

Dilemmas in drug development for tropical diseases

Experiences with praziquantel

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Abstract

This article analyzes policies that affected the availability of praziquantel, the drug of choice for schistosomiasis. The study examines how interactions among four actors (pharmaceutical producers, international agencies, non-governmental agencies, and national governments) affected praziquantel availability in poor countries. It also examines trends in praziquantel prices over time in different markets. This analysis demonstrates that the discovery of an effective new drug does not necessarily result in access to the drug for disease sufferers—especially if those sufferers are poor people in poor countries. The article proposes measures to improve international systems for making new drugs available in poor countries. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Praziquantel; Schistosomiasis; Drug development; Public–private cooperation; Pharmaceutical policy

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1. Introduction

The discovery of an effective new drug for a tropical disease represents scientific success, but it also initiates a complex economic and political struggle over how the innovation will be made available to disease sufferers. This process becomes especially problematic when the disease sufferers are people who cannot pay for the product. The search for an AIDS treatment or vaccine highlights the economic, ethical, and political dimensions of these problems [1]. Similar issues exist for pharmaceutical products that treat tropical diseases and where the disease sufferers are predominantly poor people in poor countries. This article presents the main findings of an international research study on one such product—praziquantel—for the treatment of schistosomiasis [2].

The case of praziquantel illustrates basic conflicts between public health and private business in the development of new drugs. Our analysis focuses on the interactions among four actors: pharmaceutical producers, international agencies, non-governmental agencies, and national 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) received the new treatment. Based on the experiences with praziquantel, this article suggests measures for each major actor to address the dilemmas of new drug development for tropical diseases and thereby improve access to poor people in poor countries.

2. The development and production of praziquantel

2.1. Praziquantel's discovery and development in Germany

The discovery of praziquantel represents the most important development in recent decades in the treatment of schistosomiasis. This parasitic disease, involving five species of schistosomes spread by freshwater snail vectors, is endemic in 74 countries. 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 behavior and settlement patterns in ways that increase exposure to the parasite. As shown in Table 1, schistosomiasis is estimated to infect 200 million people in the world, with an exposed population of about 600 million people [3].

Praziquantel is effective treatment for all five species and for both major types of morbidity associated with schistosomiasis (urinary lesions for *S. haematobium*, and hepatic lesions for the other species). Table 1 shows the global distribution of major waterborne parasitic diseases.

The praziquantel case demonstrates that R&D-oriented pharmaceutical firms can play a critical role in discovering new chemical entities that are significant improvements over existing therapies. Inter-firm collaboration between E. Merck and Bayer was necessary to recognize the anthelmintic properties of praziquantel. In the early 1970s, the search for effective tranquilizers with few side effects by scientists at E.

Merck led to the testing of the pyrazinoisoquinoline group, but relatively high doses of the substance had to be used in order to achieve an effect comparable to that of established tranquilizers. As a result, according to an agreement between the two firms, the compounds in this group were passed onto Bayer for veterinary screening [4]. Praziquantel was chosen from approximately 400 compounds, and found to be an effective anthelmintic against a broad spectrum of parasitic trematodes and cestodes [5].

Praziquantel was developed first for the veterinary market and then for the human market. Its curative efficacy against various platyhelminths pathogenic to man was confirmed in testing during the 1970s [6]. The compound was patented in Germany in December 1973, and in the USA in 1977 [7]. Bayer and E. Merck eventually registered the patent for praziquantel in 38 countries. For the human market, Bayer approached the WHO in the late 1970s to request collaboration in multi-center trials to demonstrate praziquantel's safety and efficacy. The resulting collaboration achieved scientific success. WHO's assistance was critical in this phase of drug development, and the case represents an important instance of public–private collaboration in drug development.

Praziquantel became available in Europe after 1978 [8], and became generally available on the international market in the 1980s. It became recognized as the drug of choice for all forms of schistosomiasis in humans, because of its high efficacy, low toxicity, and ease of single, oral administration [9,10]. A single dose of praziquantel (40 mg/kg body weight) was shown to treat schistosomiasis but not to prevent the disease; and by 1985, approximately one million persons had been treated with praziquantel [9]. But, as discussed below, problems remained in the availability of praziquantel in many schistosomiasis-endemic countries, even in the early 1990s.

