ISSN - 1744-2354

World CAB

Community Advisory Board

Meeting with the Indian Generic Drugs Industry

Mumbai, India
January 6-7, 2005

'I am proud to be Indian and proud that Indian companies make these drugs for the rest of the world, but I am paying $280 per year while people in other countries are paying $180 per year.

Because of the intervention of some Westerner [Clinton], other people are getting these drugs but our own people can't get treatment.

Will I ever be able to buy drugs at the Clinton price?'

Loon Gangte, India

World CAB: Community Advisory Board: Meeting with Indian Generic Drugs Industry

6-7 January 2005, Mumbai, India

Community participants:

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Tendayi Kureya	PATAM (Pan African Treatment Access Movement), Zimbabwe
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Thomas Zhang	AIDS Care, China
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Company participants:

Cipla	Dr Yusuf K. Hamied, Chairman and Managing Director; and Jaideep A. Gotay, Medical Services
Hetero	Shirish Phansalkar, Asst. General Manager, Intl Operations; and Satheesh Nair Asst. Manager, Intl Marketing
Ranbaxy Laboratories	Sandeep Juneja, HIV and Essential Drugs Project Manager
Strides Arcolab	Aloka Sengupta, Assistant Vice-President ATM

Report:

Written by Bob Huff and produced by HIV i-Base. Thanks to Jonathan Berger of AIDS Law Project, South Africa for comments.

Meeting coordinator: Ben Collins

The meeting and report were supported by the International Treatment Preparedness Coalition (ITPC), UNAIDS and The Monument Trust.

The World CAB meeting with Indian generics companies was organised by HIV i-Base of London and GMHC of New York on behalf of ITPC.

World CAB: second meeting

Introduction

In January 2005, an unprecedented meeting was held in Mumbai, India, between four manufacturers of affordable generic antiretroviral medicines and 30 advocates for HIV treatment access drawn from every region of the world. This was the second meeting of a worldwide HIV community advisory board (CAB) with drug companies; the first was held in San Francisco in 2004 with several multinational pharmaceutical firms.

The companies meeting in Mumbai included Cipla, the pioneer manufacturer of low-cost antiretroviral (ARV) drugs; Hetero, a large supplier of the bulk drug substance to many other generic drug makers; Strides, a small supplier of ARVs with historical ties to the African market; and Ranbaxy, an emerging powerhouse with ambitions of joining the ranks of the multinational, research-based pharmaceutical industry. The advocates traveled from Africa, South America, the Caribbean, Eastern Europe, Southeast Asia, as well as from India and Nepal, to press for lower prices and assurances of quality products.

Within the span of three years competition from the Indian generic drug industry has caused the price of ARVs to fall from over $8,000 per year, offered by the multinational originator companies, to under $200 per year, thus making large-scale plans for treating millions of people throughout the developing world feasible. But if lowered prices have brought plans to the table, the realities of actually providing therapy to so many have proven formidable and many problems remain. The meeting in Mumbai was intended to explore some of the problems that the generics industry can address, including the need for paediatric formulations of generic ARVs; the need for equally affordable second-line therapy for use when one's initial ARV regimen is not tolerable or has been compromised by resistance; and the need to address sometimes radical disparities in pricing that occur from country to country.

A key topic of discussion was the recent withdrawal of several important ARVs from a quality assurance list maintained by the World Health Organsation (WHO) that many governments rely upon when purchasing large quantities of drugs. At issue was the performance of several clinical studies designed to show that the generic drugs are absorbed into the bloodstream as well as the brand name versions. Inspectors from WHO uncovered certain irregularities with the conduct and reporting of several of these bioequivalence studies, which called into question results from all such studies performed by the Indian drug makers. This was a delicate issue for the generic companies, and while no consistent explanation for the problems uncovered by WHO were obtained, the affected companies all pledged a rapid return to the critical list.

The future of low-cost generic ARVs also came under discussion. New patent rules going into effect in India may change the way the

Subha Raghavan
India

The first World CAB meeting helped me to think about prices more locally and to express my anger towards higher prices for generics here in India when the rest of the world is paying less than we do.

This second meeting is very important for us, because we want to make sure that first-line prices are going to be comparable to what they are in the rest of the world.

We need to get the price down for efavirenz and we need to begin negotiating for second-line drugs. This is very critical for us.

Asia Russell
USA

I think activists meeting with the generic industry and communicating their concerns is long overdue, so it's a very important first step. Obviously there are huge opportunities for further pressure and activism coming out of this meeting that are all about access and pricing. I'm not happy with the answers I've been hearing. This is only the first step.

industry does business. Low-cost generic drugs have been possible because Indian patent law did not protect the final drug product, only the process of making the product. This means the generic makers have been free to copy expensive western-developed drugs by coming up with a new manufacturing process. Under the new rules, patent protection will be granted to final products first known after 1995, which means that newer ARV drugs, like tenofovir and atazanavir may never become available at the kind of prices the generic makers are able to deliver. Products known before 1995 will not be affected.

Whether licenses of right for post-1995 antiretroviral products that are already available as generics will be granted under the new rules is confusing. It seems that generic manufacturers must have already expended considerable resources on preparatory work, so licenses may extend to products that are not yet on the market in respect of the work that has previously been done. It is worrying that some companies may assume that the drugs we currently have are sufficient. We also need access to newer existing drugs and those that are in development.

All of the implications of the new patent laws are not clear, but Dr. Hamied of Cipla, the only one of the four companies serving the private ARV market within the country, thinks the outcome will hurt India by introducing monopoly patents, "It's going to be a disastrous situation for India ten years down the line."

Representatives from India pressed the manufacturers on one of the most vexing contradictions they face, "Why are drugs made in India cheaper in Africa than at home?" Each company added its piece to the puzzle, variously blaming import duties on raw materials, taxes and an indifferent Indian government. But all agreed that the key barrier to achieving lower prices, whether in India or Nigeria, is the lack of a consistent, growing commercial demand for their production. Despite widely announced plans for scaling-up treatment to reach three million people by the end of 2005, last year, one maker said, only 40,000 new patients were added to the treatment rolls. Yet with Cipla now claiming an average price of $160 per year, it may be that drug cost is no longer the limiting factor. Until the barriers of inadequate healthcare infrastructure, training and finance are removed, many fear that attainment of the kind of large-scale purchases than can bring ARV costs below $100 per year will remain unlikely.

D I S C U S S I O N S

Patents

Ranbaxy

Gopa: Have you assessed the impact of the new patent regime in India? And do you know what drugs will be affected?

Ranbaxy: Most individual ARV drugs are pre-1995. Only patent applications filed after January 1995 are affected by the new law. The drugs in our portfolio are okay except for tenofovir and abacavir. But certain combinations such as lopinavir/ritonavir are a problem. Atazanavir will be a problem. If there is a need for efavirenz in a triple combo, there could be a problem, but most products in the portfolio will not be affected. We have to take it as it comes.

Gregg: Will Ranbaxy oppose the legislation? If not, what will happen to the future of generic HIV drugs?

Ranbaxy: We are not taking a stand either way. This happened in 1995, before we were such a large company. India has decided to do this from 2005 forward, so we aligned ourselves to accommodate these new realities and prepared ourselves to operate in the world and in the US We will work with the law where ever it is.

Othman: Apparently you agree with the legislation pending in India. You are not lobbying against it.

Ranbaxy: If India has to become a high-priced market like anywhere else, patent protection would be an incentive for a company to market their drugs here. We have challenged the patent of the world's biggest drug, Lipitor, so if there is a weakness in any patent, we will fight it.

Tendayi: What is the corporate development plan? Will you abandon generics as you become more of a research-based company?

Ranbaxy: We don't see our focus on generics going down.

Hetero

Gopa: Tenofovir will probably be covered by the new patent regime; what is your strategy if it is?

Hetero: We have not heard anything new about tenofovir. Our management says our R&D people are working on this product. So I suppose that we will not face any problem but it is too early to say anything sure.

Strides

German: When world patents come to India that protects products for 20 years, what will this do to the generics industry?

Strides: Well, you have to find ways to manufacture that are non-infringing. The cost will be higher, but you will have higher returns because there will be less competition. But the preferred way will probably be to get into partnership with voluntary licenses. We will live with it. This is going to happen and there's nothing we can do about it. This is happening the world over.

Gopa: The ordinance just introduced will introduce product patents and goes beyond the requirements of TRIPS – do you have objections?

Strides: We would have to take a measured approach. We have partners in the developed world. We have many products. I will not make any comment until we know which drugs are affected.

Indian Patent Act

Cipla: After India's independence in 1947, the multinational companies were very strong in India and we were following the British Patent Act of 1911. We started fighting to change the patent law and we succeeded in 1970. We decided you can only patent a process, not a product, and then only for 7 years for health and food products. That gave us the legal freedom to make whatever we wanted. Now Indian companies now control 80% of Indian market. Unfortunately, as of Jan 1, 2005, the situation has changed concerning products invented after 1995. Whatever was known prior to 1995, we can still produce.

