Affordable Antiretroviral Drugs for the Under-Served Markets: How to Expand Equitable Access Against the Backdrop of Challenging Scenarios?

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Abstract: BACKGROUND: Threats by enforced Intellectual Property (IP) rights to equitable HIV treatment access by poor populations are impending. India and China’s policy directions in the field will be crucial in ultimately affecting the affordability and accessibility of antiretroviral (ARV) therapy in the under-served markets. These directions, together with the exploitation level of IP-bound flexibilities and the evolutionary modelling in partnerships and trade agreements between research-based and generic pharmaceutical industry, will also affect the outcomes of self-sufficiency efforts now at their beginning in the developing world as far as domestic manufacturing of generic ARV drugs is concerned.

AIMS: This paper explores key issues, implications and interaction dynamics across these challenging scenarios while attempting to provide equitable solution glimpses into the near future.

RESULTS: Access-oriented long-term drug policy strategies entitled to pass muster of governments, research-based as well as generic industries in both developed and developing countries are needed if equitable access to affordable ARV treatments by poor people has to be achieved despite enforced IP rights.

Predictable dynamics between western multinationals and transitional country generic corporations let regard IP-bound Voluntary License flexibilities as a fitting measure into just mentioned needs especially if substantial incentives to generic corporations are concurrently secured.

Efforts to equitably expand ARV drug access through exploiting IP opportunities should encompass attainment of self-sufficiency in domestic drug manufacturing whenever basic requirements are in place in the developing world as a whole. A credible industrial potential would act, indeed, as a boosting factor for drawing branded drug producers into technology transfer agreements, the terms of which would let all contractors enjoy substantial advantages.

These perspectives consistently bind up with the foreseeable long-term trade and drug policy directions of India and China according to frontier crossing implications of their key IP management trends as well as their multifaceted penetration strategies of both the wealthy and under-served markets worldwide.

As coherent with these perspectives, more disbursement by wealthy country governments and donors to basic infrastructure development in sub-Saharan African nations with stable governments in place is urged both as a priority for improving Africa’s economy and a prerequisite for allowing domestic industrial plants to take off.

Aiming at the targets just underscored, WHO’s brokering role in negotiated agreements between wealthy and developing country-based firms as well as its technical guidance in setting international standards have always to be sought if equitable and appropriate end results are to be attained.

CONCLUSION: Overall insights in this paper would mean that, while research-based corporations are to be praised whenever waiving, on humanitarian purposes, part of their profits, the trade and profit rules cannot basically be given up if long-term sustainable results are the goal to look for. Only negotiated agreements securing all contracting parties lasting advantages may ensure shifting of such a goal from mere vision to a really sustainable attainment.

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SECTION 1. ARE THERE LOOPOLES FOR MAKING UNIVERSAL ACCESS TO TREATMENTS ACTUALLY FEASIBLE DESPITE NEW THREATS POSED BY ENFORCED INTELLECTUAL PROPERTY RIGHTS?

New Threats to Still Unanswered Needs

Securing uninterrupted access to antiretroviral (ARV) drugs for all people who need them would be a landmark for effective control of HIV epidemic in low-income countries, aside from its value as an absolute ethical responsibility. Entwining it with uninterrupted prevention programmes would be the gold standard for stably attaining the most effective containment of epidemic [52, 3, 46a].

Actually, appropriately addressing the barriers to ARV treatment access requires strengthening of the health systems along with political actions focusing not only on health sectors.

Understandably, the goal of equitably expanding access to ARV treatments is deeply bound up with the urgency for national health policy strategies caring for the needs of poor populations. Improvement in national health financing, which would be the building block for help, is quite utopian currently based on the huge lack of resources suffered by the income-constrained countries, with additional damage by government policy priorities frequently away from genuine commitment in addressing poverty-related social inequities.

Practicable lines of action should include the establishment of national health system objectives more relevant to conditions in the poor, the application of pro-poor lessons learned in the worldwide scenario, as well as the issuance of government directions caring for empowering poor people to play an active role in health policy decisions [26].

Unfortunately, these ethical priorities are going unheeded, while major obstacles to HIV treatment access in developing and least-developed countries still strike hard as persistently unaffordable drug prices, inadequate financing for health, poor priority setting, inappropriate drug selection and prescription, and weak health and supply systems [19, 59].

Based on health spending is still less than US$ 10 per person per year in most African countries, these obstacles play on the whole as significant barriers in preventing poor people from getting the care they need [59].

Table 1. TRIPS Regulatory Terms and Dates for Patent Status of Drugs in Low-Income Countries*

<table>
<thead>
<tr>
<th>Patent</th>
<th>Description</th>
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<tr>
<td>TRIPS (Trade-Related Aspects of Intellectual Property Rights) 1994</td>
<td>WTO Agreement to the safeguard of Intellectual Property Rights (IPRs) around the world.</td>
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<tr>
<td>Drugs invented before 1995</td>
<td>No need for patent protection by a WTO member State if drugs were not patented before 1995, i.e. before TRIPS came into force.</td>
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<tr>
<td>1995-2005 “mailbox” drugs</td>
<td>It refers to 1995-2005 invented drugs (including second-line ARVs) for which WTO members which did not recognise drug patents before 1995 were offered diversified time limits to become TRIPS-compliant. Transitional countries have to hold patent applications on these drugs in a so-called mailbox and secure patent applicants exclusive marketing rights (EMRs) for five years once drug was in the mailbox and registration was made by the national drug regulatory authority.</td>
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<tr>
<td>Post-2005 drugs</td>
<td>All WTO members, with exception of least-developed countries (LDCs), are requested TRIPS compliance.</td>
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<tr>
<td>Dates for LDCs</td>
<td>LDCs have to become TRIPS-compliant by 2006 but, if national legislation has been consistently amended, they are exempted from accepting patent protections and TRIPS enforcement until 2016. Aside from this flexibility, even LDCs have to issue compulsory licenses (see below) for importing drugs already patented in pre-TRIPS domestic law.</td>
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<tr>
<td>Doha Declaration November 14, 2001</td>
<td>It stated that each WTO member has the right to use TRIPS-encompassed flexibilities (which include compulsory and voluntary licenses) to secure universal access to drugs in the face of a public health need.</td>
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<tr>
<td>Compulsory license (CL)</td>
<td>It is when a poor country government allows to manufacture domestically or to import copies of patented drugs at prices much cheaper than those imposed by the patent holder and without his consent. Both importing and exporting countries need to have enabling legislation in place (a corresponding CL for export has to be issued by the exporting country). Prior negotiation with the patent owner for voluntary license first is required unless for situations including extreme health crisis and not-for-profit government use. Payment of a royalty to the patent owner is encompassed by CL rules.</td>
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<tr>
<td>Voluntary license (VL)</td>
<td>Agreement negotiated with the patent’s owner for manufacturing and marketing. Notwithstanding royalty rates imposition on generic firms, these licenses only imply straightforward agreements between companies; they do not require changes in national legislation, while including non-exclusivity, openings towards technology transfer, access to owner’s data for branded drugs as well as permission for export.</td>
</tr>
<tr>
<td>Decision August 30, 2003</td>
<td>It allows non-manufacturing countries to issue a CL to import a particular medicine based on a CL for export issued by the exporting country government. Declaration by the non-manufacturing country of insufficiency in manufacturing the specific drug is required.</td>
</tr>
<tr>
<td>Parallel importation</td>
<td>Importing of fairly priced patented drugs for which the rights of the patent owner have been exhausted by the first sale.</td>
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<tr>
<td>Bolar exception</td>
<td>Permission to a generic firm for copying and registering a patented medicine before patent expiry. It could exceptionally be applied only if the normal rights of patent holder are pledged.</td>
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<tr>
<td>Data exclusivity</td>
<td>Data protection against unfair commercial use only (but five and eight year protection have been respectively requested by US and Europe).</td>
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*The regulations mentioned in this Table encompass ARVs while applying to the overall drugs for resource-limited countries.
Most worrisome, additional barriers to ARV treatment access by the poor are impending as a result of pursuance of enforced intellectual property (IP) rights inside the World Trade Organisation (WTO) Agreement on TRIPS (Trade Related Aspects of Intellectual Property Rights: Table 1) [64].

Actually, the relations between access to ARV drugs and trade policy are inflaming the international debate also because of additional challenges to the under-resourced countries by TRIPS-bound harmonisation needs. Patent harmonisation is one of the most conflicting matters currently under debate inside the Geneva-based World Intellectual Property Organisation (WIPO) [33]. Regrettably, positions among the member states continue to disagree, especially along North-South lines, while concern arises from trends by a number of developed countries to transact negotiations outside WIPO and on an exclusive basis encompassing industrialised countries only [34]. Really, this scenario alerts on the risk that the multilateral process needed for equitably harmonising patent law and procedures might substantially be undermined.

Despite their looming threats, TRIPS rules are, however, of utmost interest nowadays as they encompass flexibilities which include escapes for poor non-manufacturing countries to legally import foreign low-priced essential drugs (Table 1) [64, 15, 65, 16]. Indeed, notwithstanding the cumbersome frame and risks of blackmail by wealthy countries make most flexibilities as unsuitable or worrisome options in under-resourced countries, some of them, instead, could act, if appropriately regulated, as equitably balanced tools in achieving trade agreements securing all contracting parties substantial advantages (find later).