2.2. A new production process for praziquantel in Korea

In the late 1970s and early 1980s, a South Korean firm, the Shin Poong Pharmaceutical Co., recognized the strategic importance of praziquantel in the Korean domestic market for treating two important parasitic diseases (schistosomi-

Table 1
Global distribution of major parasitic diseases associated with water resources development

	Number of endemic countries	Exposed population (millions)	Infected population (millions)
Schistosomiasis	74	600	200
Lymphatic filariasis	69	752	75
Onchocerciasis	34	166	25
Malaria	99	2200	275 ^a

Source: WHO Division of Control of Tropical Diseases, cited in Hunter et al., 1993, p. 26, [3].

^a Only in Africa.

Table 2
Retail prices of praziquantel products in Korea: 1983 and 1994

Product	Type of Price	1983	1994
Shin Poong Distocide	Nominal	2500 Won (3.22)	2750 Won (3.53)
	Real	2500 Won (3.22)	1580 Won (2.03)
Bayer Biltricide	Nominal	3750 Won (4.83)	2500 Won (3.20)
	Real	3750 Won (4.83)	1437 Won (1.84)

Source: Shin Poong pharmaceutical company.

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

asis and liver fluke). Shin Poong worked with a government research institute and received government financial support to develop an alternative production process for praziquantel. For a remarkably low investment of corporate funds—the equivalent of about \$14000—Shin Poong succeeded in creating an alternative, innovative, and cost-saving production process for praziquantel. Shin Poong then obtained a patent in Korea to protect its new production process for praziquantel. The company also received government protection from competition in 1983, when its praziquantel was designated as an official ‘protected product’, thereby creating a legal duopoly for Bayer and Shin Poong for 5 years (1983–88).

Shin Poong designed an effective business strategy for praziquantel. In the Korean market, Shin Poong set the price for its product significantly below Bayer’s price, and squeezed Bayer’s share of the domestic market from an effective monopoly in the early 1980s to around 10% in early 1990s (while Shin Poong’s share rose from a negligible amount to around 90%). Shin Poong’s strategy significantly pushed down Bayer’s prices from 1983 to 1994, by 33% (in nominal terms) and 62% (in real terms) in Korean won (Table 2). The price drop for praziquantel (along with other factors) contributed to a major reduction in infection rates for schistosomiasis in Korea (from 41% in 1981 to 4% in 1993), and to a marginal reduction in infection rates for liver fluke (from 2.6% in 1981 to 2.2% in 1993). Table 2 shows the retail prices of praziquantel products in Korea in 1983 and 1994.

Shin Poong’s strategies with praziquantel also succeeded internationally, as reflected by its growing share of global production. By the early 1990s, Shin Poong had become the world’s single largest producer of praziquantel, with a majority of global production in 1993—a significant achievement (see below). As part of its international strategy, Shin Poong registered the new product and obtained patent rights to the production process in 12 countries, in addition to Korea. The company also established licensing arrangements with firms in other countries, while pursuing an active export strategy.

Several Korean government policies assisted Shin Poong’s development of praziquantel: the promotion of import substitution, the protection of infant industries,

and the protection of process patents but not product patents. These governmental policies created an environment that facilitated Shin Poong's success with praziquantel. But that success depended on Shin Poong's initiative: its recognition of praziquantel's potential and its efforts to pursue the product's development and sales in both domestic and international markets.

2.3. Formulation of praziquantel in Egypt

In 1987, Egypt's first private pharmaceutical company, the Egyptian International Pharmaceutical Industries Co. (EIPICO), began formulation of praziquantel, under a licensing agreement from Shin Poong. EIPICO chose praziquantel as one of its first products, because of praziquantel's strategic importance within Egypt. Praziquantel was an excellent product for a major parasitic disease in Egypt (schistosomiasis), and the product was being produced in Egypt under license from Bayer, but sold at a very high price.

