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International strategies for tropical disease treatments

Experiences with praziquantel

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International strategies for tropical disease treatments

Experiences with praziquantel

Edited by
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With contributions from:
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Bong-min Yang, Agnes Brinkmann, and Sameh El-Saharty

Action Programme on Essential Drugs
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Much research work, particularly in developing countries, at present goes unreported. The reasons for this include the intense competition to publish in the scientific press, and difficulties in matching the research resources of developed countries. The DAP research series was established to provide a forum for the rapid distribution of data and findings relevant to critical areas of drug policy and use. The Action Programme has a firm commitment to national operational research as part of its direct country support. It is also strongly committed to making the findings of such studies widely known and accessible. While every effort is made by the Programme to support studies of the highest possible quality, research skills and resources will vary from country to country. Documents in the DAP research series reflect this variation, and range from reports of very small scale studies, undertaken, with minimal

Note to the readers

The views expressed in this document are solely the responsibility of the authors. The Action Programme on Essential Drugs and the Division of Control of Tropical Diseases are publishing the report as a contribution to the debate on how best to provide access to new and needed drugs.

Abstract

International Strategies for Tropical Disease Treatments: Experiences with praziquantel, edited by Michael R. Reich, with contributions from: Michael R. Reich, Ramesh Govindaraj, Karin Dumbaugh, Bong-min Yang, Agnes Brinkmann, and Sameh El-Saharty.

This report identifies national and international policies that have facilitated or hindered the availability of praziquantel, the drug of choice for all forms of schistosomiasis occurring in humans. The report gives particular attention to questions of access for people in the world's poorest countries in Africa where schistosomiasis is endemic. The analysis of praziquantel illustrates more general problems in the design of national and international policies for tropical disease products, and suggests strategies for future research and action. The report's seven chapters are: Chapter 1: Policies for praziquantel; Chapter 2: Bayer & E. Merck: Discovery and development of praziquantel; Chapter 3: Shin Poong Pharmaceutical Co.: Process development in the Republic of Korea; Chapter 4: Egyptian International Pharmaceutical Industries Co.: Praziquantel formulation; Chapter 5: The international supply of praziquantel; Chapter 6: Demand for praziquantel and national distribution; and Chapter 7: Prices and production costs for praziquantel.

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A number of researchers in an international team contributed to the writing of this report. The introduction was written by the study's principal investigator, Michael R. Reich, and Ramesh Govindaraj. Chapter 2, on the discovery and development of praziquantel, was written by Michael R. Reich, Agnes Brinkmann, and Ramesh Govindaraj, using published materials and interviews. Chapter 3, on the discovery and development of an alternative production process for praziquantel in the Republic of Korea, was authored by Bong-min Yang. Chapter 4, on the formulation of praziquantel in Egypt, was co-authored by Michael R. Reich and Sameh El Saharty, based on interviews and data collected in Egypt. Chapter 5, on the international supply of praziquantel, was written by Ramesh Govindaraj, Michael R. Reich, and Karin Dumbaugh. Chapter 6, on the global demand for praziquantel, was written by Michael R. Reich and Ramesh Govindaraj, with assistance from John Norris on gathering national data of praziquantel availability and from Christopher Mast and Agnes Brinkmann on praziquantel distribution in Mali. Chapter 7, on global prices and production œsts of praziquantel, was written by Ramesh Govindaraj, Michael R. Reich, and Karin Dumbaugh.

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(US$ to local currency)

Chapter 1:

Policies for praziquantel*

Objectives of this report

The development of new drugs for tropical diseases occurs within a complex political and economic context. While the discovery of an effective compound represents scientific success, it also initiates a new round of negotiation and struggle over how the technological innovation should be made available to the sufferers of the disease. This social process becomes especially problematic when the disease sufferers are people who cannot pay for the product on their own. The search for an AIDS treatment or an AIDS vaccine highlights the economic, ethical, and political dimensions of these problems (Grady, 1995).

Similar issues have existed for a long time for pharmaceutical products that treat tropical diseases and where the disease sufferers are predominantly poor people in poor countries. This report explores the policies that evolved for one such product—praziquantel—for the treatment of schistosomiasis, a parasitic disease of major global public health importance. The discovery of praziquantel represents the most important development in recent decades in the treatment of schistosomiasis. This parasitic disease, involving five species of schistosome worms (*Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*), is estimated to infect 200 million people in 74 countries, with an exposed population of about 600 million people. The parasitic infection is transmitted through freshwater snail vectors (*Biomphalaria* and *Bulinus* species). The spread of schistosomiasis is often associated with water resource development projects (dams and irrigation schemes) that create new habitats for the snails through ecosystem changes and alter human behaviour patterns in ways that increase exposure to the parasite (Hunter et al., 1993). Praziquantel is effective treatment for all five species of schistosomes, and for both major types of morbidity (urinary lesions for *S. haematobium*, and hepatic lesions for the other species).

Praziquantel was the first anthelminthic drug to fulfill WHO's requirements for population-based chemotherapy of a broad range of parasitic infections. The chemical entity was discovered in 1972, and was developed first for the

* By Michael R. Reich and Ramesh Govindaraj.

veterinary market and then for human treatment of schistosomiasis. By 1985, approximately one million persons had been treated with praziquantel. Today, praziquantel remains the drug of choice for all forms of schistosomiasis occurring in humans, because of its high efficacy, its low toxicity, and its ease of

single, oral administration (compared to the two other major drugs currently available for treatment of schistosomiasis: metrifonate and oxamniquine). From these perspectives, the development of praziquantel can be considered a case of successful drug development for tropical diseases, involving various forms of public-private cooperation.

On the other hand, major problems persisted in praziquantel's availability throughout the 1980s, especially because of the product's price in countries with endemic schistosomiasis. Organizations around the world adopted different strategies to cope with the drug's initial high price set by the originating companies, Bayer and E. Merck of Germany. We seek to understand the origins of the pricing decisions, and how different organizations confronted those problems. But price was not the sole obstacle to availability. Even in the early 1990s, with significant price reductions in praziquantel, the product remained unavailable in many countries with endemic schistosomiasis, especially in sub-Saharan Africa. We explore some of the non-price factors that have affected the availability of this product in a number of countries.

This report places the production and pricing issues of praziquantel within the political and economic contexts of several national governments (Egypt, Germany and the Republic of Korea) and also within the activities of three international agencies (World Health Organization, UNICEF, and the World Bank). Using the case of praziquantel, the report raises broader issues of new drug development for tropical diseases, including the role of international agencies, the international patent system, and public/private sector interactions. Our analysis gives particular attention to the interactions among four actors: pharmaceutical producers, international agencies, non-governmental organizations (NGOs), and developing country governments. For praziquantel, the strategies of these four groups shaped the prices and the distribution mechanisms that determined whether the sufferers of schistosomiasis (and which sufferers) would receive the new treatment.

The experiences with praziquantel illustrate basic conflicts between private business and public health in the development of new drugs. The producers of tropical disease products include both originating companies and follow-on companies. The "research-oriented" pharmaceutical companies invest substantial resources in discovering and developing new drugs, and they expect significant returns for the risks involved. Those risks occur not only in the discovery phase, but also in the marketing and sales phase for new products, as companies face difficult pricing and distribution decisions. For tropical disease products, companies confront a basic dilemma: the ultimate consumers are usually very poor people in the world's poorest countries. The follow-on companies, which have operated in national legal environments without product patent protection, have had opportunities in "copying" new products that others have discovered, especially if they could discover an alternative production process that was patentable. This report examines how

praziquantel was developed by both originating and follow-on firms in Egypt, Germany and the Republic of Korea, how it was priced in different markets and market segments, and how these development and pricing strategies affected the product's availability in different countries.

International agencies are concerned with the availability of new drugs for tropical diseases for multiple reasons. Some agencies, such as the World Health Organization, have a mandate to improve global health, and new drugs for tropical diseases can offer an effective means to achieve health improvements. Other international bodies, such as the World Bank, seek primarily to promote economic growth and development, and new drugs for tropical diseases can provide a mechanism for dealing with unwanted side-effects of growth (such as water-borne diseases associated with water resource development projects) and for raising the productivity of workers, as well as improving overall social welfare. And UNICEF seeks to expand access to those pharmaceutical products that can improve the health condition of specific populations (especially mothers and children). The policy measures to achieve these diverse organizational goals also differ among the international agencies. For praziquantel, this report analyzes the different strategies adopted by these three international agencies and compares their impacts.

NGOs have, in some instances, served as viable alternatives to both the public and the private sectors in health care delivery by reaching under-served populations in developing countries. Using the example of praziquantel, this report examines the role of NGOs in the development and distribution of drugs for tropical diseases.

Finally, developing country governments seek access to new drugs for tropical diseases because those products can improve the welfare of their people. Many governments, however, have confronted extremely difficult financial situations in the 1980s and 1990s, with limited foreign exchange reserves, poorly performing economies, and external pressures to adjust their economic policies. Structural adjustment programmes sought to reduce government expenditures, which often restricted funds available for purchasing medicines. Governments that could not afford to spend major portions of their medication budget on new products either sought external aid, purchased old drugs, or directed patients to the private market. But in many poor countries, new pharmaceutical products are often not available in the private market, or are priced far beyond the means of the majority of the people. For praziquantel, this report examines the experiences of availability and distribution in a number of countries.

In sum, this report seeks to identify national and international policies that have facilitated or hindered the availability of praziquantel, especially for the world's poorest countries in Africa where schistosomiasis is endemic. Our analysis of praziquantel illustrates more general problems in the design of national and international policies for tropical disease products, and suggests

strategies for future research and action. This study of praziquantel's production and pricing involved an international team of policy analysts, with expertise in economics, political science, management, business policy, and tropical diseases, based in Egypt, Germany, the Republic of Korea and the United States of America.

Structure of the report

The report's next three chapters (2, 3, and 4) present the development and production of praziquantel by private pharmaceutical companies in Germany, the Republic of Korea, and Egypt respectively. The following three chapters (5, 6, and 7) of the report analyze the international supply, demand, and pricing for praziquantel. Most of the material in this report represents original research and includes a number of new findings. This introduction reviews the main findings of the report's six chapters, and draws some conclusions about policies for praziquantel and the broader implications of this case study.

The report begins, in Chapter 2, with a discussion of praziquantel's discovery and development, focusing on the activities of Bayer and E. Merck, and the interactions with the World Health Organization, particularly in arranging clinical trials. Bayer and WHO worked together in multicentre trials to demonstrate praziquantel's safety and efficacy, and achieved scientific success.

Chapter 3 presents the development of a different production process for praziquantel, by the Shin Poong Pharmaceutical Co. in the Republic of Korea. This chapter places Shin Poong's development of praziquantel within the context of several Korean economic policies: the promotion of import substitution, the protection of infant industries, and particularly the national policy of process patents and not respecting product patents. Shin Poong worked with a government research institute and received government financial support to develop an alternative production process for praziquantel for treatment of liver fluke in Korea. For a remarkably low investment of corporate funds—the equivalent of about US$ 14,000—Shin Poong succeeded in creating an alternative, innovative, and cost-saving production process for praziquantel. The company then registered the new product and obtained patent rights to the process in the Republic of Korea and other countries, and followed a business strategy that squeezed Bayer's share of both domestic and international markets for praziquantel. This form of public-private cooperation in the Republic of Korea resulted in significantly reduced prices for praziquantel in Korea, and in other countries as well after Shin Poong pursued exports from the mid-1980s.

Chapter 4 presents the formulation of praziquantel in Egypt, the largest single-country market for praziquantel (except perhaps for China*). The Egyptian International Pharmaceutical Industries Co., one of Egypt's few private pharmaceutical companies, formulates the drug, using raw material imported from the Republic of Korea. EIPICO began formulation of praziquantel in 1987, and its strategy, which depended on Egypt's lack of product patent protection for pharmaceuticals, resulted in major price reductions within Egypt. In 1994, for example, Bayer's product sold at less than half its entry price in 1983 (in nominal terms). EIPICO also won the government's tender for praziquantel from 1990 on (at the price of about US$ 0.26-27 per 600 mg tablet in 1992), providing the company with a major source of revenues, as the Ministry of Health purchased huge quantities of the locally formulated product.

Chapter 5 analyzes the international supply of praziquantel, since its introduction into the market in the late 1970s, and provides the first public estimate of total global supply, of 89 million tablets (600 mg.) in 1993, based on our estimates of production firm by firm. The chapter analyzes the major producers and formulators, and discusses global distribution systems, including the role of international agencies. Among international agencies, UNICEF pursued a strategy of globally concentrated bulk buying through its supply and distribution facility in Denmark, in efforts to provide praziquantel at reduced prices to developing countries, successfully pushing its purchase price for a 600 mg tablet from US$ 0.65 in 1985 to US$ 0.22 in 1994, and beginning in the late 1980s to purchase the product from Shin Poong. WHO, on the other hand, in the late 1980s and early 1990s, pursued a strategy of seeking to negotiate an arrangement with Bayer for a reduced price and for donations of the product, without yet achieving an agreement (as of December 1996). The World Bank, meanwhile, provided loans to a number of endemic countries for purchases of praziquantel through open tenders, resulting in significantly increased availability of praziquantel in several countries (especially China, Egypt, and the Philippines). Despite these efforts, in the early 1990s, many poor countries in Africa still lacked access to praziquantel for their schistosomiasis control programmes, with only limited availability in their private markets.

Chapter 6 presents the global demand for praziquantel, based on WHO's estimates of national "need," and compares those figures to availability, based on our collection of national data. The analysis shows a major gap between our estimate of international supply (89 million tablets) and WHO's estimate of global "need" (424 million tablets). The chapter also reviews the availability of praziquantel in several endemic countries, provides a critical analysis of existing cost studies of schistosomiasis control efforts, and examines various problems that affect national distribution.

* China procured a huge volume of praziquantel in the early 1990s, with a significant proportion apparently designated for treatment of cattle. We were unable, however, to obtain data on human versus veterinary consumption of praziquantel in China. For additional discussion, see Chapters 3 and 6.

Chapter 7 analyzes the prices and production costs of praziquantel, showing that the price of praziquantel declined significantly in the late 1980s and early 1990s, as product patents expired in various countries and as the number of generic producers and formulators grew. The chapter examines the market segmentation strategy used by the producers, and the price differentials that existed, especially between developed country markets, the private market in developing countries, and the tender market. In the early 1980s, the retail pharmacy price for praziquantel in West Germany was about US$ 6.50 per 600 mg tablet. At that time, Bayer offered bulk discounts to international agencies at about US$ 0.90 per tablet, which still was beyond the means of most governments in poor countries. The Bayer and E. Merck patent (dated 17 December 1973 in West Germany) began to expire in some countries in 1989, reached expiration in West Germany in December 1991, and expired in most other Western countries in December 1994, with the US patent expiring in January 1994. In late 1994, several reputable producers offered a bulk purchase price of US$ 0.13-14 for a 600 mg tablet, reflecting the increased level of competition in the global market for praziquantel. The chapter analyzes the production costs and pricing strategies used by the major producers (Bayer, E. Merck, and Shin Poong).

Lessons learned

The case of praziquantel demonstrates that the discovery of an innovative and effective new drug does not necessarily result in access to the drug for persons who suffer from the now-treatable disease—especially if those sufferers are poor people in the world's poorest countries. The case raises questions about the international systems that affect the availability of new drugs in poor countries and how those systems could be improved for each of the four major actors considered in this report.

Pharmaceutical Producers: Multinational pharmaceutical companies are the major developers of important new drugs, and they view rich countries as their core markets. These companies tend to disregard the "needs" of poor countries (particularly countries with small markets and poor growth prospects), because private firms are primarily demand-oriented and profit-driven. For example, Bayer has significantly reduced its research efforts on tropical diseases, and has focused its research on developing products for chronic diseases (such as cardiovascular products, antihypertensives, cancer drugs, and products for Alzheimer's disease). Indeed, praziquantel is Bayer's only major drug left for tropical diseases. Similarly, other companies are focusing on the more lucrative and more certain markets of rich countries or middle-class patients in poor countries. When companies discover a new drug that can benefit poor people in poor countries, they confront a series of problems, illustrated by the praziquantel case.

The first problem is pricing. Many multinational companies are seeking to set single global prices for new products—at least as much as national regulatory authorities will allow the firms to do so. This pricing strategy would effectively deny many new products to poor people in poor countries, since the governments lack the necessary foreign exchange resources to pay the full price, and poor patients cannot pay the private market prices. When Bayer launched praziquantel, it set a concessionary price for WHO, but this lower price did not have a significant impact on availability, because few countries obtained the product through WHO.

A second problem is purchasers. The private market in many developing countries at the initial launch price is very limited, and even the market at the concessionary price is limited. Donor agencies are often unwilling to provide grants for procuring new drugs on a continuing basis. Some bilateral aid agencies may be willing to provide project grants that include procurement funds for several years, as a form of indirect support for their nation's firms (as the German aid agency, GTZ, did for a number of years for Bayer's praziquantel), but this approach does not always work. For example, Merck & Co. was unable to persuade USAID to purchase ivermectin for treatment of onchocerciasis (Weiss, 1991).

One possible strategy (to resolve the pricing and purchasing problems) is for the producer to donate the new drug. Although Merck decided to donate ivermectin indefinitely for treatment of onchocerciasis, no other company has followed Merck's lead. Bayer has steadfastly resisted efforts to persuade the firm to donate praziquantel, pointing to the potentially far greater patient population and treatment costs of schistosomiasis compared to onchocerciasis. If full donation is too much to ask for a profit-driven organization, then cross-subsidization could be another possible strategy (especially for products with significant veterinary sales, which Merck receives for ivermectin and Bayer for praziquantel).

A third problem is patents. Multinational drug companies strongly supported the efforts to strengthen intellectual property protection in the Uruguay round of the GATT international trade negotiations. These companies have argued that all countries, including poor countries, should enforce product patents, and not allow the weaker protection of process patents. The companies generally consider the development of alternative manufacturing processes to be free-riding on their development costs, an infringement on their intellectual property rights, and a form of patent piracy, while many developing countries have considered this practice a fair strategy in their national efforts to catch up in the race for technology development.

A system of product patents is intended to protect the returns to inventors of products and thereby create incentives for innovation. A number of analysts have argued that tighter patent protection in poor countries will create economic growth and benefits for these countries (by creating incentives for

innovation and technological progress), and that the benefits will significantly exceed the costs (Rapp and Rozek, 1990). But these arguments tend to ignore the lumpiness and non-tangible nature of certain costs associated with greater intellectual property protection. A strict product patent regime in Egypt and the Republic of Korea would have prevented Shin Poong from developing its own version of praziquantel, would have significantly delayed the price competition in the Republic of Korea and other countries, would have prevented EIPICO from producing the drug and selling it at lower prices, and would have delayed access to the drug for many people in many countries—until after the product patent expired in various countries in the early 1990s. A tighter international patent regime may enhance economic growth in some countries (and will enhance profits for certain companies), but it will also create burdens for some vulnerable populations who have depended on reduced prices of "copies."

The experience with praziquantel suggests that pharmaceutical producers need to find ways to make some new products available to poor people in poor countries, without undermining their core business interests. Companies need to explore innovative strategies on pricing, purchasers, and patents, in order to achieve their social welfare mission, especially for highly effective products that have significant revenues from other major markets, such as the veterinary sales of antiparasitic drugs and many antibiotics.

International Agencies: For praziquantel, the World Health Organization facilitated the drug development process through its assistance with clinical trials, but then did not effectively promote access in developing countries. UNICEF and the World Bank adopted their own independent approaches. The three agencies lacked a coordinated strategy on praziquantel, and thus perhaps missed opportunities to improve availability in schistosomiasis-endemic countries. None of the agencies, for example, developed a database on consumption or procurement of praziquantel in endemic countries—not even for countries with national schistosomiasis control programmes. This instance reflects broader problems of fragmentation and competition within the UN system. Similar kinds of organizational obstacles among UN agencies may exist for other new drugs that are needed by poor people in poor countries.

Nongovernmental Organizations: NGOs seem to hold a potential for addressing both government failures and market failures (Drabek, 1987; Reich, 1994)—what Charles Wolf (1988) called the problem of "choosing between imperfect alternatives." The case of praziquantel suggests that NGOs can help provide new drugs (and other drugs) to vulnerable populations in poor countries, and thereby alleviate some of the inequities and problems discussed above.

But the case of praziquantel also suggests that NGOs are unable to affect the basic rules that shape drug development and drug distribution for tropical diseases. Some NGO supplier organizations responded to opportunities created by the availability of Shin Poong's product on the international market and by

the subsequent availability of raw materials from other sources (such as China), and thereby contributed to price reductions through their competition. But these organizations had little direct impact on the decisions taken by the major producers or the international agencies. For off-patent products, non-profit supplier organizations may be able to expand distribution in markets that multinational corporations and international agencies do not reach. Problems seem likely to remain, however, for the distribution of new (and high-priced) drugs for poor people in poor countries.

National Governments: According to the World Bank's *1993 World Development Report*, national governments can significantly improve the efficiency of their procurement procedures for pharmaceuticals through global purchases from low-cost suppliers (World Bank, 1993). The report's discussion of efficient purchasing strategies, however, made no mention of whether countries should respect product patents. Indeed, buying drugs from sources that do not observe patent laws can be highly cost-effective (as long as the products are of good quality), as the praziquantel case demonstrates.

While the World Bank's report on health maintained silence on the question of patents, the government of the United States of America has been increasingly vocal about protecting intellectual property rights in poor countries that are growing economically, especially China. Of course, rich countries have a long history of seeking to impose their intellectual property laws on the world's poorer nations (Alford, 1995). Some countries (such as Egypt and the Republic of Korea) were able to adopt national policies that protected domestic industries and disregarded international patent regimes. These countries are now being pressured to comply with the new international order on product patents (WHO, 1995). But even *The Economist* recognized the one-sided nature of intellectual property (with rights held almost entirely by rich countries) and raised questions about the fairness of expecting poor countries to honor these rights in all instances (*The Economist*, 1994).

The world's poorest countries, with the worst prospects for growth, face the most difficult outlooks. They have little leverage on donor agencies. Their domestic markets give them little leverage on multinational companies. They have extremely limited foreign exchange reserves. They face external pressures to adjust their economic policies (e.g., through structural adjustment programmes) and reduce government expenditures, which often restrict funds available for purchasing medicines. And their government organizations often lack adequate infrastructure for carrying out effective international tenders for purchasing.

In conclusion, the case of praziquantel highlights the dilemmas that result from the discovery of new drugs for diseases of public health importance in poor countries. Some new drugs, such as praziquantel, hold the potential for significantly improving human welfare in poor countries. But those welfare gains are not often achieved, due to the policies of producers, international

agencies, NGOs, and governments. This study identified specific measures that could raise the probability of achieving those welfare gains.

Our analysis shows that the greatest gaps between need and supply for praziquantel have occurred in the poorest countries of the world, especially in Africa. In these countries, the private markets for praziquantel are very limited, and the governments cannot afford to spend major portions of their drugs budget on new products. Even when price problems are addressed, non-price problems (such as inadequate distribution systems) prevent good drugs from reaching poor people in poor countries.

The praziquantel case illustrates that, for poor people in poor countries, the benefits of new drugs are achieved only after great delay, if at all. To reduce those delays significantly, simultaneous implementation of several measures discussed above may be necessary. When that happens (as shown by the cases of Egypt, the Republic of Korea, and China for praziquantel), substantial gains in public welfare can be realized.

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Chapter 2:

Bayer & E. Merck: Discovery and development of praziquantel*

The most important development in recent decades in the treatment of schistosomiasis is the discovery of praziquantel. This pharmaceutical product is the first anthelminthic drug to fulfill the World Health Organization's requirements for population-based chemotherapy of a broad range of parasitic infections (Wegner, 1981). This chapter presents some of the therapeutic precursors of praziquantel, and then describes the discovery and initial testing of praziquantel, with particular attention to the role of WHO. Competing drugs for schistosomiasis treatment and the veterinary uses of praziquantel are briefly discussed.

This report does not provide a review of the biology and epidemiology of schistosomiasis, or of the clinical and pharmacological properties of praziquantel, since a vast literature on these topics exists (for a review of schistosomiasis morbidity, see Gryseels, 1989; for a review of praziquantel therapy, see Kumar and Gryseels, 1994). Schistosomiasis is estimated to infect 200 million people in the world today, with an exposed population of about 600 million people, and occurs mainly in rural populations in frequent contact with freshwater. The disease is endemic in 74 tropical countries, and involves five species of schistosome worms: *Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. intercalatum*, and *S. mekongi.* Praziquantel is effective treatment for all five species and for both major types of morbidity (urinary lesions for *S. haematobium*, and hepatic lesions for the other species). The spread of schistosomiasis is often associated with water resource development projects (dams and irrigation schemes) that create new habitats for the snail vectors through ecosystem changes and alter human behaviour and settlement patterns in ways that increase exposure to the parasite (Hunter et al., 1993).