The mismatch between the treatment needs for HIV/AIDS in developing and least-developed countries and the current gaps in health policy strategies, national and international funding and global pharmaceutical market (Table 2) can easily be realised when considering that:

**Table 2. HIV/AIDS Epidemic in Poor Countries: Unmet Challenges and Still Unfilled Gaps**

<table>
<thead>
<tr>
<th>Challenge</th>
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<td>-National policy options (including helping HIV-infected people access health services and reducing out-of-pocket spending especially by the poor) are absent in many countries.</td>
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<td>-Government-wide support relevant to ARV drugs (e.g. strengthening government procurement, developing proper trade policies, and improving vigilance and customs services inclusive of efficient public-private-NGO mix approaches in service delivery) is largely absent.</td>
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<td>-Cooperation across government departments (health, trade, industry,…) in many developing countries is usually poor as far as the issuance of shared and harmonised policy strategies towards ARVs access.</td>
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<td>-Financing for health (both domestic and international) is still largely under-funded.</td>
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<tr>
<td>-Financing to universal HIV treatment access by donors is still under-funded.</td>
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<td>-Funding to ARV treatments is away from a comprehensive support package.</td>
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<td>-Long-term sustainability of ARV treatment access initiatives (including longer term supply of affordable drugs to the developing countries) is persistently under threat for failure.</td>
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-Table 2, contd....

-There is lack of capacity of resource-limited countries to engage in global trade.

-Challenges (economic, administrative and legal) to poor countries in making use of 30 August 2003 DECISION and other flexibilities within TRIPS are yet to be addressed (i.e. by including and applying compatible safeguards in national legislation). Achieving such a target through implementing information, technical support and advocacy would mean building capacity of developing countries to engage in global trade.

-Implementation of TRIPS-compliant flexibilities by developed countries is very poor as far as amendment of their legislation to make drug production for export available under 30 August 2003 DECISION.

-Ongoing threats to equity either through rigidly interpreting TRIPS flexibilities (such as registration data exclusivity) or through requiring registration/patent linkages have to be halted.

-The implications of stronger intellectual property (IP) rights in enhancing trends of generic drug firms towards South-South coalitions and partnerships with multinational research-based companies need, with respect to short-mid time span negative predictions on ARVs affordability for the poor, to be tackled and faced.

-Meanwhile, there is urgency, aiming to export the models, for learning from newly released South-South coalition initiatives to expand HIV treatment access in the under-served markets.

-Engagement with the business community on the issues of ARV drug affordability (including “generics” policies and mark-ups reduction) has to be implemented and harmonised.

-Discussion between multinational drug companies and developing country firms and governments is largely not enough within for-profit borders only: it should be encouraged and harmonised through further use of voluntary licensing and technology transfer aiming to promote technological catch-up and expanded access to ARV treatments.

-WHO’s brokering role in technology transfer partnerships between research-based companies and the generic firms in the under-served markets has to be enhanced: these partnerships, if appropriately regulated, are instrumental in building capacity, improving equitable access to lower priced products as well as boosting proper use of TRIPS flexibilities.

-WHO’s brokerage role with the pharmaceutical industry in negotiating ARV drug prices and supply to eligible countries should include closer relationships with generic drug companies in the light of policy implications of stronger IP rights.

-Best practice in the pharmaceutical industry as far as the demand for access to ARV drugs is currently at the beginning.

-Overwhelming challenges to African countries in building capacity for domestic manufacturing of “generics” are, apart from too few enlightening examples, still waiting for appropriate answers. These should include balance evaluation between the overall risks, requirements and costs and the direct benefit for the poor.

-Regulatory control on quality of “generics” lacks harmonised and shared guidelines among the institutions involved.

-Need is claimed for WHO’s direct training role in good manufacturing practices (GMPs) for pharmaceutical products .

-Sharing and coordination of programmes inside the international health cooperation are largely not enough.

-Antagonisms, if not rivalries, among the players inside international health cooperation still persist.

-There is urgency for far more large NGO coalitions aimed to implement the access programmes to HIV treatment.

-Threats to equity inside the distribution chain of HIV drugs are increasing.
Stringent protection regulations against drug diversion and leakage are lacking.

Funding to basic infrastructure development is urged as a priority for improving Africa’s economy and instrumental to the target of universal ARV drug access.

Building physical and human health infrastructure is urged to overcome inadequacy of systems to distribute essential medicines.

There is urgency to equitably help expand access to HIV treatments in countries with impending expansion of HIV epidemic.

Debt cancellation to poor countries has to be enhanced: debt relief savings would free large sums of money that should be used to set up more equitable fight against AIDS and further help poor countries meet the HIV treatment targets.

ARV treatment for children in the developing world suffers of neglect: efforts towards development of affordable fixed-dose combinations are urged.

Cost of second-line combination treatments with protease inhibitors (PIs) is out of reach for poor countries (ten times the average amount of first-line combination generic ARVs which is US $ 250-300 per person per year): this large disparity in price will present a challenge to the scaling up of ARV treatments.

Meanwhile, effective strategies are required to reduce the cost of first-line ARV combination therapy too: this would help overcome the monetary gap between overall needs and the funding available.

Affordability strategies for the poor of first and second-line treatments should consider the policy implications of stronger IP rights and should provide incentives to generic industries in transitional countries. These incentives are mainly expected by country governments and international players such as WHO, UNAIDS, GFATM, and World Bank.

Greater transparency is urged as far as the drug pricing policies by both research-based and generic industries.

- Five to six million people in low- and middle-income countries need ARV treatment, but only 400,000 people had access to it at the end of 2003. This means that nine out of ten patients who needed treatment were not reached. Meantime, the disparities among countries were enormous: while in Latin America and the Caribbean about 55% out of 400,000 people who needed ARVs were getting them, in Africa only 2% of an estimated 4.4 million people in need were getting treatment [55].

- In the first half of 2005, the number of people on ARV therapy in poor countries increased to an estimated 1 million thanks to the efforts of the World Health Organisation (WHO) “3 by 5” programme [58]. However, another 2 million people should have been reached (but they were not) by the end of 2005 to attain WHO’s goal.

More worrisome, in the world scenario, a total of 5 million adults needing treatment are out of reach (72% in sub-Saharan Africa and 22% in Asia) [59].

There is a tremendous need for funding to secure treatment to all people who are still waiting for. Unfortunately, notwithstanding enhanced disbursement to countries as per commitments and pledges from wealthy country governments and major donors, the monetary gap between the overall needs and the funding currently available still appears very hard to be filled up: more than US$ 2 billion have been the shortfall estimated in 2005 for the “3 by 5” goal only, while US$ 6 billion are the 2005 estimated shortage with respect to US$ 12 billion required by the same year to reach the Millennium Development Goal of reversing the HIV/AIDS epidemic by 2015 [59].

TRIPS rules are substantially affecting the list of overall factors accountable for the mismatch as reported above (Table 2).

**How Could IP Enforcement Hinder Poor Populations from Accessing ARV Treatments?**

**India and China: Insights into Frontier Crossing Implications and Outcomes of Conflicting TRIPS Managements**

As WTO member states, almost all countries are requested to follow the 1994 WTO Agreement on TRIPS (Table 1). Developed countries became TRIPS-compliant in the mid-1990s and most developing countries became so in 2000. Least-developed countries have to become compliant by 2006 but, if national legislation has been consistently amended, they are exempted from accepting patent applications or TRIPS enforcement until 2016 [64].

China implemented patent regulation in 2002, while TRIPS compliance took effect in India on 1st January 2005. Overall, these two countries account for half of the world’s poorest population. Their big industrial plants supply most of their domestic needs while exporting high volume drugs to the under-served markets [60]. India and China are, moreover, the major suppliers of active pharmaceutical ingredients (APIs) for ARV drugs to both developing and developing countries [23].

The outcomes of India and China management with enforced TRIPS requirements are of outstanding interest as they will ultimately affect the availability, affordability and accessibility of ARV drugs inside most resource-limited country markets on a planetary scale. Predictably, the rapidly growing high-technology industrial potential on the whole (not only health sector focused) of both India and China, along with their expanding world-sized attraction power towards commercial partnerships and liaisons with leading western corporations, will also play as boosting factors for equitably balanced outcomes in TRIPS flexibility negotiations should both countries transact with major branded HIV drug producers.

**India**

India, the major producer of “generics”, as of January 1st 2005 would no longer be able, consistent with TRIPS rules, to manufacture and sell generic copies (and relating APIs) of 1995-2005 “mailbox” drugs (including GlaxoSmithKline’s Combivir, Gilead’s Viread and Abbott’s Kaletra) (Table 1) [64, 27]. Likewise, the manufacturing and selling of copies of newer drugs would be forbidden [23]. Production, however, could be kept on in the sake of poor populations under TRIPS-compliant means (i.e. voluntary licenses-VLs, compulsory licenses-CLs and other flexibilities: Table 1). Meanwhile, India can continue to supply copies of drugs...
largely exceeding the WTO requirements, the decree, wide-ranging disagreement bound up with its contents. Indian government issued an executive decree comprising problems. Most worrisome, it is definitely clear that, having not fixed definite parameters and percentages for “significant” and “reasonable” actually mean? It is clear that, royalty to the patent owner [67]. But, what do the adjectives made a “significant” investment and pay a “reasonable” on manufacturing and marketing, provided that they have were submitted prior to 1st January 2005 are allowed to keep generic versions of medicines for which patent applications into force. Conversely, Indian companies now manufacturing the patent holders and Indian generic manufacturers come branded originals unless CLs or direct agreements between. Country’s big industrial potential is increasingly expanding year-by-year so allowing domestic firms to more and more penetrate the most profitable western markets [17]. At least 40% of Indian revenues come from export market and industry supplies about 20% of the world drugs in volume [60, 35, 16].