EIPICO's competition with Bayer's licensee in Egypt contributed to major reductions in the private market price for praziquantel. For example, Bayer's entry price of L.E. 4 per tablet (\$4.44) in 1983 had been reduced to L.E. 2.24 per tablet (\$0.66) in 1995 (in nominal terms), a 44% drop in local currency (representing a seven-fold drop in US dollars, from 1983 to 1995, due to devaluation).

EIPICO's strategy depended on winning the government's tender offer for praziquantel; the firm has won the competitive tenders since 1990. These contracts have provided EIPICO with significant revenues, as the government purchased huge quantities of the locally formulated product (6.8 million tablets in 1992, and 3.3 million tablets in 1993), making it probably the largest single buyer of praziquantel in the world (until recent purchases by the government of China). By 1991–1992, EIPICO was the second largest pharmaceutical company in Egypt [11], and the commercial success of praziquantel was a major factor in the company's success.

From 1988 onward, Egypt's MOH began providing praziquantel free of charge in its national schistosomiasis control program. Egypt adopted a strategy of population-based selective chemotherapy, with praziquantel provided only to infected persons, based on the results of individual diagnosis, also provided for free. This strategy significantly reduced the prevalence of schistosomiasis in several studies [12–14], suggesting that substantial reductions have also been achieved on a national level. In short, the drug is considered a major success, for Egypt and for EIPICO. By 1993, Egypt became a total annual market of about 10 million tablets of praziquantel, with sales of about 2 million tablets in the private market.

Egyptian government policies assisted EIPICO's successful strategy for praziquantel in several ways. Egypt's lack of product patent protection for pharmaceuticals made it possible for EIPICO to produce praziquantel under license from Shin Poong. National health policy gave high priority to the treatment of schistosomiasis, which required huge purchases of praziquantel. In addition, the government's financial capacity to purchase praziquantel depended on the availability of loans and grants from the US Agency for International Development, the World Bank, and other aid agencies.

3. Global supply and demand of praziquantel

3.1. Supply of praziquantel

We calculated the first public estimate of the total global supply of praziquantel: 89 million tablets (600 mg per tablet) in 1993, based on a survey of firms involved in production. The firms include the major producers; Bayer, E. Merck, and Shin Poong (all three representing 82% of global production in 1993), plus minor producers. During the 1980s, the international market structure for praziquantel changed dramatically, with Bayer and E. Merck having 100% in 1981, and then 80% in 1985. The trend continued in the 1990s, with Shin Poong achieving a 55% market share in 1993, while the combined share of Bayer and E. Merck was reduced to 27%. Fig. 1 illustrates how Shin Poong's production surged ahead from the mid 1980s while production from Bayer and E. Merck leveled off.

