Patents, Monopoly Power, and the Pricing of Pharmaceuticals in Low-Income Nations

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F.M. Scherer
Harvard Kennedy School

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F. M. Scherer*
Harvard University
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Invention patents are accorded particular importance in the pharmaceutical industry -- a role both complicated and enhanced by the adoption of the TRIPS (Trade-Related Intellectual Property Rights) agreement under the Treaty of Marrakesh in 1995. Before TRIPS was adopted, many nations did not grant patents on pharmaceuticals, and especially on pharmaceutical products. TRIPS established deadlines for the universal granting of pharmaceutical product patents. Among 32 mostly high- and medium-income nations surveyed by Edson Kondo,[1] thirteen --Argentina, Brazil, Chile, Colombia, Ecuador, Greece, India, Mexico, Peru, Portugal, Spain, Thailand, and Venezuela -- did not grant pharmaceutical product patents as of 1990. By 1996, the most highly developed World Trade Organization members were expected to begin granting such patents, and the least-developed nations were required to comply by 2006 (later extended to 2016).[2]

Patents are significant in pharmaceutical research and development for two main reasons.[3] First, focusing usually on a precisely-defined chemical or biological molecule and its uses, they provide particularly clear and unambiguous property rights, less muddled by the ambiguities that plague mechanical, electrical, and communications apparatus patents. But second, numerous surveys have shown that having patent protection is particularly important in decisions to invest R&D resources to discover and prove the therapeutic efficacy of pharmaceutical molecules. In the first of several such studies, Taylor and Silberston asked industrial interviewees in England what negative impact on their R&D expenditures a legal regime of requiring world-wide compulsory

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1. Edson Kondo, "Patent Laws and Foreign Direct Investment: An Empirical Investigation," Ph.D. dissertation, Harvard University, 1994, p. 62.

2. A semantic point: International agency terminology favors using "least developed" to characterize "low income" nations. In the context used here, "low income" is more descriptive, even if not always politically correct.

3. Some national laws also attain patent-like results by specifying minimum periods of market exclusivity before generic competition is permitted -- e.g., 12 years for so-called "biosimilars" in the United States. Limits on the uses of clinical test data by would-be imitators have similar effects.

patent licensing at "reasonable" royalties would have.[4] The weighted average reduction for all industries was projected to be eight percent, but pharmaceuticals was the outlier, with expected R&D cuts of 65 percent. There are two main reasons for this difference. For one, pharmaceutical R&D is particularly expensive, requiring discovery and testing outlays measured in the hundreds of millions of dollars to achieve a single new marketable molecule during the early years of the 21st century.[5] But second, much of the relevant expenditure is for what is best described as information, assumed to approximate unusually closely a pure public good. Once a promising new molecule is synthesized and patented, its structure is there for all to see once patent applications are published. Moreover, much of the R&D that follows discovery is devoted to clinical trials that show whether the molecule is effective or not in alleviating disease. When regulatory authorities have validated that the molecule is indeed considered safe and efficacious, others could, absent patent or other regulatory protection, synthesize the identical drug for a few millions of dollars and enter competitive (generic) production. Although the original R&D pioneer would still enjoy reputational "first mover" advantages for its efforts, these might be insufficient to deter entry and allow recovery on average of sunk research, development, and testing costs.[6] If so, incentives for original discovery could fail.

Thus, patents are unusually important in pharmaceuticals. The remaining questions are, how widespread geographically must the scope of patents be to maintain the incentives required to maintain a vigorous pace of discovery and testing? What tradeoffs are embraced when only some nations offer pharmaceutical patents? And since historically the nations with low to modest per capita incomes have also been among those not allowing pharmaceutical product patent rights, how might the extension of those rights affect the availablity of new medicines in those nations?

These questions have wide applicability, but they were particularly pertinent as the TRIPS agreement was being negotiated and then adopted during the early 1990s. Two phenomena gave the question unusual saliency then. For one, multinational pharmaceutical companies took a leading position in the advocacy, first in the United States and then on a united U.S. - Japan - European front -- to secure a TRIPS requirement

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4. Z. Aubrey Silberston and C.T. Taylor, The Economic Impact of the Patent System (Cambridge University Press: 1973). For a survey of later studies yielding similar insights, see F. M. Scherer, "The Political Economy of Patent Policy Reform in the United States," Journal on Telecommunications & High-Technology Law, Spring 2009, pp. 171-175.

