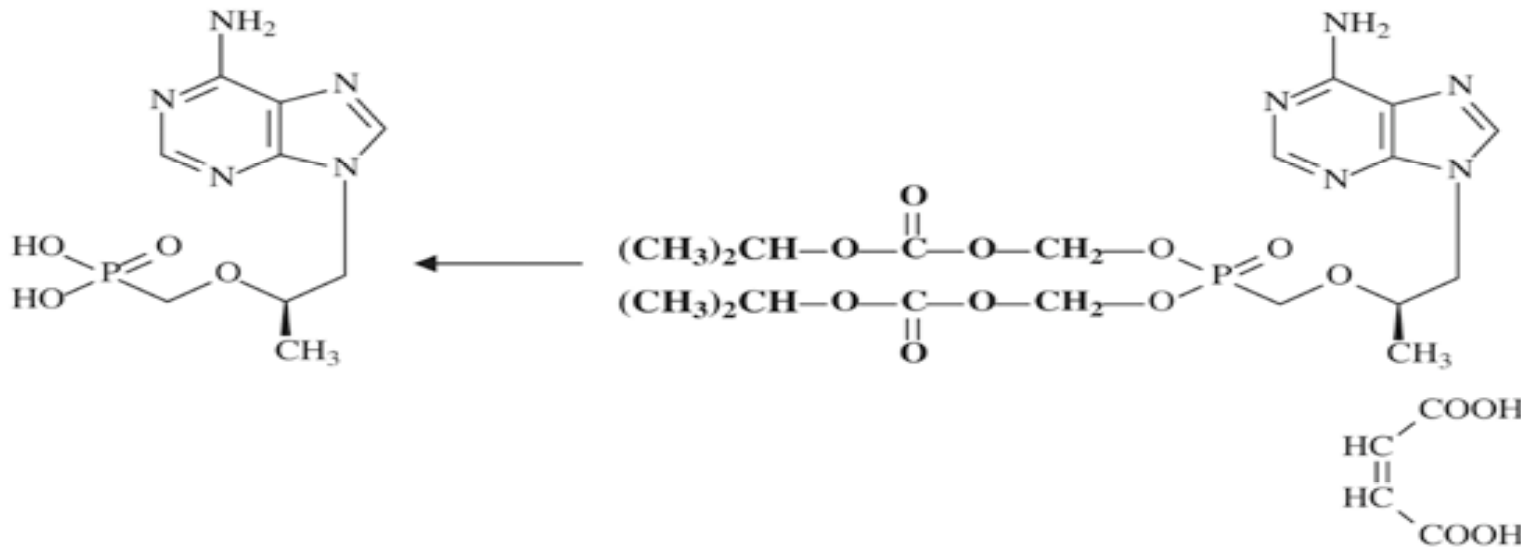
We claim:

1. A solid pharmaceutical dosage form which comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C.
2. The dosage form of claim 1 comprising a glassy solution or solid solution of said HIV protease inhibitor.
3. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.
4. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value of from about 4 to about 10 and at least one further pharmaceutically acceptable surfactant.
5. The dosage form of Claim 1 wherein said pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.
6. The dosage form of Claim 1 which comprises, relative to the weight of the dosage form, from about 5 to about 30 % by weight of said HIV protease inhibitor, from about 50 to about 85 % by weight of said water-soluble polymer, from about 2 to about 20 % by weight of said surfactant, and from about 0 to about 15 % by weight of additives.



What Can a Patent Cover?

- A new chemical entity and its salt, e.g:



PMPA (Tenofovir)

Tenofovir disoproxil fumarate (TDF)



What Can a Patent Cover?

- An intermediate compound, e.g Tenofovir Disoproxil
- Polymorphs, e.g Lopinavir/Ritonavir crystalline
- New improved formulations/dosage forms of known compounds, e.g Aluvia/Kaletra (non-refrigerable), Cardizem SR/Diltiazem (twice-daily dosage) and Cardizem CD (once-daily dosage)
- Second medical uses of existing drugs e.g Azidothymidine (AZT) - first use for cancer then HIV
- Therapeutic methods of administering a drug to a patient
- Process/methods for synthesising/making compounds and formulations