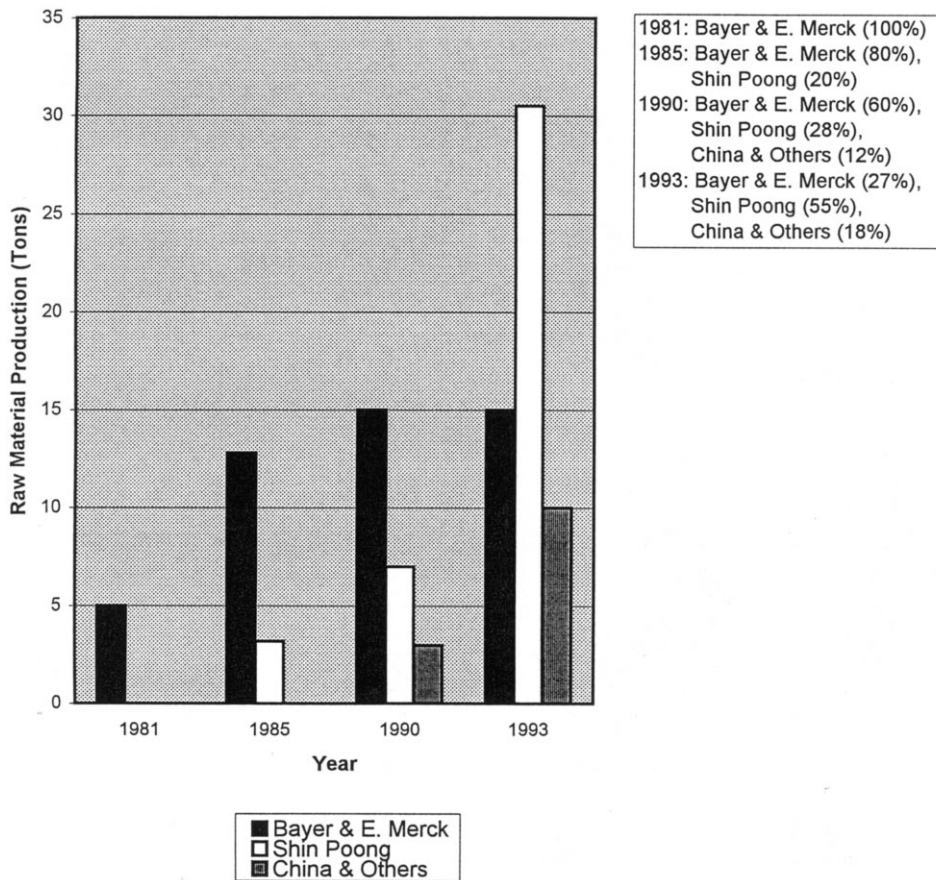


Fig. 1. Global market shares of praziquantel producers.

The changing market shares partly reflect the product's importance and pricing within the three major producers. Praziquantel is a relatively minor product for E. Merck and Bayer. For Bayer, praziquantel represented 0.001% of its total worldwide pharmaceutical sales (\$10.5 billion) in 1994 and only 0.2% of total sales to all Third World countries. According to company sources, E. Merck and Bayer have production costs of about \$170 per KG, so that their lowest price is about 50% higher than the price of other world market suppliers. The two German firms, therefore, have had a competitive disadvantage in the tender market, since decisions about purchase in the tender market are highly price-dependent.

For Shin Poong, on the other hand, praziquantel has been a major item in the company's product line, giving the firm an advantage in both production and marketing efforts. In addition, Shin Poong's more efficient production process and its lack of significant development costs presumably give the company greater profit margins for praziquantel (compared to Bayer and E. Merck), even at low prices. Consequently, Shin Poong is more willing to compete for the sales of praziquantel in developing countries, which are concentrated in the public sector, through national and international tenders. Bayer and E. Merck, on the other hand, have been less enthusiastic about tender sales and have tended to focus on sales in developed countries, which are dominated by the private sector and the veterinary market.

3.2. Demand for praziquantel

The WHO calculated estimates of national 'need' for praziquantel, based on available data for schistosomiasis prevalence and on a strategy of selective treatment for all infected persons (at 40 mg/kg body weight) [15]. As shown in Table 3, a major gap exists between WHO's estimate of need (424 million tablets) and our estimate of supply (89 million tablets), with supply providing only 21% of global need in 1993. The validity of WHO's estimate of global need is difficult to assess, because the figure was based on national data of variable quality and was calculated according to several assumptions. For example, the WHO figure would vastly underestimate global need if a mass treatment strategy were assumed, instead of the WHO's assumption of selective treatment for infected cases only. On the other hand, even if WHO overestimated global need by 100%, due to problems in estimating the number of infected cases, the global supply would still meet only about 40% of the need in 1993.

As part of this study, we conducted a survey of praziquantel availability in the top ten countries ranked according to the number of tablets needed (using WHO estimates), plus China and Korea (Table 3). This survey found very limited data on praziquantel availability, allowing us to account for only about 40% of global supply. But responses for some countries showed stunning gaps between need and availability, with very limited availability in the top three countries (Nigeria, Tanzania, and Ghana). Six of the top ten countries reported little or no availability of praziquantel, and no data were obtainable for three other countries. Of the top ten countries, only Egypt had significant availability of praziquantel; in addition,

Table 3
Estimated need and availability of praziquantel in the top 30 countries

Country	Tablets needed	Global need (%)	Cumulative global need ^a (%)	Availability in 1993	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	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	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	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	125 000–200 000	1.4
(11–20)	99 642 543	23.5	85.2		
(21–30) inc. China	43 035 263	10.1	95.4		
China only	2 826 355	0.7		24 Million ^e	8.50
Availability in Korea ^f				1–1.2 Million	
Total estimates (for top 30)	404 124 000			36 367 000 Accounted for	
Total global estimates	423 609 839			89 000 000 ^g Availability	21.0
	Need				
	Need				

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 the study by Reich et al. [2].

