

CIPLA Ltd. And the Provision of Anti-AIDS Pharmaceuticals

It's 2001, and G. G. Brereton is a busy man. He heads the Global Intellectual Property Office at GlaxoSmithKline (GSK), a multinational pharmaceutical corporation with operations throughout the world. He is tasked with defending GSK's patents against foreign imitators. In recent months he has been occupied with infringements against GSK patents for antiretroviral drugs – the pharmaceuticals used to treat the symptoms of HIV and AIDS.

This week has been especially hectic: CIPLA Ltd. of India has just announced its offer to supply an antiretroviral “cocktail” to Sub-Saharan African countries for 3 percent of the price that GSK charges for its anti-AIDS cocktail. Top management at GSK wants options for responding to this surprising offer. G. G. has been given the job of (1) coming up with potential responses by GSK to this initiative and (2) identifying that option that best assures the continued profitability of the firm now and into the foreseeable future. He has till Friday to do it!

HIV/AIDS.

One of the most vexing public-health problems of the new century has been the explosion in cases of human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS). In the year 2000, the United Nation AIDS Organization (UNAIDS) reported that 36.1 million people worldwide were living with HIV or AIDS. There were 5.3 million new cases of HIV infection in the year, and 3.0 million deaths attributable to HIV infection. Since its first diagnosis, the AIDS epidemic has claimed 21.8 million lives.

This epidemic has been centered, and has had the greatest impact, in Africa. 25.3 million of those suffering from HIV and AIDS are in Africa

The 1990s were years of pharmaceutical breakthrough in the prevention of HIV infection and the treatment of AIDS. Five large multinational pharmaceutical corporations (Merck, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, and Roche) developed a series of drugs found to be effective in treating AIDS. Each drug was somewhat effective on its own, but physicians soon found that the drugs were most effective if used in combination in a drug “cocktail”. The cost per patient per year of this “cocktail” treatment in the US and western Europe was \$10,000 to \$12,000 USD. This was a very expensive recurrent treatment for patients in developed countries, and was clearly not affordable on a widespread basis in Africa, where in some countries per capita incomes are only one percent of the cost of the “cocktail”.

CIPLA, Ltd.

CIPLA Ltd is a pharmaceutical company based in India. It is large by Indian standards, with the equivalent of \$177 million USD in revenues in the year 2000. Its ratio of after-tax

profit to revenue of nearly 17 percent indicates that it has been quite profitable. The company manufactures 400 medications for sale in the Indian and foreign markets, and in recent years has exported its products to 125 countries. It is known on world markets as a specialist in generic pharmaceuticals.

The Chemical, Industrial and Pharmaceutical Laboratories (CIPLA) Ltd was formed in 1935 in Mumbai, India by Dr. Khwaja Abdul Hamied. Dr. Hamied studied chemistry in Berlin in the 1920s and then returned to India to begin CIPLA in a rented bungalow in 1935. With the beginning of the Second World War, the supply of pharmaceuticals from Western sources was disrupted; CIPLA stepped into the breach to provide generic equivalents of those pharmaceuticals. The corporation reported its last operating loss in 1939, and has been consistently profitable since that time.

CIPLA Ltd.

Millions of rupees

| | 2000 | 1999 | 1998 | 1997 | 1996 |
|--------------------------|-------------|-------------|-------------|-------------|-------------|
| | | | | | |
| Total Assets | 5950 | 4960 | 3829 | 2964 | 3127 |
| Buildings | 1617 | 1449 | 1225 | 1067 | 944 |
| Capital | 1950 | 1404 | 728 | 305 | 32 |
| Current Assets | 2383 | 2107 | 1876 | 1592 | 2151 |
| Net Worth | 5755 | 4624 | 3643 | 2747 | 2119 |
| Total Liabilities | 196 | 336 | 186 | 217 | 1008 |

| | 2000 | 1999 | 1998 | 1997 | 1996 |
|--------------------------|-------------|-------------|-------------|-------------|-------------|
| | | | | | |
| Revenues | 7955 | 6451 | 5410 | 4779 | 3662 |
| Expenditures | 6229 | 4906 | 4060 | 3752 | 3287 |
| B.T. profit | 1726 | 1545 | 1350 | 1027 | 375 |
| A.T. profit | 1330 | 1150 | 1020 | 707 | 290 |
| Dividends | 197 | 166 | 121 | 77 | 24 |
| Retained Earnings | 1133 | 983 | 899 | 630 | 265 |
| | | | | | |
| Rupees per USD | 45 | 43 | 42 | 36 | 35 |