5. For a survey of the literature and an analysis of the many methodological problems, see F. M. Scherer, "R&D Costs and Productivity in Biopharmaceuticals," forthcoming in the Encyclopedia of Health Economics (2013).

6. For a pioneering study of first mover advantages in drugs, see Ronald Bond and David Lean, Sales, Promotion, and Product Differentiation in Two Prescription Drug Markets, Federal Trade Commission staff report, October 1979.

that patent protection no longer be denied on pharmaceutical products.[7] But second, these demands for increased patent protection coincided with a time when the world fully recognized a deadly new health scourge: HIV/AIDS. After the nature of the disease was first recognized in the early 1980s, numerous new drugs were developed to combat it. Nearly all were protected by patents and sold at prices far in excess of their production costs. The key question arose, how should a firm that has a patent-protected monopoly on some life-saving therapy price that therapy across diverse world jurisdictions, some rich like the United States and Europe, some desperately poor (as in Africa, from which HIV/AIDS spread)?

To be sure, until the requirements of TRIPS are implemented by all nations in 2016 (or later, if there are further extensions), world-wide patent protection of new pharmaceuticals will be absent. But with some important exceptions that will be addressed later, the reach of pharmaceutical patents is extensive, in part because many nations offering no local patent protection lack the internal capabilities to produce new drugs and therefore are at least partly dependent upon sources in patent-granting jurisdictions.

Pricing New Drugs under Monopoly Conditions

We begin with a normative question: What pricing strategies would one expect for a multinational drug company selling its products in a cross section of markets directly or indirectly protected from competition by patents?

Figures 1a and 1b provide an introductory perspective. They assume that a particular patented drug is sold under essentially monopolistic conditions in two nations: wealthy nation A (e.g., the firm's home nation or similar nations) and low-income nation B.[8] Assuming for convenience similar population counts between the two nations, the demand curves for the drug nevertheless differ significantly because of an income effect that shifts the less affluent nation's demand curve downward and toward the origin. Only at very low prices is the quantity demanded in the low-income nation similar to that of the high-income nation. How should the drug provider set its prices? A well-established tradition in economics suggests that it should engage in what is often called Ramsey-Baumol-Bradford price discrimination.[9] Assuming identical marginal

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7. For excellent histories, see Michael P. Ryan, Knowledge Diplomacy: Global Competition and the Politics of International Property (1998); and Michael Santoro, "Pfizer: Global Protection of Intellectual Property," Harvard Business School teaching case study (1992).

8. This analysis follows F. M. Scherer and Jayashree Watal, "Post TRIPS Options for Access to Patented Medicines in Developing Nations," Journal of International Economic Law, December 2002, pp. 913-940. The demand function for wealthy nation A is $P = 100 - .1\ Q + .00001\ Q^2$; for the low-income nation $P = 35 - .045\ Q + .00001\ Q^2$.

9. See e.g. William J. Baumol and David Bradford, "Optimal Departures from Marginal Cost Pricing, American Economic Review, June 1970, pp. 265-283.

costs in both nations of $18 per prescription delivered and no leakage of product from the low-price to the high-price nation (i.e., arbitrage or parallel trade), the firm maximizes its profits decentrally by setting a high price of say $58 per standard prescription unit in the rich nation and a low-price of $26 per unit in the low-income nation. In this way it realizes a surplus of revenues over marginal costs of approximately $17.6 million per month from sales in the high-income nation and $1.6 million in the low-income nation. If on the other hand it were to levy the profit-maximizing rich-nation price of $58 per Rx in the low-income nation, it would under the assumed demand conditions sell nothing at all there, foregoing a contribution to profits (and to the recovery of its research and development investments) of $1.6 million per month. The logic is compelling.[10] Successful price discrimination (also called differential pricing, tiered pricing, or equity pricing) is more profitable when feasible than a single-price strategy. It also has another compelling feature reflecting other well-recognized advantages of price discrimination. When a $26 price is set in the low-income nation, consumers with ability and willingness to pay more than that price realize a "consumers' surplus," shown in Figure 1b by the dot-shaded triangle above the $26 price line and below the demand curve. Under the near-linearity assumptions made, which probably underestimate the willingness to pay of especially affluent and needy consumers, setting prices well above the low-income nation's profit-maximizing discriminatory price causes consumers to forego a consumers' surplus of approximately $1.1 million per month.