^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 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.

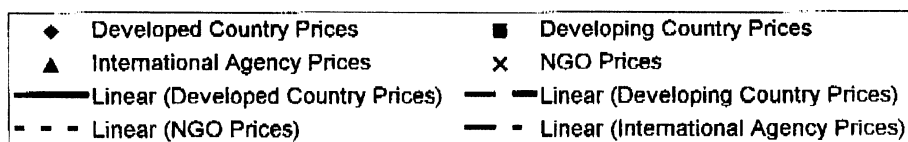
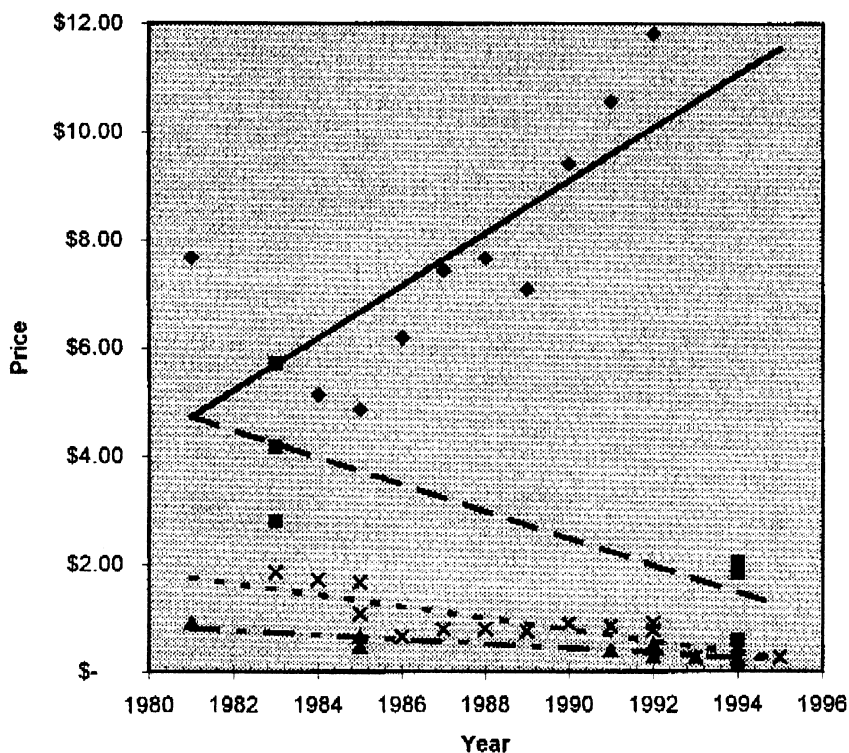


Fig. 2. Praziquantel price changes (1980–1995). All prices are for a single 600 mg tablet of praziquantel, converted into dollars. Developed country prices are German retail prices for Biltricide; source is Federal Association of Pharmaceutical Industry (Bundesverband der Pharmazeutischen Industrie [BPI] e.V. Rote Listen, 1981–1996). Developing country prices are for Biltricide and Distocide in Korea and for Biltricide in Egypt. International agency prices are purchase prices for WHO and UNICEF. NGO prices are sales prices for a single German NGO.

high availability is reported for China, and the Philippines (through World Bank loans for schistosomiasis control in these three countries). Table 3 shows the estimated need and availability of praziquantel in the top 30 countries.

3.3. Price of praziquantel

Available data on the price of praziquantel from 1980 to 1995 show distinct segmentation into three markets: firstly, a developed country market, with signifi-

cant price increases; secondly, a developing country market without product patent protection, with significant price declines; and thirdly, a concessionary market through NGOs and international agencies, with significant price declines (Fig. 2).