His son Yusuf—who obtained a Ph.D. in Chemistry from Cambridge University—joined the corporation in 1960 as the director of research and development. In 1972, with the death of K.A. Hamied, Yusuf became the chief executive officer of the corporation. Its major market is India, but it has also been successful selling its product in foreign countries. In 1985 the US Food and Drug Administration gave its seal of approval to CIPLA's bulk drug manufacturing facilities. Cipla, Ltd is currently the third largest pharmaceutical manufacturer in India, with

plants throughout the subcontinent. A map indicating the location of these plants is provided at the end of this case.

CIPLA ignited a firestorm in international pharmaceutical circles in February 2001 with its offer to sell an anti-AIDS “cocktail” to African countries for a small fraction of the price charged by Western drug manufacturers. It has offered to supply the medical group Doctors without Borders with its three-drug cocktail for \$350 USD per patient per year, and will make the same treatment available to government agencies in those countries for \$600 USD per patient per year. Other generic drug companies in India have since duplicated CIPLA’s offer at even lower price per patient.

HIV Treatments

A pharmaceutical breakthrough occurred in the mid-1980s in the search for medicines to treat AIDS. Investigators discovered that the causal organisms of the various conditions now lumped together in the diagnosis HIV shared the common classification of retroviruses. Drugs that reduce the “load” of these retroviruses in the patient, and thus suppress the symptoms of AIDS, are referred to as antiretroviral therapies. Since retroviruses mutate rapidly to counteract the effect of any one medicine, the most potent treatments currently available involve combinations of drugs.

Zidovudine (or AZT), the first antiretroviral medicine proposed for AIDS treatments, was introduced by Glaxo (now GlaxoSmithKline) in the mid-1980s. This demonstrated initial positive effects, but its effectiveness was reduced as the retroviruses developed a resistance to it. Glaxo developed two other antiretrovirals of this sort as well: lamivudine and abacavir. Each was somewhat effective when taken separately, but was markedly more effective when taken as a three-drug “cocktail”. This cocktail is quite expensive, however, with a daily cost of about \$27 USD. Other pharmaceutical companies introduced antiretrovirals as well: stavudine and didanosine from Bristol-Myers Squibb; nevirapine from Boehringer Ingelheim; efavirenz and indinavir from Merck; saquinavir from Roche; and ritonavir from Abbott. Much costly clinical research has been undertaken by the pharmaceutical companies in recent years to identify the most effective cocktail of antiretroviral medicines.

In May 2000, under intense pressure to lower their prices in Africa and other developing nations, the five large pharmaceutical corporations introduced the Accelerating Access program. Through this program they offered to reduce sharply the prices for their antiretroviral drugs to nations in sub-Saharan Africa, where the epidemic has become a human catastrophe. Negotiations with those nations have moved slowly, but three nations (Senegal, Uganda and Rwanda) have agreed with the drug makers on a set of prices for various combinations of the drugs. Only Senegal has released the negotiated prices. Patients in that nation can drug cocktails varying between \$1,008 USD and \$1,821USD per patient per year. The deals with these three countries will provide medicine for fewer than 3,000 of the 1.3 million infected with HIV in those countries. Throughout the continent, an estimated 22 million people are

infected; 11 million have already died of AIDS-related causes.

Patent protection of pharmaceuticals.

Each of these drugs has been patented by its maker; however, each drug is also available in generic form from an Indian pharmaceutical company. Prior to 2005, Indian law provided process patent protection, so that patented drugs can be (re)manufactured in India so long as the production process used is different from the one that is patented. Another manufacturer able to create an identical product through a different process will not be violating the norms of patent law in that country. Three pharmaceutical companies in India have been active in developing generic antiretroviral medicines: Cipla, Aurobindo, and Hetero. These are able to make generic versions of the antiretroviral drugs at a fraction of the price charged by the large pharmaceutical companies. The alternative form of patent production, known as product patent protection, provides protection from the creation of identical products no matter the process. While major drug makers have product patents in some African nations, such as South Africa, in many countries patent protection is either non-existent or attached to the process of production. There is a description of the coexistence of generic manufacturers and the pharmaceutical patents for the production of AZT in the appendix.