Asia: You say that partnership with the multinationals is preferred but sometimes the terms of licensing will not be acceptable if they don't serve the interests of patients.

Strides: Some multinationals are extremely good and others not so. But getting into litigation is not the way to go. I think non-confrontation way is the way to go. I'm not rejecting compulsory licensing, but I have no comment now. I think we should give voluntary licensing another shot.

Cipla

Gopa: The other companies said they are going to live with the new patent regime. What will you do?

Cipla: I oppose the whole damn thing. Strides and Ranbaxy are not selling in the Indian market so this is not their problem. If Ranbaxy only concentrates on the US market, what do you see as the future for generic ARVs from India?

I think amendment of the patents is a big mistake on the part of the government. We require a permanent compulsory licensing system for the developing world. We are willing to pay a 4% royalty, but I cannot allow a monopoly in a country the size of India. It is going to be a disastrous situation for India 10 years down the line. I would prefer an automatic patent: a 5% royalty on net sales is equivalent to a 25% ownership position.

There should be no monopoly. Evergreening is the most dangerous thing. AZT was invented in 1963. It was claimed in 1985 as an AIDS drug with a patent until 2005. GSK has said AZT should only be marketed in combination, with a patent that goes to 2017. 54 years of monopoly for AZT. We should oppose this.

Asia: What is your position on voluntary licenses?

Cipla: We live by the law of the land. We abide by the South African patent laws in South Africa. We are willing to pay the innovator a suitable royalty until the patent expires. We asked for a voluntary license, GSK resisted and now they have come around. If we sell lamivudine, we pay them a royalty.

Asia: What about your Triomune patent?

Cipla: It is a defensive patent. We would claim royalties from companies who manufacture drugs on our patents. If we get royalties in South Africa, that would go into a fund in South Africa used for treating HIV.

The Treatment Action Campaign (TAC) and patent laws

In South Africa GSK were forced to license. This was a result of the TAC case against GSK and Boehringer Ingelheim at the Competition Commission.

Further reading:

www.tac.org.za/newsletter/news_2003.htm

Registration

Ranbaxy

Rajiv: I'm from Nepal. For people with HIV in most of South Asian countries, living near India is like living close to a source of water but being unable to drink because most of the medicines you make are not registered in our countries.

Ranbaxy: We have plans to visit Nepal this month. It has been overlooked. I promised your Ministry of Health that we would file early in this year.

Rajiv: What about Pakistan?

Ranbaxy: Pakistan is not open to the Indian pharmaceutical companies. As soon as the climate allows us to open there, we will.

Subha: Bangladesh and Sri Lanka?

Ranbaxy: They have good manufacturing capacity and have approached us. If they are GMP (Good Manufacturing Practice) compliant we might do something. We are looking for a partner there.

Hanna: What is the status of registration in the newly independent states (NIS) and middle income countries? In Russia we know there have been attempts to register but what is status?

Ranbaxy: We have registered several products in Ukraine. Romania is atypical because it is moving towards the European Union and will require additional studies. Maybe we will do studies in Romania especially for them. In Russia we have started talking to people there. My estimation is that licenses would be more forthcoming to local manufacturers, not imported.

Lawan: What is the registration status in Thailand?

Ranbaxy: Registration for ARVs is very difficult to get in Thailand because they are self-sufficient and an imported ARV is not required. But we filed several years ago. Thailand has more ARVs than they need. They have been trying to offload those surplus stocks in Vietnam and elsewhere. There is a patent problem with Thailand but we could partner with a local producer.

Gopa: What is your stand on compulsory licenses?

Ranbaxy: We would use it where the law allows.

Lawan: Why not use compulsory license to export ddI to Thailand?

Ranbaxy: In Thailand, approval takes so long, that it would take ages before we could seek a compulsory license. If we don't have a registration, we have no basis to ask for a compulsory license.

Asia: We need to know where registrations are filed and their status.

Ranbaxy: This is sensitive information but I can discuss it if people in those countries write me.

Strides

Strides: Our drugs are registered or are in process in 29 countries, including most of sub-Saharan Africa. Johannesburg, Lagos and Douala have warehousing operations. We have a few offices in Latin America but none in Eastern Europe and we haven't stared registration there yet.

Marie de C: What is your comparative advantage compared to Cipla and Ranbaxy? What makes you different?

Strides: Our advantage is soft gel capsules, which lets us offer second-line therapies (PIs). We will be backward integrating into the bulk drugs. We are going to make the APIs (active pharmaceutical ingredients [bulk drug product]). But it takes time to get them stability tested. If we do, we will have

Svilen Konov
Bulgaria

The first World CAB meeting focused mainly on international issues and only to some extent on national ones, therefore it didn't produce any direct achievements in terms of access to treatment in Bulgaria. Not that it was useless; on the contrary, it enhanced our opportunities to talk to the pharmaceutical companies and helped to identify some solutions.

Gregg Gonsalves
USA

The first World CAB was helpful in getting people, particularly in the former Soviet Union, to think about registration and pricing in their countries. Also the key issue of pricing in middle income countries is now on the table in meetings between UNAIDS and all the big companies. I think the first meeting and report opened doors for advocacy and I think this one will do more because beyond price there are all these issues about quality that have to be dealt with.

Olive Edwards
Jamaica

After the first WorldCAB the information got to our government that there was a donation programme to make Diflucan available, when previously we had not had that.

Now I think there is more dialogue with the brand name companies. So much so that we now recognise that the generic companies need to do more in communicating with us. The strength of knowing that the activists from the north were going to be supporting developing countries really helped with our advocacy.

a more assured supply. We have spent a lot of time and money developing these products, so the onus can't be on the pharmaceutical company only. We can only make quality products and price them fairly.

Tendayi: What are the priorities for registrations?

Strides: We identify high-burden countries for registration. Our existing networks in Africa make it easier. But it is a very slow process. In almost all countries, the time to registration is one-and-a-half to two years.

Subha: What is the registration status in South Asia?

Strides: Vietnam has refused to accept registration; we have submitted it but they have rejected it. Cambodia will only register drugs that are pre-qualified. Myanmar is slow. You need an export permit to even send them drug samples and that hasn't come through yet. We have not tried registration in Indonesia—it is difficult to register Indian products there, too. The same in Thailand—they have their domestic production. There is little likelihood of exporting to Thailand. We are registered in India. We haven't registered in Nepal yet, but it is not difficult to do. But it is impossible to register products from India in the Middle East. And it is illegal to sell where we are not registered. We can not even give away the drugs for humanitarian purposes where we are not registered.

Tendayi: Eastern Europe?

Strides: We are not clear on the patent situation in Eastern Europe. There is widespread confusion. We have people and infrastructure in Africa, so we want to finish up there. Next year we should be starting in Russia and also Ukraine and Kazakhstan.

Subha: We are looking for solutions. We are trying to grapple with the problem that these drugs are only an hour away from where they are made, but still not available.

Strides: We are concerned. It is about the rules in these countries. We can't address these problems alone; we have to work together.

George: What about the countries around South Africa?

Strides: We are registered in Uganda and have submitted dossiers to Zambia, Tanzania, and others. It takes time. But all our products are registered in Malawi. The incidence of HIV is not as pronounced in North Africa, so we have not gone there. We focus on the high-burden countries. We have submitted in Zimbabwe and the Regulatory Authorities have acknowledged our submission and have asked questions. It is tough in the individual countries. It is hard to know the requirements and hard to get a response. The process takes two years in any country. We were able to fast track it in Nigeria. Registering 30 countries per year is good.

Rolake: How long have you had an office in Lagos?

Strides: For as long as we have been a company. We are in negotiation with the Nigerian Ministry of Health to supply the government program.

Estella: How do you sell to Latin America?

Strides: They are mainly being sold to the private market in Latin America, not to the Ministries of Health. We submit the bioequivalence studies to the Drug Regulatory Agencies in each country.

Gregg: Where are you registered in Latin America?

Strides: We are registered in Peru and are in process in Venezuela. We are in Costa Rica and the Dominican Republic. We supply to Cuba. We handle Brazil and Argentina from our plant in Brazil. We have our plant in Mexico City. Only a few countries have a fast track. You can help by advocating with these countries to have a fast-track for registering ARVs. They don't listen to us because they say we have vested interests.

Lawan: Is it possible for you to do a compulsory license if the country wants it? Could you approach countries and lobby with them about the need for a compulsory license for, say, lopinavir/ritonavir?

Strides: We need activists to do this. If we did it would be seen as us pursuing our vested interest.

Hetero

George: Are you supplying the APIs (active pharmaceutical ingredients [bulk drug product]) for local production in Zimbabwe?

Hetero: No, we sell them FDF (finished dosage form [packaged tablet form]). We have filed documents for Mali, Burkina Faso, and Angola. But every day the rules change. They take their own sweet time. They are not registered in Ethiopia. I have applied for registration of seven products in Morocco.

Tendayi: What prices?

Hetero: First we have to register. Commercial issues are secondary to registration. We are still only three years in the FDF market so we are working on it. We will focus on seven countries this year.