Praziquantel was the result of collaborative work between two German pharmaceutical manufacturers: Bayer A.G., Leverkusen, and E. Merck, Darmstadt. The anthelminthic activity of pyrazinoisoquinoline derivatives was discovered in 1972 in the laboratories of Bayer, and was followed up by J. Seubert and others at E. Merck (Andrews, 1981; Seubert et al., 1977a). Praziquantel's curative efficacy against a broad spectrum of platyhelminths pathogenic to man was confirmed in testing during the following years

* By Michael R. Reich, Agnes Brinkmann, and Ramesh Govindaraj.

(Wegner, 1984). The compound was patented in Germany in December 1973, and in the United States of America in 1977 (Seubert et al., 1977b). Praziquantel became available in Europe after 1978 (King and Mahmoud, 1989), and generally available on the international market in the 1980s. Table 2.1 presents data on Bayer/E. Merck's registration of praziquantel patents, along with the estimated patent expiry dates.

Table 2.1: Bayer/E. Merck's praziquantel patents

Country	Registration number	Expiration date
Argentina	208715	1992: 28 February
Australia	485552	1990: 16 December
Belgium	823400	1994: 16 December
Canada	1036606	1995: 15 August
Denmark	141845	1994: 16 December
Egypt		1984: 16 December
France	7441356	1994: 16 December
Germany	2302539	1991: 17 December
Greece	60708	1989: 17 December
Guatemala	3221	1994: 10 April
Hong Kong	133/79	1994: 12 November
Iran	18749	1994: 16 December
Ireland	40124	1990: 18 November
Israel	46162	1994: 29 November
Japan	1194423	1994: 17 December
Kenya	2946/79	1994: 12 November
Luxembourg	71204	1994: 29 October
Morocco	16807	1994: 9 December
New Zealand	176193	1990: 12 December
Nigeria	3044	1994: 14 December
Norway	142304	1994: 16 December
Pakistan	124888	1990: 18 November
Peru	1231	1983: 16 November
Philippines	14220	1998: 2 April
Poland	94074	1989: 16 December
Portugal	63084	1991: 27 April
Republic of Korea	8125	1992: 30 January
Romania	66907	1989: 13 December
Sweden	7415686-0	1994: 13 December
Singapore	74/1979	1994: 12 December
Spain	432974	1996: 15 October
South Africa	74/7259	1990: 12 November
Taiwan	12207	1992: 17 December
Tanzania	1969/1979	1994: 12 November
United Kingdom	1441554	1994: 12 November

USA	4001411	1994: 4 January
USSR	631070	1989: 17 December
Yugoslavia	41288	1997

Source: Bayer AG.

Praziquantel also has significant veterinary uses, and was approved in 1980 for such uses in the United States of America (*Scrip*, 1981), followed by approval and registration for human use in 1982 by the Food and Drug Administration (*Scrip*, 1981).

Precursors of praziquantel at Bayer and E. Merck

The discovery of praziquantel at Bayer and E. Merck is the latest chapter in a long series of attempts by these companies to develop drugs to combat schistosomiasis. Patients had a low tolerance toward the earliest drugs developed by Bayer and other firms, such as carbon tetrachloride, oil of chenopodium, sentonin, and pelletierine (Goth, 1976). Only in the late 1920s, when Bayer developed Fuadin (stibophen), was the firm able to offer a more broadly useful product against schistosomiasis. The drug had originally been developed for the veterinary market, and was then tested in an experiment by the Egyptian government on 150 patients (Verg et al., 1988). While it proved effective, Fuadin had to be injected in multiple doses, and thus was not appropriate for population-based schistosomiasis control programmes.

In 1953 Bayer introduced Miracil D (lucanthone hydrochloride), a thioxanthone, which used some of the knowledge gained in malaria research. This compound had been found effective against schistosomiasis (particularly against *S. haematobium*) in the Bayer laboratory in Elberfeld in 1943, but could not be tested overseas during the Second World War. After the war, once it had been tested in Egypt, the Congo, Southern Rhodesia, and Latin America, Miracil D was introduced in the market as a schistosomiside (Verg et al., 1988).

Other drugs, mostly manufactured by other firms, have been used in the treatment of schiostosomiasis in humans, including: antimonial compounds, such as antimony potassium tartarate or tartar emetic (effective against *S. japonicum*), sodium antimonyl gluconate, and stibocaptate; non-antimonials (also effective against *S. japonicum*), such as amoscanate (nithiocyaminum), and a combination of furapromidum and rectal dipterex; benzoimidazoles, such as niridazole (Ambilhar, which is effective against *S. haematobium*); and thioxanthones, such as hycanthone (Goth, 1970, 1976). The use of most of these drugs has now been discontinued, due to the availability of more effective and less toxic drugs, namely, praziquantel, oxamniquine, and metrifonate (Clark et al., 1988).

Along with their attempts to develop drugs for treatment in humans, both Bayer and E. Merck also tried to combat schistosomiasis by developing drugs to

decrease the population of fresh water snails that act as intermediate hosts in the spread of schistosomiasis. One such drug, used effectively to control snail populations, was Bayluscide (niclosamide), developed by Bayer and first marketed in 1962. Bayer carried out successful trials in eight African countries, and a large field trial in 1967 in the Egyptian oasis El Fayoum, where 1.2 million people were living. This field trial was co-sponsored by the Egyptian and German governments (Verg et al., 1988).

While Bayluscide was successful in the field trial in reducing the snail population, and thus in decreasing the proportion of the population with schistosomiasis, several limitations of molluscicides became clear (Verg et al., 1988; WHO, 1993). The only places where the host snails could be efficiently and effectively contained with Bayluscide were geographically isolated areas like oases, that is, places where water was not flowing from a non-treated site to a treated site, and where the administration of the pesticide was in the hands of one local or national government. This realization led to an increased emphasis on research for drugs for treatment of humans, which culminated in the development of praziquantel, named Biltricide by Bayer.

Discovery process and initial testing of praziquantel

At the beginning of the 1970s, the search for effective tranquilizers with few side effects was being actively pursued in the pharmaceutical industry. Scientists at E. Merck considered the pyrazinoisoquinoline substance group a promising possibility, but found that relatively high doses had to be used in order to achieve an effect comparable to that of established tranquilizers. As a result, the compounds in this group were not pursued further at E. Merck; according to an agreement between the two firms, the compounds were passed on to Bayer for veterinary screening (Groll, 1984). Using a step-by-step procedure, the most effective substance, praziquantel, was chosen from a total of approximately 400 compounds. This substance was found to be an effective anthelminthic against a broad spectrum of parasitic trematodes and cestodes (Andrews et al., 1983). The drug was first developed for veterinary use and later tested for the treatment of helminthic infections in humans.

The therapeutic potential of praziquantel for the treatment of *S. mansoni* infections was first explored by Andrews and Gönnert in 1977 at the Research Centre Wuppertal using the schistosoma / mouse model (Andrews et al., 1983). In wide-ranging preclinical studies in many animal species, they showed praziquantel to be highly effective experimentally and clinically against all species of schistosomes pathogenic to man and a wide range of cestodes (Davis, 1982). They obtained particularly good results in all of the *S. mansoni* strains (Wegner, 1979). An important observation was that the drug was also effective in the oral form. In addition, its acute toxicity was tested in rats, mice, rabbits, and dogs, and was shown to be very low compared to other schistosomicidal drugs.

Following promising results in animal experiments on toxicity and efficacy, therapeutic trials with healthy volunteers (Phase IA) were begun in 1978. In the Human Pharmacology Center at E. Merck, Leopold and co-workers performed a complex study involving 36 healthy volunteers in 1978 (Leopold et al., 1978). Tolerance and pharmacokinetics were tested for doses that were increased by steps to three doses of 25.0 mg/kg body weight each. No clinically relevant drug-related changes were detected by the extensive psychological, clinical, neurological, hematological and clinico-chemical examinations of the volunteers. The absence of toxic alterations of vital functions and organs in these pharmacokinetic studies in man confirmed the therapeutic potential of praziquantel (Wegner, 1979). Comprehensive toxicological studies, which employed a wide variety of test systems, were also carried out by WHO in collaboration with the International Agency for Research on Cancer. The tests found no mutagenic, carcinogenic, embryotoxic, or teratogenic activity of praziquantel (WHO, 1985).

WHO and Bayer cooperation

Bayer contacted WHO at an early stage of drug development and asked for advice and support for the further clinical development of praziquantel. According to Wegner (1981), "A close and fruitful cooperation was established, which resulted in the setting up of well coordinated trial protocols. Case report sheets were standardized as far as possible for the first intercontinental multicentre trials in investigational phases IIA, IIB, and III." An overview of the literature about these first stages of clinical trials and conferences is given by Dollery (1991).

In this collaboration, clinical trials of tolerance to praziquantel and of its therapeutic effects against the three common species of schistosomes infecting man (*S. haematobium*, *S. mansoni*, and *S. japonicum*) were conducted jointly by the WHO Parasitic Diseases Programme, and the Medical Department in the Pharmaceutical Research Centre of Bayer, in Africa, Japan, the Philippines and South America (Wegner, 1981). The studies on *S. haematobium* infections were carried out in Zambia, at the clinical pharmacology unit of the WHO Tropical Diseases Research Centre, Ndola Central Hospital, Ndola (Davis et al., 1979); and on *S. mansoni* infections at the Centro de Pesquisas, Belo Horizonte, Brazil (Katz et al., 1979). In the case of *S. japonicum* infections, double-blind studies of tolerance were conducted in the Koma-Kyoritsu Hospital, Yamanashi, with the advice of the National Institute of Health, Tokyo, Japan (Ishizaki et al., 1979), complemented by clinical trials of tolerance and efficacy performed by the Schistosomiasis Control and Research Team at Palo, Leyte, Philippines (Davis and Wegner, 1979; Santos et al., 1979). In all endemic areas, the double-blind trials confirmed not only good tolerance in patients but also high efficacy against the local schistosoma species (Wegner, 1981).

Dose-finding is a difficult and time-consuming process. Animals tolerate drugs quite differently than man. Mice, for example, tolerate praziquantel 20 times better than man, and in baboons a single dose of 75 mg/kg body weight was effective against *S. haematobium* (Webbe et al., 1981). The task was to determine the dose that eliminated the parasite in mice without adversely affecting humans. Phase IA studies showed that healthy volunteers tolerated the compound in oral doses of 50 mg/kg body weight as a single dose, and in three doses of 25 mg/ kg body weight each. Could these results be confirmed in schistosomiasis-infected patients who were of different ethnic origins? Was the effect on schistosome species pathogenic to man experimentally observed in different test animals the same when those parasite species were found in man? (Wegner, 1981) Did strains of different geographical areas behave differently? Could certain groups of patients be treated safely, such as young children and pregnant women? And would the dose found to be effective in healthy volunteers be appropriate for large-scale treatment? All these questions had to be addressed and answered.

The investigational clinical trials were started in selected medical centres with extensive facilities and highly trained staff, where the drug was tested for tolerance and efficacy. Then a broader spectrum of trials was conducted in hospitals without special facilities and at offices of medical practitioners. The last step was field trials.

Investigational Phase IIA studies confirmed the efficacy of praziquantel and the absence of significant side-effects in uncomplicated infections of the three major human schistosomes in people of different ethnic origin. Davis et al. (1979) conducted double-blind trials to test the tolerance and efficacy of oral doses of 20 mg praziquantel in a single dose, two doses of 20 mg each, and three doses of 20 mg each, in 79 patients with uncomplicated infections in Zambia (Davis et al., 1979; Davis et al., 1981). J.E. McMahon (1981) at the Helminthiasis Research Unit MCC/WHO found that increasing the dose above 30-35 mg/kg body weight did not increase efficacy. The findings of these studies on tolerance and efficacy were so encouraging that extended investigational Phase IIB studies were started. In these studies, patients were allotted to three strata to find out different dose levels, according to the degree of worm burden, patient's age, and the occurrence of severe adverse reactions in patients with hepatosplenic complication in advanced stages. Simultaneous infections with different schistosome species were studied, and finally the dose best suited under field conditions was identified (Wegner, 1981).

In all these trials, praziquantel was well tolerated in a battery of tests. The tests confirmed the absence of toxic effects of the drug on vital organs, systems and functions. According to a study by da Silva and co-workers (1981), praziquantel can even be safely given to patients with hepatosplenic complications. The overall results of the clinical multicentre trials showed that a single dose of 40 mg/kg body weight for *S. haematobium* and *S. mansoni*, and two doses of 30 mg/kg body weight for *S. japonicum* gave cure rates at six

months between 75% and 100% in the various samples of patients treated (Wegner, 1984). The final phase of the clinical trial programme was the use and evaluation of the preferred doses under field conditions in large-scale community projects that were undertaken by numerous investigators in different countries (Davis, 1993). In 1984, Wegner reported the safe and successful treatment of 25,000 patients in 3 continents up to 1982. Trials were conducted in as many as fifty different sites scattered over the globe (Davis, 1982). A list of trial places is given by Wegner (1984).

By 1985, approximately one million persons had been treated with praziquantel (WHO, 1985). From the discovery of praziquantel until 1983, over 400 publications were written to document the preclinical and clinical observations about the new drug (Andrews et al., 1983). Many experiments, broad clinical experience, and large-scale field control programmes all confirmed the therapeutic validity of the initial trials (Davis, 1993).

While the collaboration between Bayer and WHO was quite successful in conducting clinical trials for praziquantel, the relationship apparently did not include a written agreement on issues of pricing or distribution methods once the product was fully developed and registered. Some observers mentioned the existence of a "good faith agreement" between individuals involved in the two organizations. Our research, however, was unable to identify any documents that would support the existence of an agreement between the two organizations or the individuals on critical questions of how praziquantel would be made available.

In 1994, anecdotal reports emerged about the resistance of certain strains of schistosomes to praziquantel (Brown, 1994). However, as Cook and Reich (1996) noted, "Although there have been case reports of increased tolerance to praziquantel, resistance (in the sense of single-step complete resistance, as seen in bacterial infections) has not been reported. Tolerance to praziquantel is possible, but resistance has not been reported to be a problem." Unless the situation changes dramatically, praziquantel remains the drug of choice and the mainstay of treatment for schistosomiasis (WHO, 1993). It should be noted that the remarkable effectiveness of praziquantel against various helminthic species (including schistosomes) has directed attention away from further research and new drug development. This unintended consequence of praziquantel's success may well prove to be an Achilles' heel, should resistance to praziquantel become more widespread in the future. On the other hand, the development of an effective vaccine for schistosomiasis could reduce the demand for praziquantel significantly.

Competing drugs for schistosomiasis treatment

Currently only three drugs are used on a global scale for the treatment of schistosomiasis: praziquantel, metrifonate, and oxamniquine. All three have a

history of successful usage at the individual clinical level and in population or community-based chemotherapy (WHO, 1985), and all three appear on the WHO Model List of Essential Drugs. However, praziquantel remains the drug of choice for all forms of schistosomiasis occurring in man, because of its high efficacy, its low toxicity, and its ease of single, oral administration (Gustafson et al., 1987; WHO, 1993).

Oxamniquine is only effective against intestinal schistosomiasis (*S. mansoni*), and has been used successfully in South America. The effective dose varies between 15 mg/kg and 60 mg/kg given over two to three days, but dosage recommendations should be based on local experience (WHO, 1993). Capsules and syrup need to be kept in well closed containers, protected from light (WHO, 1993). It is a valid alternative drug for the treatment of *S. mansoni*; in fact, strains resistant to praziquantel still respond to this drug (Cioli et al., 1993; Fallon et al., 1994). However, oxamniquine has more side-effects and is more expensive than praziquantel, at least in Africa and in Latin America (Gryseels et al., 1987; Stelma et al., forthcoming).

Metrifonate is only effective against urinary schistosomiasis (*S. haematobium*), but it has been significantly less expensive than praziquantel—until recent price reductions in praziquantel. Metrifonate has been available at US$ 0.05 per 100 mg tablet in the international market, but must be given in 3 doses of 10 mg/kg two weeks apart. For a 50 kg adult, the medication cost for metrifonate would be US$ 0.25 per dose, and US$ 0.75 for three doses. The same individual would require a single dose of praziquantel (at 40 mg/kg), costing US$ 2.00 (at late 1980 prices of US$ 0.60 per 600 mg tablet), but now costing only US$ 0.50 per treatment (at the lowest available price of US$ 0.15 per tablet, in 1995)—less than the cost of a metrifonate treatment. Other factors also contribute to the choice of praziquantel over metrifonate. The metrifonate treatment schedule has a low rate of compliance, which leads to a generally lower cure rate than praziquantel (Utroska et al., 1989). Metrifonate tablets need to be kept in tightly closed containers and stored at temperatures not exceeding 25 degrees centigrade, preferably in refrigerators (WHO, 1993). A study from the Congo showed that praziquantel was more cost-effective than metrifonate in reducing schistosomiasis prevalence to a level of less than 5% of the population (Korte et al., 1986).

Veterinary uses of praziquantel

Praziquantel is used extensively in veterinary practice. The veterinary versions of praziquantel, however, may be produced by different firms, and may use different production processes. Veterinary products are not subject to the same Good Manufacturing Practices (GMP) regulations that apply to human products. In particular, the quality control standards and the sterility requirements are far less stringent.

Among the veterinary products in the market that we could identify, praziquantel is the active ingredient in Droncit (Bayer), which is used for the control of Echinococcus multilocularis, as a 34 mg tablet, or as an injectable containing 56.8 mg/ml of praziquantel (CFR, 1993b; Jordan et al., 1993). Echinococcus multilocularis is considered one of the most deadly of all zoonotic helminthic infections, and, therefore, is a zoonosis of increasing global concern. Dogs, cats, foxes, and coyotes are the most common hosts. Humans can become infected with the larval stage of this parasite, which leads to alveolar hydatid disease. Use of praziquantel for the treatment of this disease in animals, therefore, has important public health implications.

Droncit is also available in a 11.5 mg oral tablet form for the treatment of cestode-related infestations in cats (CFR, 1993a). Further, praziquantel is a constituent of a combination drug, Drontal (Bayer), which contains 18.2 mg praziquantel and 72.6 mg pyrantel, and is used in animal practice for the removal of tapeworms, hookworms and large roundworms in cats (CFR, 1993c) .

Praziquantel is also marketed by Miles Pharmaceuticals, the US subsidiary of Bayer, as Vercom, an oral paste formulation. A similar febantel-praziquantel oral paste is available for the removal of hookworms and ascarids in dogs (CFR, 1988). Finally, a US company, Mobay Corporation, manufactures an OTC version of praziquantel for use in dogs and cats, which was approved by the FDA effective January 23, 1990 (CRF, 1990).

Recently, a new use for praziquantel was proposed in veterinary practice, with public health implications. Praziquantel was used for the treatment of ducks, which are the carriers of the trematode that causes Swimmer's Itch in humans (Blankespoor and Reimink, 1991).

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Chapter 3:

Shin Poong Pharmaceutical Co.: Process development in the Republic of Korea*

Shin Poong Pharmaceutical Company Ltd.

The Shin Poong Pharmaceutical Company was established in 1962. The company has been producing various kinds of pharmaceuticals and doing research and development for more than 31 years. In 1975, Shin Poong synthesized the raw material for mebendazole, a broad-spectrum anthelminthic agent. This product marked the first time that Shin Poong produced a pharmaceutical item using self-developed technology.

In 1983, Shin Poong successfully synthesized praziquantel, the raw material for the treatment of liver and lung flukes and schistosome species. Praziquantel was designated as a "Protected Medicine" by the Ministry of Health and Social Affairs in the same year. In 1987, Shin Poong was designated as a producer approved for KGMP (Korea Good Manufacturing Practice), a government regulation to enforce high standards in pharmaceutical manufacturing.

In March 1988, Shin Poong established a joint venture company, GMC, in Sudan. GMC of Sudan is producing finished products with imported raw materials, where Shin Poong is the major supplier of raw materials. GMC began production of praziquantel products in November 1994, with plans to export the product in the near future to the African market.

In 1994, Shin Poong had about 500 employees, with total assets estimated at US$ 27 million (as of December 1994). It produced 150 items of finished pharmaceutical products, 24 items of pharmaceutical raw products, 10 items of Korean Ginseng products, and 5 items of veterinary medicine.

In 1993, Shin Poong ranked 22nd in production value among the Republic of Korea's more than 200 pharmaceutical companies. As shown in Table 3.1, its

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rank has varied over the years, but the company has consistently ranked within the 30 largest pharmaceutical companies in the country.

Table 3.1: Shin Poong's rank in total production among all Korean pharmaceutical companies

unit: million won

	1987	1990	1993
Production value	19,843 (24,498)	49,480 (61,086)	65,821 (81,260)
Rank	28th	18th	22nd

Note: Numbers in parenthesis are values in one thousand US dollars

Source: Korean Pharmaceutical Manufacturers' Association, *Annual Statistics of Production*, various years.

Shin Poong is also rated high in R&D investment among all Korean pharmaceutical firms. As shown in Table 3.2, the average annual rate of R&D investment to total production value ranges from 2.9 percent to 3.3 percent, from 1988 to 1993 among the 100 largest pharmaceutical companies in the Republic of Korea. The rate for Shin Poong in 1993 was 4.06 percent, higher than the average of the top 100 firms. Table 3.3 shows that Shin Poong is ranked 15th in R&D investment, compared to its 23rd rank in production value. A recently released report (Shin Poong's internal report on *1994 Management Strategy*) reveals that Shin Poong seeks to raise the level of R&D investment to 6 percent of total production value, estimated to be 3,600 million won, which would double the amount of its 1993 R&D investment. Whether this level of R&D investment will be achieved has yet to be confirmed.

Table 3.2: Total R&D Investment by 100 largest pharmaceutical companies in the Republic of Korea

unit: 1 million won

Year	Sales value (A)	R&D investment (B)	B/A*100 (percent)
1988	1,439,632	41,386	2.87
1989	1,658,741	54,430	3.23
1990	1,933,254	63,499	3.28
1991	2,484,277	82,909	3.34
1992	2,906,292	91,233	3.14
1993	3,241,937	104,909	3.24

Source: *Ilgan-bosa*, "Insufficient R&D Investment by Pharmaceutical Firms," June 1, 1994.

Note: Sales value = sales volume * wholesale price.

Table 3.3: R&D Investment by Shin Poong Pharmaceutical Company: 1993

unit: million won, percent

Sales		R&D		
Value (A)	Rank	Value (B)	B/A*100 (percent)	Rank
44,362	23rd	1,800	4.06	15th

Source: *Ilgan-bosa*, "Insufficient R&D investment by pharmaceutical firms," June 1, 1994.

Note: Sales value = sales volume * wholesale price.

Shin Poong's involvement in praziquantel production

In the early 1980s, about 10 percent of the Korean population, about 4 million people, suffered from liver or lung fluke infection (*Chosun-Ilbo*, August 6, 1983). Most of these affected people were residents along two major rivers, the Nak-dong and Yung-san Rivers. In the second half of 1982, Bayer Pharmaceutical Company of Korea introduced praziquantel products in the Korean market, manufacturing the final product in the Republic of Korea from imported raw materials. However, most of the people affected by liver or lung fluke infection could not benefit from praziquantel treatment because of the drug's high price in the Korean market. For example, the market price of Bayer's product (Biltricide) was 30,000 won (for eight-tablet package, equivalent to US$ 38.66, with US$ 1 = 776 won) in 1983, which represented about one ninth of the average monthly earnings of an industrial worker (273,119 won, in nominal terms, according to Korea's Department of Labor, or about US$ 352). In 1994, the same package sold for 20,000 won (equivalent to US$ 25.64, with US$ 1 = 780 won), representing only about one fiftieth of the average monthly earnings of an industrial worker (1,085,125 won, in nominal terms, or about US$ 1,391).

Shin Poong recognized a potential market in this epidemiological and economic situation. To eradicate the liver and lung fluke infection of the 4 million people in the Republic of Korea, and to address the great need for praziquantel products within the Republic of Korea and overseas, Shin Poong began an effort to find an alternative production method for praziquantel, relying on domestic R&D.

The trade situation created another incentive for seeking a domestic production method for praziquantel. If a domestic producer could manufacture the raw materials for praziquantel products, it would be possible to save thousands of dollars through import substitution. It would no longer be necessary to rely on Bayer's supply of praziquantel raw materials, which held a monopoly in the Korean market (and elsewhere as well). Import substitution was the main incentive for the Korean government to become involved in the development of praziquantel production technology.

Table 3.4 shows that the helminth egg positive rate in the Republic of Korea has declined remarkably from over 84 percent in 1971 to a mere 3.8 percent in 1993. This remarkable reduction is attributed to a number of factors, including constant government efforts at parasite control among school children and the general public, an improved standard of living, improved living environment, and reformed farming methods. It is widely believed that Shin Poong's low-cost praziquantel products made it possible for the Korean government to implement its campaign for parasite control among school children and the

general public. The data on infection rates (Table 3.4) reflect a connection between declines in positive helminth egg rates and the introduction of praziquantel, with a 50% reduction in infection rates from 1971 to 1981 (before the introduction of praziquantel) and a 10-fold reduction from 1981 to 1993.