The World Trade Organization, through its Trade-Related Intellectual Property System (TRIPS), has made standardized product patent protection a pre-condition for membership. India signed the TRIPS agreement in 1995. Signatories have until 2005 to recognize 20-year product patents for pharmaceuticals. Several nations, including South Africa, have said they are seriously thinking about importing generic drugs by applying for a special waiver from the World Trade Organization that allows the countries, in the case of national emergencies, to bypass drug-company patents.

CIPLA's drugs for HIV.

CIPLA has long been in the market for antiretroviral drugs. In 1991, CIPLA first offered zidovudine to home and foreign markets. In September 1998, it introduced its generic lamivudine in both the domestic and overseas market at less than half the prevailing global price of the time. Cipla's entry was significant because original patent holder Glaxo Wellcome (now GSK) had yet to introduce lamivudine for use in India. It had already registered its version of the drug with the Drugs Controller General of India, but had not planned to sell the product in India until January 1999. CIPLA's version of the drug was priced at \$1.16 USD per tablet as against the international prices ranging between \$2.90 USD and \$ 5.90 USD per tablet. India was estimated to have an HIV-infected population of around four million at that time.

CIPLA's ability to sell its antiretrovirals in foreign markets has been limited by the restrictions placed by patent protection. The large pharmaceutical companies have product patents on these medicines in many countries. Under those patents, the companies have the

right to dispute shipments of generic versions. In 2000, CIPLA had made shipments of a combination drug Duovir (zidovudine plus lamivudine) to customers in Ghana. In November 2000, GSK sued in Ghanaian courts to prevent the sale of Duovir in Ghana. (A copy of G.G.'s previous letter to Cipla, asking the firm to comply voluntarily with the patent restrictions, is provided in the appendix.) The ban on these imports ensures that many Ghanaians cannot afford AIDS treatment, since the price of brand-name drugs is beyond the means of most Ghanaians.

CIPLA's offer.

Dr. Yusuf Hamied announced in February 2001 that CIPLA will sell a combination of three antiretroviral drugs for \$600 USD per patient per year to governments that want to buy the therapy. Dr. Hamied said he would lower the annual price even more, to \$350 USD per patient, to Doctors Without Borders, an international nonprofit organization that provides medical services in the developing world. Both prices are much lower than the typical annual cost for the three-drug cocktail in the U.S. and Europe. The CIPLA cocktail includes generic versions of the patented drugs stavudine of Bristol-Myers Squibb, lamivudine of GSK, and nevirapine of Boehringer-Ingelheim.

Hamied says that his motivation is simple. Having witnessed a devastating earthquake that killed 17,000 people in India's Gujarat province in January, he's determined to do what he can to prevent foreseeable tragedies such as AIDS. "My idea of a better-ordered world is one in which medical discoveries would be free of patents and there would be no profiteering from life or death," he told Forbes.com. To his critics, who charge that the price war kicked off by Cipla will prevent multinationals from recouping R&D costs, Hamied protests that he's willing to pay a licensing fee for any drug he copies. As yet, though, no multinational has taken him up on his offer of 5 percent of royalties. "I've nothing against the multinationals," he recently told United Press International. "Let them do what they want to do. I'm doing my little bit."

Responding to accusations of piracy from the multinationals, Hamied says: "To say all Indians are pirates is very good PR. If I am a pirate, I am a thief. If I am a thief I have broken a law. But I abide by the laws of the land. No one can accuse me of breaking laws." He points out that no Indian drug manufacturer has been litigated against in the last 30 years. "I do not have an ulterior motive. At my age what ulterior motive can I have," protests Hamied, who is 64. "Just use the bloody thing. So what if I don't make a profit on AIDS drugs. That is not the be all or end all."

Various responses from the AIDS and pharmaceutical communities.

The Cipla offer "changes everything," said Toby Kaspar, based in South Africa as an official of Doctors Without Borders. "Every one of those countries should use the Cipla offer to help them make a better deal with the big drug makers."