Hanna: How about the Newly Independent States (NIS) and Russia?

Hetero: We are very new to business in Ukraine and Russia. We have a few non-ARVs registered there. We were invited by someone to supply lamivudine in Russia. We have visited Eastern Europe to sell APIs.

German: What is the status of registration in Central America, Latin America and Jamaica?

Hetero: In Jamaica we have submitted dossiers for 15 products, including some ARVs. In Central America, we have submitted to Honduras, Nicaragua, Panama and Costa Rica. In Latin America, we are in Peru, Columbia and Mexico. Mexico is more APIs; Peru and Columbia is a combination of API and FDF business.

Olive: What is your market like in the Caribbean?

Hetero: We are in Trinidad and Tobago, the Dominican Republic, Grenada, and the Virgin Islands. The drugs are available in the medical stores. Government sales are through the Clinton Foundation.

Subha: Where have you registered drugs in South Asia?

Hetero: Pakistan is not yet open to registration. We have not yet started the registration process in Sri Lanka or Nepal. Nepal welcomes FDF from India, but not Pakistan. Not Vietnam. The drugs are available in India.

Rajiv: What about your social responsibility to look to these countries first? Make them available first in India and then in the neighboring countries?

Hetero: In Pakistan you have patent laws. It is dominated by the multinational companies. We sell some APIs to local producers in Asia. In Thailand, GPO (the Thai Government Pharmaceutical Organisation) is our partner for ARVs. I'm doing some products in Singapore and Malaysia. The East Asian countries want finished products and the North Africans want APIs. We have a patent problem in Vietnam so we haven't started there.

Ben Cheng
USA

I think there's still much needed advocacy for the resource limited setting. But I think we're moving beyond looking for access to any drugs, to asking about which drugs should be used. I think we need to start thinking about second line therapy and beyond—soon. People are asking if d4T, 3TC, nevirapine was really the right choice for first line therapy and what the right fixed-dose regimens really are.

German Perfetti
Colombia

There have been few changes in my country because the social security system there is different than in other places. They can afford to provide the antiretrovirals. However, there are now more entities that are able to buy the ARVs at lower prices. Other countries in the region have been in negotiations with Indian generic companies to try to get better prices. There was a meeting held in Lima where agreements were signed so they can buy more ARVs, so these countries already have negotiated with some of the generics companies here at this meeting.

Hanna Khodas
Ukraine

In Ukraine there has been a tremendous change because finally the Global Fund money came and we now have gone for treatment for more than 1,000 people. It was also a tremendous success during the first World CAB meeting when we met with Glaxo Smith Kline and told them about our disruption in treatment and asked them to fill in the gap until the Global Fund came in—and they did it as humanitarian aid. That was a concrete result. Also we improved our advocacy skills and got a better understanding of the global picture. So, it was an important thing for us.

Cipla

Rolake: What is happening with registration in Nigeria and Africa?

Cipla: There was confusion on this due to a business agent we appointed in 1995. We terminated that agreement and now have registered nine ARV products in Nigeria as single molecules.

Rolake: Then why not have several business agents for a single drug?

Cipla: If an agent registers a product for us it belongs to them. If I want to market it through another agent I can't do it. We are now marketing our ARVs in Nigeria through Evans Medical. Registration for various other countries is planned.

I think the African countries in general should put their regulatory houses in order. I suggest that if a product is prequalified by WHO, then it should automatically be approved for registration in the country: if a drug is approved in South Africa then it should automatically be approved in Namibia, etc.

Hanna: Who is the local agent in Russia?

Cipla: None. The problem we find in Russia is that they are insisting on a letter from lawyers that the drugs are free of international patents. We supply Ukraine.

Rajiv: We found at our workshop that Pakistan and Nepal has no access. But we were all speaking Hindi. I think it is part of Cipla's social responsibility to supply to the poor people in these countries. Are you are supplying to Nepal?

Cipla: We can supply Nepal and Sri Lanka. Pakistan has a problem with the laws. They protect their local industry.

Lawan: Can you lobby for a compulsory license in Thailand?

Cipla: We announced in 2000 that we were prepared to give technical know-how to any country that wanted to manufacture its own ARVs. But Thailand is blocking Indian products and controlling the markets in Cambodia and elsewhere. In Thailand we cannot register unless bioequivalence studies are done against a Thai product in Thailand.

Marie de C: We understand that the procedure for compulsory licensing is so difficult that no one has applied. Will you publicly state that compulsory licensing is not available to you?

Cipla: We are not in the picture when it comes to compulsory licensing. I'll say this to the media.

Price

Strides

Loon: I'm proud India is making these drugs. I am a consumer of these products. But I am paying $280 per year while people in other countries are paying $180 per year. I'm pissed off about this.

Strides: The only way we can get costs down is to get volume and to manufacture the APIs (Active Pharmaceutical Ingredients), which we are pursuing. The government should remove sales tax and statutory levies that increase the consumer price. Wholesale and retail margins are about 20%, but 36% is going to agencies of the government. If you supply to the government of India, sales tax is exempted. But if you supply to an NGO, then you are changed 16%. The government has to be lobbied. It took us years to remove the taxes for TB products. We need to do that for ARVs.

Loon: Can the price for the stavudine/lamivudine/nevirapine combo be brought down?

Strides: I don't think you will find that the price of Strides, Ranbaxy, and Cipla will be very different from one another. Certain costs are fixed: the API, the manufacturing costs. We have all agreed to keep profits down. Just because it is a generic doesn't mean the GMP process is compromised. It is a Rolls-Royce product. You can only hope to reduce price if the volume becomes larger. Only 40,000 patients for ARVs were added last year. The economies of scale have not yet been demonstrated.

Gopa: You have two market segments; non-profit and for-profit. Can you fix the markup that the distributor takes? Most access in India is through the private sector.

Strides: None of our products are available in the retail market in India. Our supplies of TB products in India are to programmes only. That is our niche. We can't change that niche for ARVS. It is not possible. The taxes charged by the government are fixed. We can't change that. I don't think the retail market is a solution for 5 million HIV patients.

Loon: What is your plan for India? Can you compete with the Clinton price?

Strides: The last procurement by the government of India was nine months ago. We offered the government our price six months ago. I cannot give you exact prices offered because they are in confidence, but purchases by the Ministry of Health (MOH) are published. These are prices at the factory; they don't include transport. There are countries where you have to have a local agent to register and they want 10% to 15%. You have to add freight. All these things are added before it gets to the patient.

Subha: How can you help reduce these prices for the 600,000 patients in India?

Strides: If you ask me what the cost of therapy is per patient per year, it is still between $280 and $320; $150 is still a long way off. You need 200,000 patients per year to get the Clinton price.

Let me state that the benchmark is the Clinton price, but that is a price negotiated when the dollar/rupee values were different. It was also done in the context of WHO's claim of 3 million patients by 2005. This is all different now. But we would be able to work out better price structures based on volumes. I'd guess the level is about 10,000 patients for meaningful discounts—25% to 30%—not small discounts. We must also be clear on payment terms. There is a prepayment required. We have suffered in the past on this. It has happened that we didn't get paid.

Lawan Sarovat
Thailand

We use our local generic products in Thailand. We started about treating people about three years ago and already we are treating 50,000 cases. This year we will start 20,000 more and the total will be 70,000 on treatment. We try to give them the right information so they can make the right decision and not force them to take the ARVs. Then people who are taking the ARVs become strong enough to become activists in this movement.

Subha Raghavan
India

In India, a year ago, there was no free treatment available. Subsequently, in April of 2004, the government announced a free treatment programme. The programme started very slowly because they did not have adequate financial resources.

They had a limited procurement mechanism and limited infrastructure, but they applied for Global Fund money in April and were awarded $135 million. Using that money they plan to treat 135,000 people over a five year period. That is a good start for us, but that is not enough because we have another 500,000 people who require treatment now.

Things are still moving slowly, but we are trying to figure out how all the sectors can come together and help government to move forward, because it is quite complex to move forward.

Loon: Could you have non-profit prices in India for people who pay out of pocket?

Strides: It is very difficult to make small sales. It would be good if all the communities would get together and have a common basket for procurement. It then becomes much easier for us to work out a better price. If you have a buyers club, then we can do that.

Thomas: Will you sell to buyers clubs? What will be the process?

Strides: It's all about number. If someone asks for 50 bottles, I may or may not be able to offer it to them. You have different packaging specifications in different countries. In Nigeria it must have a code on it. What I produce in Nigeria, in English and French, I can't sell to Costa Rica. When you register, you include the label in the language and you can't deviate from that. Each country's label is different. You also have to have a minimum batch size. If you all get together, you can get the price advantage and better service, too. If 500 individual buyers get together the freight is the same as for 10.

Marie M: Have you had any discussions about regional procurement?

Strides: Many people talk about this proposal. It would make our life simpler.

Othman: Can you control prices where you have local distributors? We see markups that are very high.

Strides: We can't do anything about local markups. The distributor will tell me to get lost if I tell him how to price his products. He will tell me he won't carry ARVs. He carries a whole basket of our products. We are in TB, malaria and HIV because of our social responsibility.