The price declines in the late 1980s and early 1990s resulted from domestic and international competition, especially from Shin Poong in Korea and other markets (after 1985); from EIPICO in Egypt (after 1987); and from generic producers and formulators (after 1991), due to the expiry of product patents for praziquantel in various countries and to increased availability of raw material from China.

In the early 1980s, the retail pharmacy price for praziquantel in West Germany was about \$6.50 per 600 mg tablet. At that time, Bayer offered a concessionary price to WHO of about \$0.90 per tablet. In late 1994, several producers offered a bulk purchase price of \$0.13–0.14 per tablet, reflecting increased competition in the global market for praziquantel.

E. Merck's and Bayer's higher prices resulted from their higher production costs, but also reflected the relatively low priority of praziquantel in their corporate strategies and the relatively high opportunity costs they faced for praziquantel production. Corporate policies of recovering full historical costs also shaped the pricing strategies of these two firms. In effect, these two companies treated praziquantel as a normal product, and the product strategies were designed to achieve maximum economic returns for the companies, in competition with other products.

Shin Poong, as mentioned above, had extremely low historical costs of R&D to recover for praziquantel, had fewer products competing for use of its manufacturing equipment, had discovered (and patented) a less costly production process, and gave higher priority to production of praziquantel. These factors facilitated Shin Poong's competitive pricing strategy in Korea and in foreign markets. Shin Poong competed on price with Bayer and E. Merck in the late 1980s in markets that did not recognize product patents (such as Korea and Egypt), and waited until the early 1990s for the original product patents to expire to compete in other markets.

The high price of praziquantel in the 1980s represented a major obstacle to the availability of praziquantel in poor countries with endemic schistosomiasis, but it was not the only obstacle. Other factors included: low priority given to schistosomiasis control in some countries; organizational problems within schistosomiasis control programs; poorly functioning pharmaceutical distribution systems; and economic stagnation and political instability in many poor countries in the late 1980s and early 1990s. Our analysis suggests that an affordable price was a necessary, but not sufficient, condition to improve praziquantel's availability in poor countries.

3.4. Role of international agencies

Three international agencies played significant roles in seeking to make praziquantel more available in poor countries with endemic schistosomiasis: UNICEF, WHO, and the World Bank. Table 4 shows international agency spending on praziquantel.

UNICEF pursued a strategy of globally concentrated bulk buying and cost-plus sales through its facility in Denmark, in efforts to provide praziquantel (and other essential drugs) at reduced prices to developing countries. UNICEF successfully reduced its purchase price for a 600 mg tablet from \$0.65 in 1985 to \$0.22 in 1994, and began in the late 1980s to purchase the product from Shin Poong. UNICEF procured and sold a total of about 5.5 million tablets from 1985 to 1994, reflecting its main role as a purchasing agent.

WHO, in the late 1980s and early 1990s, pursued a strategy of negotiating with Bayer for a reduced price and donations of praziquantel, but did not achieve an agreement. WHO made negligible purchases of praziquantel, reflecting its role mainly in setting international norms and supporting clinical and operational research efforts.

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 Egypt, China, and the Philippines).

The different strategies of these three international agencies achieved mixed results in making praziquantel available at an affordable price and were carried out with minimal cooperation or coordination among the three agencies. The greatest increase in access occurred in countries that received World Bank loans for schistosomiasis control programs and that used the loans to procure praziquantel, except for the case of Korea.

4. Discussion

The case of praziquantel demonstrates that the discovery of an innovative and effective new drug does not necessarily result in adequate access to the drug, especially if the disease sufferers are poor people in the world's poorest countries. This analysis of praziquantel identified a series of measures for pharmaceutical producers, international agencies, NGOs, and national governments that could expand the availability of new drugs in poor countries. Table 5 shows the praziquantel supply system for developing countries.

Table 4
International agency spending on praziquantel

International agency	Annual spending on praziquantel procurement (\$ million)	Proportion of total spending by international agencies (%)
UNICEF	1.80	30.7
WHO	0.07	1.20
World Bank	4.00	68.10
Total	5.87	100

Based on spending in 1992–1993 or average yearly spending.