The infection rate for Clonorchis sinensis, however, has not declined appreciably over time, even after the introduction of praziquantel products, as shown in Table 3.4. A survey of 46,000 people nationwide in 1992-1993 revealed that the infection rate of Clonorchis sinensis remained above 2 percent (Table 3.4). Infection rates among residents along major rivers have been exceptionally high, ranging from 3 percent along the Mankyung River (Song et al., 1983) to 41.2 percent along the Nam River (Bae, 1983). A recent study compares the infection rates among residents along the Nam River between 1984 and 1992. As shown in Table 3.5, the infection rates in the adult population remain high, although the rates among school children fell dramatically during the 8-year period. The persistently high rates reflect the Koreans' raw fish diet, which is especially popular among riverside residents.

Table 3.4: Infection Rates of Intestinal Helminths: 1971-1993

unit: percent

Helminths	1971	1976	1981	1986	1993
Helminth egg positive rate	84.3	63.2	41.2	12.9	3.8
Clonorchis sinensis (Chinese liver fluke)	4.6	1.8	2.6	2.7	2.2

Source: Ministry of Health and Social Affairs, *Report of the 5th National Survey on Parasite Infection*, March 1993; and "Facts about Parasite Infection in Korea," *Journal of Korean Medical Association*, Vol. 35(11), 1992.

Table 3.5: Prevalence of Clonorchis sinensis among Nam River Residents: 1984 and 1992

unit: percent

	1984	1992
Adult residents	39.3	37.6
School children	24.4	9.7
Total	35.1	33.5

Source: Lee et al., 1993.

The role of government

Government policies in the Republic of Korea have supported general R&D promotion that could lead to the production of raw materials in medicine. Shin Poong, through joint research with KIST (Korea Institute of Science and Technology), has successfully developed new technologies for producing nine

active ingredients of pharmaceutical products, including mebendazole, albendazole, ethoxybenzamide, and niclosamide. Praziquantel is one of the success cases. For praziquantel, Shin Poong carried out preliminary research for two and a half years, from 1979 to early 1981, to explore the potential of independent development. The government of the Republic of Korea then agreed with Shin Poong about the possibility of domestic praziquantel production, and in 1982 selected the project as a government-supported special R&D project. KIST was chosen as the principal investigator of the research project, using funds jointly financed by Shin Poong and the Korean government. The total amount of research funds for the project was 30 million Korean won (equivalent to US$ 41,000, 1982 value), with one third provided by Shin Poong and two thirds financed by government tax money.

Production and consumption

In 1983, KIST and Shin Poong succeeded in jointly developing a new production technology for synthesizing praziquantel. The new method differed from the Bayer-E. Merck process in a critical step, adopting a cyclization reaction that used concentrated hydrochloric acid in the last stage of synthesis, while the Bayer-E. Merck method required high pressure catalytic hydrogenation at high temperature. The new method was significantly less expensive, with important implications for production costs. In 1985, Shin Poong's application for a process patent was approved by the Korea Patent Agency; the firm also obtained process patents in 12 other countries (Table 3.6).

Table 3.6: Shin Poong's process patent registration for praziquantel

Country	Registration number	Registration date	Expiration date
Bangladesh	1,001,626	1985: 20 May	1999: 4 July
Germany	3,324,532	1986: 24 July	2003: 7 July
India	159,586	1987: 30 May	1991: 29 May
Italy	1,193,420		2004: 7 July
Japan	1,535,215	1989: 21 December	2004: 11 April
Pakistan	128,690	1985: 28 June	1999: 28 June
Peru	3,816	1986: 20 November	1996: 19 November
Republic of Korea	20,271	1985: 13 January	1997: 23 August
Taiwan	20,498	1984: 1 March	1998: 1 December
Thailand	768	1983: 8 July	1998: 8 July
United Kingdom	2,126,212	1986: 2 July	2004: 7 July
United States of America	4,497,952	1985: 5 February	2004: 4 February
Venezuela	46,981	1988: 10 November	1998: 10 November

Source: Shin Poong Pharmaceutical Company.

In 1983, Shin Poong's praziquantel product was designated as a "Protected Medicine" by the Ministry of Health and Social Affairs of the Republic of Korea (the only one of Shin Poong's products to receive this designation). This designation usually resulted in the regulation of imports and prohibition of other production, but no actions were taken on Biltricide, since Bayer was already importing and selling Biltricide in the Republic of Korea with government approval. But the designation did prevent other manufacturers from entering the praziquantel market, creating a duopoly for the period of protection (5 years, from 1983 to 1988). This policy was a government strategy to protect domestic producers from foreign and domestic competition, to promote local firms in developing alternative production processes for existing drugs, and to produce gains from import substitution. On 1 July 1987, the

Republic of Korea agreed to adopt a product patent system, as a result of trade pressure from the United States of America. The Korean government also abolished the policy of "Protected Medicines," which depended on a process patent system. Only those process patents filed before July 1987 are still protected until expiry.

Shin Poong's development of a new praziquantel production technology contributed to a lowered consumer price in the Republic of Korea, as discussed below in more detail. The lower price resulted in increased accessibility by the 4 million people who needed the product, and thereby contributed to consumer surplus in the Republic of Korea.

Production, domestic sales, and export of praziquantel products

For Shin Poong, the sales value of praziquantel products increased over time as a percentage of total company sales, from 6.71 percent in 1991 to 10.37 percent in 1993. A single product that represents one tenth of a company's total sales is quite significant to the company. The rising importance of praziquantel in Shin Poong's total sales was greatly assisted by increases in exports, as shown in Table 3.7.

Table 3.7: Percentage of Distocide sales to total company sales

unit : 1 million won

	1990	1991	1992[b)]	1993
Total company sales value (A)	28,143 (39,306)	35,262 (46,336)	23,417 (29,717)	44,362 (54,903)
Sales from Distocide[a)] (B)	1,203 (1,680)	1,371 (1,802)	1,398 (1,774)	1,653 (2,046)
Export (C)	n.a.	(1,226)	(1,687)	(3,639)
Percentage = (B+C / A)*100	4.27[a)]	6.53	11.65	10.35

Note: a) Export volume is excluded from calculation.
b) Accounting period is changed for all pharmaceutical firms.
Numbers in parenthesis are values in one thousand US dollars.
Sales value = sales volume * wholesale price.

Source: Shin Poong Pharmaceutical Company.

Tables 3.8 and 3.9 show that Shin Poong's export volume of praziquantel doubled in 1992, compared to 1991, due to exports to China, which started in 1992. Overall, Shin Poong exports Distocide to many countries, including several European and African countries. China was the largest overseas market for Shin Poong's praziquantel products in 1993. Sudan was the largest market in 1991. Small amounts of Distocide have also been shipped to Denmark, the Netherlands, Philippines and Switzerland. Table 3.8 shows that Shin Poong has exported praziquantel raw materials to many developed and developing countries. China, again, is emerging as the main importer of Shin Poong's raw material, while Egypt has been a major market for many years. China was able

to import the huge volume of praziquantel (both raw material and tablets) in 1993 through its World Bank loan for schistosomiasis control. The tablets apparently are for use in multiple years and for mass chemotherapy for humans (in which the entire population in an endemic area receives treatment) as well as for mass treatment of cattle. Shin Poong reported to us that the volume of exports (of raw material plus tablets) plus local production (see Table 3.10) could exceed the total volume of raw material production in that year, since exports could include production from the previous year.

Table 3.8: Countries for export trade

	Raw material		Tablets	
	Country	Quantity (kg)	Country	Quantity (tab.)
1990	Egypt	4,000	Malawi	100,000
	Thailand	1,100	Sudan	91,668
	Japan	5	Switzerland	10,000
			Liberia	8,000
			Philippines	2,000
1991	Egypt	5,000	Sudan	2,306,000
	Thailand	750	Netherlands	900,000
	India	5	Uganda	200,000
	Australia	3	Malawi	100,000
			Switzerland	15,000
			Tanzania	3,000
1992	Egypt	9,000	China	(200 mg)
	Japan	35	Netherlands	34,580,000
	Australia	6	Sudan	700,000
	Italy	5	Switzerland	462,000
			Ghana	111,000
				8,000
1993	China	10,920	China	(200 mg) 82,016,000
	Egypt	3,500	Netherlands	1,063,000
	Italy	14	Switzerland	634,000
			Denmark	950,000
			Tanzania	160,000
			Uganda	125,000
			Zimbabwe	100,000

Source: Shin Poong Pharmaceutical Company.

Table 3.9 shows that the production volume of praziquantel raw material more than tripled between 1991 and 1993, due to increases in both domestic consumption and overseas exports. Between 1991 and 1993, export volume more than tripled, while the value of exports in 1993 was just three times that in 1991. This indicates that the nominal export price (not just the real price) declined in the export market during this period.

Table 3.9: Production and export of praziquantel raw material

	Production		Export	
	Volume (kg)	Value[a)] (1 million won)	Volume (kg)	Value (US$ 1,000)
1991	7,069	1,466	5,758	1,437
1992	20,435	1,861	9,046	2,412
1993	30,563	1,496	14,434	3,175

Source: For production value, Korea Pharmaceutical Manufacturers' Association, *Annual Statistics of Production*, various years; for export value, internal reports, Shin Poong Pharmaceutical Company.

Note: a) = value of praziquantel raw materials, excluding exports.

As noted earlier, Shin Poong established a joint venture company, GMC, in Sudan, in 1988, and began production of praziquantel in November 1994. In its first six months, GMC produced 1.5 million tablets (600 mg), with plans to sell the product locally to the Sudanese government and in the private market. No actual sales had occurred as of April 1995, because the Sudanese government had not issued the necessary authorization.

Three investors are participating in the joint venture in the Sudan: Shin Poong of Korea, Dae-woo Co. of Korea, and EIPICO of Egypt. Dae-woo became a partner because of its strong sales network in Sudan for the firm's electronic goods and other consumer products. Dae-woo is considered the only Korean company that enjoys both a good reputation among Sudanese consumers and a sound relationship with the Sudanese government.

Shin Poong established GMC of Sudan for the following reasons. First, Shin Poong expects that it can achieve a lower local price through production by a local manufacturer, due to lower labor costs and reduced transportation costs. The lower price should help expand praziquantel's sales volume for government procurement and in the private market. Second, in the long run, if a good sales network can be established for praziquantel in the Sudanese market, then other Shin Poong products could be introduced and sold using the same network. Third, again in the long run, Sudan could become the base for exports to other African markets of praziquantel and Shin Poong's other products.

Shin Poong is currently establishing another joint venture in China, applying a similar logic for expansion in China as the firm used in Sudan.

Shin Poong has also experienced rapid exports of finished products of praziquantel, as shown in Table 3.10 for Distocide exports in 1991, 1992, and 1993. When total production values and export values of Distocide are converted into index numbers, as shown in Table 3.10 and Figure 3.1, one finds that the value of exports expanded faster than the value of production. The increase in the overseas export market thus contributed to the rapid increase in production of Shin Poong's Distocide—the same as occurred for Shin Poong's praziquantel raw material.

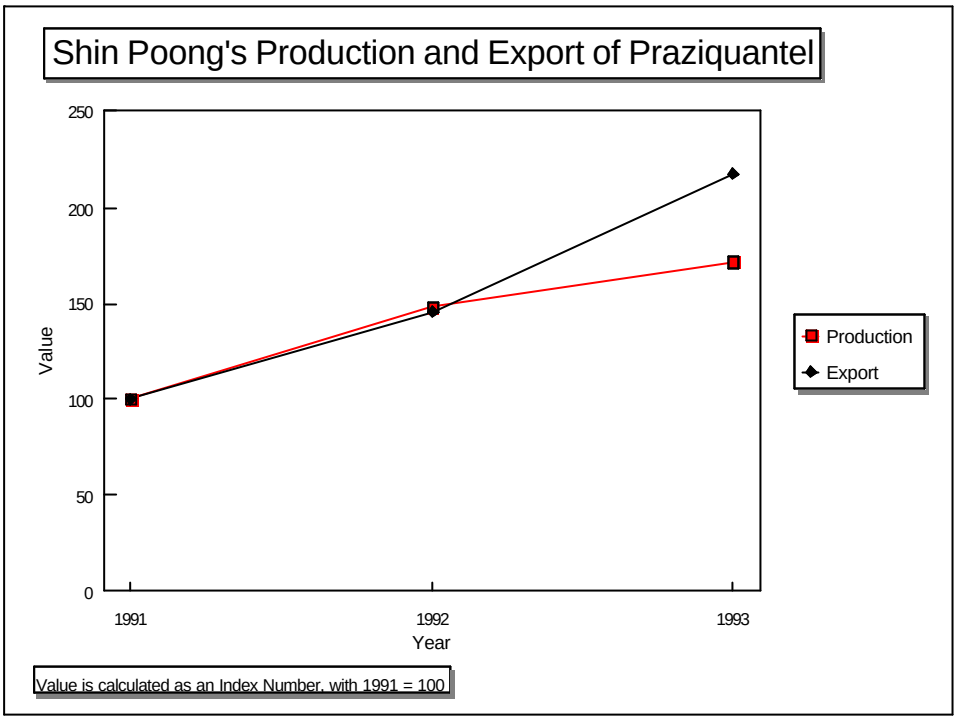
Table 3.10: Production and export of Distocide tablets

	Production		Export	
	Volume (pack units)	**Value (1 million won)**	**Volume (pack units)**	**Value (US$ 1,000)**
1991	8T: 138,040 100T: 1,633 1000T: 3,375	1,400 203 701	 1000T: 3,375	 1,226
Subtotal		**2,305 (100)**		**1,226 (100)**
1992	4T: 2,050 8T: 184,981 100T: 1,925 1000T: 1,101 1000T: (200mg): 34,580	3 2,035 209 233 940	4T: 2,000 100T: 500 1000T: 1,223 1000T: (200mg): 34,580	4 16 415 1,252
Subtotal		**3,420 (148)**		**1,688 (145)**
1993	8T: 32,914 100T: 7,552 500T: 800 1000T: 2,102 1000T: (200mg): 82,106	1,128 322 45 440 2,009	 100T : 3,700 500T : 900 1000T: 2,212 1000T: (200mg): 82,016	 95 56 566 2,922
Subtotal		**3,943 (171)**		**3,639 (217)**

Source: For production value, Korea Pharmaceutical Manufacturers' Association, *Annual Statistics of Production*, various years; for export value, internal reports, Shin Poong Pharmaceutical Company.

Note: Numbers in parenthesis are index numbers, with 1991=100. Also, according to Shin Poong, the export volume exceeded the production volume in 1992 and 1993 (for 1000T pack units) because exports included some production from the previous year.

Figure 3.1: Change in production and export



Praziquantel market in the Republic of Korea

In 1993, three pharmaceutical companies were producing praziquantel products under different brand names in the Republic of Korea. Distocide and Cestocide are Shin Poong's products, Biltricide is Bayer's, and praziquantel is Dae-woong Pharmaceutical Company's product. Shin Poong, whose process patent (effective until 1997) is still protected within the Republic of Korea, is the only company producing both praziquantel raw material and finished products. Bayer of Korea (the Seoul branch of Bayer of Germany) and Dae-woong produce Biltricide and praziquantel, respectively, with imported praziquantel raw materials. It is not known where Dae-Woong obtains the active ingredient for its production of praziquantel, although one possibility is Chinese sources.

Table 3.11 shows the production value (production volume × market price) of praziquantel finished products by the three producers. The finished products (Distocide, Cestocide, Biltricide, and praziquantel) are manufactured in three different sizes per tablet: 150 mg, 200 mg, and 600 mg. The tablets are sold in various units per pack: 4T (4 tablets), 6T, 8T, 100T, 500T, and 1000T per pack. For reasons related to tax payment, published data on sales volume by pharmaceutical firms are not readily available. This report, therefore, substitutes data on production value for sales data in most cases.

Table 3.11: Production value and market share of praziquantel products in the Republic of Korea

unit: 1 million won

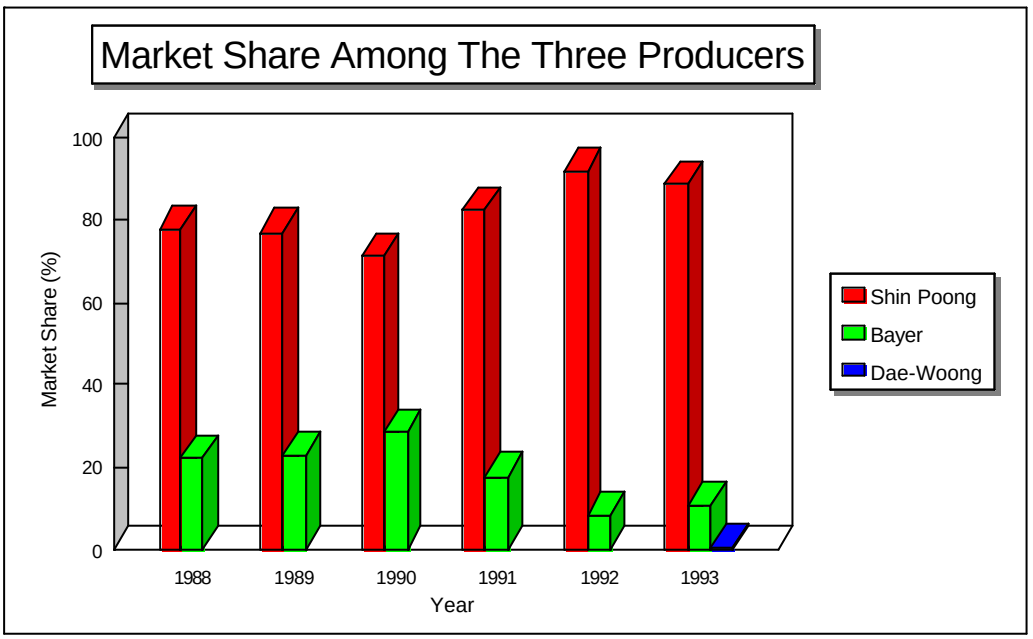
Producer	1988	1989	1990	1991	1992	1993
Shin Poong Co. (Distocide, Cestocide)	1,222 (1,509) [77.8%]	1,592 (1,965) [77.1%]	1,113 (1,374) [71.4%]	2,330 (2,876) [82.2%]	3,446 (4,254) [91.6%]	3,974 (4,906) [88.6%]
Bayer Co. (Biltricide)	348 (430) [22.2%]	474 (585) [22.9%]	446 (551) [28.6%]	504 (622) [17.8%]	315 (389) [8.4%]	483 (596) [10.8%]
Dae-woong Co. (praziquantel)						31 (38) [0.7%]
Total	1,571 (1,939) [100%]	2,065 (2,549) [100%]	1,559 (1,925) [100%]	2,835 (3,500) [100%]	3,761 (4,643) [100%]	4,488 (5,541) [100%]

Note: Numbers in parenthesis are values in one thousand US dollars.
Production value = production volume × market retail price.
Numbers in brackets are percentage of market share.

Source: Korean Pharmaceutical Manufacturers' Association, *Annual Statistics of Production*, various years.

The market shares of the three producers, and changes over time, are shown in Table 3.11 and Figure 3.2. As shown in Table 3.11, Shin Poong has been the dominant producer in the Korean market of praziquantel products. Its market share, measured by production value, has gone up over the years, with its average around 90 percent. With the entry of Dae-woong Pharmaceutical Co., one of the top-ranked pharmaceutical companies in the country (8th in 1993), into the market of praziquantel in 1993, a different picture of market shares is expected in the coming years. However, with Shin Poong's process patent still protected within the Republic of Korea and with an insignificant amount of production of finished products by Dae-woong, Shin Poong's dominance of the praziquantel market is likely to last at least in the near future.

Figure 3.2: Market share among the three producers



Price changes of praziquantel in the Republic of Korea

Shin Poong's Distocide was first introduced into the Korean market in August 1983, about one year after Bayer's Biltricide. Shin Poong's 8-tablet pack (600 mg/tablet) of Distocide was initially priced at 20,000 won (2,500 won/tablet), which was considerably below the price of 30,000 won (3,750 won/tablet) for Bayer's product (Table 3.12). Between 1983 and 1994, the nominal price for the same pack of Distocide increased by 10 percent to 22,000 won (2,750 won/tablet). However, the inflation-adjusted real price has declined by almost 40 percent, to 12,644 won (1,580 won/tablet). The price decline is even more dramatic in the case of Bayer's Biltricide. Both the nominal price and the real price of Biltricide pack in local currency have decreased remarkably, by 33 percent and 62 percent, respectively.

Table 3.12: Change in retail price of praziquantel products: 1983 and 1994

price per 600 mg. tablet

Product	Type of price	1983	1994
Shin Poong Distocide	nominal	2,500 won US$ 3.22	2,750 won US$ 3.53
	real	2,500 won US$ 3.22	1,580 won US$ 2.03
Bayer Biltricide	nominal	3,750 won US$ 4.83	2,500 won US$ 3.20
	real	3,750 won US$ 4.83	1,437 won US$ 1.84

Source: Shin Poong Pharmaceutical Company.

Note: The real price is the inflation adjusted price (using the consumer price index), with 1983=100 and 1994=174. Exchange rates used are: US$ 1=776 won for 1983, and US$ 1=780 won for 1994. The prices are based on the purchase of 8-tablet packs of the two products (600 mg / tablet).

Several market factors combined to produce the price decline in praziquantel products in the Republic of Korea:

- First, it is evident from market signals that price competition between Shin Poong and Bayer is probably the prime reason for the significant price decline for praziquantel. It is also possible that as Shin Poong emerged as the dominant producer for praziquantel, demand shifted from Bayer to Shin Poong; the drop in demand for Bayer's product could have forced a further decline in price. Dae-woong Pharmaceutical Company's entry into the praziquantel market in 1993 could cause further reductions in the price of praziquantel products, due to heightened competition, if Dae-woong survives in the praziquantel market.

- Second, the price decline in praziquantel products resulted also from increases in production volume (in the supply side), which was accelerated by Shin Poong's acquisition of a process patent for praziquantel.

- Third, a demand force (i.e., lowered demand) may have contributed to price declines for praziquantel in the Korean market. As shown in Tables 3.4 and 3.5, between 1986 and 1993 the helminth egg positive rate declined from 12.9% to 3.8%, and the prevalence of Clonorchis sinensis declined from 24.4% to 9.7% in school children from 1984 to 1992.

Both demand and supply forces thus worked together to promote praziquantel price declines in the Korean market. The impact of supply factors may have been more important than demand factors. This conjecture is supported by the market signals that the lower price has been accompanied by greater volumes of praziquantel consumption and export over time.

Conclusion

The development and sale of praziquantel in the Republic of Korea, by the Shin Poong Pharmaceutical Company, resulted in significant benefits for the Korean people and for people in other countries, as well as substantial returns for Shin Poong. The firm's success in the domestic and international markets for praziquantel depended on three policies adopted by the Korean government: 1) the lack of product patent protection and provision only of process patent protection for pharmaceutical products; 2) the promotion of R&D, through public-private collaboration, to develop alternative production processes for important pharmaceutical products; and 3) the ability to designate some products as "protected medicines" and restrict both foreign and domestic competition. But these were primarily enabling conditions. The success story of praziquantel in the Republic of Korea could not have been achieved without Shin Poong's recognition of the potential of praziquantel and its vigorous efforts to pursue the product's development and sales in domestic and international markets.

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Chapter 4:

The Egyptian International Pharmaceutical Industries Co.: Praziquantel formulation*

The Egyptian International Pharmaceutical Co. (EIPICO) began as an idea in 1979, emerged as a project in 1982, and started production of pharmaceuticals in March 1985, in the 10th of Ramadan City—an industrial zone in the desert some 50 kilometers outside Cairo. Since its inception, the company has concentrated on the formulation of generic products, those pharmaceuticals that are no longer protected by patents, and has sought to maintain its production at international standards of quality. Production value at EIPICO grew from L.E. 19.7 million in 1985 (US$ 20.52 million), to L.E. 60 million in 1988 (US$ 34.09 million), to L.E. 88 million in 1992 (US$ 26.51 million), to L.E. 224 million in 1994 (US$ 66.47 million), and the company became known as a success story within the Egyptian pharmaceutical industry. One of EIPICO's most successful products is praziquantel, the drug of choice to treat schistosomiasis, a major health problem in Egypt and in many African countries.

History of EIPICO's development

Egypt first sought to promote a domestic pharmaceutical industry in the late 1930s, with the establishment of the Misr Pharmaceutical Company in 1939, followed by the Memphis Pharmaceutical Company in 1940 and the CID Pharmaceutical Company in 1942. By 1952, at the time of the Revolution, Egyptian companies provided 10% of the national drug needs (MOH, 1986:41-48). That same year, the Revolutionary Council cut the price of drugs by 15% in an effort to make pharmaceutical products accessible to the majority of the population. In 1957, the government established the Supreme Organization for Pharmaceuticals, to set basic principles for a national drug policy. And in 1960, a Presidential decree ordered that all drug imports would be channeled through the Supreme Organization for Pharmaceuticals, and that prices would be cut by 25%. Through this time, the Egyptian pharmaceutical industry was mostly small laboratories.