Coherently, Indian firms are increasingly being involved with research-based industries in manufacturing and research & development (R&D) partnerships that include provision of APIs or final products, “generics” such as vaccines and insulin, as well as innovative re-formulations of already known molecules [23].

Deeply entwined interests with research-based corporations aimed to support India’s expensive and risky forays into the major markets make it easy to foresee that Indian government will hardly issue streamlined CLs (Table 1) on a routine basis because of their negative commercial impact based on multinational corporations would be detracted from keeping their profits.

Consistently, the 23rd March 2005 new patent legislation (as in its 5th April 2005 amendment), though provides openings into equity, does still sound as compliance with the interests of transnational enterprises [67].

Based on the new Bill, indeed, 1995-2005 “mailbox” medicines and newer drugs whose generic versions have not yet been produced by Indian firms can only be sold as branded originals unless CLs or direct agreements between the patent holders and Indian generic manufacturers come into force. Conversely, Indian companies now manufacturing generic versions of medicines for which patent applications were submitted prior to 1st January 2005 are allowed to keep on manufacturing and marketing, provided that they have made a “significant” investment and pay a “reasonable” royalty to the patent owner [67]. But, what do the adjectives “significant” and “reasonable” actually mean? It is clear that, having not fixed definite parameters and percentages for unequivocal interpretation, the Bill will predictably boost excessive demands by the patent holders and litigation problems. Most worrisome, it is definitely clear that, without substantial incentives by Indian government, the prices of “generics” produced under such a royalty imposition will increase sharply making these drugs unaffordable by the poor.

Furthermore, notwithstanding, the new Bill no longer requires issuance of CLs for import by poor non-manufacturing countries making requests to India for generic drugs, it does still require that, aside from national emergencies, Indian generic manufacturers must wait for three years after a patent is granted to a particular medicine before they are authorized to apply to the Controller for a CL to produce it [36, 67]. Actually, overall time will predictably be even longer because of an average six-month unavoidable prior negotiations with the patent holder for VL first (Table 1) and, possibly, additional delay bound up with Controller’s discretion as the Bill has provided no timeline to deal with CL applications once they have been made [67].

Moreover, though the new Bill has restored the pre-grant opposition (so allowing ideally any member of the public to oppose frivolous or invalid patent applications before their grants) [67], unfortunately the access to information on applications is quite complicated so basically taking away any opposition ability.

It might therefore be argued, according to overall insights above, that this quite equivocal new regime, which would sadly bar poor populations from keeping access to life-saving medicines, is far from being devised by chance. Really, it looks like the governments answer to awareness, based on country’s strong biotechnology and drug industry, that India might profit more than it would lose from enforced patent protection.

Accordingly, the effects of enforced IP rights in the Indian market are expected to stably result in reduced access to affordable medicines by the poor, unless setting up appropriate strategies promptly.

In this environment, indeed, if by some unfortunate chance Indian firms did close down production of generic “mailbox” drugs, the unaffordable branded originals would monopolize the market.

Furthermore, if appropriate government incentives will be lacking, Indian firms are expected to skyrocket either the prices of generic versions of “mailbox” drugs currently being produced or, possibly, those of “generics” off-patent (invented before 1995) only looking at middle-income Indian social classes (about 300 million people) who can afford out-of-pocket spending [16]. Should the government insist requiring fixed low prices, firms could simply withdraw from production.

This scenario could additionally converge in Indian firm coalitions and in enhancement of currently working manufacturing and R&D partnerships either on a South-South basis or by spreading to multinational research-based corporations. As a consequence, the drug prices would probably mount further as effect of diminished market competition just in reply to joining of forces.

Such an environment would also encompass unaffordable prices for newer drugs in case their domestic manufacturing and selling did pass muster of the patent’s holders by agreements (such as VLs) whose economic charge (Table 1) had not been softened through government incentives including tax allowances to Indian firms.
China

China is the world’s tenth largest market. The country has the lowest-cost primary ingredient manufacture and is a key supplier of APIs to India, to several developing country firms and to some multinational drug manufacturers [16]. Differently from India, Chinese pharmaceutical industry currently shows deeper government involvement, less technological expertise in chemical synthesis and lower capacity in commercialising innovatory drug formulations.

Although IP legislation was introduced in 2002, pursuance of TRIPS rules is quite weak in China and production of “generics” is still being permitted, despite IP rules, if the patent holders lack domestically sourced APIs [16].

These realities, which may undermine the requirements for partnerships with international industrial giants, help explain why, with respect to India, manufacturing and R&D partnerships with research-based corporations are still less represented in China. That said, it might be argued, on the contrary, that the latitude of China in ignoring IP rights agreements, along with its role as the world’s cheapest API supplier, would assign the country a critical function in helping overcome some challenges to the taking off of domestic plants for “generics” in sub-Saharan Africa (find later).

Epidemic in China is on the edge of a surge in growth: about 840,000 people are still being estimated as HIV-infected (though current number could be significantly larger because survey was conducted in 2003) and more than 10 million would become infected by 2010 without effective measures for containment [32].

Chinese firms produced in 2004 five generic low-cost HIV drugs (DDI, D4T, AZT, NVP and IDV) as their patents had expired. Based on these drugs, four cocktail treatments were possible, each of which cost about 3,500 yuan (US$ 423) per patient per year; still beyond the reach of infected people most of whom are farmers [32]. Nonetheless, these “generics”, together with imported brand name drugs (3TC, AZT+3TC, EFV) are currently being involved in the National Free Anti-Retroviral Treatment Program covering HIV drugs directly by some western corporations within the China boundaries [32].

Nonetheless, Chinese government (apart from its understandable reluctance to issue commercially risky CLs) would possibly be attracted by some opportunities inside TRIPS-related technology transfer flexibilities, namely VLs (Table 1), just for a number of reasons:

- the need for technological catch-up while aiming to compete with multinational giants in the exceedingly sophisticated western markets.
- the need for trustworthy relations with research-based companies while looking for attainment of the standards as mentioned above.
- the need, based on the looming epidemic expansion in China, to enhance and diversify the number and quality of HIV drugs available (including children formulations as well as newer and second-line drugs).
- the need to achieve sustainable self-sufficiency in pharmaceutical manufacturing: with such an overwhelmingly mounting domestic epidemic, it would be silly to fully depend on fickleness and price fluctuations by foreign corporations.
- the awareness that reduced prices as per cutting by western drug producers would hardly be, even in the most favourable cases, as affordable as those of “generics” produced domestically under VL agreements equitably softened in their economic charge through, for instance, government fiscal incentives to firms.

Despite orientation towards wealthy markets, as reported above, Chinese and Indian industries are expected to still be attracted by the under-served markets based on relatively low costs and expertise already achieved in such environments. Consequently, Indian industry will likely continue with its engagement with southern markets also looking for revenues supporting its expensive forays in the wealthy western markets. Such a perspective would apply, in a short while, to Chinese industry too if the premises for its technological catch-up and increasingly competitive partnerships with the big multinational producers will translate into politically long-term directed actions.

TRIPS-Related Factors Interfering with Access to ARV Treatments

While looking at the possible effects on a world perspective, the major risk following enforcement of IP rights is that poor people in resource-constrained countries could be prevented from accessing life-saving drugs because of raised prices.

Moreover, countries are expected to be barred from using most of TRIPS-compliant flexibilities unless national legislation has been appropriately amended (Table 1): unfortunately, as the majority of developing and least-developed countries are lacking skilled political, administrative and legal networks, a suitable implementation in domestic law is very unlikely to be attained [24, 38, 39]. Additionally, although some countries possibly have well-crafted laws already into force, they lack, however, human
boost to implement them (i.e. viable social environments and political will as well as trained staffs long lasting in public services) [37].

Such a background would partly help explain why, notwithstanding extant TRIPS-compliant flexibilities, very few developing countries have declared a state of national AIDS emergency and issued CLs so far [44].

More difficult to accept, most developed countries producing generic ARV drugs still have to amend (with exceptions including Norway and Canada) their national legislation to meet TRIPS requirements as far as production for export is concerned [16]. This delay is unethical as poor populations are being detracted from getting life-saving medicines: in the light of TRIPS enforcements, indeed, CLs are expected to increasingly be issued by least-developed countries with no manufacturing capability so as to import “generics” from western producers based on issuance by the exporting country of CLs for export as per national TRIPS-consistent legislation (Table 1).

Implementation of TRIPS flexibilities is also being limited in most under-resourced countries because they lack effective cooperation across government departments (health, trade, industry...) as far as the issuance and harmonisation of policy strategies to equitably expand access to ARVs are concerned [16]. This poorly coordinated environment also suffering from inadequate sharing of information would hardly be capable of appropriately managing with TRIPS rules (Table 1).