Recognizing these advantages, a conference organized in April 2001 by important but unusual partners -- the World Health Organization and the World Trade Organization -- concluded:[11]

> Differential pricing can and should play an important role in ensuring access to existing essential drugs at affordable prices, especially in poor countries. In doing so, it could help to reconcile affordability with incentives for research and development.

The Extent of Differential Pricing

Do pharmaceutical firms actually differentiate their prices in nations of diverse affluence, as suggested by Figures 1a and 1b? Several studies suggest that there is some such tendency, although the evidence is mixed and the reasons for price variation are much more complex than a pricing-to-reflect-income hypothesis can support.

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10. For extensions to differently shaped demand curves but retaining the assumption of an "income effect," see Scherer and Watal, "The Economics of TRIPS Options for Access to Medicines," in Brigitte Granville, ed., The Economics of Essential Medicines (United Kingdom: Royal Institute of International Affairs, 2002), pp. 45-46.

11. WHO-WTO, "Differential Pricing and the Financing of Essential Drugs" (presumably written by the conference rapporteur, Jayashree Watal), reprinted in Brigitte Granville, ed., The Economics of Essential Drugs (U.K.: Royal Institute of International Affairs, 2002), p. 218.

It was the HIV/AIDS crisis of the 1990s, with its highest incidence in low-income African and Asian nations, that focused attention most sharply on the determinants of national price differences. A particularly impressive effort was mounted by Stephane Luccini et al.[12] Supplementing data collection efforts by international health care agencies, they went into the field to obtain point-of-entry transaction prices for seven anti-retroviral drugs in 13 sub-Saharan African nations (plus Brazil). The most striking result of their study was a series of charts tracking the dramatic price decreases observed between 1997 and 2001 -- on average from their regression equations (Table 3), by 82 percent, with an especially sharp decline in 2001. Among the variables they tested for explanatory power was GDP per capita in the target nations. Consistent with the differential pricing hypothesis, they found a positive relationship between prices and GDP per capita, but the relevant coefficient was not statistically significant. Its role, however, might have been blurred by the fact that their sample focused almost exclusively on low-income nations. Among other findings, prices tended to be systematically higher in sample nations with drug product patent protection and lower for drugs with significant generic competition.

Another study analyzing the prices of AIDS drugs in 18 intermediate- and low-income nations, with benchmarking to prices in the much richer United States, was conducted by the author of this paper and Jayashree Watal.[13] Data were obtained from IMS, a pharmaceutical industry data compiler, on wholesale prices, usually charged to retailers, for 15 AIDS anti-retrovirals across the years 1995-1999. The sample differed from that of Lucchini et al. by emphasizing South and Central American nations, mostly with low to intermediate average GNP per capita, and only two sub-Saharan Africa nations. The main analyses focused on the ratio of observed prices in sample nations as compared to the wholesale prices of comparable formulations in the United States. The central question was, were prices in those low- and medium-income nations systematically lower than those in the wealthy United States? The evidence of Ramsey-like discriminatory pricing was weak. On average, prices in the sample nations were 85 percent of reported U.S. wholesale prices, which tended to be 15 to 25 percent higher than actual U.S. transaction prices. There was a weak positive correlation (+0.127) between the ratio of sample to U.S. prices and gross national product per capita in the sample nations, declining to essentially zero in the last covered year. In an unreported analysis of the original data, the United States prices to which the sample nations' prices were compared were found in most (but not all) cases to have fallen substantially between 1995 and 1999, mirroring the similar price decreases observed by Lucchini et al. in sub-Sahara African nations.