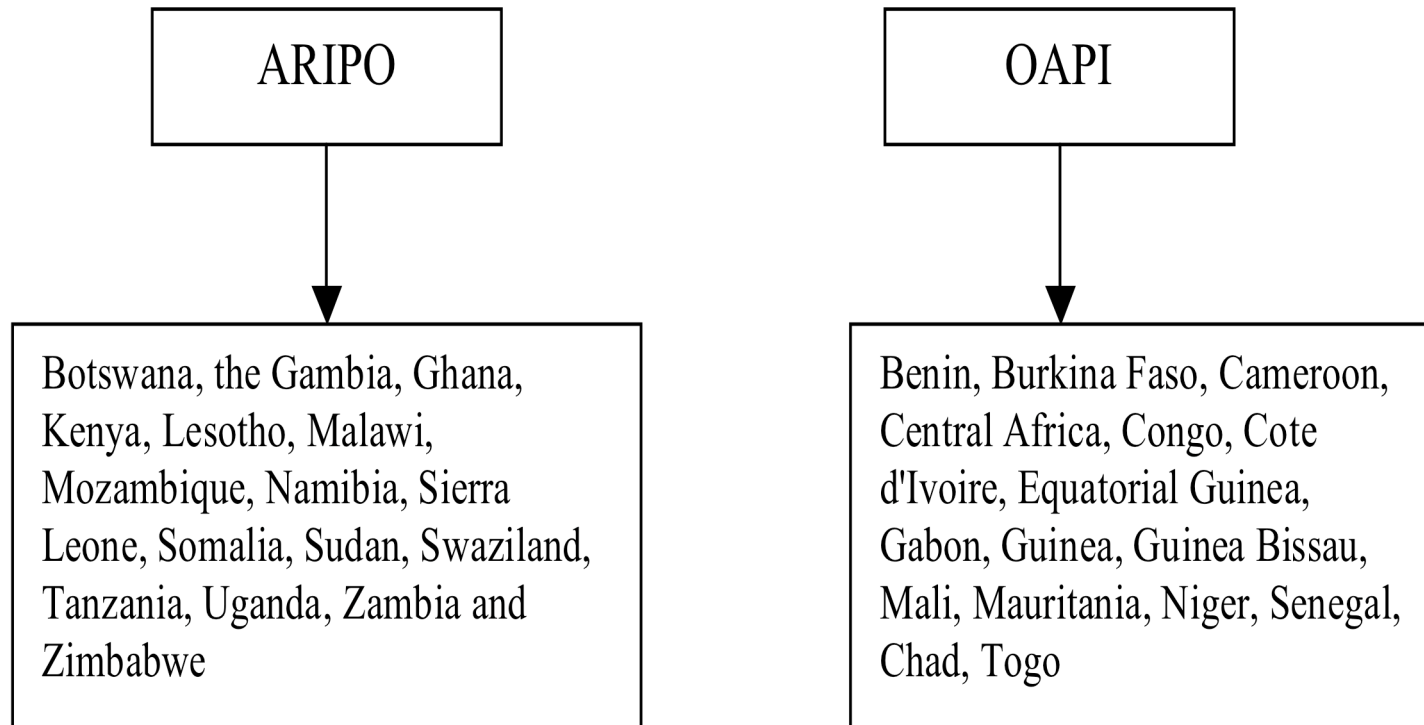


How Are Patents Granted

- Patents are administered at national patent offices and/or through central filing systems e.g World Intellectual Property Office, African Regional Intellectual Property Organisation (ARIPO) or the Organisation Africaine de la Propriete Intellectuel (OAPI)



How Are Patents Granted in Africa



Other African countries with active patent laws administer patents through their national patent offices, e.g Nigeria, S. Africa, Egypt, Morocco, Namibia



Are Patents a Barrier to Production and Access to Medicines?

Pharmaceutical companies viewpoint:

- Patents are not barriers or cause undue increase in prices. Without the exclusive rights patents give companies would have no incentive to invest in R&D for newer, innovative medicines to benefit patients.
- The problems with production and access are a result of all those barriers listed in Slide 3.



Are Patents a Barrier to Production and Access to Medicines?