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In the 1960s, the government under President Gamal Abdul Nasser embarked on an aggressive policy of nationalization and promotion. In 1961, the pharmaceutical industry was nationalized, and the government then started to gather the small companies into larger firms, establishing a series of companies in 1962 and 1963. Egypt's strategic geopolitical location placed it at the crossroads of the Mediterranean, the Third World, and the Arab World. Physicians throughout the Arab countries came to know Egyptian pharmaceutical products, in part because of the country's location, but also because many Arab physicians were trained in Egypt and because many Egyptian physicians worked in other countries. During the 1960s, the Egyptian pharmaceutical industry became very powerful, one of the country's most developed industries, with domestic production covering about 28% of the market in 1960 and reaching over 85% by the late 1970s (Table 4.1). The country had a number of active Schools of Pharmacy, and the Ministry of Health acquired advanced quality control laboratories.

Table 4.1: Pharmaceutical supply by foreign and local drugs

(L.E. million at retail prices)

Year[1]	**1952-53**	**1960-61**	**1970-71**	**1978[2]**	**1979-80**	**1980-81**	**1991[3]**
Local drugs	0.5	4.3	44.5	124.1	188.7	267.8	1,500
Imported drugs	4.3	10.6	7.2	17.4	31.6	62.3	103
Total	4.8	14.9	51.7	141.5	220.3	330.1	1,603
Percentage of local drugs to total	10%	28%	86.3%	87.7%	85.7%	81.1%	93.6%
Percentage of local drugs privately produced[4]	100%	0	21.9%		29.4%	27.3%	

Source: Henry E. Cole, Robert H. Smith, and Sohair Sukkary, *An Overview of Pharmacies, Pharmacists and the Pharmaceutical Distribution System in Egypt: An Executive Summary*, Prepared for the US Agency for International Development, by the Futures Group, Washington, DC, May 1982: 5.

1 Source for 1952-71, 1979-81: Technical Secretariat of the Drug Sector, Ministry of Health, Egypt.

2 Source for 1978: Study of Health Financing and Expenditures: Egypt, Publication No. 1G, Ministry of Health, Egypt, Health Profile of Egypt, April 1980.

3 Menas Associates, "Economy & Business," *Egypt Focus*, 1992.

4 Unofficial Statistics for the Technical Secretariat of the Drug Sector, Ministry of Health, calculated from producer prices.

Egypt has a high domestic production capacity, but remains heavily dependent on imported raw materials for pharmaceuticals. In 1988, Egypt's 19 main pharmaceutical companies produced 80% of national pharmaceutical

consumption; yet the industry still imported 90-95% of the necessary raw materials (El Shafei, 1990:13). According to one report, if raw materials and machinery are considered, then "perhaps only 35 percent of value added in pharmaceutical sales are derived locally" (Thomas et al., 1994:2). Imports are particularly important in certain therapeutic areas: insulins, cancer medicines, and infant milk formula (Menas Associates, 1992). A key government entity is The Egyptian Drug Organization, which owns the nation's public sector drug companies (including 7 production firms), and supervises the private sector companies (including 15 production firms).

The Egyptian pharmaceutical industry has four types of firms (Thomas et al., 1994:2-3):

Public sector: seven government-owned firms provide about 60 percent of consumption, along with two small public firms that import drug products and another public firm that makes bulk chemicals.

Multinational sector: five multinational firms produce and sell pharmaceutical products in Egypt, with two having 100% foreign ownership, and three including minority Egyptian ownership (since they entered the Egyptian market in the early 1960s when 100% foreign ownership was prohibited).

Private sector: fifteen privately owned Egyptian firms operate in the pharmaceutical industry, with EIPICO a prominent example, ranking as the second largest firm in 1991, and as the largest firm from 1992 to 1994.

Scientific offices: most of the 250 firms in the pharmaceutical industry in Egypt do not directly manufacture or sell drugs, but market their products and contract with other companies for local production; this category includes many multinational companies.

The Egyptian International Pharmaceutical Industries Company (EIPICO) was Egypt's first private company in the pharmaceutical industry. The company started production in 1985, and licensed many products from various multinational corporations (Tables 4.2 and 4.3).

Table 4.2: Local versus licensed products for EIPICO

(as % of total sales)

	Local products	Licensed products*
1985	44%	56%
1986	54%	46%
1987	68%	32%
1988	68%	32%

Note: Licensed products are manufactured using licensed technology (see Table 4.3 for a list of companies that have agreements with EIPICO).

Source: EIPICO, 1989.

Table 4.3: License agreements for EIPICO

From the USA:	*From Switzerland:*
Merck Sharpe & Dohme (and Chibret)	Roche
Smith Kline & French	Ginseng Products Ltd.
Upjohn	Pharmaton
Allergan	*From Sweden:*
From the United Kingdom:	Leo
Riker	Pharmacia
From France:	*From Denmark:*
Rhöne Poulenc - Theraplix	Biogena
From West Germany:	*From Italy:*
Degussa Pharma G.P. (Chemie Homborg-Asta)	Angelini
Dolorgiet Arzneimittel	Lisapharma
Hek Pharma	Zambeletti
Dr William Schwabe	Luso Pharmaco
	From the Republic of Korea:
	Shin Poong

Source: EIPICO, 1989.

EIPICO, from the beginning, sought to meet international quality standards, through the implementation of Good Manufacturing Practice (GMP) in the factory's design and production processes. GMP rules are observed in the ventilation, and in the control of temperature, humidity, air pressure, air suction, and air purity. These procedures are particularly important in the pharmaceutical industry, in order to assure cleanliness, product quality, and to prevent cross-contamination between products.

EIPICO selected its products according to four principles:

- The new products should replace imported products.
- The new products should meet market demand not covered completely by local production of the pharmaceutical industry.
- The new products should represent new technology in the pharmaceutical industry and research.
- The new products should provide mutual cooperation between Egyptian experts, scientists and researchers of EIPICO, and those of foreign international pharmaceutical companies, according to license agreements.

By 1994, EIPICO production covered all pharmaceutical dosage forms: the traditional dosage forms (such as tablets, capsules, emulsions, and ampoules) as well as nontraditional forms (such as soft gelatin capsules and long-acting capsules). About 70% of products was in tablet form, the most common dosage form for most pharmaceutical companies. The company performed its own bioequivalence studies and stability studies. The products covered all therapeutic classes, with the range of products increasing from 50 products in 1985 to 128 products in 1992. EIPICO continues to import most of the raw materials—especially the active raw materials—and is primarily engaged in

formulation. The company has sufficient land area for another manufacturing facility, if it decides to begin production of active ingredients.

While the pharmaceutical industry in some developing countries (Brazil, India, Indonesia and Republic of Korea) can manufacture raw materials, the Egyptian industry has not reached that point yet. One state-owned company in Egypt makes active raw ingredients (El Nasr for Chemicals and Drug Raw Materials Company, which was started in 1960), but it manufactures only a limited number of active ingredients, such as analgesics (paracetamol and aspirin) and other products. In addition, one private sector company in Egypt manufactures active ingredients (Acopharm). A future challenge for the Egyptian industry is how to begin domestic manufacture of pharmaceutical active ingredients.

EIPICO is considered a private company in Egypt, and ranked second among all Egyptian pharmaceutical firms (Table 4.4) in 1991-1992.

Table 4.4: Egypt's leading pharmaceutical manufacturers (Oct 1991-Sept 1992)

	Rank	Value (LE million)	Value (US$ million)	%	% growth
Total		1,560	469.88	100	7.6
Bristol Myers Squibb	1	108	32.53	6.9	(9.5)
EIPICO	2	88	26.51	5.7	12.5
Ciba-Geigy	3	78	23.49	5.0	2.0
Hoechst	4	67	20.18	4.3	10.6
Sandoz	5	61	18.37	3.9	(11)
Misr*	6	61	18.37	3.9	(3.6)
Nile*	7	59	16.87	3.8	(3.9)
Pfizer	8	59	16.87	3.7	(2.3)
CID*	9	49	14.76	3.2	(16.3)
Alex*	10	47	14.16	3.0	5.2
Glaxo	15	35	10.54	2.2	13.2

* Public sector
Exchange rate of US$ 1 = L.E. 3.32 for 1992.

Source: Glaxo Egypt, cited in: Menas Associates, 1992.

EIPICO's largest share-holder is ACDIMA (Arab Company for Drug Industries and Medical Appliances), a share-holding company originally generated by a group of Arab governments (Table 4.5). After the 1979 Camp David accord, however, ACDIMA split into two companies, because other governments opposed Egypt, and 3/4 of the company moved to Jordan, while the remaining 1/4 stayed in Egypt. The Egyptian firm now holds 11 separate companies, involved in all aspects of pharmaceutical production, including manufacture, supplies, packaging, and glass. EIPICO buys its glass, capsules, some active materials, packaging materials, and other items from various ACDIMA companies. ACDIMA is a pan-Arab company owned by governments. The founder and Chairman of the Board of Directors of ACDIMA, Dr Abdul Salam, died in 1992, and the post remained vacant for two years, until the retiring Minister of Health, Dr Ragheb Dewidar, decided to fill the position himself.

Table 4.5: Share holders of EIPICO

ACDIMA	33.91%*
Kahira Pharmaceutical Company	27.65%
Egyptian Trading Company	18.75%
Arab Drug Company	8.75%
Memphis Chemical Company	4.38%
Medical Union Pharmaceutical	4.38%
Members from EIPICO	2.18%
Total	**100%**

Note: The proportions are rounded to two decimal places and to total 100%.
Source: EIPICO, 1989.

Private pharmaceutical companies in Egypt have complained about economic difficulties, due to a combination of continued price controls (to provide low-cost pharmaceuticals as part of social welfare objectives) and the devaluation of the

Egyptian pound in 1987 followed by the implementation of a free foreign exchange market, which has resulted in sudden and substantial cost increases for raw materials (El Shafei, 1990:12; Menas Associates, 1992). Foreign companies in particular have complained about low and even negative profit rates (Table 4.6).

Table 4.6: Private sector companies in Egypt: Economic health in 1989

L.E. million

Company	Sales	Net profits	Net worth	Return on sales (%)
Adwia	5.2	0.65	8.9	12.4
EIPICO	76	8.0	41.2	10.5
Hoechst	93	2.5	15.1	2.6
Pfizer	52	1.7	12.9	3.2
Pharco	44	13.3	11.8	20.2
Rhone Poulenc	18	0.75	15.2	4.2
Squibb	66	(6.2)	9.0	(9.4)
Swisspharma	91	(1.2)	12.1	(1.3)

Source: El Shafei, 1990, p. 20.

The squeeze between product prices and production costs applies to domestic private companies and public companies as well, resulting in major losses for private companies and for public sector companies, although good statistics for public sector companies are not easily obtained (Menas Associates, 1992). According to one report, "Public sector firms lose money on over 700 of the 1300 products they sell, largely because the prices for those products were set in the 1970s and have been adjusted only marginally since" (Thomas et al., 1994:11). Prices for pharmaceutical products are set for both public and private companies by a committee within the Ministry of Health, based on a cost-plus formula, as part of the registration process. The committee includes several MOH officials, representatives of the drug control agencies, the First Undersecretary of the Ministry of Supply, and the First Undersecretary of the Ministry of Economics, according to Dr Zakaria Gad, President of the Egyptian Syndicate of Pharmacists (Gad, 1995). (This information contradicts the report by Ravenholt and Russell (1993:29), which states that the committee also includes representatives of public sector firms and local private companies.)

Multinational firms have also complained about inadequate patent protection in Egypt. Patent law in Egypt provides legal protection for processes for 10 years, but does not provide protection for products. Egyptian firms therefore can legally manufacture products—such as praziquantel—that are protected by patent law in other countries. This practice is considered to be "patent piracy" by multinational pharmaceutical firms (Thomas et al., 1994:8). Egyptian policy in this area has recently undergone some changes, since Egypt has agreed to comply with the Trade-Related Intellectual Property Rights conditions and will respect international product patents. Consequently, the MOH will not approve new drugs that violate international patent laws,

although currently marketed products will continue to be sold until 2004 (Nathan Associates, 1995).

In its 1991 agreement with the World Bank and the International Monetary Fund, the Egyptian government agreed to liberalize most of its economy, including the pharmaceutical sector. But the government has resisted efforts to liberalize prices in the pharmaceutical sector, because it is considered a sensitive industrial sector, in which sudden price rises could have sharp political consequences. As reported in December 1992, "liberalization and privatization has moved extremely slowly in Egypt even in non-sensitive areas and that of the pharmaceutical sector is still a long way off" (Menas Associates, 1992).

Schistosomiasis in Egypt

Schistosomiasis has a long history in Egypt, and the government has over sixty years of schistosomiasis control efforts. In 1922, the government of Egypt began a major control effort for schistosomiasis control, soon after the discovery that snails play an essential role in disease transmission—and the same year that Egypt received formal but limited independence from Britain. In the 1930s, the Ministry of Health created a department for endemic diseases, and in the 1940s the country passed a number of ordinances and decrees to control snails and to require examinations for at-risk populations. In 1955, the government recognized schistosomiasis as the largest health problem in Egypt and initiated a comprehensive control programme.

In 1972, the Minister of Health, Dr Mahmoud Mahfouz, presented Egypt's first official report on national health policy, which included an analysis of economic losses from schistosomiasis. The report drew attention to the need for a comprehensive control programme, not only from a health and social perspective but also for purposes of economic development. Since 1969, the government of Egypt has expanded its schistosomiasis control efforts to Upper and Middle Egypt and the Suez Canal area, relying heavily on foreign assistance. In 1984, the government spent just over 8% of the per capita public health expenditure on schistosomiasis control; in 1988, expenditure was cut to 5.2% (Cochrane and Liese, 1992).

The many years of efforts in Egypt have had an impact on schistosomiasis prevalence. According to a World Bank report, prevalence of schistosomiasis was reduced in Middle Egypt from about 30% in the late 1970s to about 10% in the late 1980s (Cochrane and Liese, 1992:37), based on a study in 1977 that found positive samples in 29.4% of 2.7 million persons examined, and a study in 1988 that reported positive samples in 8.6% of persons examined. In Upper Egypt, the figures dropped from 21.7% positive samples in 1980 (in 775,000 persons examined) to 14.4% positive samples in 1988 (in over 3 million persons examined). The Ministry of Health reported that from 1982 to 1992 the

prevalence of *S. haematobium* declined from about 15% to 1% in the Nile Delta and from 13% to 3% in Upper Egypt, and the prevalence of *S. mansoni* declined from about 40% to 20% in the Nile Delta (El Khoby, Galal, and Fenwick, 1993:2). Table 4.7 shows a collection of studies on declining prevalence of *S. haematobium* in three districts in Middle and Upper Egypt.

Table 4.7: Prevalence of S. Haematobium in three districts in Middle and Upper Egypt

	Beni Suef %	Menya %	Assiut %	Weighted positive* %	Estimated prevalence [4]
1977 Baseline	27.7	33.6	19.3	29.3	
1979[1]	16.4	17.4	11.8	16.1	
1980	14.4	17.3	9.9	15.3	
1981	15.5	14.7	10.4	14.1	
1982	15.2	14.0	7.0	13.2	
1983	9.3	11.6	8.9	10.5	
1984	6.8	9.1	10.4	9.2	
1985[2]	5.1	7.3	7.3	6.8	
1986	4.9	6.2	9.1	6.0	
1987	4.8	4.9	5.0	4.9	
1988	4.2	4.6	9.0	4.6	16.8
1989[3]	2.6	4.6	2.7	3.9	14.8
1990	1.8	3.7	4.3	3.1	12.0
1991	1.7	3.4	3.2	2.9	10.7
1992	1.7	2.9	2.9	2.7	10.5
1993					11.2
1994					9.9

Prevalence rates in Beni Suef, Menya, and Assiut determined from annual 10% sample surveys.

* The weighted positive % is the overall prevalence taking into account the different sample sizes.

Source: "Ministry of Health Schistosomiasis Control Activities in Egypt," *Schistosomiasis Research Project* 3(2):1-3, 1993.

1 "Report of an Independent Evaluation Mission on the National Bilharzia Control Programme in Egypt," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 81(supplement):1-57, 1985.

2 G. Webbe and S. El-Hak, "Progress in the Control of Schistosomiasis in Egypt (1985-1988)," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 84(3):394-399, 1990.

3 Ministry of Health, unpublished data.

4 Adapted from Ministry of Health data, cited in EIPICO, 1995.

Studies in Egypt have demonstrated the effectiveness of praziquantel. Starting in 1983, selective population chemotherapy, using a single dose of praziquantel, was carried out in two highly endemic districts (with an overall prevalence of 73.5%) in the Beheira governorate in the Nile Delta, with sponsorship from UNICEF, the government of Egypt, and WHO. The study

assessed the prevalence of schistosomiasis among school children, and the impact of a single dose of praziquantel (40 mg per kg of body weight). The study found that prevalence among school children declined from 75.4% to 40.9% in one district and from 80.5% to 30.8% in the other (El Malatawy et al., 1992). The same study carried out community surveys, which showed peak prevalence for schistosomiasis in the 15-24 years old age group in one district, and in the 15-44 years old age group in the other district. The report concluded, "The results of this operational research augur well for the future of large-scale chemotherapy in the control of schistosomiasis" (El Malatawy et al., 1992:55).

A separate report on the same research project, however, reached a somewhat different conclusion. This report, issued from UNICEF, argued that chemotherapy alone is not effective in reducing prevalence, concluding, "Schools where the prevalence was not reduced due to single treatment [were] usually located in villages with poor sanitation, no water supply and have no active health education; therefore, we cannot depend on diagnosis and treatment without having snail control, water and sanitation and health education activities" (El Malatawy, 1989:16). This report showed data for the second survey in which 7 primary schools (out of a total of 194 schools) continued to have high prevalence rates of 70-99%. These results would suggest that an integrated control approach is necessary to reduce schistosomiasis prevalence rates in some areas and that praziquantel administration alone is not sufficient in some situations.

The Ministry of Health began providing praziquantel free of charge in its schistosomiasis control programme on a nationwide basis in 1988, using a strategy of population-based selective chemotherapy. With this strategy, the MOH provided praziquantel only to infected persons, based on the results of individual diagnosis, also provided for free. Before 1988, the MOH used praziquantel only in some governorates and for certain age groups. The MOH began using praziquantel in school children in Middle Egypt, Beni Suef, Minya, and Assiut, in the early 1980s; one year later, Suhag and Kena were added. At that time, the MOH used about 0.5 to 1 million tablets a year, purchased directly from Bayer, at about double the current price (perhaps about US$ 0.57 per tablet). In 1992, the World Bank provided a loan of US$ 26.84 million over a period of six years, mainly to extend the national schistosomiasis control programme to five governorates in the Eastern and Western regions of the Nile Delta, with approximately US$ 12.87 million for purchase of praziquantel.

According to MOH policy, treatment is provided only on proof positive of infection. Annual surveys are carried out by MOH rural health personnel. Some rural residents may buy praziquantel on the private market, if they do not want to provide stool or urine samples to MOH personnel or if they disbelieve the MOH exam. The MOH exams are generally considered fairly accurate, although they vary depending on the quality of the technician, and the intensity of the infection. To promote treatment with praziquantel, the

MOH has advertised on television, provided free diagnosis and free drugs, and made a particular effort to diagnose the disease in children (1-2 times a year). In urban school children, the MOH School Health Department has been responsible for the exams; in rural school children, the MOH Primary Health Care Department has been responsible.

The population is reported to be satisfied with praziquantel as treatment, considering the drug to be safe, effective, and good quality. Praziquantel is considered to cure 70-80% of people infected with schistosomiasis. The MOH purchases its praziquantel through open tender, and is required by law to have at least three bids and to accept the lowest price. Funds for praziquantel procurement by the MOH are provided by the World Bank. And the MOH has purchased approximately 6 to 9 million tablets a year, making it probably the largest single buyer of praziquantel in the world (Table 4.8), until recent purchases by the government of China. In 1992, the MOH examined about 22 million people in outpatient clinics and schoolchildren surveys, and treated about 2.3 million people who were diagnosed positive with praziquantel. Egypt's strategy of population-based selective chemotherapy significantly reduced the prevalence of schistosomiasis in several studies (Barakat et al., 1995; El Malatawy et al., 1992; Farag et al., 1993), suggesting that substantial reductions have also been achieved on a national level. In short, the drug is considered a major success.

Table 4.8: Procurement of praziquantel by Egypt's MOH

	Number of tablets	Estimated value in L.E.	Estimated value in US$
1992	6.8 million	L.E. 5,984,000	US$ 1,802,410
1993	3.3 million	L.E. 2,904,000	US$ 872,072

Estimated value is calculated based on a procurement price of one tablet at L.E. 0.88
Estimated value in US$ is calculated based on an exchange rate in 1992 of US$ 1 = L.E. 3.32, and in 1993 of L.E. 3.33

Source: EIPICO.

Praziquantel production

In 1983, in EIPICO's start-up phase, its research staff began looking for new products and identified praziquantel as a good prospect. The product provided excellent treatment for all forms of schistosomiasis—a disease that affected millions of Egyptians—and EIPICO's staff identified a "price problem" confronted in Egypt. In 1983, when Bayer entered the praziquantel market in Egypt, it sold four tablets (of 600 mg.) for L.E. 16 (US$ 17.78). Praziquantel was produced in Egypt under license from Bayer by a public sector company in Alexandria, and sold on the Egyptian market as Biltricide. If EIPICO could obtain a low-cost source of the active ingredient, the company could undercut

Bayer and compete effectively both on the private market and in government tender sales. Praziquantel was identified as a major strategic opportunity.

Praziquantel was not the only anti-schistosomiasis drug available in the Egyptian market. Two other products were sold: Bilarcil (metrifonate 100 mg.) against *S. haematobium* and produced by Bayer; and Vansil (oxamniquine HCL 250 mg.) against *S. mansoni* and produced by Pfizer-Egypt. From a clinical point of view, however, praziquantel was considered a superior product, with significant potential for market growth compared to the two competitive products.

Because Bayer was already heavily involved in the Egyptian market, EIPICO needed to look elsewhere for praziquantel active ingredients. A Chinese source was identified and samples were obtained, but technical staff at EIPICO determined that the material was inferior to Bayer's and contained about 1% impurities, perhaps from residual solvent. Another source was Shin Poong Pharmaceutical Company in the Republic of Korea, and its samples, once tested, showed very good quality. EIPICO then prepared the dosage form, as tablets, and asked the Tropical Diseases Institute in the Egyptian Ministry of Health to conduct a clinical trial, compared to Bayer's Biltricide. EIPICO officials reported some efforts by Bayer to interfere in the clinical trial—but the results nonetheless showed Shin Poong's product to be excellent, and EIPICO successfully registered the product in Egypt.

EIPICO's entry into the praziquantel market in Egypt in 1987-1988 pushed the prices down, and gave EIPICO a majority share of the private and public markets. EIPICO sold a four-tablet package at L.E. 7 (US$ 0.52 per tablet) in 1994, less than half the price in local currency of L.E. 16 (US$ 4.44 per tablet) that Bayer charged for the same four-tablet package in 1983, when they entered the Egyptian market. Bayer had no choice but to cut its prices in response to the competition. In 1995, in private pharmacies, Alexandria/Bayer sold its product (Biltricide) at L.E. 8.95 (for four tablets, US$ 2.65), while EIPICO/Shin Poong sold its product (Distocide) at L.E. 9.45 (also for four tablets, US$ 2.80). By contrast, the competing products of metrifonate (Bilarcil) and oxamniquine (Vansil) in 1995 were sold at much lower prices per treatment, L.E. 0.80 (for three tablets, US$ 0.24) and L.E. 1.75 (per capsule, US$ 0.52), respectively. Metrifonate requires three doses one week apart, so that a full course of treatment costs L.E. 2.40 (US$ 0.71). The recommended treatment for oxamniquine is six capsules given over one day, and a full treatment has been available in Egypt in a box of six capsules for L.E. 9.00 (or US$ 2.65, although oxamniquine is no longer produced in Egypt, probably because of competition from praziquantel).

For 1993, EIPICO reported private market sales of about 22,000 (four-tablet packages) per month, or about 1 million tablets per year. In that year, praziquantel was ranked number 6 among EIPICO's products, according to

sales including government tenders, and number 20 for private market sales only.