Table 5
Roles of major players in the praziquantel system for developing countries

Activity	International Agencies		Developing country government	Private supplier (inc. NGOs)	Pharmaceutical producers
	UNICEF	WHO World Bank			
Development: discovery of new drugs and 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 programs	X		X		
Procurement: for research		X	X		X
Technical support: for control programs		X	X	X	X
Distribution: provision within countries	X		X	X	X

4.1. *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 give lower priority to the needs of poor countries (particularly countries with small markets and poor growth prospects), because private firms are primarily demand-oriented and profit-driven. As noted by the Institute of Medicine, pharmaceutical companies face serious disincentives to investment in drugs for diseases that primarily affect people in poor countries [16], and the firms tend to respond accordingly. For example, Bayer has significantly reduced its research efforts on drugs for tropical diseases, and has focused its research on products for chronic diseases. 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 and of 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 launch prices for new products. This pricing strategy effectively denies many new products to poor people in poor countries, since these governments usually lack the foreign exchange resources needed to pay the full price, and poor patients cannot pay the private market prices. A second problem is purchasers. The private market in developing countries at the launch price is very limited, and most governments are reluctant (or unable) to spend major portions of their health budgets on a few new drugs for a limited number of patients.

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 strictly enforce product patents, in addition to 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. Many developing countries, on the other hand, have considered this practice a fair strategy in their national efforts to catch up in the race for technology development and to improve the health of their people with limited resources.

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 [17]. 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 Korea and Egypt would have prevented Shin Poong from developing its own version of praziquantel, would have significantly delayed the price competition in Korea and other developing countries, would have prevented EIPICO from producing the drug and selling it at lower prices in Egypt, and would

have delayed access to the drug for many people in many poor 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.”

Producers could adopt several measures (related to pricing, purchasers, and patents) to improve the access to new drugs in developing countries.

One strategy is for the producer to donate a new drug that has remarkable effectiveness for diseases of public health importance in poor countries. Merck’s decision to donate ivermectin indefinitely for treatment of onchocerciasis is often cited as unprecedented [18,19]. Until the late 1990s, no other company followed Merck’s lead in making single-product donations for developing country markets. Now, however, several firms are considering similar single-product donations. Glaxo-Wellcome announced a program to donate its new antimalarial drug in developing countries, under certain conditions, and SmithKline Beecham announced its donation of albendazole for treatment of lymphatic filariasis. Even Bayer is considering a donation program for praziquantel, reflecting changes in the firm’s structure and vision. As shown by the Merck example, a successful donation program can produce substantial benefits in public relations, corporate morale, and human welfare.

A second strategy is to use multi-tiered pricing—in short, to sell the product at different prices in different markets [16,20]. Companies fear that this pricing strategy will create incentives for transshipment (from low-priced to high-priced markets) and will lead to political criticism (as in the US Congress) in countries with high-priced markets. In addition, concessionary pricing may not result in expanded access. For example, 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. On the other hand, single global prices can also result in political criticism and ethical problems, by denying health improvements to poorer people and countries.

A third strategy is to find a third-party purchaser. Some bilateral aid agencies may be willing to provide project funds 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 donor agencies are often unwilling to provide funds for procuring new drugs on a continuing basis. For example, Merck & Co. was unable to persuade USAID to purchase ivermectin for treatment of onchocerciasis [18]. On the other hand, World Bank loans may be an effective source of funds for procurement, as in the case of praziquantel for the Philippines, Egypt, and China.

A fourth strategy is to sell the product patent to a third party, for specific markets or uses [21]. This approach could make new pharmaceutical products available to poor people in poor countries in ways that would protect development incentives for new drugs, by compensating firms for innovations, and would not undermine core business interests.

4.2. *International agencies*

For praziquantel, the WHO 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 missed opportunities to improve availability in schistosomiasis-endemic countries. International agencies should consider the following measures to improve access to new drugs in poor countries:

One strategy is to develop an information system on the consumption or procurement of specific drugs that have the potential for major welfare improvements in poor countries. This effort did not occur for praziquantel in schistosomiasis-endemic countries.