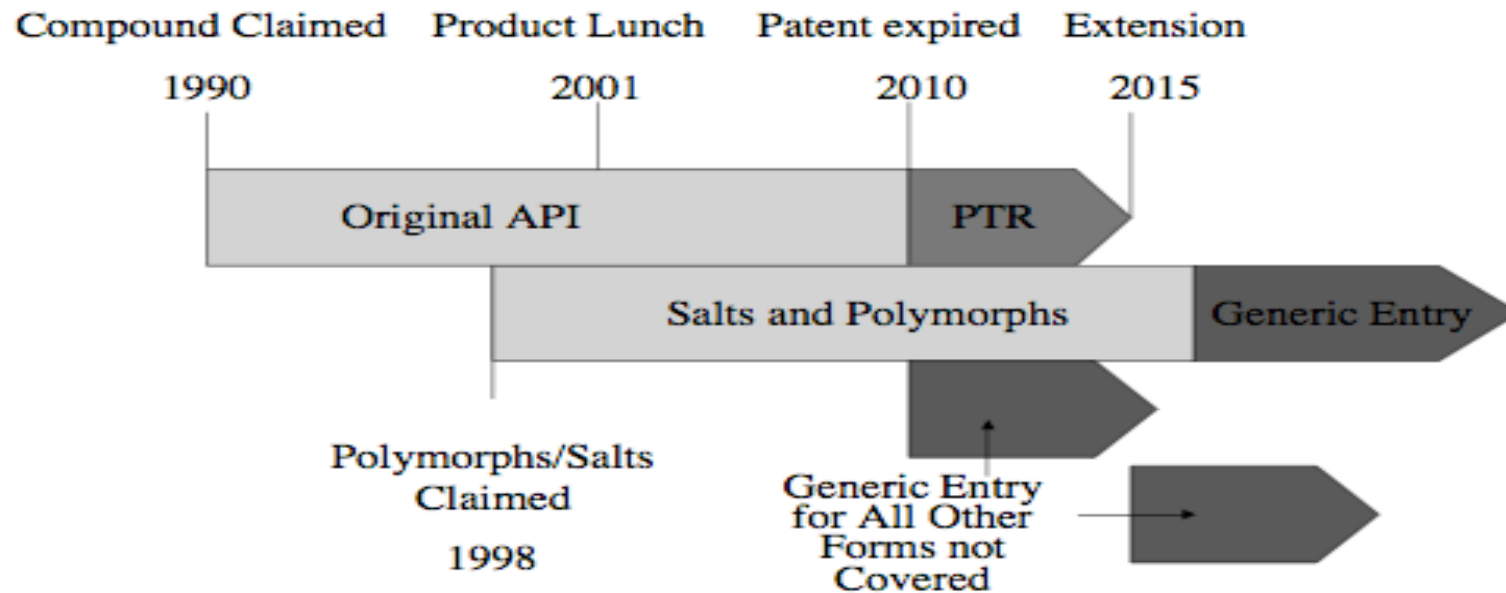
“Patents are the best and most effective means of controlling the competition. They occasionally give absolute command of the market, enabling the owner to name the price without regard to cost of production.”

Edwin J Prindle (US Patent Attorney), *Quoted in Noble D.F, America by Design, 1979*



Are Patents a Barrier to Production and Access to Medicines?

How can Salt and Polymorph Patents Provide Additional Patent Protection?



PTR: Patent Term Restoration = half of the investigational period + all of the FDA review period

Ref: Lucas J and Burgess P., PharmVOICE, Feb., 2004



Are Patents a Barrier to Production and Access to Medicines?

The other side of the debate:

- Evidence shows that expiration of patents can significantly reduce drug prices by ~30% (*Frank and Salkever*)
- Between 1993-2004, 68% of NDA's filed at the FDA were for non-NME's i.e modifications of existing drugs." (U.S Government Accountability Office, *New Drug Development, Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, 2006)
- A number of pharmaceutical patents that are used to extend patent life over patent for original molecule are held invalid when challenged e.g Norvasc (Amlodipine Besylate) and Viread (Tenofovir Disoproxil Fumarate)



Overcoming the Patent Barrier

- Implementing public health and domestic industry friendly patent laws
- Improving the patent information asymmetry and expertise of examiners at patent offices
- Challenging of poor quality patents by domestic companies, science community and public
- Voluntary licenses
- Compulsory licenses
- Effective competition laws



Implementing Patent Legislation

- Implement patent laws that safeguard public health needs and allow domestic industries to develop technical knowledge to 'catch-up'.
- Governments should not be induced by the myth that implementing stronger IP laws will automatically result in more foreign direct investment (FDI). Various studies show FDI flows into Africa have decreased since the 70s, despite ARIPO and OAPI (UNCTAD, 1999). See also case studies on Jordan Pharmaceutical Industry (Oxfam).
- WTO Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) allows flexibility for countries to define what is an invention. E.g India's strict definition of patenting new forms of known substances, broad provisions for compulsory licensing (see below), research/bolar exemptions and parallel importation.