In such a context, the under-resourced countries are being urged to undergo economic pressure by wealthy countries towards TRIPS-plus legislation through bilateral or regional agreements whose impact on equitable fulfillment of TRIPS flexibilities is, unfortunately, quite negative. These agreements, indeed, often require constraining conditions such as limiting CLs to domestic non-commercial use or to national emergencies, as well as enforcing protection for clinical trial data (i.e. several year data exclusivity) and strengthening patent status/registration rights linkage, so actually delaying registration of “generics” produced under CLs and fully holding market exclusivity (Table 1) [29, 16, 18].

On the other hand, increased patent protection rules clearly favour the patent’s holders as they get rid of competition on “mailbox” medicines by securing patent’s owners at least 5 years exclusive marketing rights (EMRs) (Table 1). In such a perspective, it may be worth mentioning that provisions opposing EMRs are included in the 5th April 2005 published Indian Patent Act amendment [67].

What Could Be Done to Meet the Challenge?

Long-term equitably balanced strategies should be equipped to pass muster of all involved parties (governments, research-based as well as generic industries in both the developed and developing world) and to encompass support to markets development in resource-constrained countries while, at the same time, bringing these countries into the global pharmaceutical market. These requirements should first be looked at whenever seeking sustainable ways to help poor populations in the under-served markets access essential therapies for widely striking epidemic conditions. Additionally, these requirements would mean, in economic terms, an incentive for either research-based or leading generic companies to approach these markets with existing products while concurrently investing in new products for them.

Exploring the Ways

Incentive- Bound VLs as a Viable Choice

Understandably, governments in developing and least-developed countries are reluctant to issue CLs because of the risk for withdrawal of investments and economic support by multinational drug industries and wealthy country governments. Likewise, other options inside TRIPS flexibilities lack general agreement because of insufficient profitability guarantees or cumbersome and unwieldy frames (Table 1).

Otherwise, VLs (Table 1) can be regarded as a better option notwithstanding they provide for royalty rates imposition on generic firms: these licenses, indeed, only imply straightforward agreements between firms; they do not require changes in national legislation, while including non-exclusivity, openings towards technology transfer, access to owner’s data for branded drugs as well as permission for export (Table 1).

Really, VLs appear as a viable choice nowadays because research-based corporations are secured economic profits at least, while advantages to developing country firms are enjoyable as well: these include domestic market expansion as well as technology transfer and R&D partnerships, which play as prerequisites for enhanced competition capability in the western markets. So compounded, VLs fit well into requirements as set out at the top of this sub-section.

Intriguingly, the growing potential of Indian and Chinese plants (encompassing their bilateral partnership as part of wider South-South and North-South partnerships) could act at once, in such a perspective, as a catalyst for bilateral VL agreements grounded on quite more profitable conditions for the developing country firms as a whole [5b, 68].

Attention should be paid, however, that VL agreements encompass signed statements securing expanded access to treatments by poor people as well. Aiming at this, the WHO’s brokering role in partnerships between research-based companies and generic firms in the under-served markets has to be enhanced: so regulated, indeed, these partnerships are expected to become really instrumental in building capacity, improving equitable access to lower priced products as well as boosting proper use of TRIPS.

Clearly, based on the inherent royalty rates imposition, VL frames should always provide for a combination of various incentives to transitional country-based generic firms if effective drug affordability by the poor has to be the end result. Provision of these incentives, aimed first to keep prices as lowest as possible, is mainly expected by country governments and leading international players such as the Global Fund to Fight AIDS, TB and Malaria (GFATM), the World Bank (WB), WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS). These incentives should include:
Warranties of Market Expansion and Safety as per “Generics” Exclusive Sales Agreements with Donors Such as WB and GFATM, Based on Acceptance by Firms of WHO’s Prequalification Surveillance

As a reply to extremely urgent humanitarian needs, these agreements would ethically be warranted and would predictably result in reduced drug prices, thanks to the certainty of a growing market. Transparency and accuracy enjoyed, in the sake of users, through expanded WHO’s prequalification check would make such a model quite trustworthy.

Warranties of Fiscal Relief by Country Governments

Such a measure would likely deter firms from raising drug prices as a reply to stronger IP protection policies. But, where from could governments draw the equivalent for such a tax allowance? Apart from enhanced disbursement by international donors and engagement in domestic expenditure priority reallocations, the debt relief savings from debt cancellation to poor countries would free large sums of money that should partly be used to further help poor countries meet HIV treatment targets like these [48, 47, 30]. WHO and UNAIDS, following acknowledgement of country pledges to channel debt relief savings towards tax allowances, should engage in promoting approval of debt cancellation by the G8 Heads of State and Finance Ministers and closely checking for pursuance of the pledges.

Warranties of WHO’s Brokerage in VL Agreement Negotiations with the Research-Based Corporations

As channelled towards technology and knowledge transfers along with new R&D partnership opportunities, these regulated agreements mean at once as incentive for technological catch-up and easier access to more profitable wealthy markets by developing country firms while ensuring equitable drug access by the poor.

So conceived, VL agreements would play as a working measure to overcome the constraints and conditions by stronger IP rights and research-based industry, while egging firms in transitional countries to keep low prices for generic ARVs and the corresponding APIs. As a result, poor populations, both in domestic and foreign under-served markets, would be given feasible channels (as per export allowances, should engage in promoting approval of debt cancellation by the G8 Heads of State and Finance Ministers and closely checking for pursuance of the pledges).

Warranties of WHO’s Prequalification Check

This model, securing provision of low-cost APIs to developing country-based (Brazil, Singapore, Chile, Thailand, South-Africa …..) generics firms depending on major APIs producers (namely China and India), would help allow these firms to keep on with their ARV drug production.

Such a policy would also be essential in helping least-developed countries with no manufacturing capability still import affordable generic ARVs for their poor population settings without engaging in hardly feasible TRIPS-bound changes in national law (Table 1).

Equally important, high-grade predictability of HIV resistance mutations in the developing world does allow VLs to be assigned another critical spin-off, which links in with the need for second-line and newer ARV drugs for the under-served markets. Indeed, as viral resistance is expected to begin as a worrying problem in the mid-time span (about 20% of patients in three years time from beginning the first-line course), effective ways are to be found quickly so as to allow poor countries to access fairly priced generic copies of these drugs despite enforced IP rights [28]. This is a valuable reason supporting VL use as instrumental in keeping provision of second-line and newer generic ARV drugs. These copies, again, would additionally result in quite cheaper prices than branded originals even in case of most favourable price cuttings through bilateral agreements.

Based on their multifaceted potential including suitability for meeting requirements and needs by all involved parties, VLs actually appear as an appropriate formula nowadays with global advantages over more limited strategies such as CLs, differential pricing or donations (Table 3) [14].

That’s why new applications for VLs by generic producers in developing countries are increasingly adding to currently working VL agreements [14, 45, 43b, 46b].

Intrinsic Value of Self-Sufficiency in Domestic Drug Manufacturing

Thoughtfully, whole insights in this section also highlight the reasons for building domestic plants for ARVs in the developing world. Working domestic plants, indeed, would definitely play (aside from their value as a bargaining tool with research-based industry for cheaper branded-drug prices) as a substantial prerequisite for negotiating profitable VLs encompassing technology transfer channels that are the basis of partnerships grounded on both manufacturing and R&D. These partnerships in turn would result in technological catch-up, enhanced knowledge and better use of TRIPS flexibilities, as well as raised job opportunities, improved marketing power and, under contractually defined regulations, expanded domestic drug access by the poor.

Unfortunately, the overwhelming challenges to African countries in building capacity for domestic manufacturing of “generics” are, apart from too few promising examples (see section 3. Technology Transfer for Local Production of HIV/AIDS-Related Drugs in African Countries: A Long-Term Solution), still waiting for appropriate answers. These should include detailed balance evaluation between the overall risks, requirements and costs and the direct benefit for the poor.

Actually, a preliminary study concluded recently that domestic production for HIV medicines in sub-Saharan Africa has the potential to be financially viable and offer increased access to ARV drugs if specific requirements are met: competitive prices with imported drugs, market share enough for domestic production, and stable governments in place [25]. The viability of the enterprise, based on access to financial capitals has been secured, would depend, anyway, on a couple of both difficult to control and fluctuant factors, i.e. the APIs price and the market share [25]. In such a light, the Chinese APIs, based on their current affordability and availability, could definitely serve as a reliable source for allowing domestic sub-Saharan plants to take off.
Table 3. Synopsis of Reasons Supporting Voluntary License Use by Comparison with Compulsory License, Differential Pricing and Donation Options