For example, I can't find a distributor in Togo! He says he won't take less than 20% — then he disappears. In some countries you need to have a local agent. We have asked to be exempted from having a local agent and governments have said no. There are countries where you don't get paid for six months.

Marie de C: We understand the logic of your pricing policy, but we need concrete data. What is the biggest purchase that has been made?

Strides: The biggest sale was to the government of Chad, for about 3,500 patients. It was about 300 Euros per patient per year. It took us one year to get paid from them with a great deal of difficulty.

Ranbaxy

Subha: We are proud that India produces these drugs, but Marie from Cameroon buys them for less than Loon here in India. What can we do today?

Ranbaxy: When we export we get an export benefit, so that is why prices are lower in Africa than in India. Most countries in Africa and Southeast Asia don't have import duties and value-added tax (VAT). India has abolished most taxes on ARVs, but there are still some and we are working with them to have them abolished. By policy, India does not have import duties on finished ARVs or raw materials. But multipurpose intermediates are not exempt, so some raw materials for ARVs have escaped the exemption and we're working on those. We tried to find every way to remove these duties and one proposal was to give a subsidy—cash back for import duties. But then the government changed and that idea disappeared.

Loon: We are the largest producers of drugs; we have so many patients; but we have the least number getting treated.

Ranbaxy: The previous Ministry of Health called us and said you have to give us the Clinton price. The government planned to reach 200,000 patients but the infrastructure was not ready. The government changed and now they too say they are trying to reach 200,000. But the new government has not talked to us. We have gone to meet them but they don't speak to us. They are going

to NGOs and foundations to get better prices. We worked it out with the old government, but the new guys don't know that. We are still trying to talk to the government.

Products for the private market are distributed through established distribution channels, which have certain markups. We recommend that ARVs be distributed through a public health channel so that patients get the best prices. In some cases we have made product available from our own distribution centers, and the prices were lower.

Marie de C: What quantity and price was offered to the Indian government under the Clinton agreement?

Ranbaxy: The Clinton prices are theoretical prices based on volumes that have not materialised. They said they would reach 100,000 patients after 2004, then 200,000 after 2005. We said our price is based on 40,000 patients. This is where we could enter into contracts with our suppliers. But the volumes haven't been realised yet.

Marie de C: Which countries have really gotten the Clinton price?

Ranbaxy: Very few. In Rwanda the price went from our NGO price to the Clinton price but there was no increase in volume. Only the distributor lost out because his commission shrank.

Othman: Why are there differences in prices from one country to another? In Africa, if there is no difference in duties between countries, are the differences due to your distributors? Do you have a plan to control your distributors' markup?

Ranbaxy: Our price mechanism is dual: one price for the private market; one price through NGOs. We make the product available through distribution channels for the private market. The private market is a free market. In some countries, such as Kenya, we have convinced distributors to lower prices. In some countries we have some existing exclusive agreements with distributors. But we need to have a local agent. When the consignment reaches that country we have to have someone there. So they need to get paid and make a profit. For the not-for-profit market, the prices are much more uniform. You won't see a fluctuation of prices upwards of 25% for the NGO products. If you do, please bring it to my attention.

Rolake: In Nigeria we see the Ranbaxy drugs selling inside the government hospitals for $75 a month. For the government patients in the same hospital, it is $25 a month. There is a 22% tax, but that does not explain a 300% increase.

Ranbaxy: We have not controlled the not-for-profit sector, which supplies to NGOs and government. There are low margins there. You have to have differential pricing to even things out, which is why private prices are higher.

Marie M: What price did you offer in Cameroon?

Ranbaxy: Sometimes we get the business from Cameroon, other times we don't when others have a better price.

German: There was a meeting in the Andean region and prices were agreed upon. How are you monitoring these prices?

Ranbaxy: We thought there would be tenders coming out of that meeting, but there was only one tender. In Argentina, there was a dispute because the agent was not making enough margin. We changed to an agent who was willing to go with the margin. But the tender was cancelled for some reason. We quoted a good price, but the supply didn't happen. Whenever tenders come from that region, we quote at that price or better.

German: How do you monitor prices in the region? Why are there higher prices in some countries than others?

Ranbaxy: If the tender comes to us, we decide the price and can monitor it. If the tender goes to the agent, and he doesn't tell us what he is quoting, it can

Thomas Zhang
China

Because we don't have good negotiations with the drug companies, and because there is no local production of 3TC, efavirenz and the other ARVs, the cost of treatment is very high. We used to only have the 100mg dose of 3TC for hepatitis B, but about three months ago we started having the 300mg dose for HIV. But this costs about $130 a month.

Olive Edwards
Jamaica

There are more people on treatment than a year ago. The government says there about 600 people on treatment in Jamaica, but there were many others who were traveling to purchase who didn't realise that they can get it locally. And there are also those who would never discuss their medications with anyone, so they are private patients. I think that there are at least 800 or 900 people on drugs and that's because people now have more information.

be difficult to monitor. Some countries have a system where only local companies can quote, and you get this problem.

Thomas: You mention that Ranbaxy was selling to buyers' clubs. Are you or will you sell to buyer's clubs in China at Clinton prices?

Ranbaxy: We sold to MSF in China. We are open to selling to buyers' clubs in China if the laws allow it. I don't know about the Clinton price, because the volumes will be low. I will put you in contact with our China office. The problem with ARVs is that orders are fragmented and small. When you get small orders from an area the cost of logistics is higher than the cost of the medicines.

Hetero

Hetero: There are two markets: the private and government sectors. Private sales are only a small part of Hetero's business—governments and NGOs are the major buyers. MSF has started buying from us. We want to give the rock bottom prices everywhere. If you give us the number of patients you want to treat, we can give you a price.

Gregg: What is your price for Ukraine, Morocco and Uganda?

Hetero: It is very difficult to say. If it is a private market sale, then it goes to our distributor and they mark it up. Also, all the countries have different tax structures.

The best price is the Clinton price. It has been offered to some Caribbean islands and to Swaziland. Not in India because the Clinton Foundation has not yet started operations here. But we have given it to some of the missionaries.

Loon: I am from India and I am a consumer for the past three years. Will we ever be able to buy your product at the Clinton price in India?

Hetero: That is a management decision, not mine. We have been following the Clinton prices, but it is dependent on conditions. We apply the prices when we have more than 10,000 patients. Prices have still been going down and most of them are at par with Clinton prices, even though not purchased through the Foundation.

Othman: Do you have any strategies to reduce the margins that make the drugs unaffordable in many countries? We see prices marked up very high by local distributors. Also, in Morocco, there are intermediaries between you and the MOH (Ministry of Health) that increase the prices.

Hetero: If the MOH does not have its own clearing facilities, then the agent clears them. Those expenses are taken care of and a royalty of 1% or 2% is given to the distributor.

Marie de C: How do you control abuse of the markup?

Hetero: A price is set comparable to the prices set by the multinational companies. We try to see that the pricing is affordable to the local people. The minimal margins across the board are around 15% for the distributors.

Gopa: What part of your business comes from APIs (active pharmaceutical ingredients) and what part from FDF (finished dose forms [pills])? You should be able to bring down the price further because you are producing the API.

Hetero: About 70% of our business comes from APIs and 30% from FDF.

Marie de C: What is your biggest client for both API and FDF? How dependent are the other Indian generics on you?

Hetero: Our biggest clients are countries like Argentina and Brazil for APIs. FDFs are sold mainly in the African region; Burundi, Kenya, Nigeria and Namibia are the biggest clients there. About 40% of FDF ARVs made by Indian companies use API purchased from Hetero.

Estela: Some of the Argentinean companies that buy your API don't have bioequivalence data.

Hetero: We know. But they buy our API for ARVs.

Thomas: Will you sell to buyers clubs?

Hetero: We are getting ready to sell to NGOs. If we come across an NGO that knows our products and is interested we will sell to them. Cambodia is an example. In Cambodia we are working with MDM (Medicins du Monde).

Othman: Do you need to have a minimum number of units or patients to sell?

Hetero: Our benchmark is 250 patients.

Cipla

Cipla: If you want to treat a million patients, we can manufacture 2 million tablets a day. But where will you get the API? The bottleneck in the large scale supply of ARVs in is the manufacture of actives. You need 30 tons of stavudine; 146 tons of nevirapine per year. If you change to efavirenz, you need 220 tons annually. Nelfinavir, you need 900 tons annually for a million patients. Who is there to finance these quantities? One hundred companies like Cipla

cannot cope with this situation. The problem is the manufacture of the actives.

Marie de C: We heard feedback about stock-outs, problems with timely delivery, etc. What can you do about delivery and payment problems?

Cipla: The national Ministries of Health (MOH) have to be more proactive and inform us of what they need and let us know ahead of time. The problems we have faced are irregularities of payments. Many governments are not paying us on time. We have a $2 million payment outstanding from Congo. Do we stop the supply? Some governments will only buy from the local agent. I might supply to the agent at $150 but I don't know what the government pays. We need time. We can't supply you millions of doses overnight. We need to plan, particularly with the API. And I need to be paid!