Improving Patent Offices

- Improving access to patent information (information asymmetry) in ARIPO/OAPI and national patent offices will help local companies and procurement agencies make informed decisions on whether to enter the market with generic products.
- Many patent offices in the region need better qualified examiners and examination systems to improve patent quality. E.g Morocco does not examine applications before grant. South Africa grants patents based on preliminary examination reports from WIPO.



Challenging Poor Quality Patents

- On closer scrutiny, a number of pharmaceutical patents are unmerited because of procedural irregularities at filing, broad claims, are inventions already in the public domain or are not inventive .



Challenging Poor Quality Patents

Case 1: Tenofovir Disoproxil Fumarate (TDF), Gilead Sciences

The TDF patent claims the fumaric acid of the ester derivative bis(POC)PMPA (Tenofovir Disoproxil). Gilead claims that obtaining the fumarate salt, particularly its crystalline form, showed surprising advantages in stability over citrate salt.

A number of prior publications suggest/teach that obtaining a salt with the properties similar to that of fumaric acid i.e low solubility and hygroscopicity would be better suited for improving stability for a basic drug like PMPA/bis(POC)PMPA than citric acid (see P. Gould, *Salt Selection for Basic Drugs*, International Journal of Pharmaceutics, 1994).



Challenging Poor Quality Patents

Case 2: Benflumetol and Artemisinin (Coartem), Ciba-Geigy/Novartis

Ciba-Geigy claim in patent no. WO1992/002217 (also ARIPO Patent No.0000231A) a composition of Benflumetol with Artemisinin, Dihydroartemisinin, Arteether, Artemether or Artesunate that is suitable for synergistic action.

Cipla Ltd subsequently filed for a patent claiming a composition of Artesunate and Lumefantrine (Benflumetol) in a suitable synergistic amount and in a single unit dosage form. Cipla identified, through its own tests against the information in Ciba's patent, that Ciba's patent does not provide an enabling disclosure for claiming the composition Artesunate and Lumefantrine.



Challenging Poor Quality Patents

Other examples:

- Glivec (Imatinib Mesylate)
- Ziagen (Abacavir Sulfate)
- Combivir (Zidovudine and Lamivudine)
- Norvasc (Amlodipine Besylate)



Making Better Use of Compulsory Licensing

- Compulsory licenses (CLs) **legally** allow third party manufacturers to produce patented drugs, without consent of the patent owner, if negotiations for a voluntary licence are unsuccessful and on payment of adequate remuneration.
- CLs for national emergencies or health crises can be issued without the need for negotiations with the patent holder.
- CLs can be issued for the national market or for countries with no manufacturing capability to meet public health needs and emergencies.
- Better use of CLs can help local companies develop manufacturing skills for particular drugs.
- Requires strong political will to act on part of Governments, e.g Thailand and Brazil for Efavirenz



Voluntary Licensing

- Entering into voluntary licenses (VLs) with patent holders can help in the transfer of technology and know-how
- VLs can help speed up access to medicines and bring more competition to the market place
- Restrictive aspects of VLs: geographical, inflated royalties, unsuitable transfer in technology, restriction on API sourcing for manufacture, can detract from the need for CLs and to date limited largely to ARVs



Voluntary Licensing

Licensor	Licensee	Year	Product*	Terms and Conditions***	Price US\$ (ppy)**
GlaxoSmithKline	Cosmos Limited	September 2004	Lamivudine (Retrovir®) Zidovudine (Epivir®) Lamivudine and Zidovudine (Combivir®)	Manufacture and distribution in Kenya, Uganda, Tanzania., Burundi and Rwanda.	N/A
	Cosmos Limited	October 2004	Nevirapine (Viramune®)	Manufacture and sale in Burundi, Kenya, Rwanda, Tanzania and Uganda.	N/A
Boehringer-Ingelheim	Memphis	November 2004	Nevirapine (Viramune®)	Egypt and neighbouring countries.	N/A
	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
Roche	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



Effective Competition Laws

Can help prevent abuse of IP by:

- Ensuring patent holders do not insert anti-competitive terms in licenses, e.g. exclusive grant back clauses, clauses precluding the challenges to the validity of the patent, price restrictions, production restrictions
- Agreements struck between patent holders and generic companies for generics not to enter the market.



“The logic of patent monopoly is to have a safe and secure distribution system aimed at selling smaller numbers of expensive medicines to a wealthy class, rather than try distribute large numbers of cheap medicines at a few cents to the poor. When large companies speak about ‘growing the market’ in developing countries, it is the wealthy segment they have in mind.”

Peter Drahos/John Braithwaite, *Information Feudalism: Who Owns the Knowledge Economy*, 2002