Keith Maskus and Matthias Ganslandt approached the price discrimination question from a different perspective.[14] Their focus was on 20 typically well-known

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12. Stephane Lucchini, Boubou Cisse, Segolene Duran, et al., "Decrease in Prices of Antiretroviral Drugs for Developing Countries," in Jean-Paul Moatti et al., ed., Economics of AIDS and Access to HIV/AIDS Care in Developing Countries (International AIDS Economics Network: 2003), pp. 170-211.

13. Supra note 8.

14. "Parallel Trade in Pharmaceutical Products: Implications for Procuring Medicines for Poor Countries," in Granville, ed., The

brand-name drugs, explicitly excluding AIDS anti-retrovirals, in 14 nations, of which only five fell into the low- or medium-income per capita category. They found only weak support for the income-correlated differential pricing hypothesis. Some lower-income nations did benefit from reduced average prices, but others paid even more than in the wealthier nations. Variables influencing the prices at which nations were supplied included the existence of national price controls, drug makers' strategies in targeting diverse income groups within national markets, the extent of competitive pressure from imports of the same drugs from lower-price jurisdictions, the way procurement efforts were organized, and the competitive efficiency of nations' wholesale distribution channels.

Reasons for the Paucity of Differential Pricing

There are several reasons why pharmaceutical prices have not been systematically adjusted to different nations' income per capita, reflecting ability to pay, under Ramsey pricing strategies.

One that has received particularly intense attention is so-called "parallel trade," that is, arbitrage transactions by middlemen who acquire pharmaceuticals (or other products) at sharply discounted prices in low-income nations and divert them from their intended recipients to the consumers of rich nations, needless to say, reaping an arbitrageur's profit by doing so. During the 1990s, European Community authorities actively encouraged parallel trade in pharmaceuticals, hoping that the redirection of supplies from low-price Community member nations (most notably, Spain) to nations in which prices were higher would help perfect the Common Market.[15] A decade later, however, it was recognized that a policy suitable for encouraging parallel trade among rich nations was inappropriate to meeting the needs of consumers in low-income nations. The consensus report of a 2001 WHO-WTO conference concluded that:[16]

> Markets for differentially priced drugs need to be tightly segmented to prevent leakage of differentially priced drugs to high-income markets.... High-income countries may need additional legal authority in order to prevent the import of products marketed elsewhere at differential prices.

Economics of Essential Medicines (supra note 8), pp. 57-80. See also Patricia Danzon and Li-Wei Chao, "Cross-National Price Differences for Pharmaceuticals: How Large, and Why?" Journal of Health Economics, vol. 19 (2000), pp. 159-195, which focuses mainly (with the exception of India) on high-income nations and has no test of how income per capita differences affect prices.

15. See EC Commissioner Sir Leon Brittan, "Making a Reality of the Single Market: Pharmaceutical Pricing," speech before the IEA Health and Welfare Unit, London (December 1992).

16. "Differential Pricing and the Financing of Essential Drugs," in Granville, supra note 11, at pp. 226-227. For a graphic analysis of how parallel trade undermines rich-nation prices and resultant profits, see Scherer and Watal, in the same volume, p. 42.

In an apparent response to the conference sponsors' urging, European national customs officers soon thereafter executed a well-publicized confiscation of drugs re-imported from low-income nations back into European markets.[17] More systematic policies were subsequently adopted to encourage "tiered pricing" and to discourage the parallel importation of low-priced drugs into Europe from less-developed nations.[18] Among other things, it was recognized that low-price shipments to the least developed nations should have distinctive packaging.

A possibly more serious obstacle to the differential pricing of drugs comes from the formal price control systems some wealthy nations use to prevent the makers of patented drugs from exploiting their full pricing power. This is the so-called system of "external reference pricing," under which national price regulators set the maximum allowable price for a drug to approximate the level of prices observed in several "reference" nations. Intricate inter-national reference price networks have been mapped.[19] The available evidence suggests that the least-developed nations have seldom been included among the reference nations. However, this could change, and if the low prices offered under income-correlated differential pricing were incorporated in reference-based price control systems, the rich-nation price-reducing effect could substantially impair multinational pharmaceutical companies' incentives to offer drugs in low-income nations at prices approaching marginal cost.