<table>
<thead>
<tr>
<th>VOLUNTARY LICENSES (VLs)</th>
<th>COMPULSORY LICENSES (CLs)</th>
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<tbody>
<tr>
<td>- suitable for attaining (through technology transfer) technological catch-up while securing transparent relations with research-based companies.</td>
<td>- frequently feared by governments in the developing world because of risks of blackmail and withdrawal of investments based on multinational corporations and wealthy country governments would be detracted from profits.</td>
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<tr>
<td>- suitable for breaking away from dependence on fickleness and drug price fluctuations by foreign corporations.</td>
<td>- cumbersome and unwieldy frames requiring enabling national legislations already into force.</td>
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<tr>
<td>- suitable for keeping generic drug prices more affordable than those of branded originals even after cutting by patent's owners.</td>
<td>- risks that offers are not available in the private sector notwithstanding most people in developing and least developed countries access healthcare through private organisations (lack of transparency).</td>
</tr>
<tr>
<td>- suitable for securing both research-based and generic industries lastling advantages which may include market expansion, economic gains as well as manufacturing and R&amp;D partnerships.</td>
<td>- risks that discounts might preclude the use of &quot;generics&quot; (exclusion from the market of generic competitors: lack of transparency).</td>
</tr>
<tr>
<td>- suitable (as per export authorization) for expanding access to affordable ARV drugs in foreign under-served markets lacking capability for domestic manufacturing.</td>
<td>- risks for diversion and leakage (need to modify packages, labelling and instructions.</td>
</tr>
<tr>
<td>- suitable for securing supply of low-cost APIs to developing country-based (Brazil, Singapore, Chile, Thailand, South-Africa,...) generic firms depending on major APIs producers.</td>
<td>- discounted drugs not always available in every country.</td>
</tr>
<tr>
<td>- suitable for enhancing manufacturing of appropriate fixed-dose ARV combinations for children.</td>
<td>- discounted drugs sometimes not registered in specified countries.</td>
</tr>
<tr>
<td>- suitable for achieving, by native language instruction enclosed, the proper use of medicines.</td>
<td>- discounted drugs not always available in every country.</td>
</tr>
<tr>
<td>- suitable (through making generic copies of new and second-line ARVs readily available) for appropriately tackling impending viral resistance expansion in the developing world.</td>
<td>- cumbersome distribution channels for some discounted medicines.</td>
</tr>
<tr>
<td>- suitable for helping domestic plants for ARVs in sub-Saharan Africa take off and engage in R&amp;D partnerships encompassing technological catch-up, exploitation of TRIPS flexibilities, raised job opportunities, as well as improved marketing power.</td>
<td>- discounted drugs sometimes not registered in specified countries.</td>
</tr>
<tr>
<td>- suitable for supporting markets development in resource-constrained countries while bringing these countries into the global pharmaceutical market. In economic terms this means as incentive for either research-based or leading generic companies to enter these markets with existing products while concurrently investing in new products for them.</td>
<td>- risks for diversion and leakage (need to modify packages, labelling and instructions).</td>
</tr>
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REQUIREMENTS (UNDER VLs) FOR EFFECTIVELY EXPANDING ACCESS BY THE POOR INCLUDE: 1) WHO'S BROKERING ROLE IN NEGOTIATIONS, 2) SUBSTANTIAL INCENTIVES TO GENERIC FIRMS (I.E. "GENERICS" EXCLUSIVE SALES AGREEMENTS WITH MAJOR DONORS, FISCAL RELIEF BY COUNTRY GOVERNMENTS).

DIFFERENTIAL PRICING (GOAL: PRICES CLOSE TO THE MANUFACTURING COST)
- promotion of local market by keeping competition with domestic and foreign manufacturers.
- support to R&D.
- risks that offers are not available in the private sector notwithstanding most people in developing and least developed countries access healthcare through private organisations (lack of transparency).
- risks that discounts might preclude the use of "generics" (exclusion from the market of generic competitors: lack of transparency).
- risks for drug price fluctuations depending on fickleness and policy strategies of research-based corporations.
- drug prices unlikely to be as affordable as those of "generics" domestically manufactured.
- risks for diversion and leakage (need to modify packages, formulations and instruction languages).
- discounted drugs not always available in every country.
- discounted drugs sometimes not registered in specified countries.
- cumbersome distribution channels for some discounted medicines.
- discounted price quoted by the manufacturers may not constitute the final price for reasons including (though not limited to) exceeding mark-ups and lack of monitoring.

DONATIONS
- no suitability to long-term needs in the developing world where consistency of supply is crucial for chronic conditions.
- risks to undermine the development of local markets by locking out competition.
- no sustainability; it would be impossible by the patent’s owners to give away their products indefinitely.

Really, the overall factors implied in the taking off and working of domestic plants for ARVs in sub-Saharan Africa also encompass the presently weak technological know-how as well as the production costs and the uncertainties due to the insufficiency, if not lack, of basic infrastructures such as energy power plants and railway and traffic road systems. In such environments, indeed, it is easy to fear production breaks based on refrigerator chain malfunctions or power cuts recurrences with no back ups.

Therefore, while access to financial capitals remains a critical point, the technological catch-up, skilled workforces, economies of scale and infrastructure building are essential as well for allowing domestic ARV drug manufacturing in the developing world to stably take off [51, 48].

WHO’s Technical Guidance to Help Attain International Production Standards

Under perspectives as outlined above, the WHO’s direct training role in good manufacturing practices (GMPs) for pharmaceutical products has to be enhanced to provide resource-limited countries with appropriate skills and capacities for attaining international production standards. Enhancement should encompass WHO’s overall partnership activities in the field because of their value in appropriately addressing the challenges posed by TRIPS (Table 4) [60, 61, 62, 63].

Table 4. WHO’s Leading Activities to Appropriately Expand ARV Treatment in the Developing World

<table>
<thead>
<tr>
<th>WHO’s Leading Activities to Appropriately Expand ARV Treatment in the Developing World</th>
</tr>
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<tbody>
<tr>
<td>- Information, Technical Support and Advocacy broadly covering all topics in the field and addressing the needs of country governments as well as public and private institutions and organisations.</td>
</tr>
<tr>
<td>- ARV Drugs Prequalification Programme: the programme, through listing drugs proven to meet international standards for quality, safety and efficacy, aims to make them suitable, first and foremost, for procurement by United Nations Agencies; it also facilitates training for regulators from developing countries.</td>
</tr>
<tr>
<td>- AIDS Medicines and Diagnostics Service (AMDS): with a secretariat based at WHO headquarters and a wide partnership*, AMDS activities include a) the negotiation of affordable high quality HIV/AIDS treatments with research-based industries, b) updated drug information encompassing patents, prices and registration data, c) ARV drug procurement, stockpiling and supply, d) development of technical packages to help approval of fixed-dose combination treatments by national drug regulatory authorities, e) technical support to improve the efficiency of drug supply chain.</td>
</tr>
</tbody>
</table>


In such a context, closer relations with generic drug companies should be undertaken by the WHO-bound AIDS Medicines and Diagnostics Service (AMDS) to effectively supply eligible under-served markets with appropriate paediatric and adult ARV drug formulations (Table 4) [5a, 59].

SECTION 2. CHINA FACED CHALLENGES IN OVERCOMING THE OBSTACLES TO EXPANDED ANTI-RETROVIRAL DRUG ACCESS

The Current Situation of HIV/AIDS in China

By the end of 2004, the cumulative number of reported HIV positive cases in China since 1985 was 106,990, of
whom 23,955 (22.4%) were AIDS patients and 5,598 patients (5.23%) died of AIDS [53]. The cumulative number of HIV cases was estimated 840,000 corresponding to a total rate of 0.07% [53]. The HIV/AIDS-infected patients were distributed in 31 different provinces, autonomous regions, cities, and municipalities directly under the Central Government, mainly in rural areas. The top five provinces in number of the infected were Yunnan, Henan, Guangxi, Xinjiang and Guangdong, with the infected patients put together occupying 79.2% of the total infected in China (Fig. 1). The top five provinces in number of AIDS patients were Henan, Anhui, Yunnan, Hubei and Guangxi, with AIDS patients accounting for 87.6% of the total AIDS patients in China. The top five provinces in number of deaths caused by AIDS were Henan, Anhui, Yunnan, Hubei and Shanxi in turn, put together, occupying 78.1% of the total deaths. These five provinces once had a serious problem of illegal blood collection and supply. Considering the vast land and the huge population in China, the hidden peril of AIDS spread shall be paid enough attention to, although compared to other regions with high HIV infection rate in the world, the HIV infection rate of China is much lower.

**Clinical and Epidemiological Characteristics of HIV/AIDS in China [53, 7]**

Since 2001, the Increasing Number of AIDS Cases and AIDS-Related Deaths has been Presenting a Pattern of Clustering in Some Parts of China

Clinical data showed that in China, the asymptomatic period of those infected through sexual activity and intravenous drug use (IDU) is 6-10 years, while the period of those infected through blood transfusion is 6 years or so. Compared to patients in other countries and regions, the survival time of Chinese AIDS patients is shorter, especially for those in rural areas [43a]. A main reason is that most patients are not aware of their infection, thus delaying its treatment. The transmission of infection through IDUs is speedy, and the infections are aggravated by repeated drug abuse. If one is infected through blood transfusion, a large number of viruses assemble in the body and replicate dramatically. Thus, CD4 cells are devastated in a very short period of time, the immune function destroyed and infections soon occurring. In this sense, symptoms of infection in those infected through blood transfusion appear earlier, and their asymptomatic period is much shorter.

HIV is Beginning to Spread From Significant Groups in China to the General Population

The HIV/AIDS is spread from high-risk population, such as IDUs and prostitutes, to general population, such as family members and sexual partners of the drug users, illegal blood-selling and blood transfusion people and their family members and partners. People’s open attitudes toward sex brought by social opening make many people get HIV infection unwarily. In East China, especially in Shanghai and Jiangsu province, hemophilia patients get HIV infection through the transfusion of blood and blood products.