Rolake: Because of stock-outs in Nigeria, we have increasing drug resistance. Is there a possibility to have donated drug put aside to cover stock-outs?

Cipla: How do you know how much and for how long? The basic problem has been MOH want product yesterday. If we get orders consistently on a monthly basis, we can avoid stock-outs. Sometimes the consignments get lost after they land.

Estela: I would like to know why the prices are different between the different sectors within the country.

Cipla: By and large our prices are regional. I think of our pricing system as a window. Today it fluctuates from $140 to $200 (even though the dollar has depreciated in the last 2 years). The price depends on if you buy directly or through an agent. There is a window.

Hanna: In Ukraine, Duovir was bought by the government for $3,572 per year while the Combivir was $119 per year. Cipla's agent sold it to government at this high price.

Cipla: I was not aware. Why don't you ask the agent what he bought it for? If we sell for price X, and then that company sells for price Y, then I am not responsible.

Hanna: Of course we will ask the local agent, but it impacts on your reputation.

Cipla: Ask me and I will sell it to you at $20 per month. We are supplying to 90 countries, what can we do?

Lawan Sarovat
Thailand

Initially we had to import our drug illegally, but now the government makes it and we are trying to scale up more to help our friends in neighboring countries. The logistics costs are quite high if they just buy from the other countries. But the problem at the moment is that we need to amend our patent laws to allow the export of our generics to other countries where they are patented.

Tendyai Kureya
Zimbabwe

Whether people take generic or originator drugs depends on which programme they are on. A lot of programmes in Africa are externally funded and sometimes the external requirement is such that they use branded drugs. For example there is a small program funded by the American CDC that uses branded drugs from the US. But the national programmes in the countries in the region are mainly using generic drugs, those that have been prequalified by WHO, because most of the money is coming from the Global Fund.

Othman: You can impose markups on your distributors. In Morocco, your products are more expensive than the originators'.

Cipla: It is the job of your country to see that there is less corruption and fewer kickbacks. There are shady governments out there.

Gregg: You talk about windows. We see that the African countries get the best prices, but middle income countries pay more than they can afford.

Estela: Did you know that Triomune is $1,000 in Peru?

Cipla: We are supplying through a non-profit organization called IDA (www.ida.nl). We supply through MedPharm (www.medpharm.net). IDA just marks up 5% to cover costs. If I give them Triomune at $180 then you should buy it for $200. Supplies we have made through IDA to the MOH have gone to the MOH in Peru. They were goods consigned to MOH.

Gopa: It was a year ago that we heard of the Clinton price at $140 per year. What assumptions went into that pricing? Are those assumptions still in effect?

Cipla: When we were approached by the Clinton foundation—I don't think the Clinton Foundation has funds of their own to buy ARVs—we were told that seven countries were in partnership with Clinton for supplies, and that the total demand would be 2 million patients in the next two years. On that basis we arrived at a price of $140 per patient per year for Triomune. But that was a conditional price. They announced that price but not the conditions.

The conditions were: the price of the APIs were fixed; no payment of royalties or licensing fees; no litigation over patent infringements; the specification of the product was fixed; any variations were higher. Supplies were point to point; no intermediates. These were subject to large confirmed irrevocable orders. Payment terms were to be agreed in advance: advance payment or against supply. Then the fluctuation in currency would be considered. If the dollar went down, the price would increase. The dollar is already down 25%. It was to be FOB basis, for only three products in only seven countries.

So they are nice people at the Clinton Foundation, but I don't know how effective as an NGO they are, because no business has developed from them.

Marie de C: So the market is not what we thought. I'm surprised that you believed what Clinton told you.

Cipla: He is a very good talker.

Marie de C. The Clinton deal is not working. Can we talk about what will work?

Cipla: First, who will invest in the API? I'd suggest the Global Fund and World Bank should invest in API. The South African government has given a loan of $50 million to a company to make APIs. I think it is a public mission to fund this.

Marie de C: What is the best price you can give?

Cipla: Why do you only talk about pricing? There are other issues. What is the cost of medication? The medicine is only a small part of the costs of treating the people.

Subha: In India there are 58,000 registered cases and 252 VCT centers. If $140 is not realistic, what is the best price right now?

Cipla: I have written to the Indian Prime Minister to say: let us import raw materials duty free to make ARVs. No answer. We still pay 25% to 30% import duties. The average price is $160 per patient per year. FOB Bombay $160.

Loon: Will we ever get below $140 in India?

Cipla: India is in a unique position—we have a large industry, over 20,000 pharmaceutical companies—but there is also a public drug sector. I suggest

that the public sector takes over ARVs. We have reduced the price dramatically in Triomune over the last four years. If the duties go away, then the price will be lower.

Loon: Will the Indian patients ever get $140 per year?

Cipla: In a word, Yes. We have supplied $250,000 worth of Triomune to the government that they are distributing free.

Gopa: Only a few people access drugs under the free ARV programme, but the rest access drugs in the private sector.

Subha: We have made a list of prices. The reality is we are paying $240 to $300. We need to change that. The government programme will only reach 25,000, and the need is to reach 500,000.

Cipla: Use your influence with the government and get the import duty released. If you are selling Triomune at $140, the total coast of APIs is around $100—if there was no import duty. If we have to import, that makes it $120 or $130, then add another $40. Under the general system in India, if we supply at $65, the customer pays $100. In the case of ARVs, the wholesaler and pharmacist have agreed to lower margins and some states have eliminated sales tax. We also have to add at least 10% for defaulted payments.

Simon: Cipla makes hundreds of drugs. Are default payments a problem with other products?

Cipla: We specifically find that defaults are much higher on the AIDS drugs.

Estela: What are the opportunities for reducing the price of APIs?

Cipla: I mentioned the manufacture of APIs. Twelve to fourteen APIs are being used extensively for ARVs. It is not humanly possible for any one company to produce all of them. Understand the scale of operation: stavudine requires 30 tons but nelfinavir requires 900 tons. If I make Triomune for 1 million patients I need 110 tons of lamivudine. Last year GSK consumed 26 tons of lamivudine, and their sales were $135 million. It requires a team effort. I buy from my competitors as well. I don't want to produce protease inhibitors, but I market a range of them by buying them from others like Hetero.

We import and make APIs and intermediates. We sell very few APIs. From India, the countries buying APIs are Brazil and maybe Thailand. The problem will come when WHO begins to inspect APIs; that will be a major problem. Before they said they only approve the end product. The responsibility for the API was ours. Now they are going to inspect the API factories. If we have to use FDA approved factories, it will be difficult.

Marie de C: I take your suggestion is to get the World Bank to fund API production.

Cipla: What you should do is have a consortium that sets up a manufacturing base. Choose a least developed country with no patents until 2016. Bangladesh, Ceylon, Mauritius. If governments do not actively participate, then little can be done. You need a long term partnership because it is a life-time illness. Why doesn't the Indian government use its factories?

Let me ask you an important question. What contingency plans do you have to assure that you have medications 20 years down the line? One of our main partners in producing ARVs is China. If China decides to stop supplying chemicals for ARVs then we are all out of business. The China patent rule is that they can not sell the patented drug in China but they can export it to countries where it is legal to sell, like India. That could change. Today the China currency is linked to the dollar. Tomorrow, if the currency is delinked and starts floating, the prices of all ARV drugs will raise very high. What happens if the companies stop selling at cost? If they leave the field? If China stops selling APIs? What contingency plans do you have?

Olive Edwards
Jamaica

Although we did not meet with Merck, it was at the first World CAB meeting that I learned that there was a 600mg tablet of Stocrin available. Where before we could only get the 200mg dose, within three months after I got back we were able to get the 600mg table - and the price was less! So I was able to buy my Stocrin at a lower price and was only taking one pill instead of three. I told the people in my group and they all said, "We don't want the 200mg dose, we want the 600mg Stocrin." Now the Minister of Health buys the 600mg Stocrin from Merck.

Hanna Khodas
Ukraine

I know many people who have started treatment because they come to our organisation for counseling. People are feeling better and getting better. The community knows that treatment is accessible but we have cases where people refuse therapy, so we are working to persuade them. I know two people who had less than 100 CD4 cells and now they have 300 or 400 and they are feeling much, much better and looking much better. So they are a good advertisement for treatment.

Quality

Ranbaxy

Asia: We want to talk about the crisis over WHO prequalification. The entire Ranbaxy ARV portfolio has been withdrawn from the WHO pre-qualified list. This has caused disruptions to treatment programmes. Nigeria is deregistering all Ranbaxy products. We saw that a new CRO (Contract Research Organisation) was contracted for PEPFAR purposes. This seems to establish two tiers of quality. Can you comment on the apparent double standard?