This disincentive could also work without formal reference pricing control systems. If drug X is sold at $65 per 30 capsules in a rich nation and only $15 in a low-income nation, procurement authorities in the rich nation are likely to say, "See here. You're only charging $15 for this drug elsewhere. You're discriminating against us. We demand that you reduce your prices here too." The multinational pharmaceutical manufacturer may be forced to concede, in which case, its incentive to offer the drug at low prices in less-developed nations is undermined.

Apart from the rich linkages among nations in systems of pharmaceutical pricing, the segmentation of consumers within a particular low-income nation market can also lead to conscious drug manufacturer strategies favoring relatively high prices. Income inequality is pervasive, within rich nations and poor. Many low-income nations (South Africa comes to mind as an example) can with some oversimplification be divided into two groups: a rich minority often employed by multinational enterprises at high wages and, very importantly, with generous health insurance; and the vast majority who toil at low wages and lack formal health insurance plans. Figure 2 illustrates the elemental economic theory. It shows a national market in which consumers can be segmented into

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17. See "Nearly $18M in Discounted AIDS Drugs Allocated for Africa Diverted by Wholesalers and Sold on European Markets," Kaiser Health News, October 3, 2002, p. 1.

18. See e.g. European Commission DG Trade working document, "Tiered Pricing for Medicines Exported to Developing Countries: Measures To Prevent Their Re-importation into the EC Market," Brussels, April 22, 2002.

19. See the WHO-WTO conference report, "Differential Pricing and the Pricing of Essential Drugs," supra note 11, at p. 229, reproducing a chart presented at the conference by Ed Schoonveld.

two groups: sub-market 1, comprising the rich, well-insured consumers (corresponding to the aggregate of consumers in Figure 1a) and another sub-market 2 in which are clustered the less affluent and poorly-insured potential consumers.[20] In this case, the combined demand curve for both classes of consumers is kinked, with demand in the less affluent sub-market D_2 being added to demand in sub-market 1 only below the "choke price" of $35 per unit in the lower-income sub-market. If the supplier is able to engage in price discrimination across the two sub-markets, its profit-maximizing strategy must include ensuring that the marginal revenues in the two sub-markets are equalized. Otherwise a reallocation of output from the lower-MR to the higher-MR sub-market is profitable. Under the assumed circumstances, the supplier will compute its combined marginal revenue function (with a kink where the two sub-market functions intersect). It then sets a price of $58 in the rich segment and $32 in the low-income segment. However, within a single national entity, arbitrage is much more likely than across geographically separated nations, and so the effort at differential pricing may fail. In that case, the pharmaceutical supplier faces two alternative single-price options. It can try to serve all customers at a price of $32, or it can confine its sales to the rich consumers comprising sub-market 1 at $58. The surplus of revenues over marginal costs is approximately $4.6 million per month if both consumer classes are served at a uniform price. If sales are directed only toward affluent consumers, profits are $6.6 million per month. If arbitrage is probable and successful market segmentation unlikely, the producer will be inclined to charge a high price and exclude low-income consumers, whose "choke price" of $35 precludes their participation in the high-price sub-market. Among other things, the high-price strategy sacrifices substantial consumer surpluses for both rich and poor consumers even as it maximizes producer profits.

A complication overlooked in the analysis by Scherer and Watal[21] was articulated by Maskus and Ganslands.[22] Especially in the least developed nations, but also in China,[23] distribution channels linking pharmaceutical manufacturers to eventual consumers are often inefficient and infused with monopoly elements. In many sub-Saharan African nations, exclusive franchises are awarded, often as the result of political corruption, to drug wholesalers and sometimes to private companies that receive drugs at the initial importation node and then relay them to wholesalers. Competition at the drug retailing level is also limited. Given their monopoly positions, middlemen charge extraordinarily high prices for their services, raising the prices ultimately paid by retail consumers. The more monopolistic stages pyramided between the original product source and the consumer, the more the ultimate quantity supplied is likely to be

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20. The demand function for Market 1 is P = 100 - .25 Q; the demand function for the low-income is identical to the low-income nation demand function assumed in Figure 1b.