The Existence of Dangerous Factors Transmitting HIV

1. In the years to come, IDU will still be the main channel for HIV/AIDS transmission in China. The phenomenon of sharing needles is common, and people who get infected by sharing needles take up 63.7% of the total infected patients. At present, there are altogether 520,000 drug abusers registered. The Department of Public Security estimates that the actual number of drug users may be several times
larger than the registered number. Statistics show that HIV infection rate of the drug users in the year 2000 is 10%, 500 times higher than that of 1995.

II. Unprotected sex may gradually become the main infection factor in HIV/AIDS transmission. The increase of promiscuity and prostitution and the decrease of condom use, plus people’s lack of knowledge on HIV/AIDS, make the situation more serious. The reproductive tract infection rate of women in rural areas is considerably high. Statistics showed that from the year 1995 to 2000, HIV infection rate of the prostitutes in the year 2000 was 1.32%, an increase of 66 times in five years.

III. Since the fist case of maternal-infant HIV transmission was found in 1995, the Rate of maternal-infant HIV transmission has been growing steadily each year, rising from 0.1% in 1998 to 0.6% in 2003. With the increase of female HIV-infected patients by sexual transmission, maternal-infant HIV transmission will rise. At present, maternal-infant HIV transmission mainly occurs in seriously epidemic areas. In some counties and villages in Yunnan province and Xinjiang Autonomous Region, the HIV infection rate of pregnant and maternity women reaches 1.3% and 1.2% respectively [8, 71].

Co-Infection of HCV Being Serious Among HIV-Infected Patients

In China, over 90% of the HCV/HIV co-infection is transmitted by blood transfusion. Like HIV infection by blood transfusion, HCV infection tends to be regional, and it is characterised by genetic diversities [69]. Till 1997, 9 main HCV genotypes and over 30 HCV sub-genotypes have been found. At present, it is found that HCV in Xinjiang and Yunnan mostly is of genotype 1, 3, and 4, while HCV in Henan mostly is of 1 genotype and 2, whereas HCV in Guangdong and Hongkong mostly is of genotype 1 and 6 [70]. HCV infection is an important reason for the constant increase of inpatient rate and death rate of the HIV infected. The incidence of chronic HCV infection and HCV-related liver diseases of the HIV infected are also rising constantly. Often, these patients with mixed infection cannot stand highly active anti-retroviral therapy (HAART), thus losing the chance of receiving HAART.

HIV/AIDS and Tuberculosis Co-Infection

Tuberculosis is a complication that cannot afford to be neglected. Tuberculosis is one of the most common opportunistic infections of the HIV/AIDS patients. It is also the only opportunistic infection easy to be transmitted without intimate contact. Based on current statistics, we can infer that in the coming ten years, tuberculosis epidemic will be aggravating again. 8,000 new cases of tuberculosis get added to the list each day worldwide, and 3,000,000 people die of tuberculosis each year. Although the death rate of tuberculosis has dropped in China, which ranked the 7th in 1990, but ranked the 11th in 2000. One thirds of the population has latent tubercle bacillus. In some poor areas and ethnic group regions, especially in the 12 provinces in west China, tuberculosis epidemic is awfully serious with the incidence as high as 197/100,000.

The Current Situation of HIV/AIDS Treatment in China

Treatment of HIV/AIDS is an important approach to control the source of infection and prevent HIV/AIDS transmission. HAART has greatly improved the living of the HIV-infected patients, and has lowered the morbidity and mortality of AIDS. HIV/AIDS treatment and care is an urgent task facing both China and the world, because the development of HIV vaccine has not been successful till now. Even from the perspective of AIDS prevention, AIDS treatment is still the main approach to control the source of infection, though not perfect enough yet. What’s more, AIDS treatment improves the living of the AIDS patients, and checks maternal-infant transmission. By AIDS treatment, the second generation of the AIDS patients may keep healthy. Finally, AIDS treatment is beneficial to the economy of both China and the world. Treating HIV/AIDS patients is an important measure to prevent and control HIV/AIDS, which is put forward in China’s medium- & long-term strategy for HIV/AIDS prevention and control (1998-2010) issued by the Ministry of Health of China [11].

Since 1999, China has carried out HAART of international standard, which can be divided into three stages:

1) The first stage started from May 1999 to December 2001, right before the first price drop of anti-AIDS drugs. 150 patients received HAART, including those in the clinical trial with free anti-AIDS drugs provided by the pharmaceutical factories and those buying anti-AIDS drugs at their own expenses. Twelve patients continued to take the HAART for 5 years. The scope of HAART was expanded from Beijing to Shanghai, Guangdong, Henan, Yunnan, Fujian, and Xinjiang [9, 40-42].

2) The second stage started from December 2001 to 2003, after the mass scale price drop of imported AIDS drugs. Because of the price drop, some patients were able to afford anti-AIDS drugs at their own expenses. Hence, people receiving HAART increased, especially in more prosperous provinces and areas like Beijjing, Shanghai and Guangdong. Around 350 patients received HAART.

3) The third stage started from the year 2003 when domestic generic drugs came to the market and the China's Action Plan for Reducing and Preventing the Spread of HIV/AIDS (2001 - 2005) came on [11]. In this stage, a project aiming to establish comprehensive AIDS prevention, care and control demonstration zones was launched, so as to provide health education, AIDS prevention, medical care and consultation service to AIDS patients. Till the end of 2004, this project had covered 29 provinces, including 127 cities and counties, with a population of 83,250,000. 11,377 HIV/AIDS patients in 19 provinces had received free anti-retroviral drugs from the government. Every province established a simple technical scheme for AIDS prevention and treatment, including inclusion criteria, exclusion criteria, case records and follow-up files. Four pharmaceutical factories were involved in providing 5 kinds of
generic drugs (DDI, D4T, AZT, NVP and IDV) for free to HIV/AIDS patients. The Ministry of Health of China also imported from GSK and Merck a considerable amount of Combivir (3TC+AZT), 3TC and EFV for free use.

Strategic Progress in Clinical HIV/AIDS Treatment in China

With the situation of HIV/AIDS epidemic changing, responsibility of leading HIV/AIDS prevention and treatment work has also shifted. The State Council is directly leading the HIV/AIDS prevention and treatment campaign. We shall enhance the awareness of the leaders and the public on HIV/AIDS prevention and treatment, strengthen the government intervention, and encourage the active cooperation from all sections of the government, like the Ministry of Health, Ministry of Civil Affairs, Ministry of Public Security, Ministry of Finance, Ministry of Education, and Ministry of Science and Technology. Comprehensive measures are being taken to carry out overall HIV/AIDS prevention and treatment work. HIV/AIDS monitoring in cities and ports on the border is reinforced; overseas blood products are forbidden to enter the Chinese market, and domestic blood and blood products, visceral organs, and artificial insemination are to go through strict test and inspection; blood products are required to be inactivated. Drug trafficking and drug abuse are prohibited; drug addiction treatment is forced; and prostitution is to be clamped down. Drug treatment to pregnant HIV-infected women is to be enhanced to cut down vertical maternal-infant transmission.

On special sessions of the UN General Assembly on AIDS, the Chinese government made the promise to provide free AIDS drugs to those patients suffering economic difficulties. In cities, the government will provide free anti-AIDS drugs for low-income citizens, while in rural areas, the government will provide free AIDS drugs for all infected farmers (there is no medical insurance in most of the rural area of China now). The central government and local government have already invested over ten billions yuan in the establishment of a medical relief system for those who suffer from communicable diseases to carry out overall HIV/AIDS prevention and treatment. In order to fully carry out HIV/AIDS prevention and treatment, special HIV/AIDS prevention and treatment centers, equipped with necessary facilities, shall be established, and special medical teams and test personnel shall be trained. Since 2003, a nationwide systematic anti-retroviral drug and anti-infection training programme has been held for the medical staff, including physicians, nurses and lab technicians. As a result of this training programme, a community health protection team has formed and is growing up.

The Future of HIV/AIDS Prevention and Control

HIV/AIDS is not a disease of a particular country or region, but a kind of serious worldwide contagious disease unable to be controlled effectively so far. Looking back into the HIV/AIDS history in the past twenty years, since the time when HIV was defined as AIDS, scientific researches and clinical practices on AIDS prevention and treatment have made great progress, though many challenges still remain. Difficulties remain in discovering the pathogenesis of HIV/AIDS and in preventing and treating HIV/AIDS. Anti-retroviral therapy is a great task nowadays. In this HAART era, HIV/AIDS has become a chronic disease that people can handle, and the task of establishing further treatment plans and discussing the goals of treatment will become more complicated. The challenge that we are facing now is to integrate HIV/AIDS treatment with symptom control in all clinical settings.

Admittedly, only relying on AIDS treatment cannot eliminate HIV infection in the world. The transmission channels of HIV infection are well established. Therefore, HIV infection can be prevented. Adults can change some of their acts to prevent HIV infection. Research has shown that HIV infection can be prevented if prevention measures are implemented properly. These prevention measures include education on appropriate behaviour and sex health, encouraging protected sex acts, prohibiting drug use, promoting the using of clean needles and injectors, and adopting anti-retroviral drugs to cut down maternal-infant HIV transmission. Developing microbicides agents is another preventive measure. All these preventive measures are the most economic investment in health and worth popularising.