Ranbaxy: Double standard? We didn't realise our delisting would be interpreted that way. PEPFAR was knocking at the generics' door—due to your pressure. We have good relations with the US FDA. We understand that process very well. They have approved 100 of our products. We were in middle of assessing data for the FDA and we wanted to harmonise everything to the US market and consolidate manufacturing in one place. If a product is approved by the FDA then it is accepted anywhere. It's not a double standard, but exactly the same product made at the same locations.

Asia: We understand the need to recreate the bioequivalence studies with a reputable CRO. But these tests take weeks, not months. If your registration department is crowded, maybe you need to increase resources.

Ranbaxy: Most of our CROs are in the US They are already inspected and approved by FDA. The person entrusted with the re-submissions to WHO is our guy who handles bioequivalence studies for the US. He has his contacts

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World Health Organisation (WHO)

In 2004, the World Health Organisation (WHO) removed several Indian generic drugs from its prequalification list after irregularities with one company's bioequivalence data cast suspicion on the prequalification system and generic drugs in general. In November 2004, two doses of lamivudine made by Cipla that had been previously removed were returned to the list. However at that same time, several drugs made by Ranbaxy Laboratories and Hetero Drugs were removed.

As of July 1, 2005, results of newly conducted bioequivalence studies for several delisted drugs made by Ranbaxy have been resubmitted to WHO and were under evaluation. Also in 2005, new products manufactured by Strides Arcolabs, including stavudine capsules, lamivudine tablets and nevirapine tablets were added to the list. As of April 2005, the WHO list contained 53 antiretroviral products, including 19 drugs made by generic manufacturers.

US Food and Drug Administration (FDA)

As of July 1, 2005, the FDA has granted tentative approval to seven generic antiretroviral products. Although these drugs may not be sold in the United States due to patent restrictions, the agency has certified that they are equivalent to the originator versions according to federal quality, safety and efficacy standards, and may therefore be purchased by the US-funded PEPFAR program.

The drugs include efavirenz tablets, nevirapine tablets, stavudine capsules and lamivudine tablets made by the Indian generic maker, Aurobindo Pharma, Ltd.; and nevirapine tablets and lamivudine tablets made by Ranbaxy Laboratories. Earlier in the year, FDA granted tentative approval to a co-packaged product produced by Aspen Pharmacare of South Africa that includes generic nevirapine tablets plus a fixed-dose combination tablet of lamivudine/zidovudine. The Aspen drugs are produced under licenses issued by the originators.

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in the US and can get research slots in the US CROs because we have worked with them in the past. It is an efficient process. We are also using our in-house clinical facilities, which are reserved for FDA submissions. We use that unit to do WHO and FDA submissions.

Gregg: It is not okay for you to wait to go back to WHO until after you have filed with the FDA. Many AIDS programmes are in disarray. You need to get these drugs back on the WHO list and not wait for FDA. You are creating havoc until they are re-listed.

Ranbaxy: The two are not linked. The US asks for less stability data than the WHO does, so filing for WHO prequalification could actually happen later. WHO requires certain additional data to be generated which is being done. There are bioequivalence studies running today and you cannot be 100% sure when the data will come out.

Simon: What is the rough timeline?

Ranbaxy: Normally our bioequivalence studies are planned well in advance. If you are developing a product, you know when you will need bio studies, so you reserve a slot. The CROs are fully booked well in advance, so you reserve a slot. If you approach them in a crisis they normally don't have slots unless they knock someone else out. So you have to wait for your bio to start. Normally it takes weeks, but it can take several months if there are wash-out periods or outliers where you have to repeat the test with that outlying subject. But before you start the study you have to wait several weeks for the CRO to give you a slot.

Simon: But a company like Ranbaxy must have many slots booked for other projects.

Ranbaxy: We have knocked out slots for other projects to make room for ARVs.

Asia: Is there a timeline?

Ranbaxy: WHO filings will start in January 2005. There have been three filings with the FDA so far. We plan to complete the majority of re-filings with WHO by March and the balance should happen by June. After we have done our first filings we plan to engage with them to see how this can be fast-tracked. We will share any developments with the media. From the communication we have had with them, WHO is keen on fast-tracking our filings.

Olive: Community people may not see that press release. You want to benefit from WHO prequalification. Yet we hear that your products are no good. What do we do? Return them? All we hear is your drugs are no good.

Ranbaxy: WHO recommends that patients on those treatments continue on them. Some treatment programmes chose to continue despite the media reaction. A lot of orders have been reinstated.

Simon: Was there compensation for returned stocks or for drugs that were unable to be used?

Ranbaxy: We are okay with taking stocks back but we strongly urge using them.

George: If you encourage use of these de-listed products, isn't that a health risk?

Ranbaxy: WHO says the bigger risk is in not continuing to use ARVs.

Marie de C: What really happened?

Ranbaxy: Those three products were supported by bioequivalence data from a particular CRO in India, which had been used by several different companies, pharmaceutical and others, doing various kinds of analyses, including bioequivalence studies. It was a very reputable, publicly listed company. The CRO had some issues with GCP (Good Clinical Practice) and GLP (Good Laboratory Practice) and consequently those studies were not

Tendyai Kureya
Zimbabwe

In southern Africa access to antiviral medicine has been ad hoc, in the sense that in some countries you have universal provision for access, in that anyone who needs antiretrovirals should be able to get them through the national programmes. That's for Zambia and Botswana, the two countries that are pioneering in that direction.

But in other countries, such as Zimbabwe and Malawi, there are national programmes but they are going very slowly, mainly because of funding issues. But even in the countries where we have said there is universal access, the uptake is very limited.

Thomas Zhang
China

The government is planning to have free treatment with ARVs, but the problem is that the lower-level healthcare providers and officials don't really understand why they should provide free treatment and spend so much money for these people. There are two reasons: one is the stigma and discrimination against HIV-positive people.

The second reason is that China's healthcare system has become highly commercialised. Nothing is free. So now you can imagine that they resent spending so much money to treat these people and so they reject the government policies. So they are very reluctant about implementing the treatment programme.

passed by WHO. And WHO de-listed the products.

Marie de C: What issues? If we know what happened, then maybe we can calm down the concern that you are selling bad products. Can you be more specific?

Ranbaxy: What I can say is there were issues with noncompliance and handling of data. You can get a copy of the WHO report from your Drug Regulatory Authority. This issue has caused everyone a lot of trouble. It has been a breach of faith and a breach of contract and once everything settles down we might need to take legal action against the CRO. Anything I say now would be a breach of confidentiality. That's why I can't share it right now.

Bob: We have heard that fraud was involved.

Ranbaxy: We received a report from WHO and with that data we inspected the CRO. The findings of WHO were confirmed and we decided we did not want to trust any work done by that CRO on antiretrovirals. So we decided to withdraw all our ARVs from the WHO list. It is not that the drugs are poor quality; the issue is that we are not sure if they are bioequivalent, because the tests done at that lab are inadmissible.

We are repeating even those bioequivalence studies for which we had not received WHO prequalification because, as a company, we lost faith in that CRO and we decided to repeat all of the work they did on ARVs.

Marie de C: You have to find a way to speed the process.

Ranbaxy: We won't spend an extra day in submissions, but we don't want to cut corners. We don't want to compromise our reputation nor the reputation of the generic industry. A second failure would be disastrous.

The most expensive bioequivalence study in India costs $30,000. We pay $150,000 to $200,000 to the US CRO, which is standard for them. We have not put a limit on the budget on this. The biggest problem is finding enough people to work on this. We have a team of senior level people working on this monitoring it continuously.

Estella: We are concerned with communication about bioequivalence.

Ranbaxy: Before we were de-listed, our bioequivalence data were on our website for anyone to see. Pharmaceutical companies tend not to do that. We will do that again once our products are re-listed.

Strides

Strides: We are happy with our CRO—it is approved by Brazil, inspected by the FDA and WHO. Monitoring of the bioequivalence protocol is the responsibility of the drug company, not the CRO. No CRO objects to having a company-appointed monitor in place. There are absolutely no issues with our bioequivalence studies.

Let me explain the process of developing a product. We do preformulation studies; we study the compatibility with excipients, do dissolution tests, etc. We compare with the innovator product. There is no pharmacopoeia, so there are no reference standards other than by comparison with the innovator. Twelve months of stability studies are required by WHO. From the day you identify a product to having approval is 18 months to 2 years. We are underway with efavirenz and will be ready by the end of the year.

We have sent stavudine/lamivudine to the FDA. The problem with FDA has been their inability to accept bioequivalence studies that were carried out using European innovator products. They don't have the right of reference. This means every bio study has to be repeated with US approved innovator product. We just completed a bioequivalence study with one.

Svilen: Can you publish your scientific data?

Strides: Our bioequivalence studies are on our website. We are in the process of doing clinical trials. When they are finished the results will be made available.

Hetero

Marie M: We are concerned that some products have been de-listed from WHO prequalification. What is the timeline for re-listing?

Hetero: We had an audit but decided not to go ahead. But there were aspects of the GCP standard and GMP standard. But certain documents were different. After consultation we withdrew. Bioequivalence was done five years ago. The WHO and FDA standards were not inline. A new bioequivalence study is being done and should be complete by February or March. Then we will invite the WHO inspectors for the audit. The WHO has said that the quality of the drugs is adequate. Our associations with MSF and the Clinton Foundation have continued and we have delivered those products.