21. Supra note 8.

22. Supra note 14 at pp. 68-69 and 78-79.

23. See the chapters by Mingzhi Li and Kai Reimers and by Yanfen Huang and Yiyong Yang and my own synthesis of their findings at pp. 376-379 in Karen Eggleston, Prescribing Cultures and Pharmaceutical Policy in the Asia-Pacific, Walter Shorenstein Asia-Pacific Research Center, Stanford California (2009).

restricted, all else equal.[24] One consequence is that price concessions offered by manufacturers can be dissipated and hence blurred in the analysis of prices paid by retailers and consumers. This blurring is more likely in analyses that use data sources such as IMS, which focuses its efforts on the prices paid to wholesalers by retailers, than in studies such as that of Luccini et al.,[25] who ventured into the field to obtain original source pricing data.

The Ultimate Triumph of Differential Pricing

Despite these problems, needy consumers in low-income nations ultimately became the beneficiaries of greatly reduced prices for life-saving drugs and vaccines, especially during the 1990s and the first decade of the 21st Century. For example, the cost of providing three-drug therapy to persons afflicted with HIV/AIDS in the poorest nations fell from approximately $15,000 for a year's treatment in 2001 to an average of $127 in 2012.[26] These price reductions made possible an increase in the number of low- and middle-income nation citizens treated with anti-retrovirals from the low hundreds of thousands in 2001 to an estimated 6.6 million in 2010, along with an appreciable decrease in the number of persons dying from AIDS following peak mortality levels in 2005.[27] Similar price reduction trends can be observed for vaccines (beginning in an earlier decade) and drugs targeted inter alia against malaria and tuberculosis.

Several developments led to these changes. For one, increases in the cumulative and ongoing quantity of drugs procured probably led to economies of scale, although detailed information on cost-volume relationships are lacking.[28]

Second, life-saving drugs became available to an increasing extent from government clinics and from international health care organizations rather than through

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24. These propositions were initially proved mathematically in a famous work by Augustin Cournot in 1838 and a much less well-known monograph by Charles Ellet Jr. in 1839. The phenomenon was recognized in less rigorous form by U.S. Treasury Secretary Alexander Hamilton in Federalist Paper No. 22 (December 1787).

High tariffs on drugs imported into the least-developed nations also had a negative impact, albeit without a pyramiding effect.

25. Supra note 12.

26. "A New Approach to Solicitations for a Troubled AIDS Charity," New York Times, July 10, 2012, p. D6.

27. "The 30 Years War," The Economist, June 4, 2011, pp. 89-91. Later estimates put the number treated in the range of 8 million as of 2011.

28. On the substantial cost reductions achieved in early penicillin production, see the Federal Trade Commission staff report, Economic Report on Antibiotics Manufacture, June 1958, pp. 162-163.

private-sector pharmacies, avoiding many of the distribution channel inefficiencies characterized earlier.

Accompanying this change was an increase in the bargaining power of entities purchasing essential drugs from manufacturers. Organizations such as the World Health Organization, UNAIDS (an affiliate of the United Nations); the multi-national Global Fund To Fight AIDS, Tuberculosis, and Malaria; UNICEF (at work already in the 1990s to obtain and distribute vaccines at rock-bottom prices), Medicines sans Frontieres, Oxfam, the Gates Foundation, the Clinton Foundation, and PEPFAR (the U.S. President's Emergency Plan for AIDS Relief) brought to bear both moral and large-purchaser pressure on pharmaceutical manufacturers and then ensured that the purchased drugs reached utilization points expeditiously.[29]

By no means all of the dramatic reductions in AIDS drug prices came from price discrimination favoring low-income nations. Moral suasion and large-buyer pressure also had an impact in the rich nations home to research-based pharmaceutical companies. In the United States, for example, AZT (original brand name Retrovir), the first drug shown to be effective against AIDS, was sold in 1987 at prices amounting to approximately $10,000 for a year's treatment of a single patient. A patient advocacy group, the ACT UP (AIDS) coalition, disseminated information on the large disparity between estimated production costs and prices and mounted highly visible protests. Its activity stimulated investigatory hearings in the U.S. Congress, eventually leading to substantial domestic market AZT price reductions. Similar pressures were exerted with respect to the numerous AIDS drugs reaching the market during the ensuing decade and a half.