SECTION 3. TECHNOLOGY TRANSFER FOR LOCAL PRODUCTION OF HIV/AIDS-RELATED DRUGS IN AFRICAN COUNTRIES: A LONG-TERM SOLUTION

The Problem of HIV/AIDS, Tuberculosis and Malaria in Africa

Africa’s 785 million people continue to suffer from a huge burden of preventable and treatable disease due to HIV/AIDS, tuberculosis (TB), and malaria. These diseases cause incalculable human suffering with devastating human and economic impacts.

Globally, there are 39.4 million people living with HIV, and 25.4 million are in Sub-Saharan Africa. There were 2.3 million deaths in Sub-Saharan Africa due to AIDS during 2004, with 3.1 million deaths occurring globally [2].

As well as a profound impact creating enormous human suffering, the burden of disease due to HIV, TB and malaria in Sub-Saharan Africa stands as a major barrier to economic growth. There is a clearly defined cause-effect relationship between malaria and poverty, so that growth of per capita income from 1965 to 1990 for countries with severe malaria transmission was 0.4% per year, whereas economic growth for countries with fewer malaria infections was 2.3% per year, more than 5 times higher [6]. Africa’s Gross Domestic Product (GDP) would have been up to 100 billion US$ greater today if malaria had been eliminated years ago. The TB epidemic is fuelled by the AIDS epidemic, and a nation can expect a decline in GDP of 1% per year when more than 20% of its adult population is infected with HIV. As the economic gap between industrialized and low-income countries widens, so too is the health gap between rich and poor. This is particularly evident in relation to the HIV/AIDS, tuberculosis and malaria epidemics in Africa.
These epidemics represent unique moral and practical challenges of unprecedented urgency to the global community. The disease burden in the developing world can be reduced with a concerted global investment strategy that increases access to essential health services. The Commission report [49] on Macroeconomics and Health details the investment needed to scale-up health systems in developing countries. The report concludes that by 2007, donor grants to low-income countries must be increased from 6 billion US$/year to 27 billion US$ per year (or 30 – 410 US$ per capita). To ensure success, this strategy must include access to essential medicines, and especially to existing treatments for HIV/AIDS, TB, and malaria. When appropriately used, existing medications for these diseases can be highly effective for both individual patient treatment and for epidemic containment and control.

While access to medicines is a complex process requiring manufacture, delivery infrastructure, monitoring, and patient compliance, it nevertheless begins with the tangible availability of affordable, high quality medicines in the countries where they will be used. A combination of importation and local production strategies can be used to achieve this, as is the cases, for example, in Brazil and Thailand for the treatment of HIV/AIDS.

**Thailand’s Experience in Local ARV Production: a Long-term Solution in Implementing Successful ARV Programmes**

**HIV/AIDS Situation in Thailand**

About 700,000 people are infected with HIV in Thailand, out of a population of 63 million. It is estimated that 2 % of men and 1 % of women are currently living with HIV. There are 30,000 to 50,000 new AIDS and HIV infected patients each year [31]. As a result of successful prevention campaign, the incidence of newly HIV infected has stabilised. Now, Thailand is moving into a more “mature” phase of the epidemic. More and more people are showing symptoms and requiring care. The health care system in Thailand has sufficient resources to treat many common opportunistic infections.

Thailand has experience with antiretroviral therapy since 1988, but the experience has been mixed because of the involved costs and initial poor implementation of treatment in clinical practices.

**Government Pharmaceutical Organization**

Government Pharmaceutical Organisation (GPO) is a state enterprise under Ministry of Public Health. Its function is to manufacture and supply pharmaceuticals and other medical products to support health services activities of Ministry of Public Health throughout the country.

GPO manufactures more than 300 items of pharmaceuticals especially drugs in the National List of Essential Drugs including biological products. Total number of employees is 2,200 and annual sale volume is about US$ 100 million. GPO spends about 1.6% of the sale to research and development [22].

GPO realizes that one of the factors that is critical for access to anti-retroviral drug is affordable prices. Drugs should be available at affordable prices so that they fall within the financial reach of health services and individual in need.

The Research and Development Institute of GPO performs basic, applied and pilot scale research, which is essential not only to develop new pharmaceutical products but also to compliment and improve existing technologies.

The Research and Development Institute has been working on the formulation development and bioequivalence studies of HIV/AIDS-related drugs since 1992. Thailand is the first developing country to make generic ARV available in 1995.

In 2001, a fixed-dose generic combination drug known as GPO-VIR was invented, which contains either 30 or 40 mg of stavudine, 150 mg of lamivudine and 200 mg of nevirapine.

This fixed-dose combination did:
- simplify treatment
- increase patient compliance
- reduce the emergence of drug resistance HIV
- lower the price.

At the time, patients receiving this regimen took 6 pills a day at a cost about 85 US$ a month for generic drugs and 474 US$ for original drugs.

Production of GPO-VIR began in April 2002. Patients took two pills a day at a cost of 27 US$ a month, or 324 US$ a year. GPO-VIR is now used by about three quarters of the more than 70,000 people being treated for HIV infection in Thailand.

**GPO's Generic Production**

Manufacturing of any generic product is possible only after bioequivalence study. All production phases take into consideration the ever more stringent Good Manufacturing Practice (GMP) on manufacturing and quality assurance. GPO now manufactures 6 types of anti-retroviral medication in 24 dosage forms, with sufficient production for 100,000 patients. Increased production is planned, as well as a new production facility with improved quality standard [22].

**Conclusion**

Attempts to reduce the price from 5 to more than 20 times of its original price depending on the sources of raw materials are now possible due to GPO’s generic production of these drugs.

Thailand will achieve the goal of improving affordability through the increase of local production where the costs are lower and quality can be maintained.

In 2004, the Thai government established a policy of universal coverage for anti-retroviral treatment and also offered to supply drugs to 30,000 patients in Cambodia, Laos and Vietnam.

**Technology Transfer for Local Production of HIV/AIDS-Related Drugs in African Countries**

In April 2001, the 57th Session of the United Nations Commission on Human Rights adopted Resolution 2001/33, on “Access to Medication in the Context of Pandemics such as HIV/AIDS” [56].
The Commission calls upon States, at the international level, to take steps individually and/or through international co-operation, in accordance with applicable international law, including international agreements acceded to, such as: (i) to facilitate access in other countries to essential preventive, curative or palliative pharmaceuticals or medical technologies used to treat pandemics such as HIV/AIDS or the most common opportunistic infections that accompany them wherever possible, especially in times of emergency. On 21st May 2001, the 54th World Health Assembly in the resolution “Scaling Up the Response to HIV/AIDS” (WHA 54.10) recalled “efforts to make drugs available at lower prices for those in need” and urged Members States “in order to increase access to medicines, to cooperate constructively in strengthening pharmaceutical policies and practices, including those applicable to generic drugs and intellectual property regimes, in order to promote innovation and the development of domestic industries consistent with national law” [54].

In the Resolution “WHO Medicines Strategy” (WHA 54.11), the World Health Assembly recognizes the efforts of Members States to expand access to drugs and promote domestic industry, cooperate constructively in strengthening pharmaceutical policies and practices, including those applicable to generic drugs and intellectual property regimes in order further to promote innovation and the development of domestic industries, consistent with applicable international law” [54].

The UNGASS Declaration of Commitment on HIV/AIDS 25-27 June 2001, with regard to care support and treatment recommends members to cooperate constructively in strengthening pharmaceutical policies and practices (including generic drugs and IP regimes) [50].

Further, Article 7 of the November 2001 WTO DOHA Declaration reaffirms the commitment of developed countries to provide incentives to its industry for transfer of pharmaceutical technology to least developed countries [15].

Because of economies of scale, the market demand for raw materials required to manufacture pharmaceutical products is currently met by India, China and South Korea. And yet, the potential utilization of antiretrovirals is so large in high HIV/AIDS endemic African countries that developing the additional capacity required to meet this demand would likely lower the price of raw materials even while maintaining the economic viability of this sector. This will have a dramatic cost lowering impact, making antiretrovirals even more affordable in Africa. Similar considerations apply to the availability of medicines for tuberculosis and malaria.

**Building Pharmaceutical Production Capacity in Africa**

A major limitation that many African countries face in pharmaceutical production is lack of capacity and infrastructure in the manufacturing process required to produce quality drugs. In Africa, the generic pharmaceutical industry requires:

1. Increased availability of trained human resources for quality manufacturing;
2. Greater depth of expertise in multilevel Standard Operating Procedures for quality manufacturing;
3. Higher levels of quality manufacturing and analytical technologies;
4. Improved local sourcing of raw- or semi-finished materials, with tariff barriers eliminated for importation;
5. Enhanced capabilities for local chemistry synthesis procedures;
6. Improved quality monitoring skills at National Drug Regulatory Authorities;
7. Greater government incentives;
8. Improved access to ample donor support.

**Transfer of Pharmaceutical Technology and Drug Quality**

Drug quality is a critical issue, and local production must meet national and international standards for GMPs. Achieving this would create several advantages beyond an increased supply of affordable essential medicines. Such a capacity would improve national pharmaceutical policies, and diminish the supply of, and demand for counterfeit drugs. In more general terms, it would foster scientific capacity at large, exert a positive impact on efforts to promote value-added manufacturing activities, and increase employment and education levels.