From 1990 on, EIPICO won the Egyptian government's tender for praziquantel. In 1992, EIPICO sold the Ministry of Health about 6.8 million tablets of praziquantel, at a price of about 88 piasters per tablet (or about US 0.26-0.27 per tablet), and in 1993, about 3.3 million tablets, due to budgetary problems. According to EIPICO, the company sold the Ministry of Health a total of about 64 million tablets of praziquantel through tenders from 1987 to 1994, "at approximately one-half the imported drug price" (EIPICO, 1995).

In the early 1990s, EIPICO began to consider export opportunities for praziquantel. The licensing agreement from Shin Poong apparently contained no restrictions on export, and EIPICO registered its product in a number of countries: Sudan, Uganda, Yemen, and the six countries on Lake Victoria (Burundi, Kenya, Rwanda, Sudan, Tanzania and Zaire). If true, then Shin Poong apparently gave EIPICO the right to export praziquantel, in exchange for Shin Poong's access to the Egyptian market (through EIPICO) for sales of its raw material.

The biggest problem EIPICO confronted in exports to African countries was timely payment by the governments, which tended to be chronically short of foreign exchange. EIPICO also needed to consider export opportunities for praziquantel as part of a broader export strategy for all its products, because the Egyptian government did not guarantee exports as done by some other countries. By 1994, EIPICO had opened two foreign offices—one in Romania, and one in the Russian Federation—because of rapid growth potential. Neither country, however, had significant demand for praziquantel. EIPICO's efforts to expand exports reflected a broader recognition about the importance of this strategy for the development of the Egyptian pharmaceutical industry. The growing demand for pharmaceuticals in the Middle East and the difficulties of rapidly increasing raw material production led one report to conclude: "Export promotion of drugs was considered the strongest medium for development of the [Egyptian] Industry" (El Shafei, 1990:21).

EIPICO was also exploring other sources for praziquantel's active ingredient. In 1994, once Bayer's main patent expired, a number of new sources appeared, with some very low prices. EIPICO's management, however, wanted to assure product quality and also wanted to protect its existing license and procurement relationship with Shin Poong. The availability of other sources, however, might persuade Shin Poong to provide its active ingredient at a lower price, especially if EIPICO could gain access to larger markets outside Egypt, through international agencies or to African governments directly.

For the future, EIPICO's management believes it can compete with Shin Poong's own product on quality and formulation, and can also compete on price, because of the Republic of Korea's comparatively high-cost labor. But so

far, EIPICO has not secured any significant sales of praziquantel outside Egypt, either to an international agency (like UNICEF or the World Bank) or to an African country government. EIPICO also needs to maintain its government tender in Egypt, in order to protect its overall sales of praziquantel as among its top ten products. If the international market becomes highly competitive, then there is a small chance that EIPICO could lose this domestic contract, which would put a sizable dent in praziquantel's history as a successful product for EIPICO.

Another option for EIPICO is to explore other domestic markets for praziquantel. As the result of a new law passed in July 1992, establishing a School Children's Health Insurance Programme in Egypt, the Health Insurance Organization (HIO) has assumed responsibility for school health services (Reich and Swelam, 1994). EIPICO could approach HIO about sales of praziquantel for the treatment of school children in rural areas. In addition, since HIO purchases enormous quantities of pharmaceuticals, EIPICO could explore sales of other products as well, with special packaging for HIO. EIPICO could also consider marketing praziquantel for its treatment of other helminthic diseases, which would require different dosage and packaging. While these markets are relatively small (compared to the anti-schistosomiasis market), they could provide some protection to EIPICO in case it loses the MOH tender in the future.

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Chapter 5:

The international supply of praziquantel*

This chapter provides a description of the supply of praziquantel since its introduction in the international market in the late 1970s. It first presents basic data on producers and formulators of praziquantel, including firms that manufacture the drug's active ingredients and firms that only formulate tablets from purchased raw materials. The chapter next describes the global distribution of praziquantel, with particular attention to the role of bulk suppliers in developing country markets.

Producers and formulators

The major producers

Praziquantel has been available since 1978 in the European market (King and Mahmoud, 1989)—(although information is scanty on when it was introduced in different European countries)—and has been registered and licensed for use in the USA since 1982 (Scrip, 1981). Until 1983, only two companies were marketing the product: Bayer, Germany (and its subsidiaries in France, the Netherlands, South Africa and the USA; and licentiates in Egypt, Indonesia, the Republic of Korea and Thailand), and E. Merck, Germany (and its subsidiary in South Africa; and licentiates in South America). In 1983, the Korean company, Shin Poong, entered the praziquantel market—initially within the Republic of Korea and later in the global market, as described in Chapter 3.

Shin Poong developed its own production process for praziquantel—which differed from the original Bayer process in a critical step (see Chapter 3). Shin Poong was able to patent this process in a number of developing and developed countries worldwide, including in the Republic of Korea (Kim et al., January, 1983) and in the USA (Kim et al., February, 1985) (see Chapter 3 for dates of registration in various countries).

By the mid-1980s, the brand-name products of praziquantel (for human use) on the market were:

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- Biltricide (600 mg) [Bayer];
- Cysticide (500 mg), Cesol (150 mg), Cestox (150 mg), Cenaride, Cisiticid [E. Merck];
- Distocide (600 mg), Cestocide (150 mg) [Shin Poong].

These three firms—Bayer, E. Merck, and Shin Poong—are considered the "major producers" of praziquantel in this report. According to our estimates, these firms represent the major share of global production of praziquantel (82% in 1993), as discussed below.

Formulators and other producers

From the late 1980s on, praziquantel was being formulated under license from Shin Poong by two other companies (EIPICO in Egypt, which started production in 1987; and GMC in the Sudan, which started production in 1994) (see Chapters 3 and 4). On the expiry of the Bayer-E. Merck patent (which has been expiring in various countries since 1989, as noted in Chapter 2), the production process for praziquantel was included in the US Pharmacoepia (*US Pharmacoepia*, 1993—USP No. 22), and the product became available in generic form. A number of generic producers refer to the USP No. 22 production process for praziquantel as the basis for their own manufacturing of the active ingredient. Moreover, the raw materials required for the formulation of the tablets are now freely available in the international market from several sources, including from the major producers. Sources of raw materials for the formulation of praziquantel are listed in the International Trade Centre's Market News Service (MNS), a publication that is co-managed by UNCTAD/GATT and WHO/DAP, currently funded by WHO/DAP.

A number of other producers and formulators of praziquantel emerged in the late 1980s and early 1990s. These firms include Medochemie in Cyprus, Pharmamed in Malta (a subsidiary of the International Dispensary Association - IDA), Dae-Woong in the Republic of Korea, Laboratoria Wolfs and Pharmachemic in Belgium, Athlone Labs in Ireland, and Chempharma and Rivopharma in Switzerland. Praziquantel is also currently being produced by a company in Shanghai, China, as Pyquiton (200 mg tablets), entirely for domestic use. We found no evidence of any export of the Chinese product, although the raw materials are exported (and reportedly are used by some formulators of praziquantel). In the 1980s, there were three Chinese manufacturers (Shanghai Pharma Factory # 6, Nanjing, and Tiangsang factories), but two of them stopped production, suggesting that the Chinese companies did not find the market profitable. Not much is publicly known about the production process used by the Chinese firm that continued production. EIPICO, however, reported that it tested and rejected the Chinese raw material for praziquantel on the basis of quality (see Chapter 4).

Our study found verbal reports that praziquantel has been produced or formulated by companies in other countries (including Italy, Japan, Russian

Federation, Switzerland and Thailand), but details of the companies and their production processes were not available. These companies probably have limited production capacities. Many of the products, particularly those produced in developing countries, are reportedly of untested or dubious quality, and therefore, WHO has not approached these companies for procurement (Interview No. 8). Sales of these products (for example, sales of praziquantel produced by Thai companies) are probably directed mainly to domestic markets, and, to some extent, to markets in other developing countries.

We obtained verbal reports that some international agencies, bilateral agencies, and developing countries have procured drugs from generic producers in some developed countries in the past (an unnamed Italian company; and the two Swiss firms, Rivopharma and Chempharma). If current trends are an indication, generic production is likely to increase significantly in the future, particularly with the expiry of the Bayer patent (between 1989-1994 in most developed and several developing countries) and the Shin Poong process patent (in 1997 in the Republic of Korea, and by 2004 in most other countries). The major producers are already exploring mechanisms to introduce generic versions of the drug, as discussed below. This expansion of the generics market should auger well for the price of the product on the international market.

Production capacity and markets of major producers

As part of this study, all the known producers and formulators of praziquantel were contacted for information on the manufacture, marketing, and pricing of their products. An initial mailing of a questionnaire was followed up by telephone interviews in all cases, and by in-person interviews (when feasible) with firms that agreed to participate in the study. In general, firms were reluctant to provide information about their production processes, pricing structures, and sales figures. However, the three major producers, Bayer, E. Merck, and Shin Poong, along with EIPICO, all agreed to cooperate with the study, to provide internal data on production, pricing, and sales, and to meet with members of the study team. Other firms, mostly formulators, refused to provide data and often refused to cooperate.

Based on the data collected, we were able to calculate the first public estimate of the total global production of praziquantel, and the first estimate of total global supply of praziquantel tablets for use in the treatment of human schistosomiasis. We assumed that 1 kg. of raw material yields approximately 1600 (600 mg) tablets (allowing for an approximate 3% production loss from the normal 1:1 ratio of conversion of raw material to tablets). This assumption allowed us to estimate a total global production of 89 million tablets of praziquantel in 1993. Table 5.1 summarizes our calculations of the global production of praziquantel.

Table 5.1: Estimates of global praziquantel production (1993)

	Volume of raw material (in tons = 1000 kgs)	No. of tablets (millions) [including tablets manufactured by subsidiaries, licentiates, and formulators]	% of global total
Major producers			
E. Merck	1.5	2.4	2.7%
Bayer (using raw materials from E. Merck)	13.5	21.6	24.3%
Shin Poong	30.5	49[a]	55%
Other producers			
China & others[b]	10	16[c]	18%
World total	55.5	89	100%

[a] Includes tablets formulated by EIPICO (about 10 million tablets).

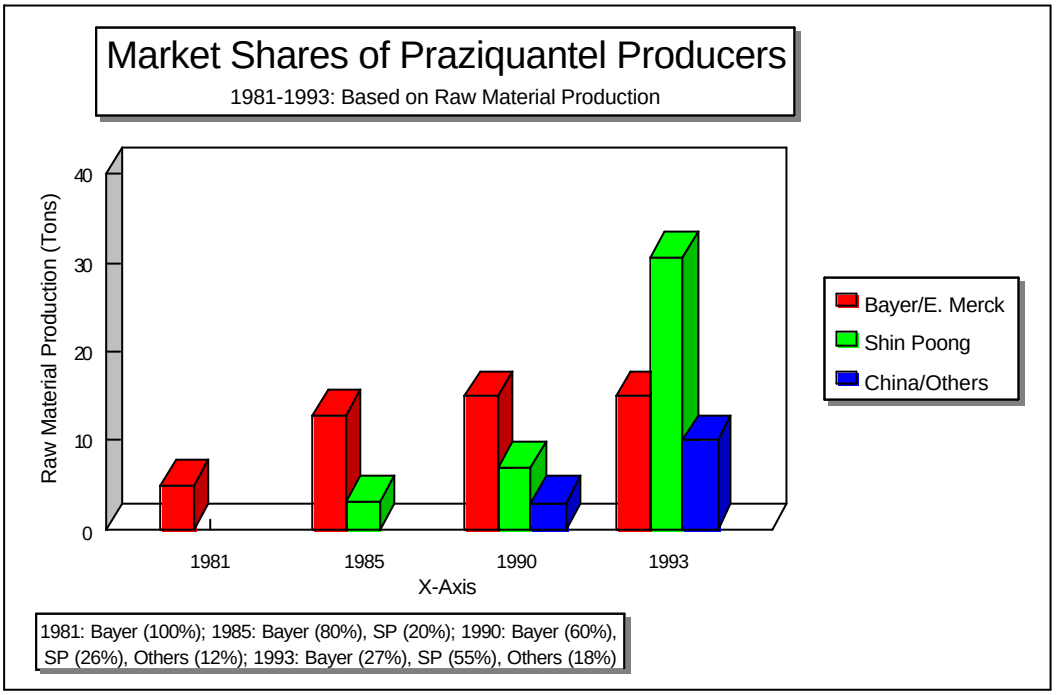
[b] Includes production of raw materials by Medochemie.

[c] Includes tablets formulated by Pharmamed, the IDA subsidiary.

Assumptions:

1. Estimates of total production of raw materials are based on data collected in interviews with company officials.
2. We estimate that the 3 major producers were responsible for 82% of total global production of raw materials in 1993 (45.5 tons of the total 55.5 tons of raw materials produced).
3. The number of tablets is based on a conversion factor of 1600 tablets from 1 kg of raw materials, which includes 3% production losses.

Figure 5.1: Global production of praziquantel



From 1981 to 1993, the global market for praziquantel underwent a dramatic transformation. Prior to 1983, the praziquantel market was provided solely by Bayer and E. Merck, with a total supply of approximately 8 million tablets of praziquantel a year. With the entry of Shin Poong in 1983, the market situation began to change rapidly. The global market share of Shin Poong increased consistently each year. In 1985, Bayer and E. Merck had about an 80% share of the market, producing about 10-15 tons of raw materials for praziquantel out of the estimated global total of 12.5-19 tons, with Shin Poong producing the balance. By 1990, Bayer and E. Merck's share of the market had dropped to 60%, with their production of raw material totalling 15 tons of the estimated global total of 25 tons. In the early 1990s, Shin Poong overtook the original producers and became the dominant producer and global supplier of praziquantel.

The most recent production figures show Shin Poong's striking dominance of the praziquantel market. In 1993 (see Table 5.1), Shin Poong was estimated to

be producing about 30.5 tons of raw materials, out of a global total of 55.5 tons of raw materials (or in tablets: about 49 million of the total global production of 89 million praziquantel tablets). Figure 5.1 gives the estimated market shares of the major producers in 1993: Shin Poong (55%) and Bayer/E. Merck (27%). In addition, in 1993, the Chinese company was estimated to have a 13% share of the praziquantel market, while the other producers had an approximate 5% market share. The production data show that the entry of formulators and generic producers has significantly altered the global structure and composition of the praziquantel market, although these firms still represent a small proportion of the total global supply. These statistics also express the recent stagnation of Bayer and E. Merck, and the stunning growth of Shin Poong in the global market for praziquantel. The current production volumes, sales, and markets of the three major producers are described below, followed by a brief discussion of formulators and generic producers.

Bayer

Praziquantel sales constitute an insignificant share, possibly 0.001%, of the overall pharmaceutical sales of Bayer worldwide, estimated at US$ 10.5 billion. Bayer has 88% of its total pharmaceutical sales within only 8 countries: 6 countries in Western Europe, plus Japan and the USA. About 12% of all sales are to the remainder of the world, and only 4% of Bayer's pharmaceutical sales are to developing countries. Most of these sales go through private markets, although a small proportion is sold through tenders to governmental or institutional markets (Interview No. 2).

Praziquantel sales constitute a small 0.2% of all sales to the Third World. Between 80-85% of these developing country sales (in contrast to E. Merck's sales of praziquantel, and unlike Bayer's sales of other pharmaceuticals) are through competitive tenders, and directed towards institutional markets. Since the mid-1980s, competitive producers (such as Shin Poong) have offered lower priced praziquantel on the global market; from this point on, Bayer has had to compete on price, with considerable losses in market share.

Bayer currently provides raw materials (obtained from E. Merck) to a number of developing countries, including Egypt, Indonesia, the Republic of Korea and Thailand, for local production of Biltricide under license. Licentiates receive know-how as well as raw materials from Bayer. Local production of praziquantel is probably most important in terms of volume in Egypt (where Alexco formulates praziquantel under license from Bayer, with volume varying between 1.5 and 2 million tablets a year). Another country where praziquantel could be produced in the future by Bayer is India. In general, however, Bayer sees limited markets where this product could be manufactured in sufficient quantities to reap benefits of economies of scale.

E. Merck

In a 1978 contract between Bayer and E. Merck, it was decided that E. Merck would be responsible for producing the basic raw materials required in the formulation of praziquantel tablets. Further, the companies determined that

they would each formulate and market praziquantel in their respective "historical" marketing areas in the developing world: E. Merck in Latin America, and Bayer in Africa and South East Asia (Interview No. 3). Thus, E. Merck sales have concentrated in the Latin American and European regions (praziquantel sales in these two regions constitute about 10% of the total global praziquantel sales of Bayer and E. Merck). Besides Germany, E. Merck has supplied praziquantel to Brazil, Chile, Colombia, Ecuador, Mexico, Peru, and Venezuela.

Nonetheless, praziquantel remains a minor product in the overall production of E. Merck. Moreover, the firm's share of the global praziquantel market has been shrinking in the past decade. E. Merck's limited role in the international trade of praziquantel could be due to the way it produces and markets the drug. The raw materials are produced only in Germany; tablets are manufactured in Germany and, to some extent, in Latin America. Sales of praziquantel in Latin America, however, are relatively limited, because oxamniquine is the preferred drug for the treatment for schistosomiasis in those Latin American countries (especially Brazil) with significant prevalence of this disease (World Bank, 1989).

E. Merck's current production capacity is between 25 and 28 tons. The actual production of the basic compounds is just over half of that amount, or about 15 tons, at a production cost of US$ 170 per kilogram (Interview No. 3). According to its agreement with Bayer, E. Merck retains about 10% of the raw materials for the formulation of praziquantel tablets to be sold in Europe and Latin America. The other 90% is passed on to Bayer for the formulation of praziquantel tablets that are sold to countries in Africa, Asia, Europe and North America.

According to interviews at E. Merck, the lowest price that the firm can set for praziquantel raw materials (US$ 170 per kg) is 50 per cent higher than the prices at which the raw materials are offered by other world market suppliers, because of E. Merck's higher production costs (Interview No. 3). E. Merck has no current plans to expand its production capacity or its production, because the firm produces primarily for the private market, which is not growing. Less than 20 percent of E. Merck's production is sold on tender bids. E. Merck has a competitive disadvantage in the tender market, since purchase decisions are made based primarily on price.

According to company representatives, two future scenarios are possible: the company could market aggressively and expand sales to its current capacity; or the company could work more closely with international agencies, expanding capacity beyond its current size, so that it could reengineer for larger quantities, produce at a lower cost, and compete effectively. According to E. Merck's representatives, option one, of marketing enough praziquantel to fully use the current capacity, would be a major undertaking, since E. Merck's cost and pricing structure is much higher than that of its international competitors

(see also Chapter 7). And option two, of creating additional capacity and expanding the production programme for praziquantel, would take about 10 years and would only be feasible with sales guarantees from international agencies.

Given this situation, does E. Merck plan to continue to produce praziquantel in the future? According to company sources, the answer is yes, in order to have a full line of products, and because praziquantel is a life-saving drug. The company is also making attempts to develop a lower cost production process. In addition, E. Merck has been working for the last five years with WHO and others to develop a new therapy that would combine another drug, albendazole, with praziquantel.

Shin Poong

Since its entry into the praziquantel market, Shin Poong has gone from strength to strength. The company successfully developed a new low-cost production process for praziquantel, with Korean government support (see Chapter 3). Between 1991 and 1993, the production value of Distocide tablets (Shin Poong's praziquantel brand used in schistosomiasis treatment) went up from 2305 million wons (approx. US$ 3.03 million) to 3943 million wons (US$ 4.88 million); the export value for Distocide tablets in the same period increased from US$ 1.2 million to US$ 3.6 million (see Chapter 3).

Shin Poong has continued to gain new overseas markets for its praziquantel products (Distocide and Cestocide, a praziquantel formulation used in treatment of flukes). Besides supplying international agencies (UNICEF and WHO) and other organizations such as IDA, Shin Poong has been supplying praziquantel, in raw material and tablet forms, to a number of developing countries, with China ranked as the top importer. In 1992, Shin Poong manufactured praziquantel raw materials in excess of 20 tons (see Chapter 3), making it the world's largest producer. In 1993, Shin Poong was producing about 55% of the total praziquantel manufactured globally. In addition, as noted above, Shin Poong has licensed EIPICO (Egypt) and GMC (Sudan) to produce the drug in their countries and for export (see Chapter 3).

Formulators and generic producers

Among formulators and generic producers of praziquantel, EIPICO's entry into the market in 1987 was the most significant development, because of the size and importance of the Egyptian market for this product. Of the estimated total annual world market of 89 million tablets in 1993, Egyptian consumption of about 10 million tablets comprises over 11%. From 1990 on, EIPICO won the Egyptian government's contract for the procurement of praziquantel (which constitutes more than 75% of total sales in Egypt), giving EIPICO a hugely dominant position over Alexco, Bayer's licensee in Egypt. In 1992, EIPICO sales totalled almost 8 million tablets of praziquantel—about 7 million in the public sector and 1 million in the private sector (Chapter 4). Alexco's total sales of

praziquantel in Egypt (all in the private market) are estimated at about 1.5 to 2.0 million tablets.

Limited data were obtained for two other generic producers: Laboratoria Wolfs in Belgium, and Medochemie Pharmaceuticals in Cyprus. Laboratoria Wolfs started production of praziquantel in 1991, and only manufactures praziquantel for human use. The company produces its own raw materials based on USP 22 specifications, and also formulates the drug from raw materials supplied by its customers. Praziquantel constitutes approximately 2% of its overall sales of drugs.

Medochemie Pharmaceuticals, according to its representatives, has been producing praziquantel for the last 10 years, averaging 4-5 million 600 mg. tablets per year. Medochemie produces its own raw materials for praziquantel using its own technology. The company reportedly has the capacity to increase production to as much as 25 tons of praziquantel raw materials or approximately 40 million tablets annually. The company does not consider praziquantel sales as important, compared to overall drugs and pharmaceutical sales. Medochemie considers Bayer and Shin Poong as its main competitors in the praziquantel market. The company is currently supplying praziquantel to WHO, and could supply UNICEF in the future. It also supplies the drug to relief agencies that provide praziquantel to developing countries. Medochemie has also supplied several developing countries directly, but declined to identify these countries.
Unfortunately, we could obtain only limited data from the International Dispensary Association (IDA), which formulates praziquantel in its subsidiary (Pharmamed) based in Malta, and is a significant player in the global supply of praziquantel. IDA is a "foundation for non-profit procurement of medical supplies," according to an IDA brochure (IDA, n.d.). The organization's managing director, however, did not provide us with any data on its procurement sources or its production volumes of praziquantel, stating that those figures by product "are regarded as being confidential and can not be shared" (den Besten, March 1996). Our estimates of IDA's role in the praziquantel market, therefore, are based on other sources.

Global distribution of praziquantel

Distribution to developing countries

The distribution of praziquantel to developing countries takes three forms:

- bulk sales to national governments, typically for use in schistosomiasis control programmes

- sales to bulk suppliers, including international agencies, and private and nongovernmental organizations, which then sell to national governments; and

- direct private sector sales, either through subsidiaries, or through licensees, distributors, wholesalers, and retailers.

Of these, in most developing countries, bulk sales to governments (usually through tendering) probably represent the major avenue for distribution of praziquantel. In some countries, distribution through bulk suppliers represents the main national source of praziquantel, which is then distributed through government channels (in a schistosomiasis control programme, primary health care programme, or essential drugs programme). In general, the private market is rather small for praziquantel, compared to government distribution of the product. More details on the distribution of praziquantel in developing countries are provided in Chapter 6.

Most of the competition over praziquantel distribution to developing country markets hinges on price. The higher costs of Bayer and E. Merck have created difficulties for these firms in competing with lower cost producers, including Shin Poong and the minor producers. In an attempt to overcome some cost problems, in 1994, Bayer, together with other pharmaceutical firms, formed a company named Sanavita that offers generic products (Interview No. 2). This company provides more than 180 products that are sold to Third World countries. Its products will eventually be registered in several African countries. This company also supplies praziquantel in a package with other products. A similar approach was successfully used by the Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) for projects in Cambodia, Mali and Yemen.

Distribution in developed countries

Praziquantel distribution channels in developed countries differ significantly from those in developing countries. Most developed country markets are supplied by Bayer and E. Merck and their subsidiaries. This situation, however, is changing with the expiry of their patent, as more generic producers and distributors become involved in these countries. Government tenders do not represent a significant market in developed countries, except to aid agencies involved in provision to Third World countries. Private market sales are relatively limited, since schistosomiasis and other tropical diseases for which praziquantel is used as treatment are minor health problems in most developed countries. In these countries the veterinary sales of praziquantel are much larger than sales of the human product.

In developed countries, distribution of both the human and veterinary products occurs through:

- direct sales by Bayer and E. Merck to hospitals (including veterinary hospitals),

- sales to wholesale and retail pharmacies, and
- sales to food stores (for OTC veterinary products).

In the 1990s, the expiry of the praziquantel patent has led to a proliferation of smaller manufacturers in developed countries. For example, about 10-20 German companies now produce praziquantel tablets on order. The patent expiry has also led to an increase in the number of distributors of praziquantel in Germany. Consequently, there is an increasingly active and complex market for both raw materials and final product for praziquantel. Even Bayer occasionally buys from the raw material market.