Marie de C: I don't understand the story about the change in WHO standards.

Hetero: The CRO did not follow the current GCP standards. The regulatory process is slow at WHO because of their bimonthly process. It all went into a little hiccup after the Ranbaxy de-listing. WHO is now more stringent with CRO inspections.

Subha: What was the previous WHO requirement and what are the current requirements? What changed? What was the problem with the CRO?

Hetero: I'm more from the marketing side. Any statement from my side would be wrong. I can't give you any kind of a statement.

Tendyai: You have the ultimate responsibility for the CRO's behavior.

Hetero: I agree. We have the responsibility to see to the bioequivalence data. The issue is meeting the current standards. It takes time to correct this.

Othman: In February or March, will your entire portfolio be prequalified?

Hetero: Only some of it. Single-dose and double-dose will be ready by March. The triple combinations are already submitted to WHO.

Estella: I represent the Latin American community. They are not sure of the quality of the drugs if they are not prequalified.

Hetero: The quality can be assessed only by use. We have supplied the drugs to many countries.

George: You are telling us the quality can only be proved by using it?

Hetero: I meant that we wouldn't still be in this business if they weren't good quality.

Marie M: There was news in Cameroon that the drugs were of poor quality. We were embarrassed. What are you doing to address these concerns in our communities?

Hetero: We have traveled to several countries and are educating people. We met with the Ministry of Health in Cameroon. We want to eliminate any ambiguity. We could not survive in this business if they weren't good quality.

Cipla

Marie M: We are glad to hear that you have resubmitted your products to the WHO. But we are concerned about the other products that you have not yet submitted.

Cipla: Are you aware that WHO hires out inspectors for prequalification? We have been disillusioned by the type of inspectors coming to inspect. There are two types of qualification: the facilities and the products. When we give work to an outside agency, then we need to have them independently

Lawan Sarovat
Thailand

We have problems with side effects, mostly with d4T and lipodystrophy, which you can see in people's faces.

We are trying to get the doctors to talk more with the patients about the side effects.

Thomas Zhang
China

I have seen greater access to ARVs in the past year, but at the same time I have seen a lot of problems with adherence and the management of side effects.

Because ARV treatment is a lifelong process and because it is a toxic treatment, people need follow-up on the adherence counseling issues.

In China, we still need to have a commitment to do that. In some of the counties there is one doctor to treat hundreds of patients.

Thomas Zhang
China

Because of the limited local choice, most of the drugs are nevirapine, ddI and d4T, which is very toxic, and most of the people can not tolerate that and then they give up.

They have side effects of neuropathy of the feet and hands. The maximum time people can take the drugs is about one year and then they start having problems. Then they need to stop or they have to swap to another therapy, but that is usually too expensive.

certified. We asked WHO, why not certify CROs too?

Also, WHO does not qualify the active ingredient going into the end product. So any prequalification is meaningless unless they also qualify the APIs. Now they are going to start qualifying the APIs and the cost will double. We will have to produce every API according to FDA good manufacturing practice (GMP).

I would really go into the qualification system of WHO. Individual countries also have their own qualification protocols. Suddenly Americans wake up and say these protocols are not good enough.

Four or five products are in process of submission. The FDA refuses to answer if US money will go toward buying drugs that are FDA approved, but are still under international patent protection. Lamivudine expires in 2007; stavudine in 2005. So will US money buy drugs which are FDA approved, but are governed under U.S. patent laws?

George: You seem to say that it is difficult to manage a large number of countries. Why did it take you so long to take back the drugs that were delisted?

Cipla: That is a sore point with us. We submitted our revised bioequivalence data to WHO on August 10. They didn't answer until September 10. They said they don't have the manpower. The Triomune was done previously and there was no problem at all.

Gregg: A the end of last year, we sent a letter to Dr. Lee of the WHO to ask why he was not reacting more aggressively. How and why did three companies have drugs delisted? With each day that goes by, it becomes harder to have confidence in them.

Cipla: It is very simple. If you go to the US FDA and say you want to re-review a drug approved in 1995, a 2005 reviewer will find fault in what he found in 1995. Three labs in Canada were delisted for bioequivalence mistakes. It happens all the time. Bioequivalence is a new science in India. We set up the first bio lab in 1986. Bioequivalence is showing the single-dose equivalence. How do you keep records? The CRO's record keeping was faulty. It is a delicate point. The WHO and other drug regulatory authorities should investigate and prequalify the CROs.

Asia: How can you say you are not responsible for the CRO's performance? You are accountable. Other companies have taken the responsibility.

Cipla: This is an evolving science. We have learned a lot from this.

Pipeline

Ranbaxy

Elena: In Romania there are many AIDS cases in children; I am the mother of a child with HIV; there are no generics, although the government is obligated to pay for ARVs. I want to know what is planned for paediatric formulations in Romania and the rest of the world?

Ranbaxy: Romania follows the European Union, which requires different kinds of data for registration that we haven't done yet, but we will.

On paediatrics, I want to have your suggestions on what kinds of products we should develop. The costs of pediatric drugs are higher. For example, carrying liquids in glass across the globe raises the cost. We have dedicated resources in R&D that we can put to work on developing paediatric formulations.

Polly: What paediatric formulations do you have so far?

Ranbaxy: We have conventional zidovudine, and are working on a stavudine. These are available in India and produced in Nigeria for local use. Volumes are very low and achieving economy of scale will be slow.

Olive: Are you working on a paediatric triple combination?

Ranbaxy: The ratio of the drugs in the combination changes with the child's weight. We can't get people to agree on the needed doses, so we decided on a product which will exclude some age groups. It will apply to a weight of about 20-30kg, but not above and not below. Some paediatricians agree with this and some don't. If we develop something that is not necessary we will lose a lot of time and resources. Another challenge is to create a formulation that is not a liquid. But then access to clean water becomes an issue.

Simon: You know that in practice, children are being treated by crushing adult formulations. This is due to cost, storage and also lack of availability.

Ranbaxy: That's off-label use. To get it approved, you have to clinically prove it, and that is where the challenge is.

Loon: What are your new products?

Ranbaxy: We are close to introducing lopinavir/ritonavir and nelfinavir. You will hear announcements in the future. But these won't be triple fixed dose combinations (FDCs) because there are problems with some combinations. Second-line is based on PIs, which have high doses, and frequent doses. So they don't lend themselves to FDCs as well as the first-line.

We will do original research on new ARVs and a booster, if that is needed.

Gregg: The price of generic efavirenz needs to match the price for nevirapine. Why is there such a great difference?

Ranbaxy: Prices of originator efavirenz were lower than the generic because our price could not match the innovator's cost. If we start getting volume we can improve the price. We sold at a loss for a while to match the innovator until we could lower our costs. But not much was purchased at 95 cents. If you look at the volume of efavirenz supplied to Africa, it is very small at this time.

Loon: Lots of people have to take TB medication and need an alternative to nevirapine.

Ranbaxy: We have the technology to make efavirenz at a much lower cost. Now we are beginning to make a tiny profit, so there is progress. We will buy raw materials more efficiently and lower the prices.

Svilen: You say you have nelfinavir in the pipeline. When will it be available?

Ranbaxy: The problem with PIs is the high dose and difficulty to combine into a swallowable tablet. There are no other manufacturing problems that can't be solved.

Tendyai Kureya
Zimbabwe

There is a lady I work with in my office and she used to look upon herself very lowly. Literally she had given up on life. She used to wonder, "I don't know what it will be like at my funeral. I don't know what people will really think about me when I'm gone." That has all changed. Only recently she was talking about wanting to have a baby and she was exploring the different options that are available to make sure she gets an HIV-negative baby. And she was not the only one. I think almost everyone I have been working with has had that attitude after they have gone on treatment.

Thomas Zhang
China

In one village, almost 90% of people stopped taking the ARVs within a sort period of time. The main reason is because of the way they distributed the drugs without any education. They just passed them out with no information. So some of the people had the side effects and the others watched them and stopped. So there is a lack of understanding and no treatment literacy and rumors start to come out of the village, 'the government is trying to poison us.' There is a lot of misunderstanding.

Svilen: Generic tenofovir? Enteric coated ddI?

Ranbaxy: We already make enteric coated ddI. Tenofovir is in the patent mailbox. So it may be not possible to manufacture in India. Presently it looks that way. We are trying to figure out a way we can manufacture it and export it to countries with no patents.

Simon: What about abacavir, zidovudine, lamivudine? The market is for use in TB patients.

Ranbaxy: Abacavir is not widely used because doctors in India don't like to use it. A small number use it but it is growing slowly. We found that in Latin America governments are asking for abacavir.

Strides

Polly: What are your plans for developing paediatric formulations?

Strides: We made a proposal to WHO a year and a half ago for a triple drug paediatric formulation. WHO never got back to us. We need people to tell us if we are doing the right thing, making the right doses; but not much has happened. We can develop granules in sachet, which UNICEF was excited about. Clean water is still an issue. Temperature and humidity are issues. The granules can't clump together. On fixed dose, we need someone to tell us what doses, etc.