Peter Mugenyi, director of the Joint Clinical Research Centre in Kampala, Uganda said,

"It's a good offer but it's still not good enough." Dr. Mugenyi, a leading African AIDS physician and researcher, said the price of the drugs "is finally coming into the reach of top government salaries," noting that in Uganda there is no health insurance or government drug-buying program. As a result, even at \$600 USD very few Ugandans will benefit from the offer, he said.

Others worry about the restrictions that patent protection may impose on the program. "We wonder what sacrifices are going to be made at the altar of profit," said Chris Ouma, a Nairobi physician with Action Aid Kenya. "Which is more deadly to Africa? Is it HIV, or is it the businessmen who have briefcases of patent applications?" Indeed, Mr. Hamied of Cipla said he isn't worried about violating patent law or of drawing a legal challenge from the companies in African countries. Instead, he said each country must deal with the legality of importing his products. "I'm not a salesman, I'm a scientist," he said. "I've made an offer. It's up to individual countries to decide, that's the way I look at it."

Guy Macdonald, a vice president at Merck, Whitehouse Station, N.J., said there remain too many variables in the Cipla offer to fully estimate its impact. "Are they going to provide it to 20 or 30 countries in Africa? Are they going to provide sustainable products? And what about quality?" Mr. Macdonald asked.

Doctors Without Borders announced it will distribute CIPLA's anti-AIDS drugs in 10 countries. Doctors Without Borders will buy the three-drug anti-retroviral cocktail for \$350 a person per year, will distribute it for free, and will take care of the legalities of importing it. "In general, where the CIPLA drug will be used, it will be supplied free of cost. Wherever it is purchased by governments, it would be sold at reduced prices," Daniel Berman of the agency's Access to Essential Medicines campaign said Friday. Berman said the agency will begin distributing the drugs in the next couple of months. He wouldn't name the 10 countries but said the program is under way in Thailand and Cameroon.

Jesuit priest Rev. Angelo D'Agostino, a former Georgetown University Hospital medical professor who runs the small Nyumbani home for orphans with AIDS or HIV in suburban Nairobi, said on 22 February 2001 that he will import deeply discounted antiretroviral medicines from CIPLA. "I am sick and tired of doing funerals," D'Agostino said. Although he estimated that the discounted drugs might be sufficient to treat only 20 of the 70 children at his orphanage, his efforts reflect increasing willingness of non-governmental organizations and AIDS activists to defy national regulations and international patent rules to buy cheaper, generic AIDS drugs. "It's really the darker side of capitalism, the greed that is being manifest by these drug companies holding sub-Saharan Africa hostage," said D'Agostino. "People are dying because they can't afford their prices."

CIPLA's announcement stirred up its Indian competitors as well. Shortly after the announcement, Hetero Drugs of India announced that it would sell the three-drug cocktail for \$347/patient/year. Hetero Drugs is a small, privately held, company. Aurobindo is also rumored to be developing a generic cocktail for \$295/patient/year. Aurobindo is based in the

southern city of Hyderabad, and is well respected in the industry as a low-cost producer of bulk drugs, those that go into ready-to-take medications or formulations. It started making AIDS formulations only three months ago. Managing Director Ramprasad Reddy was quoted in Reuters as saying "ours is probably the lowest price in the world." Asked how his company managed to offer the drugs so cheap, he said it was partly because it made all the ingredients itself. "We are just about breaking even or making small profits on these drugs. It is more of a humanitarian initiative," he added.

GSK's cost of producing the cocktail.

It's not cheap to develop new pharmaceuticals. GSK has a large research team devoted to the identification, purification and testing of new drugs for the world health market. As G. G.'s colleagues in Accounting tell him, the costs of producing the "cocktail" are relatively minor compared to the costs of testing, research and development, and marketing. While those in Accounting guard their privacy on GSK costs, they use the example in the appendix entitled "Accounting for Research and Development in Pharmaceuticals: an example" to illustrate the contribution of production costs and R&D costs to pricing a new pharmaceutical.

They ask him: "Where will we be as a corporation if we stop developing new drugs?"

Back to the Task.

G. G. has his work cut out for him. What are GSK's options in response to this CIPLA initiative? Which one will be best for the company? And, also important: will he still have a job after Friday?

Sources:

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Cipla, Ltd.