Bulk suppliers for developing countries

A number of international agencies and for-profit and non-profit organizations act as bulk suppliers of praziquantel for developing countries. These include: UNICEF, the World Health Organization (WHO), the International Dispensary Association (IDA) in the Netherlands, IAPS in the Netherlands, Orbi-Pharma in Belgium, Action Medeor in Germany, ECHO in the UK, and INMED in the USA. In addition, the World Bank provides assistance for the procurement of praziquantel through long-term loans.

Table 5.2 presents a summary of the roles and activities of the bulk-supplier organizations, along with the pharmaceutical multinational companies (MNCs) and the developing countries themselves, in the global system of drug development and supply for praziquantel.

Although many of the bulk supplier organizations are public sector institutions in many ways (except the pharmaceutical MNCs and private suppliers), they publish very limited information on their pharmaceutical activities, and most of them refused to provide us with data on their praziquantel purchases (volume, sources, or prices) or national destinations, despite numerous requests by mail, telephone, and in person. Indeed, many public organizations were more secretive than the major private manufacturers of praziquantel (Bayer, E. Merck, Shin Poong, and EIPICO). Among the bulk supplier organizations, our data indicate that UNICEF, WHO, and IDA are the most important players, and that they distribute the major share of praziquantel that is provided to developing countries through bulk suppliers. The World Bank makes an important contribution in financing direct procurement by countries. Below we review the procurement and distribution strategies of UNICEF, WHO, the World Bank, and several NGOs and private organizations.

Table 5.2: Roles of major players in the praziquantel system for developing countries

	International agencies			Developing country	Private suppliers	Pharma-ceutical
	UNICEF	WHO	World			

Activity			Bank	governments	(inc. NGOs)	producers
Development: discovery of new drugs & processes				X		X
Development: clinical trials for new products		X		X		X
Procurement: negotiations with producers	X	X		X	X	
Procurement: provision of financing			X	X		
Procurement: through int'l tenders	X			X		
Procurement: for control programmes	X			X		
Procurement: for research		X		X		X
Technical support: for control programmes		X		X	X	
Distribution: provision of essential drugs	X			X	X	X

UNICEF

UNICEF is the most important bulk supplier of praziquantel to developing countries (other than the major producers Bayer, E. Merck, and Shin Poong). From 1985 to 1994, according to UNICEF officials, UNICEF sold approximately 5.5 million tablets of praziquantel (600 mg)—averaging about half a million tablets a year (Interview No. 6). UNICEF, however, refused to provide us with annual procurement or sales figures.

UNICEF purchases drugs through international tender, using its bulk purchasing power to obtain prices that are significantly below market prices. Through the UNICEF Supply Division in Copenhagen, Denmark, UNICEF supplies praziquantel to national schistosomiasis control programmes that it supports. In these cases, supply lists for praziquantel are prepared, based on established guidelines, in UNICEF's country offices, and sent to the Supply Division for procurement, packing, and shipment actions (UNICEF, 1992). Complementary to its supply of praziquantel to UNICEF-assisted schistosomiasis programmes, UNICEF also supplies countries, other United Nations agencies, and third parties with praziquantel, on a cost-plus basis, through a purchasing service (Interview No. 6; UNICEF Annual Report, 1993). In this latter situation, developing country governments and third parties (mainly NGOs and non-profit organizations) provide the necessary funds (usually in advance, and preferably in a fully convertible currency) for the procurement of drugs by UNICEF on their behalf. The money paid to UNICEF by the purchasers, in these instances, is the purchase price plus a handling charge of 6 percent (UNICEF Supply Division, 1995). In an effort to support Essential Drugs and PHC programmes in developing countries, UNICEF has

also established a Special Working Capital Fund which allows eligible countries to pay for praziquantel (and other essential drugs) on delivery, rather than in advance as is required for regular UNICEF purchasing services (UNICEF Supply Division, 1995). Whether through purchasing services or for UNICEF-supported programmes, UNICEF's sales are restricted to the public and non-profit sectors, since UNICEF does not sell for the private market (Interview No. 6).

Price is an important consideration in UNICEF's sourcing decisions for drugs, but it is not the only criterion. For quality assurance, UNICEF requires drug registration in the country of origin and drug manufacture conforming to Good Manufacturing Practice (GMP) standards. But UNICEF has no independent assessment capabilities, and relies on the recommendations, as specified in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (WHO, 1994). UNICEF also relies on the services of experts from Denmark's National Board of Health in the assessment of companies, although these experts do not undertake drug testing. Because of UNICEF's policy on quality assurance, UNICEF has not engaged in joint procurement with private bulk purchasers (such as INMED, ECHO, etc.), and UNICEF also does not compete with these agencies on price.

UNICEF perceives its role in drug distribution to developing countries as that of an agent: procuring drugs through international competitive tenders and then selling the products to developing countries at a minimal charge (cost-plus basis), with no "manipulation" of the drug in any way (e.g., no modifications of the drug or its packaging).

UNICEF's conservative policy on drug quality results in a risk averse procurement pattern. Due to this policy, UNICEF may ignore potential suppliers from countries where GMP standards are not strictly enforced and where quality control can vary from company to company (such as China and India). Furthermore, while UNICEF procures drugs from companies approved by WHO, there is often a time lag between a company's initial offering of a product and WHO's approval of its quality. These factors combine so that UNICEF does not necessarily procure at the lowest available global price.

UNICEF's policies on procurement initially restricted purchase of praziquantel to German firms (Bayer and E. Merck), and subsequently added a firm in the Republic of Korea (Shin Poong). For a brief period of time, UNICEF reportedly did procure praziquantel from a firm in Italy, but the company involved evidently had some legal problems with its process patent, involving a possible infringement of the Bayer-E. Merck patent. UNICEF was unable to provide us with information on the nature of the patent infringement by the Italian firm. The problems with the Italian producer led UNICEF to shift to Shin Poong in the early 1990s, after Shin Poong's product registration and patent were approved by WHO, and no evidence was found of infringements of the German patent.

Although UNICEF is the largest bulk supplier of praziquantel, the drug does not represent a high priority for UNICEF. The total annual expenditure on all UNICEF essential drug purchases in 1992 was about US$ 61 million. An additional US$ 62 million was spent on vaccines (UNICEF Annual Report, 1993). Praziquantel constituted less than 1% of the expenditure on essential drugs and vaccines. While UNICEF recognizes schistosomiasis as a major health problem in developing countries, the agency does not include schistosomiasis treatment as a top priority in the health sector. According to a UNICEF official (Interview No. 6), investment on a single praziquantel treatment is significantly more expensive compared to immunization doses or ORS treatments for the same number of people (although no good comparative cost-effectiveness studies exist, to our knowledge). Moreover, immunization has a lifelong impact, while praziquantel has to be used repeatedly in the same population for the control of schistosomiasis. Finally, immunization, unlike schistosomiasis, represents a UNICEF priority.

WHO

Although WHO assists member countries in the formulation and implementation of schistosomiasis control programmes, it is not involved in the procurement of praziquantel for these control programmes (Interview No. 8). WHO procures relatively small amounts of praziquantel, primarily for research studies of the Special Programme for Research and Training in Tropical Diseases (TDR).

WHO's procurement of praziquantel is much smaller than UNICEF's scale. In 1991, WHO bought 28,000 tablets of praziquantel, while in 1992, a total of 186,000 tablets were purchased for the equivalent of US$ 72,500 from various sources (Interview No. 8). WHO did not agree to provide us with information on the prices paid for its praziquantel procurement. As for sources, over the last 10-12 years, WHO has procured praziquantel from Bayer, IDA, Medochemie Pharmaceuticals and Shin Poong.

World Bank

The World Bank has provided assistance in the form of long-term loans at concessional rates for the purchase of praziquantel by several developing countries. This assistance has occurred as part of grants for health projects (e.g., schistosomiasis control or infectious disease control programmes), and in loans linked to irrigation projects (Interview No. 7). Details of the World Bank's involvement in the distribution of praziquantel as part of national schistosomiasis control programmes are provided in Chapter 6, with a brief summary below.

Countries that have received assistance for praziquantel procurement include: Cameroon, China, Egypt, Ivory Coast, Kenya, Malawi, Nigeria, Philippines, Senegal, Tanzania and Zambia. Of these, China, Egypt, and the Philippines comprise more than 90% of all World Bank-supported purchases of praziquantel.

The World Bank has standard procedures for the procurement of pharmaceuticals using World Bank loans or grants. For example, countries using World Bank loans to procure praziquantel must submit tender documents to the World Bank for review and obtain a "no-objection" certification. Further, the countries are required to publicize the tenders widely, including the placement of advertisements in at least seven international journals and newspapers. Details of the procedures to be followed are provided in a document entitled "Standard Bidding Documents for Procurement of Pharmaceuticals and Vaccines" published by the World Bank (World Bank, 1993).

Our study calculated, for the first time, the relative contributions made by UNICEF, WHO, and the World Bank to the total spending on praziquantel purchases by these international agencies, as shown in Table 5.3 below. The table highlights the dominant role played by the World Bank in the procurement of praziquantel by developing countries, in comparison to the other two international agencies.

Table 5.3: International agency spending on praziquantel

International agency	Annual spending (US$) on praziquantel procurement	Proportion of total spending by international agencies
UNICEF	1.80 million	30.7%
WHO	0.07 million	1.2%
World Bank	4.00 million	68.1%
TOTAL	5.87 million	100.0%

Note: Based on spending in 1992-1993 or average yearly spending.

NGOs and private organizations

Various private organizations produce or formulate praziquantel or purchase the drug in bulk and sell the drug to developing countries. Examples of these organizations are: IDA and IAPS in the Netherlands, Orbi-Pharma in Belgium, Action Medeor in Germany, ECHO in the UK, and INMED in the USA. Other than IDA, these organizations purchase praziquantel in bulk, but their shares of the total bulk procurement are likely to be comparatively small.

These organizations procure praziquantel from numerous producers and formulators, with price as the primary criterion for selecting the source. With some exceptions (e.g., Action Medeor), considerations of drug quality and adherence to patent laws are usually secondary to price. For example, Orbi-Pharma in Belgium—which has supplied praziquantel to several countries in Africa, including Burundi, Equatorial Guinea and Zaire —procures the drug from two generic producers, namely Athlone Labs in Ireland, and Pharmachemic in Belgium.

In the Netherlands, IDA works with the Dutch Government and Dutch development aid, provides praziquantel (and other drugs) to many NGOs, and also bids on tenders issued by developing countries. IDA is a private non-profit foundation, with an annual turnover of about US$ 60 million in 1991. IDA has two warehouses in the Netherlands, and is subject to the full control and inspection of the Dutch government, similar to any other Dutch wholesale organization. IDA's facilities in the Netherlands have been fully inspected and approved for both Good Manufacturing Practices and Good Distribution Practices. IDA procures active raw materials on the international market, and then formulates its own praziquantel tablets in IDA's subsidiary in Malta, Pharmamed. According to IDA, its praziquantel active ingredients are procured only from sources that meet international pharmacopoeial specifications, but the foundation refused to disclose the source and origin of its raw materials, "for economical reasons" (den Besten, April 1996). According to other agencies, IDA has reportedly procured raw materials and praziquantel tablets from Bayer, Shin Poong, and Chinese producers. Among private organizations, IDA is probably the biggest supplier of praziquantel (after the major producers and UNICEF) to developing countries and also to international agencies, such as WHO. But we could not confirm this statement, since IDA refused to provide us with data on its praziquantel production, purchases, or distribution.

One example of a smaller NGO involved in pharmaceutical procurement for Third World countries is Action Medeor in Germany. This NGO has a warehouse, with an annual turnover of US$ 14 million, through which it can supply packages of small amounts of drugs and other supplies (Interview No. 1). Medeor ships praziquantel in its own containers of 250 tablets of 600 mg. The tablets are made to order for Medeor by 7-8 small contract pharmaceutical firms, with raw ingredients purchased by Medeor on the world market. For example, Medeor has purchased praziquantel raw materials from Pharmamed, the IDA subsidiary in Malta. Medeor is subject to German pharmaceutical laws and regulations, which apparently is a requirement for any German organization that imports raw materials.

Medeor previously purchased Biltricide from Bayer, but this proved too expensive. Before the expiration of the Biltricide patent, Medeor entered into price negotiations with Bayer, but was unable to obtain concessions; it therefore switched suppliers on the expiry of the patent. Praziquantel constitutes a relatively small part of Medeor's supplies, although its expenditure of US$ 75,000 on the product is relatively important in terms of Medeor's drug budget. In 1993 Medeor mailed 728 containers with 250 tablets of 600 mg, and in 1994, it mailed 754 containers. Medeor sells Biltricide at approximately US$ 0.88 per tablet and generic praziquantel at about US$ 0.25 per tablet.

German law restricts Medeor's activities in several ways. Medeor has a special license that allows it to have raw materials made into tablets and to ship tablets

overseas, but the tablets cannot be sold in the German market. These overseas shipments, however, must meet German GMP requirements, which increases the costs of formulators and distributors such as Medeor, and raises the price that purchasers in developing countries pay for a drug like praziquantel. The restrictions also open up opportunities for competitors who can avoid strict quality standards and can ship directly by placing their formulating and distributing facilities outside of Europe.

Conclusions

The key lessons emerging from this analysis of the global supply of praziquantel may be summarized as follows:

- The 1985 entry of Shin Poong Pharmaceutical Company into the global praziquantel market has had a major impact on market structure. Shin Poong has gained market shares almost continuously over time, at the expense of the original producers of praziquantel, Bayer and E. Merck. In the early 1990s, Shin Poong became the world's largest producer of praziquantel, responsible for 55% of global production in 1993.
- The expiry of the Bayer/E. Merck praziquantel patent in various countries, between 1989 and 1994, is the second notable event in the market history of praziquantel. The patent expiry has resulted in the emergence of a growing number of generic producers and formulators, mostly based in Europe, and has created an increasingly competitive market for praziquantel.
- In the near future, it is unlikely that Bayer and E. Merck will expand their production capacity for praziquantel significantly, for several reasons: because of the higher cost structure of their production process, because of the marketing effort that would be required, because their request for a sales guarantee from international agencies is not likely to be met, and because the availability of an effective vaccine in the near future seems likely and would have a major impact on the market for praziquantel.
- The distribution channels for praziquantel in developed and developing countries differ significantly from each other. Sales to developing countries are concentrated in the public sector, through national and international tendering, while sales in developed countries are dominated by the private sector and the veterinary market.
- Various international agencies and for-profit and non-profit organizations play important roles as bulk suppliers of praziquantel to developing countries.
- Among international agencies, according to expenditure figures, the World Bank plays a dominant role in financing praziquantel procurement, UNICEF plays a major role in selling the drug on a cost-plus basis, and WHO plays a minor role in providing technical assistance related to praziquantel (although WHO provides technical assistance for essential drugs programmes, which include praziquantel). Little coordination occurs

among the three international agencies on activities related to praziquantel.

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Chapter 6:

Demand for praziquantel and national distribution*

This chapter provides an assessment of the global demand for praziquantel, and describes national distribution of the drug in several developing countries. The section on demand focuses on the striking gap between the high potential demand for the drug (as evidenced by the prevalence of schistosomiasis in developing countries), and its limited supply by the existing producers and formulators of the drug. The chapter also discusses the impact of praziquantel's high cost on the operation of schistosomiasis control programmes. The section on distribution of the drug discusses: the role of international agencies and bilateral aid organizations in assisting national schistosomiasis control programmes; the role of the private market in ensuring the availability of the drug in developing countries; and the role and success of national schistosomiasis programmes (using the example of Mali) in making the drug available to people afflicted by the disease.

The demand for praziquantel

Non-schistosomiasis demand

The non-schistosomiasis demand for praziquantel can be considered along several dimensions, as noted below: human versus veterinary use; developed country versus developing country markets; and within the human market, use for treatment of schistosomiasis versus treatment of other helminthic infections.

- First, the veterinary market may be smaller in terms of volume, but is probably comparable in terms of sales value to the human market, because of the higher prices of veterinary products. In 1993, the total value of global veterinary sales of praziquantel were about US$ 90 million. This compares favourably with our approximate estimation of the global value of sales of human praziquantel formulations in the same year. Assuming an average price per tablet (based on the prices and relative sales in developed and developing countries) of the human formulations of about

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US$ 1,[**] our estimate of global supply in 1993 of 89 million tablets (see Chapter 5) would suggest that a global sales value of human praziquantel formulations is about US$ 89 million. The veterinary market probably also offers higher profit margins to producers of praziquantel than the human market.

- Second, veterinary sales of praziquantel are dominated by the developed world, although China does use the drug for the treatment of schistosomiasis infections in cattle (World Bank, 1991) as a means of reducing disease transmission. Given that the veterinary market is comparable to the human market and is located primarily in developed countries, developed country praziquantel sales (veterinary plus human) may well exceed sales in developing countries.

- Third, the demand (both potential and realized) for praziquantel for schistosomiasis treatment dominates that for other helminthic infections, although the potential demand for praziquantel for treatment of these other diseases is significant and increasing. WHO's global estimates of prevalence of these other helminthic diseases in 1993 are shown below:

Table 6.1: Estimated global prevalences for selected helminthic diseases

Helminthic diseases	Estimated global prevalence
Clonorchiasis	7.0 million
Opisthorchiasis	10.3 million
Paragonimiasis	20.7 million
Various intestinal fluke infections	1.3 million
Schistosomiasis	200.0 million

Source: Schistosomiasis Control Unit, WHO, 1994.

These estimates would suggest that praziquantel may have other potential markets in the future. For this report, however, the non-schistosomiasis market and the veterinary market are not discussed further, due to the limited availability of data and the study's focus on schistosomiasis.

Potential demand for praziquantel for schistosomiasis treatment

In 1989, WHO compiled an estimate of the global "need" for praziquantel, based on country by country estimates of the prevalence of schistosomiasis and assumed treatment of all infected people (Utroska et al., 1989). This represents the only public effort to calculate the potential demand for praziquantel. The

[**] The estimate of an average price per tablet of about US$ 1 should be taken as very rough, based on three main assumptions: very small market share in developed countries at full price; relatively small private market share in developing countries (perhaps 20%); and predominantly tender market for developing countries (perhaps 80%) at deeply discounted prices. See Chapter 7 for more data on prices.

analysis compiled studies from developing countries to estimate the global prevalence of schistosomiasis. Estimates of the population at risk (population in endemic areas of the country) and the average prevalence of schistosomiasis in the country were used to estimate the total number of people infected. The infected people were then separated into two groups, persons below 15 years and those above 15 years. Then, using standard national weight charts for these two groups, estimates of the total body weight of each group were made. Finally, the total weight for each group was divided by the standard dosage of praziquantel of 40 mg/kg body weight, to arrive at the total number of 600 mg praziquantel tablets needed. The analysis calculated that about 424 million tablets were needed annually to treat all people estimated to be infected with schistosomiasis in endemic countries.

The validity of the WHO global estimate is difficult to assess, because the figure is based on variable data and several assumptions. A potential for bias exists at each step of the analysis, and, therefore, in the overall results, although it is difficult to know what the extent and overall direction of the bias might be. For example, the quality of the prevalence estimate differs by country, depending on whether a scientific study was undertaken or the country simply provided its own assessment. Some countries have reassessed WHO's point estimate of prevalence, and found it either too high or too low. Cameroon's estimates, for example, were found to be too high (Ratard et al., 1992). One factor that could contribute to under-estimates is that schistosomiasis is not a reportable disease—except in a few countries—which would reduce the level of reliable reporting. On the other hand, some countries calculated national figures based on projections from pilot studies in endemic areas; this method would tend to generate over-estimates of prevalence. To deal with these problems, future estimates of schistosomiasis prevalence by WHO could include ranges.

While WHO's estimates for specific countries may have wide margins of error, the ordering of countries is probably reliable. Table 6.2 lists the top countries according to WHO's global estimate of praziquantel need, along with each country's share of global need, and the overall global need. Table 6.2 also includes the limited data that we could collect on the estimated availability of praziquantel in the national markets of the top 30 countries, plus data for the Republic of Korea. It should be stressed that these estimates of national supply are very rough, based on incomplete data. Also, substitutes for praziquantel are used in some countries. Brazil, for example, makes its own oxamniquine, and therefore does not use much praziquantel.

Market data for praziquantel in developing countries are extremely difficult to obtain. For example, WHO does not have figures on praziquantel procurement by the 24 national schistosomiasis control programmes that it supports (WHO, 1993). And estimates of private market sales are limited and spotty at best. In seeking these data, we mailed questionnaires to MOHs and government offices in the top 30 endemic countries, to experts in schistosomiasis, and to others involved in national schistosomiasis control programme operations. Few responses were received, however, with even fewer reliable estimates of public

procurement or private market sales for praziquantel. The responses included partially completed questionnaires from three schistosomiasis experts, and from seven countries (Botswana, Brazil, Egypt, Ghana, Nigeria, South Africa, and Zambia). In addition, information was received that eleven questionnaires had been forwarded to the proper authorities, although no response was received from these sources by April 1995. A few additional questionnaires were returned with suggestions that other people be contacted; these leads, however, did not produce usable data. As shown in Table 6.2, we were able to collect very limited market data on only 8 of the top 30 countries (plus the Republic of Korea), accounting for about 40% of the global supply of praziquantel (36 million tablets out of the estimated total supply of 89 million).

Table 6.2: Estimated need and availability for praziquantel in the top 30 countries

Country	Tablets needed	% of global need	Cumulative % of global need[a]	Availability in 1993	% of need met[b]
1. Nigeria	61,827,176	14.6%	14.6%	negligible	negligible
2. Tanzania	31,409,269	7.4%	22.0%	160,000	0.5%
3. Ghana	27,611,179	6.5%	28.5%	200,000	0.7%
4. Mozambique	27,311,159	6.4%	35.0%	n / a	
5. Egypt	26,316,941	6.2%	41.2%	10 million	38.0%
6. Zaire	23,945,287	5.7%	46.8%	n / a	
7. Brazil	19,680,000	4.6%	51.5%	negligible[c]	negligible
8. Madagascar	15,413,514	3.6%	55.1%	n / a	
9. Mali	13,962,618	3.3%	58.4%	607,000[d]	4.3%
10. Uganda	13,900,410	3.3%	61.7%	125-200,000	1.4%
Nos. 11-20	99,642,543	23.5%	85.2%		
21-30 (inc. China)	43,035,263	10.1%	95.4%		
of which China	2,826,355	0.7%		24 million[e]	850%
Availability in the Republic of Korea[f]				1-1.2 million	
Total estimates (for top 30)	**404,124,000 need**			**(36,367,000 accounted for)**	
Total global estimates	**423,609,839 need**			**89,000,000[g] availability**	**21.0%**

Source: Estimated need is for use of praziquantel in treatment of schistosomiasis, based on a case treatment strategy, from Utroska et al., 1989; estimates of praziquantel availability are mostly for 1993, and are based on various sources, including a survey distributed to governments and schistosomiasis experts, as part of this study.

[a] The cumulative % of global need refers to the percentage of total global need accounted for by that country and all countries above.

[b] The % need met is based on the highest estimate of availability as a percentage of the estimated need.

[c] Brazil has wide availability of oxamniquine, which is produced in Brazil and is used for treatment of S. mansoni.

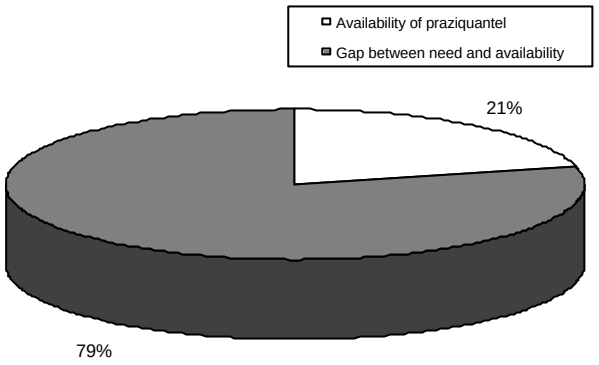
[d] The data for Mali are for 1995 and include purchases for projects and for the Ministry of Health.

[e] This figure for China is based on import and production estimates; the high volume is partly explained by China's strategy of mass treatment for schistosomiasis in endemic areas, not only for infected cases, and by China's treatment of cattle (which require large dosages of praziquantel).

[f] the Republic of Korea is included because praziquantel is widely available (for treatment of schistosomiasis and liver fluke).

[g] This figure of 89 million probably overestimates the global supply of praziquantel for human usage, since it includes the quantity used in China for both human and veterinary treatment.