Polly: What ages or weights of babies and children were you developing formulations for? Paediatric dosing is complicated, guidelines differ from licensed dose and paediatricians don't always agree. Liquid formulations present problems in terms of volume, storage and transport and can be 3 to 10 times more expensive than the equivalent for adults. And d4T for example is not stable at higher temperatures.

Strides: We had two doses for FDCs. But we need a clinical organisation to tell us what they need.

Gregg: What other drugs do you have in the pipeline? We need tenofovir, and a better formulation of ddI.

Strides: On tenofovir, it depends on the patent situation. We don't want to market these then get into litigation. We want work with the innovator companies. The best thing is if they give voluntary licenses, then we will make them. They need to be more considerate with giving voluntary licenses. There is an advantage for them, too. The cost of making tenofovir in India would be much cheaper. It works both ways.

Svilen: So the newer products are less certain, but what about older products like abacavir and nelfinavir?

Strides: Nelfinavir is in the pipeline. WHO has said not to pay much attention to abacavir. Also there is less API available. The cost is prohibitive because the raw materials must be from an approved source. The Chinese are good at making materials at a low cost but their standards are not accepted. They don't have DMFs (Drug Master Files) that are acceptable to WHO or the FDA. So we depend on a few Indian API makers.

With our soft gel capabilities, we have ritonavir and lopinavir/ritonavir and saquinavir. Two are prequalified and five more are under evaluation. We expect prequalification in the next three months. Bioequivalence studies are completed.

Simon: If lopinavir is covered under the new patent regime, will you stop producing it?

Strides: It is not clear what would happen. Would we have to stop manufacturing until we develop a non-infringing process? We can't say yet. We sell a lot of ritonavir but not a lot of lopinavir. Making non-refrigerated ritonavir is very difficult.

Hetero

Elena: Can you speak about paediatric formulations?

Hetero: We have just recently started in this; only for the last couple of months. We have efavirenz syrup, nevirapine syrup, lamivudine syrup. But these are only available in India. We haven't gone abroad yet. It is a process that takes time. We need to have a separate facility for syrups.

Svilen: What new medications do you have in the pipeline?

Hetero: The latest is lopinavir/ritonavir and tenofovir.

Simon: Atazanavir is listed in your book. What about the legal problems?

Hetero: The APIs for atazanavir and tenofovir are absolutely ready today, but we have to see what will happen with the patent situation. We can do anything we want in R&D, but for commercialisation, patents are an issue.

Cipla

Elena: What can you tell us about paediatric formulations?

Cipla: It is not easy to make FDCs for kids. If the FDC were in the same ratio of APIs as Triomune, then it would be another matter; we could make tablets.

Simon: If the WHO guidelines for PMTCT change and recommend four or seven days of Duovir after the nevirapine dose to reduce resistance risk for mothers, would you be able to supply that too? Would you consider co-packaging?

Cipla: We will provide seven days of Duovir with nevirapine if that is what is needed.

Subha: About 20% of our patients require efavirenz as first-line therapy. When will it be ready in FDC?

Cipla: I don't think efavirenz will be so easy in FDC. Co-packaging it in the kits will improve patient adherence. We are concentrating today on kits containing didanosine, lamivudine, efavirenz: one capsule and two tablets, once a day, packaged together in a kit. We have Odivir 250 and Odivir 400. We introduced another kit: Duovir E, which is one tablet in the morning, and two at night. These types of kits with efavirenz can't be marketed for less than $700 or $800 per year.

Marie de C: When are you going to submit these new kits to the FDA?

Cipla: We are in the process of submitting the efavirenz kit for prequalification.

We have submitted Duovir and Triomune, and we hope to submit efavirenz within the next 4 to 6 months. Some of these bioequivalence studies are tricky—including ddI.

We will be introducing tenofovir, also FTC soon, then a combination of the two. Then abacavir plus lamivudine.

Gregg: Will the patents of tenofovir and FTC stop you?

Cipla: FTC was known before 1995; tenofovir is 1997. I think we can make it and see how it works out. Kits are not FDCs, so no one can stop you.

I'm a firm believer in the automatic patent of right. You don't have to ask, you just pay a fair royalty. Canadians used to be able to copy any drug they want and pay 2% royalty. They could do this until they joined NAFTA.

Quote:

Cipla: I think it is very important to work out what drugs you want for the future. What are your criteria? T-20 costs $20,000 per year. I can make T-20 for $5,000 a year. Are you interested in T-20? You have to look at efficacy and affordability side by side. We go by what is the easiest to produce, but that may not be what you need.

Tendyai Kureya
Zimbabwe

Stigma is still one of the main barriers. Many people would not like to come out in the open with an HIV-positive status. Hence, by the time they finally say - 'Okay try me on the antiretrovirals' - it is usually too late.

And the second big problem is that of literacy. A lot of people who are HIV-positive, even if they know their status, they are not literate about the medications and hence they haven't move quickly towards treatment.

Further information

Organisation websites of the participants are:

AIDS Treatment Activist Coalition (ATAC), USA
http://www.atac-usa.org
Agua Buena Human Rights Association
http://www.aguabuena.org
AIDS Foundation East-West (AFEW), Russia
http://www.afew.org
All-Ukrainian Network of PLWH, Ukraine
http://www.network.org.ua
European AIDS Treatment Group (EATG)
http://www.eatg.org
Forum for Collaborative HIV Research, USA
http://www.hivforum.org
Georgian Plus Group, Georgia
http://www.georgia-plus-group.port5.com
Gay Men's Health Crisis (GMHC), USA
http://www.gmhc.org
HIV i-Base, UK
http://www.i-base.info
Jouranlists Against AIDS, Nigeria
http://www.nigeria-aids.org
Legal Assistance Centre, AIDS Law Unit, Namibia
http://www.lac.org
Network of African People Living with HIV/AIDS (NAP+), Zambia
http://www.naprap.org
National Association of People with AIDS (NAPWA), Australia
http://www.napwa.org.au
Plus and Minus' Foundation, Bulgaria
http://www.aidsbg.info
Solidarity and Action Against the HIV Infection in India (SAATHII), India
http://www.saathii.org
Treatment Action Group (TAG), USA
http://www.aidsinfonyc.org/tag
Treatment Action Campaign (TAC), South Africa
http://www.tac.org.za

Further reading:

The Médicins Sans Frontières publication *Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries* begins by stating: "The lack of clear information on pharmaceutical prices on the international market is a significant barrier to improving access to essential medicines in developing countries. The situation is particularly complex in the case of antiretrovirals." This excellent document provides clear and verified information for potential buyers and the 8th edition can be accessed on the MSF website.

The report from the *International Treatment Preparedness Summit* in Cape Town 13-16 March 2003 which includes extensive recommendations from the community for successful antiretroviral treatment programmes can be accessed on the SAATHII website.

Other websites:

Global Fund to fight AIDS, Tuberculosis and Malaria
http://www.theglobalfund.org
MSF—Médicins Sans Frontières
http://www.msf.org
UNAIDS
http://www.unaids.org
WHO
http://www.who.int
World Bank
http://www.worldbank.org
WTO
http://www.wto.org

Companies at the meeting:

Cipla
http://www.cipla.com
Hetero
http://www.heterodrugs.com
Ranbaxy
http://www.ranbaxy.com
Strides
http://www.stridesarco.com

While preparing a presentation for the second WorldCAB meeting we went through many documents on purchasing ARV drugs in Ukraine. We found serious inconsistencies between the prices of medications purchased by the Ministry of Health and international prices. At the meeting in India we met with the top management of Cipla and found out that Cipla doesn't influence the prices of ARV drugs in the countries and that the prices are formed locally.

After we came back we conducted a thorough analysis of purchases by the MoH and prices proposed by the Global Fund. Comparison of the prices showed a difference between them of up to 27 times- the price for of nevirapine from Cipla, including all taxes, was to be $225.34 for one package, the price recommended by the Global fund was $7.65!

In 2004 a tender for 3TC was held. MoH decided to pay $169,17 but the Global Fund price was $6.48. The difference – 25 times. In 2005 3TC/AZT cost 13.5 times more. If Ukraine bought medicines according to Global Fund prices, the state would save up to $1 million, 423 thousand US dollars.

After finding such outrageous facts we started an advocacy campaign. We prepared and distributed press-releases among NGOs and government institutions in order to inform the public about severe violation of tender procedures and to advocate for the rights of PLWHA in Ukraine to receive high quality and accessible treatment. The All-Ukrainian Network of PLWHA demanded that government revise the tender for purchase of the ARV-drugs of proper quality at the world prices. Also the Network demanded to include representatives of PLWHA community into the tender committee to escape such situations in the future.

As a result of the advocacy campaign conducted by the Network the tenders were cancelled. But community representatives are still not included into government tender commission so the Network continues its work in the field of drug purchase.

Hanna Khodas
Ukraine

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