A second strategy is to develop cross-agency coordination mechanisms and broader alliances with the private sector and NGOs, to support national control programs, through a combination of loans, procurement assistance, and control program support. Again, this effort did not occur for schistosomiasis, but has occurred for onchocerciasis. These efforts could be expanded into a broader collaborative R&D venture, to develop, register, and manufacture new drugs, as proposed in the Tropical Diseases R&D Alliance (a not-for-profit organization that would seek to discover and develop new pharmaceutical products for tropical diseases, based on a public–private partnership). This proposed alliance, however, suffered a major setback in December 1997, when a group of leading pharmaceutical firms refused to support the plan [22].

A third strategy is to assure that international agencies receive significant benefits (such as agreement to assist in distribution as well as concessionary pricing or donation) in exchange for assistance in arranging multi-center clinical trials. For praziquantel, WHO provided assistance with clinical trials, but received few tangible benefits in return.

4.3. *Non-governmental organizations*

NGOs hold the potential for addressing some of the government failures and market failures [23] that affect tropical disease control programs in poor countries. NGOs can help provide new drugs to vulnerable populations in poor countries, through the following kinds of measures:

For off-patent products, NGO supplier and manufacturing organizations may be able to expand production and distribution for markets that multinational corporations and international agencies do not reach. Governments and international agencies could support NGOs that are seeking to address these markets.

For some off-patent products, NGO supplier and manufacturing organizations may be able to respond to opportunities created by the availability of raw materials and products from non-traditional sources (such as Shin Poong in the late 1980s, and Chinese sources in the 1990s, for praziquantel), which can contribute to price competition and price reductions in the international market.

For new (and on-patent) drugs, NGOs can assist in the distribution of donated drugs (as done with ivermectin) and drugs sold at concessionary prices, so that available supplies are received and used appropriately by poor people in poor countries.

4.4. National governments

The national governments of poor countries have an important role to play in making new drugs more available, in assuring that available resources are used more efficiently, and in seeking to obtain additional resources.

National governments can significantly improve their disease control programs by increasing the efficiency of procurement procedures for pharmaceuticals, for example, through global purchases from low-cost suppliers [24]. These efficient purchasing strategies could include buying drugs from sources that are not bound by product patent laws, a strategy that can be highly cost-effective (as long as the products are of good quality), as the praziquantel case demonstrates.

National governments can also obtain loans from bilateral and multilateral aid agencies, to assist in the procurement and distribution of new drugs. The World Bank loan in Egypt, for example, made it possible for the Ministry of Health to purchase praziquantel from EIPICO (under a process patent regime in Egypt and under license from Shin Poong in Korea), and significantly expanded access to the drug for treatment of schistosomiasis in Egypt. A disease program that depends entirely on loans, however, may have problems with long-term sustainability.

In the past, many governments (such as Egypt and Korea) adopted national policies that disregarded international product patent regimes but still protected process patents, in order to promote the development of domestic industries. Some governments (such as Korea) also provided subsidies to promote the development of alternative production processes for drugs of public health importance. These countries are now being pressured to comply with the new international order on product patents [25,26], with potential negative health effects for some populations. In some cases, compulsory licensing of patented pharmaceuticals may provide an alternative policy for governments seeking to enhance public health under a product patent regime [27].

Finally, the governments of rich countries can give increased attention to the unintended consequences of strict enforcement of intellectual property rights for pharmaceuticals. The US government, for example, has pushed for protecting intellectual property rights in poor countries, especially those countries growing economically (such as China). Rich countries have a long history of seeking to impose their intellectual property laws on the world's poorer nations [28]. But even *The Economist* has raised questions about the one-sided nature of intellectual property (with rights held almost entirely by rich countries) and the fairness of expecting poor countries to honor these rights in all instances [29]. It would seem reasonable, therefore, for middle-income and low-income countries to call for alternative approaches to intellectual property rights, especially for products that promise significant benefits to poor people in poor countries.

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.

This 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 Korea, Egypt, and China for praziquantel), substantial gains in public welfare can be realized.

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