Figure 6.1: Current global availability of praziquantel compared to total need



Total need	= 424 million tablets
Current availability	= 89 million tablets

Gap between need and supply of praziquantel

Table 6.2 and Figure 6.1 show a striking disparity between WHO's estimated need for praziquantel, and our estimate of the supply of the drug in developing countries. As noted above, WHO estimated that the total global need for praziquantel is approximately 424 million tablets annually. This figure contrasts with our best estimate of the current annual supply of praziquantel, of about 89 million tablets (based on production data)—representing only 21.0% of the WHO's estimate of global need. If WHO over-estimated the global need for praziquantel by a factor of two (about 210 million tablets), then the current global supply of praziquantel would still meet only about 40% of the revised global need. The gap is even more marked within certain individual countries.

The situation in six countries is reviewed next (in the order of estimated national "need" for praziquantel), to illustrate the gap that exists between the demand for praziquantel and its supply in developing countries with endemic schistosomiasis.

Nigeria (#1): According to WHO's estimates, Nigeria has the greatest national need for praziquantel, about 62 million tablets annually, which is almost 15% of the total global need. However, according to a report received from the Nigerian MOH, and other informed sources, very little praziquantel is available in Nigeria—in either public or private sectors (Nigeria MOH, 1995). The high cost of praziquantel, and Nigeria's huge requirement for the drug, has limited the country's ability to procure the drug from Bayer and from international agencies (despite the concessional prices offered by these agencies). The same holds true for a number of other Sub-Saharan countries, such as Mozambique, Tanzania and Zaire.

Ghana (#3): According to WHO's estimates, Ghana requires approximately 28 million tablets of praziquantel annually, which is about 6.5% of the estimated global need, ranking Ghana in third place in terms of need for praziquantel. The government has procured praziquantel through UNICEF and WHO, though the procurement has been irregular, and the annual supply has never exceeded 100,000 tablets. In 1993, however, the Ghana Partnership for Child Development project in the Volta region procured 200,000 tablets of praziquantel. Reportedly, praziquantel is available in the private market in Ghana (along with metrifonate, and Ambilhar (niridazole), a drug not officially recommended for schistosomiasis), although the volume of private sales is unknown.

Egypt (#5): Egypt is the world's second largest single-country consumer of praziquantel, according to our estimates (approximately 10 million tablets in 1992), and ranks fifth in the world in its need for praziquantel, according to WHO's estimates. But even the current level of praziquantel supply in Egypt provides only 38% of WHO's estimate of national need (26 million tablets per year). It is difficult to gauge whether this gap reflects an over-estimation of need in Egypt by WHO, or a shortfall in supply. Starting in 1988, Egypt's MOH procured praziquantel from Bayer, and later from EIPICO. Since 1990, however, the MOH has obtained almost all of its praziquantel from EIPICO. Praziquantel is distributed by the MOH to the local health units. Cases of schistosomiasis identified through field tests are treated with the drug in primary health care and endemic disease units. A follow-up is undertaken after three months through a re-examination and testing of the treated patients.

South Africa (#16): According to WHO estimates, South Africa has a need of almost 10 million tablets, placing it 16th among the countries needing praziquantel. Though exact figures were not available, South Africa's procurement of praziquantel for schistosomiasis is probably considerably lower than its need, although the procurement might increase in the future with the expanded implementation of the government's mass parasitic treatment projects. Praziquantel is used in South Africa for a number of parasitic infections, including schistosomiasis, cysticercosis, and various other cestode infections. Although the Bayer patent has expired in South Africa, it still holds a trademark registration, and evidently is, to date, the sole supplier to South Africa of praziquantel for treatment of schistosomiasis (although Merck, South Africa, produces a praziquantel-containing drug for treatment of cysticercosis). Praziquantel is sourced from Bayer, Germany, as a finished product and is then packaged locally in Bayer's South African subsidiary and distributed through its own distribution company. Bayer supplies praziquantel to the South African government at a tender price, and also supplies the private sector, offering discounts based on the volume of purchases.

Zambia (#23): Zambia, according to WHO, has an annual need of about 5 million tablets, placing it 23rd in the list of countries needing praziquantel. Zambia, however, purchases hardly any praziquantel. The small quantities

purchased are used for research purposes in Zambia's attempts to find the best strategy for community-based control of schistosomiasis. Annually, about 1,000 tablets have been purchased for the last several years from Bayer, IDA, and WHO. Oxamniquine and metrifonate are reportedly available in the private market. Praziquantel is distributed by Medical Stores, Ltd., a pharmaceutical company run by the Ministry of Health.

China (#29): In China, the Schistosomiasis Control Programme in the MOH's Department of Endemic Disease Control is responsible for the distribution of praziquantel to the provinces, through a special provincial office for schistosomiasis control. In 1993, China was the largest single-country consumer of praziquantel, with approximately 24 million tablets, according to our estimates of imports (10 tons of raw material) plus domestic production (5 tons of raw material), although this figure includes veterinary uses (for cattle) as well as human uses. We were unable to obtain any estimates of human versus veterinary consumption of praziquantel in China (or number of cases treated), despite numerous attempts with Chinese authorities and international agencies.

Several factors help explain the large gap between WHO's estimate of the theoretical "need" and our estimate of the current supply of praziquantel:

- First, the relatively low profile of schistosomiasis as a disease priority has helped to constrain demand in many countries. Though it affects about 4% of the world's population (with three times that number at risk), schistosomiasis is often perceived as a relatively low public health priority, because of the insidious nature of the disease and its tendency to affect morbidity without dramatically increasing mortality.

- Second, the availability of praziquantel may not reduce incidence rates of schistosomiasis, despite the drug's high cure rates, because reinfection remains a major problem. If praziquantel availability does not affect the transmission of schistosomiasis, then the need for praziquantel would not decline and could even increase over time. Consequently, the gap between need and supply would persist in the foreseeable future at current production levels.

- Third, the high cost of praziquantel has created an irregular and uncertain supply in many countries. The problems of high cost are compounded by the low purchasing power (and limited foreign exchange) of most developing countries with endemic schistosomiasis. We explore price problems and cost issues in more detail in the next section.

- Finally, even when praziquantel is "available," the public and private distribution systems may not work effectively in countries with endemic schistosomiasis. Major obstacles exist in the delivery of praziquantel to infected populations in rural areas.

The cost of praziquantel within schistosomiasis control programmes

The high procurement cost of praziquantel is commonly identified as the biggest obstacle to implementation of a successful schistosomiasis control programme. Table 6.3 summarizes information from the limited number of studies that have estimated the costs of praziquantel as a proportion of the total costs of schistosomiasis control programmes using different control strategies.

Table 6.3 demonstrates the paucity of good studies on the costs of schistosomiasis control programmes. Undertaking such studies in different country settings could help explain the role of praziquantel costs in national control programmes for schistosomiasis. Some studies suggest that the structures and strategies of control programmes affect the total cost of praziquantel as well as the proportion of total programme costs devoted to praziquantel. If the schistosomiasis programme is decentralized and integrated with local health delivery systems, in a horizontal approach, then the delivery costs are often reduced, while the proportion of praziquantel cost to total programme costs increases (Gryseels, forthcoming). A vertical programme, on the other hand, is more efficient at providing mass screening and preliminary sample surveys in a developing country, while the proportion of praziquantel cost to total programme costs decreases, because of the high cost of other inputs, such as vehicles and personnel (Gryseels, forthcoming).

Table 6.3: Studies on the cost of praziquantel compared to overall costs of schistosomiasis control programme

Study location	Year	Authors	Praziquantel as % of total costs	Comments
Mali	1988	Brinkmann et al.	8.5 to 17.3%	Range based on whether programme involved targeted or mass chemotherapy.
Global	1983	WHO study	10 to 30%	Estimate of costs not based on data collected in a specific setting.
Madagascar / Mali	1989	Rohde	39 to 47%	Estimated costs of alternative scenarios for control programmes, for a hypothetical population, assuming various expenses and using data collected in Madagascar and Mali.
Kilombero, Tanzania	1994	Guyatt et al.	30.9% 58.1% 83.5%	Lower estimate is for reagent strip testing of schoolchildren. Middle estimate is for passive testing & treatment at PHCs. Higher estimate is for mass treatment of schoolchildren using mobile teams.
Pemba, Tanzania	1986-87	Savioli et al.	80 to 89%	Estimate of total costs calculated with only drugs and urinary reagent strips included.

Congo	1986	Korte et al.	Not calculated	Model-based cost estimates for metrifonate and praziquantel.

Table 6.3 highlights the great variability across studies of the relative costs for praziquantel. While part of this variation can be explained by different control strategies (e.g., mass chemotherapy versus targeted strategies), as explained above, the variation also results from inconsistency in the cost categories. The two most widely cited, and probably more reliable, studies (Brinkmann et al., 1988; and WHO, 1983) show that the costs of praziquantel as a proportion of overall programme costs are significant (8.5 to 17.3%; and 10 to 30%).

The cost of praziquantel within government health budgets

Can countries with endemic schistosomiasis afford to pay for praziquantel from the government health budget? Below we briefly consider this question for the countries of Sub-Saharan Africa.

In 1990, average per capita expenditure on health in all of Africa was about US$ 23 (Murray, Govindaraj, and Musgrove, 1994). Of this, spending in the entire public sector (including social insurance and spending by parastatal agencies) was just over US$ 10 per capita. If only the Ministry of Health expenditures are considered, then the average annual per capita expenditure would be about US$ 5-7 per capita. If one were to disregard countries like Botswana, the Seychelles and South Africa, which are significant outliers in terms of health spending, then the annual spending on health by the Ministries of Health would be under US$ 4 per capita. For several countries, like Mozambique, the level of spending is even less.
If about 20% of the MOH health budget is spent on drugs and medical products (Murray, Govindaraj, and Chellaraj, 1994), then the average spending on drugs in Africa by Ministries of Health would be about US$ 0.80 per capita. If, for example, Nigeria were to procure as much praziquantel as it needs annually to treat all schistosomiasis cases (62 million tablets, according to the WHO estimate), at the UNICEF price of about US$ 0.22 per tablet, then the MOH would require an annual expenditure of US$ 13.6 million, or a per capita spending of almost US$ 0.14—about 17.5% of all MOH spending on drugs and medical supplies. This rough calculation demonstrates why it would be difficult to expect Nigeria's MOH to pay for the praziquantel "need" out of the government's health budget.

The study in Tanzania by Guyatt et al. (1994) provides roughly similar figures for the cost of praziquantel compared to total government per capita health spending. The cost per capita of praziquantel in the three types of programmes evaluated by the authors can be calculated at approximately US$ 0.02-0.07 (from 30.9% of US$ 0.05, to 58.1% of US$ 0.11). Per capita government expenditure on drugs would be US$ 0.24, based on the estimate from Guyatt et al. of per capita government health spending of US$ 1.20, and assuming (as in the previous example) 20% expenditure of this amount on drugs. Once again, expenditure on praziquantel alone would constitute a substantial proportion

(8-29%) of the government's total spending on drugs, probably putting it beyond the means of the Tanzanian government.

National distribution of praziquantel

WHO support

According to WHO, starting in 1983, a total of 24 countries have established schistosomiasis control programmes (WHO, 1993). These countries are: Algeria, Brazil, Botswana, Burundi, China, Dominican Republic, Egypt, Ghana, Indonesia, Laos, Madagascar, Malawi, Mali, Mauritius, Morocco, Nigeria, Philippines, Saudi Arabia, Sudan, Suriname, Tunisia, United Republic of Tanzania: Zanzibar, Venezuela, and Zimbabwe (WHO, 1993). WHO provides technical assistance to these programmes, but does not become involved in the funding of control programmes or in the procurement of drugs for the programmes. As part of a global monitoring effort, a computerized global database has been established in the Schistosomiasis Control Unit of WHO, with information on the epidemiology of schistosomiasis, control activities, and people responsible for control, water resources, and chemotherapy for each endemic country (WHO, 1993).

UNICEF support

UNICEF has provided some assistance to distribute praziquantel in certain countries, mainly in Asia and Africa, as a part of UNICEF-assisted schistosomiasis control programmes. UNICEF, however, does not directly become involved in the distribution of praziquantel within a country, except through an essential drugs programme. In general, UNICEF relies on each country to arrange for the effective distribution of drugs procured through its supply service. In some cases, UNICEF might provide technical support, if requested by the government.

World Bank support

The World Bank has provided significant financial support to schistosomiasis control efforts in Egypt, China, and Brazil. These activities are briefly described below.

Brazil: The schistosomiasis control project in Brazil is part of a WB-funded Endemic Diseases Control Project (Interview No. 7). Oxamniquine remains the most important chemotherapeutic agent used in schistosomiasis control in Brazil. According to the World Bank, in 1989, the price of oxamniquine was about three times the price of praziquantel in Brazil (World Bank, 1989). Even at the estimated price of US$ 2.84 for a course of praziquantel, it was calculated that Brazil could save several million US dollars by switching to praziquantel. However, the Brazilian programme has not procured

praziquantel, despite strong pressure from the WB. Sales of praziquantel in the Brazilian private market are relatively small.

According to WB sources, physicians in Brazil are reluctant to prescribe praziquantel, despite evidence that praziquantel is superior to and cheaper than oxamniquine, and despite successful clinical trials in Sao Paulo. One reason for resistance is complaints about the large size of praziquantel tablets, which makes it difficult for children to swallow them. In addition, there is a general feeling that oxamniquine is a satisfactory drug for the treatment of schistosomiasis and it has been used for a long time. Further, oxamniquine is packaged locally in Brazil by a subsidiary of Pfizer, which may provide an incentive to continue the drug's use in the national programme.

According to the Brazilian Ministry of Health, about 300,000 people are treated annually in the national schistosomiasis control programme. Each year the programme uses approximately 40,000 vials of 12 ml. oxamniquine syrup and 960,000 capsules of 250 mg. oxamniquine.

China: The WB-supported schistosomiasis project in China involves 8 provinces, which together represent almost 90% of WHO's estimated total need for praziquantel in China (Interview No. 7). According to WB sources, almost all the consumption of praziquantel in China occurs through the government's schistosomiasis control programme, with no significant sales in the private sector or through non-MOH sources.

The project in China is being implemented in three phases: in high intensity areas, control of schistosomiasis is through chemotherapy (praziquantel) and health education; in medium intensity areas, control is through chemotherapy, health education, and molluscicide (using primarily niclosamide); in low intensity areas, control involves limited chemotherapy, a lot of molluscicide, and a limited number of environmental interventions. The project also involves operations research, particularly in relation to drug efficacy and economic analysis of different interventions. According to the WB, a significant share of the project's expenses (about 42%) are for the procurement of praziquantel, for a total of US$ 3.8 million over the course of the project, but we could not obtain estimates of the procurement volume.

When the project started in 1991, praziquantel was procured from Bayer. In 1992, Shin Poong won an international tender bid to supply all praziquantel for the project, including praziquantel tablets for human consumption and praziquantel powder for cattle. According to WB sources, the Chinese initially tried to disqualify Shin Poong and substitute it with a local supplier, but did not succeed because of WB objections on the grounds that such substitution would be an infringement of the WB's procurement procedures (see Chapter 5) (Interview No. 7). The niclosamide used for the project was initially supplied by Bayer, but a Chinese company subsequently submitted a bid at 80% below the

Bayer price. The quality of the Chinese product was found to be good, and Chinese niclosamide is now used in the project (Interview No. 7).

According to the WB, the project has been very successful. An initial survey was undertaken in 1989 by the WB, with a follow-up survey in 1992. The second survey showed that the schistosomiasis control measures had achieved a major impact—the focus was therefore shifted from chemotherapy to molluscicides and environmental measures. Further, the recent price declines for praziquantel have resulted in significant savings, which have been used to purchase niclosamide for expanded mollusciciding.

Egypt: The World Bank (WB) programme in Egypt was initiated in 1992, in order to extend the ongoing Egyptian schistosomiasis control programme to the Nile Delta region (Interview No. 7). The WB project has been funded for a period of six years (1992 to 1997), and the total project costs are estimated at about US$ 43 million, with the WB providing a loan of US$ 26.84 million. This independent project is attached to a larger Water Drainage and Irrigation project, also funded by the WB. The WB loan funds the entire procurement of praziquantel by the Egyptian government (the estimated cost of the procurement being about US$ 12.87 million), in addition to funding provided for the other components of the control programme.

The prevalence of schistosomiasis in the delta area at the start of the programme, in 1992, was estimated at over 35%. The goal of the programme is to reduce the prevalence of schistosomiasis by 75% (from >35% of the population to <10%) at the end of the six years. In 1991, the Egyptian government budgeted about L.E. 14 million (US$ 4.65 million) for the purchase of praziquantel tablets and pesticides. Since 1990, all government procurement has been from a local source (EIPICO) (see Chapter 4).

Other countries: In addition to the three countries discussed above, the World Bank has played a major role in the schistosomiasis control programme in the Philippines (providing US$ 7.3 million from 1983-1992 for the purchase of praziquantel). The World Bank has made limited contributions to national programmes in Cameroon, Côte d'Ivoire, Kenya, Nigeria and Senegal. We do not have estimates of praziquantel procurements in these countries through WB loans, due to the lack of a central database in the WB on praziquantel procurements.

Bilateral aid agencies and national schistosomiasis control programmes

Bilateral aid agencies have also assisted national schistosomiasis control programmes in improving access to praziquantel. Unfortunately, we could find no database or studies on the role of bilateral aid agencies in schistosomiasis control—including technical and financial assistance. Here we discuss only the activities of the German bilateral aid agency, since it seems to have been most

active with regard to praziquantel. USAID has supported schistosomiasis control efforts in Egypt, but has devoted little attention to praziquantel procurement. The Bilharzia Fund, a German government-sponsored agency (although not technically a bilateral aid agency), has also supported national schistosomiasis control programmes.

The Health, Population, and Nutrition Division of the German Agency for Technical Cooperation (GTZ) has participated in several schistosomiasis projects in Africa. While each project was a "separate entity with its specific national background, structure and strategies," most of GTZ's efforts were directed at testing and implementing population-based chemotherapy with praziquantel, using specialized mobile teams (Gryseels, forthcoming). For example, in the early 1980s GTZ-assisted schistosomiasis control projects were initiated in Mali, Congo, and Madagascar, and were evaluated by external experts in 1987, 1988, and 1989, respectively (Gryseels, forthcoming). These projects were among the first large-scale applications of praziquantel for population-based chemotherapy, and showed that schistosomiasis prevalences could be quickly and safely reduced by mass or selective treatment. The evaluations also demonstrated, however, that reinfection occurred and that repeated treatment was necessary, making the vertical structures and strategies of the projects difficult to sustain in the long term (Gryseels, forthcoming). GTZ is not currently purchasing or supporting procurement of praziquantel (Korte, 1994).

Role of the private sector in praziquantel distribution

Private industry associations have also supported some schistosomiasis control programmes. The German Pharma Fund, for example, is an organization used by the German pharmaceutical industry to donate products and services to developing countries and to specific development projects. One successful project of the Fund was carried out in collaboration with WHO in Pemba, Madagascar, to supply praziquantel for the schistosomiasis control programme there.

Little information is available on the private market for praziquantel in developing countries, except that there is considerable variation in the size of the private sector by country. In Mali, for example, about 30 percent of praziquantel consumption is private, according to WHO sources (Interview No. 8). In Egypt, the private praziquantel market is between 10-15% of total consumption by volume (see Chapter 4). Certain countries, such as China, have practically no private sales of praziquantel. On the other hand, in a few countries, such as the Republic of Korea, most praziquantel consumption is through the private sector (see Chapter 3). Three points can be made regarding the size and role of the private market for praziquantel in developing countries:

- First, private market sales of praziquantel are generally quite small in most developing countries, compared to public sector procurement, in part

because the public sector often provides praziquantel to patients free of charge or at nominal prices, which reduces demand in the private market.

- Second, in general, the price in the private sector tends to be much higher than in the public sector. Those consumers who are concerned about the quality of praziquantel in the public sector, or who do not want to wait in long lines at public sector clinics to receive the drug, may choose to purchase the drug on the private market.

- Third, the large gap between the private market price and the public sector price can be an incentive for pilferage of public sector supplies. Similar problems of leakage for subsidized goods occur for other pharmaceutical products as well as other commodities.

National schistosomiasis programmes

As mentioned above, by 1993, national schistosomiasis control programmes had been established in 24 countries (WHO, 1993). The experience of Mali's schistosomiasis control programme is briefly discussed below, because that country's programme has been extensively studied. The case of Mali suggests lessons that may apply to other countries in Sub-Saharan Africa.

The case of Mali

The national schistosomiasis control programme in Mali began with a small programme initiated in 1978 with the assistance of WHO and GTZ, to treat commercial farm workers residing around the small dams and irrigation schemes of Bandiagara (Brinkmann et al., 1991). By 1982, a national programme, under the administrative umbrella of the National Institute for Public Health Research, was developed as part of the Ministry of Health's ten-year plan. Four regions, which were significant to Mali's economy and where prevalence of one or more of three varieties of schistosomiasis exceeded 20%, were chosen as priority intervention areas (Brinkmann et al., 1991).

Until 1990, the schistosomiasis control programme in Mali was a vertical programme and used mobile teams to test individuals for schistosomiasis and to administer praziquantel—as part of selective or mass chemotherapy. The goal was to lower the incidence of debilitating disease (to control morbidity), rather than to reduce general prevalence (Brinkmann, et al., 1991). The programme's praziquantel was ordered on an as-needed basis by the local GTZ office through its headquarters in Germany. GTZ's office in Germany then ordered the tablets from WHO, which in turn acquired them from Bayer. The pills were delivered to GTZ in tins of 1000 tablets each.

The control programme in Mali had no formal logistics system. Doctors travelling to parts of the country where the drug was to be distributed simply took as many tins as they thought might be needed, put them in their trucks, and drove to the site. Yet no shortages were reported. From 1980 to 1987, approximately 75,000 antiparasitic treatments were administered, representing

an average of three tablets per person, after allowing for losses (Brinkmann, 1988). This effort delivered roughly 255,000 tablets or about 255 tins.

All procurement in Mali was through the schistosomiasis control programme, and only individuals enrolled in the programme could obtain the drug. There was no organized private market for the drug, but a demand emerged for praziquantel (supported by the control programme's widespread advertising of the programme, and the drug's beneficial effects on morbidity), which created a flourishing black market. Physicians working in clinics were believed to contribute to this market through illegal sales of praziquantel to their patients.

The control programme in Mali achieved a major impact in reducing morbidity associated with schistosomiasis, and significantly lowered prevalence in the programme areas (Brinkmann et al., 1988). By 1992, however, GTZ had withdrawn completely from the control programme, and the programme was integrated into the primary health care system. The responsibility for mass chemotherapy and health education was handed over to district health teams, while the central team retained control over evaluation and future programming (Brinkmann et al., 1991).

This transition from a vertical programme dedicated to schistosomiasis control to a horizontal primary health care-based system had both advantages and disadvantages. As a horizontal programme, the delivery costs of the programme were drastically reduced, and a much greater population coverage was achieved (Gryseels, forthcoming). However, the move to a horizontal approach also created problems:

- First, the regional health offices, which were expected to pay for the programme's recurrent costs, excluding drugs, were often unable to fund this portion (Brinkmann et al., 1991).

- Second, the district teams, given their multiple responsibilities, could not sustain the level of motivation displayed by the vertical programme workers (Gryseels, forthcoming).

- Third, the delimited areas of high infection did not necessarily correspond to recognized administrative demarcations, thereby hampering effective implementation.

- Finally, the supply of drugs became irregular and problematic (Brinkmann et al., 1991).

The experience in Mali suggests that more work needs to be done on the cost-effectiveness and trade-offs between horizontal and vertical approaches to schistosomiasis control. The study by Guyatt et al. (1994) in Tanzania represents a useful and important contribution in analyzing and understanding these issues. The challenge is to design an effective distribution

and monitoring system that can function after the aid donor has withdrawn its human resources and material aid. Sustainability requires not only continued provision of praziquantel (because of reinfection) but also an organizational structure that will continue to administer the treatment in high-infection areas. The experience in Mali, after GTZ's withdrawal, indicates serious problems with a decentralized approach that depends mainly on national resources for schistosomiasis control.

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Chapter 7:

Prices and production costs of praziquantel*

This chapter examines the prices of praziquantel in various market segments, and the production costs of praziquantel. The section on pricing traces changes in praziquantel prices over time, and presents data on: current prices at which praziquantel is purchased by bulk suppliers; prices obtained by developing countries through tenders; and prices at which the drug is sold by producers in the private market in developed and developing countries. The section on production costs discusses the costs of manufacturing praziquantel faced by the major producers, and their pricing strategies. The section also explores problems experienced by Bayer and E. Merck in competing in the international market with lower-priced producers, who have successfully used process patent laws to develop alternative (and much cheaper) processes for producing praziquantel.

The price of praziquantel

Market segmentation and price reductions

This study of global prices for praziquantel in the 1980s and 1990s identified two striking features: a) a sharp segmentation of the international market, based on price; and b) a significant decline in prices in the 15 years since the product's introduction on the international market.