Although there is no cure for HIV infection, antiretroviral drugs (ARVs) can dramatically reduce HIV-related morbidity and mortality and improve quality of life. The progress that has been made in the global response to treatment needs for HIV/AIDS is real—but inadequate (see section 1. Are There Loopholes for Making Universal Access to Treatments Actually Feasible Despite New Threats Posed by Enforced Intellectual Property Rights?).

One of the possibilities of increasing access to ARVs is transfer of technology for domestic production. Experiences so far indicate that technology transfer is not widely applied to the African continent. Enabling factors for building local manufacturing capacity through technology transfer are local technical expertise, incentives for mutual technical cooperation, and “warming up” of the local market.

**Examples of Technology Transfer Projects**

**Democratic Republic of Congo**

**Technology Transfer for Local Production of HIV/AIDS-Related Drugs: A Private Entrepreneur with Social Missions in Collaboration with German Medical Aid Organization-Action Medeor**

Pharmakina (PK), originally owned by Boehringer-Mannheim and Roche respectively, has been taken over by the management of PK in the beginning of 1999. PK is not only the largest private employer in Eastern Congo, but also the world’s largest producer of quinine. PK has put into operation a diagnostic centre for malaria, tuberculosis and pregnancy tests which is already open to the public. It also
operates 12 Health Centres spread over North and South Kivu.

Aim of this humanitarian project is to reduce the morbidity and mortality of AIDS patients in Bukavu, Eastern Congo by offering cost effective diagnosis and low-priced ARVs, which is a today’s best available choice of fixed-dose combination of stavudine, lamivudine and nevirapine and is taken as bi-daily tablets. It is well tolerated in most cases, has few contra-indications and is appropriate for use in women of child-bearing age. It has proven efficacy under actual field conditions, is affordable and is easy to take.

This is part of an on-going PPP project (Public Private Partnership) in association with the GTZ (German Agency for Technical Cooperation) that will include the screening, counselling and therapy of patients. A total sum of around US$ 1 million will be invested. Production of the HIV/AIDS-related drugs was planned to start by July 2005.

Action medeor works in close partnership with Pharmakina by providing treatment to a minimum of 50 to 100 patients and monitoring of 250 to 500 patients. It has appointed a project manager who will be responsible for the implementation of anti-retroviral therapy. Laboratory has been equipped with flow cytometer and the training of personnel has been provided. Treatment has been planned to start as soon as locally manufactured drugs are available.

**Tanzania**

**Local Production of HIV/AIDS-Related Drugs: Fill in the Gaps of Technical and Human Resources**

Of the 37.6 million people living in Tanzania, an estimated 1.6 million people are living with HIV/AIDS. By 2010, AIDS is expected to increase the death rate in Tanzania by more than 50 %, and life expectancy will drop from 56 to 47 years. Nine percent of Tanzania’s active labour forces were HIV-positive as of the end of year 2005. Each year in Tanzania, approximately 50,000 to 60,000 children are born HIV-positive. Some 140,000 Tanzanians living with HIV/AIDS are children under the age 15 and younger [4].

Currently, only one third of the sub-Saharan African countries have capacities for secondary manufacturing. Very often when they do have capacities, they are not in full GMPs. Today’s best available choice is fixed-dose combination of stavudine, lamivudine and nevirapine for which local production capacities are not available in Tanzania. In order to reduce the morbidity and mortality rates among the Tanzania population, the local production of HIV/AIDS-related drugs would provide a long-term solution.

Tanzania Pharmaceutical Industries (TPI), a pharmaceutical manufacturing company, 40 % owned by the government, 60 % by private entrepreneurs, having its operations in Arusha has teamed up to manufacture artemisinin-based antimalarial drugs at affordable prices. Because Tanzania is one of the countries hardest hit by HIV/AIDS, Tanzania has decided to start manufacturing life prolonging drugs for AIDS patients. Since the country has an acute shortage of highly qualified technical and industrial pharmacists, TPI has entered into an agreement with experts from Thailand who have agreed to cooperate and transfer knowledge and know-how and all the necessary information to support the production of pharmaceuticals and in particular antimalarials, antiretrovirals and anti-TB drugs.

**Technology Transfer and Local Manufacture of Affordable Antimalarial Drugs in Collaboration with German Medical Aid Organization-Action Medeor**

Tanzania spends 5.9 % of its GDP on health. Each year, the fight against malaria costs the country US$ 100 million. Thirty percent of the people who go to clinics have malaria. Thirty eight percent of the children under five who die in hospitals, die of malaria [13].

The objective of this project is the development and implementation of newly formulated antimalarials (Artesunate) with TPI including:

1. The technical backup for TPI in areas of production and system development, such as standard operating procedures
2. The formulation of finished dosage forms
3. Quality improvement and quality assurance.

These drugs will be made available by action medeor at low cost for the public health sector.

The newly developed drug name Thaitanzunate was launched officially by Tanzanian Minister of Health in September 2003. The cost of treatment for adults is 0.80 US$. Paediatric dry syrup formulation has been manufactured in May 2004.

Action medeor acts as partner and is responsible for the technology transfer and for non-profit procurement in Tanzania. TPI has been audited by action medeor with respect to GMP status.

**Conclusion**

There are technical and human resources gaps that need to be filled up via technology transfer. Creation of local good manufacturing site capable of receiving the technology transfer represents the best viable and long-term sustainable option for greater access to medicines in African countries. It will also represent the focal point of knowledge and skill oriented society and for a transition into value added manufacturing.

To improve access to essential drugs in Africa, the stimulation of local manufacturing of essential drugs provides a win-win solution to all involved parties and, most importantly, it represents a viable and sustainable means of tackling the problem at its source.

In each country, unique challenges have been found.

TPI’s 40 year-old plant will never make WHO standards for drug safety and quality, which means that the Tanzanian government will have to fund the local production until the facilities can be upgraded. There is difficulty of establishing a suitable trained workforce. The recommendation will be to apply a grant to purchase a ready-to assemble modular production plant designed to internationally acceptable specification.

The facility in the Democratic Republic of Congo is new, and would meet WHO standards, but production of
ARVs has been delayed because of the conflict in the country. The poverty, cultural and language barriers in the country still remain problems.

Annual medical cost in Democratic Republic of Congo, where initial production would be sufficient for only several thousand patients, might be about 240 US$ per person per year. In Tanzania, where the goal is medication for 30,000 patients, the annual cost might be 120 US$ per person.

In spite of overall deeply threatening challenges as depicted, production of ARVs did actually start in both nations between July and September 2005 (Fig. 2).

Clearly, to replicate the success in Thailand, it is necessary to demonstrate that antiretrovirals can be produced in these countries without interruption, that production can be scaled up, and that the quality of the medications meets international standards. These remain daunting challenges.

SECTION 4. CLOSING REMARKS

Access-oriented long-term drug policy strategies entitled to pass muster of governments, research-based as well as generic industries in both developed and developing countries are urgently to be found if universal and equitable access to fairly priced ARV treatments has to be achieved, despite enforcement of IP rights, in the sake of poor populations. Hopefully, these strategies should encompass support to markets development in resource-constrained countries while, at the same time, bringing these countries into the global pharmaceutical market. These requirements should always be taken into consideration whenever seeking sustainable ways to help poor populations in the under-served markets access essential therapies for widely striking epidemic conditions. Additionally, these requirements would mean, in economic terms, as incentive for either research-based or leading generic corporations to enter these markets with existing products while concurrently investing in new products for them.

Present and predictable connection dynamics inside the pharmaceutical industry, namely between western multinationals and transitional country generic corporations, let regard technology transfer-grounded VL agreements as a working measure fitting well into the targets just mentioned especially if substantial incentives to generic firms are concurrently secured.

Efforts to equitably expand ARV drug access through exploiting TRIPS opportunities should encompass attainment of self-sufficiency in domestic drug manufacturing whenever basic requirements are appropriately in place in sub-Saharan Africa as well as in the developing world as a whole.

A credible industrial potential would act, indeed, as a boosting factor for drawing branded drug producers into technology transfer agreements, the terms of which would let predictably all contractors enjoy substantial advantages.

These perspectives are consistently bound up with the foreseeable long-term trade and drug policy directions of India and China according to frontier crossing implications of their key TRIPS management trends as well as their multifaceted penetration strategies of both the wealthy and under-served markets worldwide.

As coherent with these perspectives, more disbursement by wealthy country governments and donors to basic infrastructure development in sub-Saharan African nations with stable governments in place is urged both as a priority for improving Africa’s economy and a prerequisite for allowing domestic industrial plants actually to take off.

Likewise, building for physical and human health infrastructures in the developing world is urged as instrumental in overcoming current inadequacy of the systems to distribute care and essential medicines.

Aiming at the targets just underscored, WHO’s brokering role in negotiated agreements between wealthy and developing country-based firms as well as its technical
guidance in setting international standards have always to be sought if equitable and appropriate end results are to be achieved.

Conclusively, overall insights in this paper would mean that, while research-based corporations are to be praised whenever waiving, on ethical purposes, part of their profits (i.e. by voluntarily fixing differential drug pricing, donating, investing further in low-cost production, as well as not enforcing or avoiding registering patents in poor countries), the trade and profit rules cannot basically be given up if long-term sustainable results are the goal we are looking for. Only negotiated agreements securing all contracting parties lasting advantages may ensure shifting of such a goal from mere vision to a really sustainable attainment.

REFERENCES
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