GlaxoWellcome

10th August, 2000

Cipla Ltd
Mumbai Central
Mumbai 400 008
India

FAO: Mr Amar Lulla, Director,

Dear Sirs,

Re: Lamivudine/Zidovudine combinations

It has come to our attention that you have imported your product Duovir, which contains lamivudine and zidovudine, into Ghana.

Glaxo Group Limited has exclusive rights under the following patents that cover lamivudine and zidovudine formulations in Ghana: AP11, AP136, AP162, AP300.

Importation of Duovir into Ghana by Cipla or any of its affiliates represents an infringement of our Company's exclusive patent rights. We understand that, to date, imports of Duovir into Ghana have been of limited scope and have been characterised as a "donation". We therefore do not intend to seek immediate redress. However, we reserve the right to enforce our patent rights against any further acts of infringement.

Yours faithfully,

G G Brereton
Head of Patents
Global Intellectual Property Department

AZT – a generic drug

A few other countries manufacture AZT, including Spain, Canada, Russia and Benin. AZT was first invented in 1964 as an anti-cancer drug. In the course of the early 1980s it was tested against HIV, which led to the discovery of its antiretroviral effect.

The original patent on the AZT molecule occurred in 1974: a US government-funded laboratory which made the discovery therefore applied, in 1985, for a patent on the use of AZT to treat people with HIV. A patent on the use of a molecule gives to the patent holder a monopoly on selling all drugs containing that molecule and intended to be used for the indication that is the object of the invention. It does not cover drugs that contain the molecule but intended for other indications (e.g. cancer as opposed to HIV). The American authorities then decided to grant to the British pharmaceutical company exclusive licensing rights on the AZT use patent: from then on, in every country where the AZT use patent was in force, doctors could exclusively use Glaxo's AZT to treat their HIV+ patients.

Nevertheless, in 1985 a great number of countries did not recognize patents, or did not recognize product patents, or patents on medicines, or patents on the uses of a therapeutic molecule. Thus, in many countries there is no patent on AZT: copycat versions of Glaxo's AZT may be freely imported or manufactured.

In addition to this, it remains perfectly legal in countries where there is a patent on the use of AZT in the treatment of HIV, to manufacture all the ingredients necessary for making AZT tablets at HIV indication dosage, and export these " kit-form tablets " to countries that have no patent on AZT, and that can easily and in perfect conformity with the law reformulate the ingredients into the final tablets. However, it should be noted that AZT remains an old-generation HIV drug and that nowadays it is used by a small share of HIV patients. Indeed, it is the later-generation HIV drugs, and especially third-generation antiretrovirals, that are of greatest value to people living with HIV and AIDS.

Source: www.genericsnow.org

Accounting for research and development in Pharmaceuticals: an example.

Consider the Excello pharmaceutical company. During the year, it offers four drugs on the market (A, B, C, D). It produces and sells 1 million tablets of each and has the following costs. How should it price its products?

a. Labor costs for producing:

| | |
|---|-----------|
| A | \$110,000 |
| B | \$110,000 |
| C | \$180,000 |
| D | \$100,000 |

b. raw material costs for producing

| | |
|---|----------|
| A | \$45,000 |
| B | \$65,000 |
| C | \$50,000 |
| D | \$75,000 |

c. depreciation of machinery in producing

| | |
|---|----------|
| A | \$65,000 |
| B | \$85,000 |
| C | \$40,000 |
| D | \$75,000 |

d. management, sales, advertising, legal, accounting: \$500,000

e. research and development for new drugs: \$2,500,000.

Cost allocation by profit center:

| | A | B | C | D |
|---------------------------------|--------------------|--------------------|--------------------|--------------------|
| Labor | 110 | 110 | 180 | 100 |
| Raw Materials | 45 | 65 | 50 | 75 |
| Depreciation | 65 | 85 | 40 | 75 |
| R&D | 550 | 650 | 675 | 625 |
| Overhead | 110 | 130 | 135 | 125 |
| Total cost | \$880,000 | \$1,040,000 | \$1,080,000 | \$1,000,000 |
| 20 % profit | 176,000 | 208,000 | 216,000 | 200,000 |
| Total revenue | \$1,056,000 | \$1,248,000 | \$1,296,000 | \$1,200,000 |
| Average cost per tablet | \$1.06 | \$1.25 | \$1.30 | \$1.20 |
| Marginal cost per tablet | \$0.22 | \$0.26 | \$0.27 | \$0.25 |