Price segmentation can be observed across four dimensions: the prices of praziquantel in the veterinary and human markets; the prices of the human formulations in developed and developing country markets; the prices provided to bulk purchasers versus smaller buyers; and the prices in the public and private sectors in developing countries. The price structure of praziquantel from highest to lowest prices paid, in general, is as follows:

- private market in developed countries,
- veterinary market in developed countries,
- insurance market in developed countries,
- private market in developing countries,

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- generics market, and
- tender market for governments and institutions.

Producers seek to set the price in each market segment according to the price level that buyers in the segment are expected to bear. For example, because the veterinary market for praziquantel is confined primarily to the developed world (except for the veterinary market in China), the prices of veterinary formulations tend to be higher than the prices in the insurance market for the human formulations. Similarly, the tender market prices for developing countries tend to be much lower than the prices charged in the private market, either in the developed or developing world.

The second feature of praziquantel prices is their significant decline, globally, over time— although not necessarily at the same rate in each market segment. As mentioned in Chapter 5, the price of praziquantel has fallen continuously in most market segments since the product's introduction in 1978—except for branded products in the developed country market segment (illustrated by the German market). The process of declining prices has been accentuated in the 1990s by the expiry of the Bayer-E. Merck patent between 1989 and 1994 (see Chapter 2), and by the increase in the number of generic manufacturers and greater price competition.

Both the price segmentation of the market and the differential price declines in these segments reflect a strategic effort on the producers' part to maximize overall profits from the different market segments. Producers seek to protect higher prices in more profitable market segments, but are still willing to participate in more competitive market segments, especially if they have the potential for large volume sales.

These two features of the praziquantel market (market segmentation and price declines) are discussed below in more detail.

Producer and supplier prices

This research project made considerable effort to obtain information on praziquantel prices. Questionnaires were mailed to producers, suppliers, and purchasers of praziquantel that we could identify, and the mailings followed up through telephone calls and in-person interviews when feasible. Library searches were undertaken for published material on the prices of praziquantel. Various databases were searched for praziquantel price-related information.

In general, we experienced great difficulty in obtaining accurate and reliable price data on praziquantel, due to three main factors: (1) the lack of public databases related to pharmaceutical products and prices; (2) the lack of good private databases on pharmaceutical products and prices in developing country markets; and (3) the reluctance of producers, suppliers, and purchasers to disclose price-related information, which was accentuated by the increasingly competitive nature of the praziquantel market. Still, our research

yielded some information on changes in the prices for praziquantel between 1981 and 1994 in several market segments, and differences in the prices across market segments. Figure 7.1 provides a summary of these price changes for the major producers and suppliers of praziquantel.

Figure 7.1

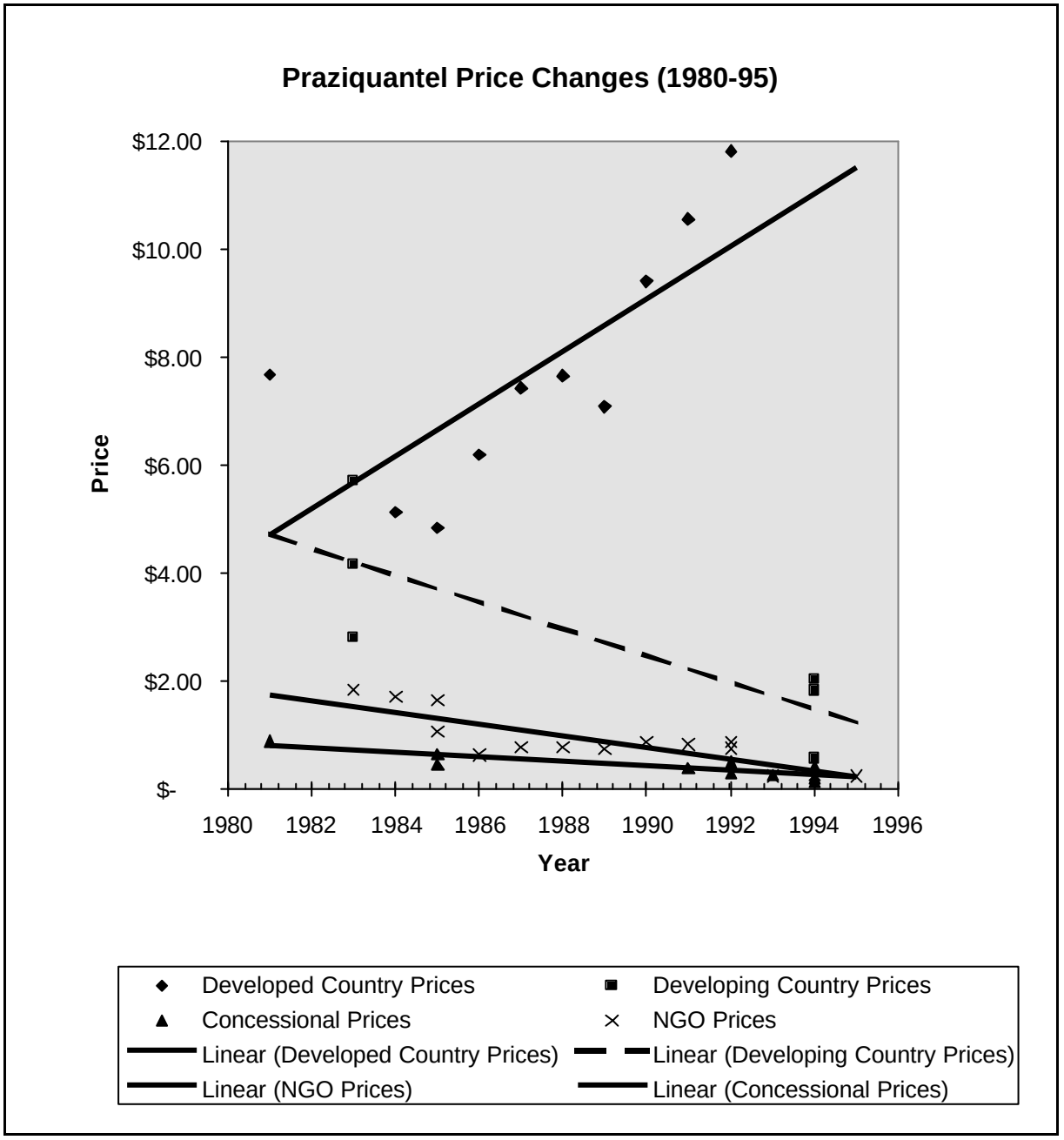

Figure 7.1 shows that prices for praziquantel have dropped significantly in most market segments since the drug's introduction. When the product was introduced by Bayer in 1978, it was priced at approximately US$ 6.50 a tablet in Germany in the private retail market (*Scrip*, 1981). Also in 1981, Bayer was selling the drug to WHO at a concessionary price of about US$ 0.90 a tablet (*Scrip*, 1981). Since then, the price has fallen substantially in the private market in most developing countries. Similarly, the concessionary price has dropped as well.

The drop in prices in the private market in developing countries has also been substantial. In the Republic of Korea, when Shin Poong entered the

Prices are for a single 600 mg tablet of praziquantel, converted into dollars. Developed country prices are German retail prices for Biltricide. Developing country prices are for Biltricide and Distocide in Korea and for Biltricide in Egypt. Concessionary prices (international agency) are purchase prices for WHO

praziquantel market in 1983, Bayer was selling the drug at US$ 4.83 a tablet (see Chapter 3). By 1994, in an attempt to compete with Shin Poong, Bayer had dropped its price in the Republic of Korea to US$ 3.20 per tablet—a price lower than Shin Poong's in the Korean market (Chapter 3). Shin Poong's entry into the market, thus, had a dramatic impact on the price of praziquantel in the Republic of Korea. Similarly, in Egypt, the entry of EIPICO forced Bayer to drop its price from L.E. 4 per tablet in 1983 to L.E. 2.24 per tablet in 1994, reflecting an almost 50% drop in local currency—and a nearly seven-fold price reduction in dollars (from US$ 4.44 in 1983 to US$ 0.66 in 1994) due to the devaluation of the Egyptian pound. Bayer was also beaten out of the public market by EIPICO, which was able to win the MOH tender at a price of 88 piasters (US$ 0.26), in 1992 and 1993 (see Chapter 4).

In the market for bulk sales to international agencies, the price at which Bayer was willing to sell praziquantel to WHO in 1994 was US$ 0.42—a greater than 50% drop from its original concessional price. But Bayer is in a poor position to compete in the tender market because of its high production costs (described in the next section), and because other producers have been able to offer even lower prices to international agencies. For example, Shin Poong sold praziquantel to WHO and to UNICEF in 1994 at a price of US$ 0.21-0.22, while producers like Medochemie and IDA were offering prices of US$ 0.14 and lower to WHO.

Figure 7.1 also demonstrates the differential pricing used by producers in the different human market segments. As early as 1981, Bayer sold praziquantel to international agencies at 1/7th its private market price (*Scrip*, 1981). Similarly, in 1994, Shin Poong was pricing the product at US$ 3.53 per tablet (nominal price) in the Korean private market, and was selling to international agencies at about 6% of that price (Chapter 3). A similar market segmentation is reflected in the prices of praziquantel in developed and developing countries. While Bayer currently sells praziquantel in the USA for between US$ 10-19.50 a tablet in retail pharmacies (depending on the volume of purchase), its price in the Republic of Korea is US$ 3.20 per tablet (nominal price) (Chapter 3).

The purchase volume, which forms the basis for bulk discounts offered by producers, determines to a significant extent the differences in the prices at which praziquantel is sold in developing country markets. For example, in 1994, UNICEF, because of its large volume purchases, obtained prices (US$ 0.22/tablet) significantly below those offered to Ministries of Health in developing countries, even below the tender price in Egypt where EIPICO won a bid to supply the Ministry at a price of US$ 0.26 per tablet.

An added consideration, which probably explains the difference in price in the developed and developing œuntry markets, is the purchasing power of the country, and the ability of an individual market segment to sustain a particular price.

The strategy of producers to provide differential pricing across countries raises important issues related to the possibility of trans-shipment of products from lower priced to higher priced countries. Although we were not able to obtain a completely satisfactory explanation for the absence (or at least the relatively low level) of such secondary markets, it seems that factors related to transport costs, and possibly some quality considerations, may have a role.
Along with a reduction in producer prices, there exists a declining trend in prices from international agencies and private suppliers to developing countries. The declines in the sales prices from bulk suppliers can be explained by the drop in manufacturers prices, and the increasing competition among private distributors and suppliers.

For example, WHO was initially selling praziquantel to developing countries at a price close to US$ 1 per tablet in 1981 (*Scrip*, 1981). This price dropped to about US$ 0.51 in 1992 (MSH, 1993). The current price is probably closer to US$ 0.20-0.25. Similarly, the UNICEF sale price has dropped from US$ 0.65 in 1985 to US$ 0.29 in 1992 and US$ 0.27 in 1993.

Among private suppliers, a similar fall in the sales price of praziquantel is observed over time. This price decline is shown in time-series data obtained from Action Medeor, and in data collected by Management Sciences for Health for other private suppliers. These data are presented in Tables 7.1 and 7.2 below.

Table 7.1: Price Changes of praziquantel sold by Action Medeor

Year	Price (DM)	Percent change from previous	Exchange rate (DM = US$ 1)	Price (US$)
1983	4.8	0	2.6	1.85
1984	4.8	0	2.8	1.71
1985 (Jan)	4.8	0	2.9	1.66
1985 (Feb)	3.06	-36%	2.9	1.06
1986	1.4	-54%	2.2	0.64
1987	1.4	0	1.8	0.78
1988	1.4	0	1.8	0.78
1989	1.4	0	1.9	0.74
1990	1.4	0	1.6	0.88
1991	1.41	+1%	1.7	0.83
1992 (Jan)	1.42	+1%	1.6	0.89
1992 (Feb)	1.24	-13%	1.6	0.76
1993	0.42	-66%	1.7	0.25
1994	0.42	0	1.6	0.26
1995	0.36	-14%	1.45	0.25

Note: These are sales prices from Medeor; from 1983 to 1992 the product was obtained from Bayer and E. Merck; from 1993 on, from generic producers.

Source: Action Medeor, Germany.

In addition to demonstrating the decline in the price of praziquantel over time, Table 7.1 illustrates the impact of two significant events in the market history of praziquantel: the entry of Shin Poong in the international market (in 1985); and the expiry of the Bayer/E. Merck patent in many countries, resulting in a dramatic increase in the number of generic producers (in 1992-1993). These two events were accompanied by sharp cuts in the price of praziquantel by the existing manufacturers, in response to the increased competition, and by a corresponding decrease in the sales price of suppliers. Thus, in February 1985 (roughly corresponding with the entry of Shin Poong in the praziquantel market), Medeor's sales price dropped sharply by 36% in the course of a month, and in 1986 fell again by a further 54%. Following this period of rapid price cuts, prices tended to stabilize for the next 6 years. In 1992 and 1993 (corresponding with the expiry of the Bayer/E. Merck patent in many countries), Medeor's praziquantel prices once again fell sharply, by 13% and 66%, respectively.

Table 7.2: Price changes of praziquantel sold in concessional market by private suppliers

	Price (US$) per tablet and (% change from previous year)						
Private supplier	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**
IDA	0.62	0.59 (-4.8%)	0.60 (+1.7%)	0.49 (-18.3%)	0.38 (-22.4%)	0.30 (-21.1%)	0.15 (-50.0%)
IAPS	--	--	--	--	--	0.34	0.17 (-50.0%)
ECHO	0.85	0.70 (-17.6%)	0.87 (24.3%)	0.59 (-32.2%)	0.41 (-30.5%)	0.34 (-17.1%)	0.19 (-44.1%)
ORBI	--	--	0.91	0.57 (-38.5%)	0.52 (-8.8%)	0.34 (-34.6%)	0.26 (-23.5%)
INMED	0.71	--	--	--	0.61 (-14.1%)	0.61 (0%)	N/A

Note Suppliers are listed in Table 7.3 according to price level for 1995, with the lowest first, and highest last.

Source: Management Sciences for Health, 1989-1995.

Table 7.2 shows that IDA, the largest of the private suppliers, was selling praziquantel at US$ 0.62 in 1989, and dropped its price to US$ 0.15 by 1995 (MSH, 1995). Similar drops in the sales prices are also observed for all the other

suppliers of praziquantel. These data show that supplier prices dropped sharply after 1992 (similar to the pattern of Table 7.1), suggesting a causal link between the fall in the price of praziquantel and the expiry of the Bayer/E. Merck patent. In 1995, the price quoted by these private agencies for the supply of praziquantel to developing countries and relief agencies ranged from a low of US$ 0.15 per tablet (from IDA) to a high of US$ 0.26 per tablet (from ORBI), just below UNICEF's price of US$ 0.28 per tablet. However, even with these suppliers, the quoted price can reportedly be negotiated downwards, depending on the size of the order, the company from which the drug is procured, and the size of the package (e.g. 8-tablet, 100-tablet, 1000-tablet packs) that is being purchased (MSH, 1994).

Prices in individual countries

A notable feature of the price of praziquantel across countries is the markedly higher prices charged by producers for praziquantel in the developed world as shown in Figure 7.1. While the prices in the developed nations do vary by country and market segment, they tend to be much higher than the prices in developing countries. As explained above, this phenomenon is explained by the market segmentation strategy of producers.

Thus, in 1993, the price in the private market for the Bayer product was US$ 9.02 per tablet in Japan, US$ 5.95 per tablet in Taiwan, US$ 4.61 in Austria, US$ 3.97 per tablet in France, and US$ 2.17 in Australia. These are to be contrasted with the price for the same product in the private markets in the developing world, where they ranged from US$ 0.57 in Egypt to US$ 1.82 in Jordan, and US$ 2.11 in francophone Africa.

In developing countries, the public sector's procurement price of praziquantel tends to be 25-50% below the retail price in the private market, depending on the effectiveness of the tender process in the public sector, and on whether the brand of praziquantel sold in the private sector is produced by a domestic or foreign source. For example, in Egypt, the procurement price in the public sector in 1994 was about US$ 0.26, while the retail price in the private market varied from US$ 0.51 (EIPICO) to US$ 0.57 (Bayer). Public sector stocks diverted to the black market tend to be sold at a price between the public sector procurement price and the private sector retail prices. It is difficult, however, to estimate the size of the black market.

Production costs and pricing strategies of major producers

This section briefly examines the production costs of the three major producers for praziquantel (Bayer, E. Merck, and Shin Poong), to help explain the competitive positions and pricing strategies of these firms.

Bayer

Praziquantel was first produced and marketed in Germany by Bayer, and then rapidly moved to other parts of the world, including developing countries. The prices set by Bayer in the late 1970s and early 1980s took into account the market potential, the expense in developing the product, the realization that the patent would expire in the early 1990s, and the expectation that competitors would establish their own production capacity (Interview No. 2).

In the late 1980s and early 1990s, Bayer confronted competitive challenges in the international market, because Bayer's cost and pricing structures are much higher than those of its competitors. Bayer officials explained the cost differential using the same factors cited by officials at E. Merck. For example,

Bayer uses a "full costing" approach for all of its products, and no exceptions are made even for special, life-saving drugs developed for economically disadvantaged clients. Bayer officials also mentioned the uncertainties of the demand by governmental and other international institutions for the product, especially the problems of forecasting demand in a market with tenders, and the lumpiness with which contracts are awarded and won.

In addition, Bayer's overall drug development strategy has moved away from tropical diseases, making it difficult to justify the opportunity costs of disrupting the production line to shift to praziquantel, and making it difficult to justify a price based on less than full costs (Interview No. 2).

According to company officials, Bayer has had several discussions with WHO to make praziquantel available, where needed, at a reasonable price, but those discussions have not reached a successful conclusion. Bayer representatives reported that some WHO officials were trying to persuade Bayer to provide the drug as a donation for all cases of schistosomiasis worldwide (Interview No. 2). However, according to company representatives, this donation is not likely to occur, since it would require perhaps 256 tons of the raw materials annually (based on WHO's assessment of global need for praziquantel tablets). According to Bayer estimates, even at the best production cost at E. Merck of US$ 170 per kg, this amount would require 256 x US$ 170 x 1000, or US$ 43.5 million annually. At the normal Bayer price of US$ 450 per kg, the figure would increase to US$ 115.2 million per year. This figure, according to Bayer officials, represents a request for a donation of a multiple of the annual expenditures of Merck & Company (USA) to donate ivermectin (Mectizan), and still does not solve the issues of where the tablets would be manufactured or how the drug would be distributed. Bayer representatives also suggested that, given the financing capacities of developing countries and international agencies, the market could sustain a maximal production of about 100-150 tons of praziquantel.

Recently, Bayer has embarked on a new agreement for public-private cooperation related to praziquantel. According to a Bayer official, "Bayer, under a revised philosophy of addressing the needs of endemic countries, started talks with UN agencies regarding a new type of public-private cooperation. This will include, besides the supply of the drug at a price comparable to the major competitors, the definition of a bundle of additional services which could be rendered by a research-based pharmaceutical company to those countries and organizations pursuing schistosomiasis control programmes in the context of their national drug policy" (Interview No. 9). It is not yet certain what this effort will yield, or how other competitors will respond, should this initiative be implemented.

Bayer's pricing strategy in the developed world is to have a common price at the consumer level in all countries, to the extent possible (Interview No. 2). Different prices of Bayer's products at the wholesale level will often reflect

different margins at the pharmacist's level. Other price differentials stem from different inflation rates and VAT rates, so that a product which is available for US$ 100 in Germany can cost US$ 10 in Portugal. Distributors sometimes take advantage of these price differences between countries, so that an Italian distributor might purchase Bayer products in Spain, for an additional profit. Bayer Italy, however, cannot do so, according to company policy, which also constrains Bayer's attempts to compete successfully in the world market.

E. Merck

The prices for E. Merck's praziquantel products tend to be much higher than those of its competitors, due to two factors: production process and cost structure (Interview No. 3).

According to E. Merck representatives, Shin Poong uses a different process, with one less production step, which makes the process inherently cheaper. Production costs are also affected by the number of products. At E. Merck, praziquantel is only one of many product lines, and praziquantel does not have top manufacturing priority. Every time praziquantel is to be manufactured, the production line (the chemical vats and equipment) must be cleaned and prepared. A company (such as Shin Poong) that manufactures relatively fewer compounds, one of which is praziquantel, has fewer opportunity costs, and may be able to manufacture one compound almost continuously on one production line. E. Merck representatives suggested that if production could be expanded, then some savings could also be realized by the company (Interview No. 3). But the company currently has no plans to expand production, because of the cost and price disadvantages of E. Merck in the world market (see Chapter 5), catching the company in a vicious circle.

E. Merck's policy on costing structure also places the company at a significant competitive disadvantage. The company sets the price based on full historical costs, so as to recover the original investment in research, development, and manufacture of the drug. Companies (such as Shin Poong) with a smaller initial investment, with a more efficient process, and with fewer other products on the production line, have a definitive cost structure advantage in pricing the drug. This price advantage is particularly important in bulk purchasing markets, where purchasing decisions are made primarily on price.

E. Merck seeks to maximize its profits through price discrimination in different market segments, as described above. E. Merck's price structure (from highest to lowest prices) is as follows: private markets (pharmacy purchase or the equivalent), veterinary markets, insurance markets (in Germany a "reference" or "Festpreis" price), generics market, and bulk sales to non-governmental agencies or developing country governments.

E. Merck company officials suggested that the development of drugs for developing country markets has usually been considered a significant risk, because of inadequate patent protection (Interview No. 3). If a product attains

wide acceptability, other manufacturers start to produce it and thus reduce expected profits for the original developer. E. Merck has seen this cycle not only with praziquantel, but also with other drugs (e.g., certain cancer drugs which were produced by firms in India and the Republic of Korea). It is not clear whether the new patent regime established by the Uruguay trade round of the GATT, with increased product patent protection, will change the perceived risks of drug development for tropical diseases.

E. Merck representatives also suggested that government or non-profit programmes that supply drugs free of charge have an adverse impact on the firm's private markets. A policy of free drugs at the consumer level can contribute to irrational drug use and can make it difficult to charge full costs for the drug in the private market.

Shin Poong

Shin Poong has competed very successfully in the global praziquantel market since its entry in 1983. Shin Poong has benefited from much lower development costs (a total of only about US$ 14,000 to develop the alternative production process), and from the lower costs of its manufacturing process for praziquantel (see Chapter 3). These two factors have enabled Shin Poong to market its product at much lower prices in the Republic of Korea and in the international market.

Shin Poong's entry into the international market in the mid-1980s caused Bayer and E. Merck to drop their sales prices significantly in almost every market where they competed with the Korean company. Despite their lowered prices, however, Bayer and E. Merck have been unable to regain their position as the leading producers of praziquantel, and, indeed, in the 1990s they have lost further ground around the world. By the mid-1990s, Shin Poong had established itself as the world's largest producer of praziquantel and was expanding into new markets and new production opportunities, while Bayer and E. Merck were retreating (see Chapter 5). In short, Shin Poong's strategy succeeded for the firm and also resulted in making praziquantel more readily available and affordable for poor consumers in poor countries.

Conclusions

Several significant lessons emerge from this chapter's analysis of the global price trends of praziquantel and the production costs for different producers:

- Prices for praziquantel, at a single point in time, vary greatly across market segments, with the highest prices generally found in the developed country private markets and the lowest prices in the tender market for developing country governments and other institutions. This pricing strategy of market segmentation was found for all the major producers, and reflects broader patterns in the pharmaceutical industry.

- Over time, the prices of praziquantel in several market segments have declined significantly, ranging from 50% in some markets to a decline of 90% of the initial price over a decade—except for developed country markets (such as Germany) where prices for brand-name products have increased over time. The substantial price declines reflect the heightened competition from Shin Poong in the Republic of Korea and in other markets (after 1985) and from generic manufacturers (following patent expiry from 1991 on).

- Price data about praziquantel (and other products for tropical diseases) are not readily available, although the *International Drug Price Indicator* (Management Sciences for Health) provides an important compendium of some prices. Better price information on praziquantel (and other products) could improve the efficiency of government procurement efforts and tenders and could improve the functioning of the market for tropical disease products.

- The pricing strategies of Bayer and E. Merck are the result of higher production costs (associated with their manufacturing process for praziquantel, but also due to the relatively low priority of praziquantel in overall corporate strategy and the opportunity costs of praziquantel production). In addition, corporate policies of seeking to recover full historical costs have shaped the pricing strategies of Bayer and E. Merck.

- Shin Poong, on the other hand, had relatively low historical costs of R&D to recover for praziquantel, had fewer competing products, had discovered a less costly production process, and gave higher priority to production of praziquantel, all of which facilitated an aggressive pricing strategy both in the Republic of Korea and in foreign markets. Shin Poong took advantage of these factors to compete on price with Bayer and E. Merck in the late 1980s in those markets that did not recognize product patents (such as Egypt and the Republic of Korea) and to wait until the early 1990s for the original product patents to expire to compete in other markets.

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