Differentially, however, the producers of drugs with patent protection were induced to reduce prices in less affluent markets more than in rich nations not only through appeal to the logic of Ramsey-type price discrimination, but also by the stern discipline of competition. Some nations, we have seen earlier, did not issue patents for pharmaceutical products at the time the TRIPS agreement was signed in 1995. Among these were India and Brazil. Although it was not required to do so at an early date, Brazil extended patent protection for pharmaceutical products shortly after the ratification of TRIPS. India chose not to do so until 2005. Even for Brazil, however, only the newest pharmaceutical products were covered by patents; older molecules remained patent-free while protection continued in the nations that had earlier coverage. This made it possible for Brazilian companies not bound by patent rights to begin competitive generic supply and (more importantly) for Brazilian health authorities to draw upon Indian supplies at greatly reduced prices. The multinationals were required either to follow suit or confine themselves to severely reduced market shares when they tried to maintain high prices in no-patent jurisdictions.

The history of India's role in these developments is particularly interesting. The chronicle begins much earlier in Europe, however.

For more than a century until 1978, Italy's laws expressly excluded pharmaceutical products from patent protection. In 1978, however, the Italian Supreme

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29. Noticeably absent from the history is collaboration among the least-developed nations to leverage their purchasing power collectively.

Court ruled in a law suit brought by both multinational and some Italian pharmaceutical firms that this exclusion was unconstitutional. The Italian parliament passed a law implementing the court's decision in 1982, and from that time on, new pharmaceutical products tended to receive Italian patent protection. Before that change, Italy was home to the world's leading export-oriented generic pharmaceutical industry. With no domestic patent barriers, Italian firms were able to supply new drugs competitively in their home market. But in so doing they also enjoyed a first-mover advantage in supplying those products to other nations (including Greece, Spain, and Argentina) that did not grant product patents. As the almost certain consequence of these 1978-82 legal changes, Italy's balance of trade in pharmaceuticals turned sharply negative beginning in 1982 as the export advantage of its domestic producers faded.[30]

India's industry rose to fill the gap. It became the world's leading generic drug supplier.[31] The AIDS crisis amplified that role. As the 21st century dawned, anti-retroviral prices in most of the world, including severely-impacted African nations, were so high as to be unaffordable for most AIDS sufferers. With the encouragement of William Haddad, president of the U.S. Generic Pharmaceutical Manufacturers Association; Medicins sans Frontieres, and an organization created by U.S. consumer activist Ralph Nader, Indian firms, led by generic specialists Cipla and Ranbaxy, began exporting substantial quantities of anti-retrovirals and other important drugs to Africa and some southeast Asian nations at prices as low as two percent of those quoted by multinational patent holders.[32] Again, the consequence was a dramatic decrease in drug prices for low-income nations and indeed the emergence of the kind of cross-nation price differences implied by the theory of differential pricing.

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30. See Sandy Weisburst and F. M. Scherer, "Economic Effects of Strengthening Pharmaceutical Patent Protection in Italy," International Review of Industrial Property and Copyright Law, vol. 26, no. 6 (1995), pp. 1009-1024. The analysis in that paper shows also that pharmaceutical R&D in Italy rose subsequently at an annual rate well below multinational company trends. See also Pablo Challu, "Effects of the Monopolistic Pricing of Medicines in Italy Since 1978," International Journal of Technology Management, vol. 10, no. 2/3 (1995), pp. 237-250.

31. An illustrative anecdote: In 1994 I made an extended visit to Czechoslovakia, which at the time provided no pharmaceutical product patents. I discovered that I had failed to bring with me an important drug whose monthly cost in the United States, for myself and my insurer, was approximately $70. I obtained a prescription and presented it to a Prague pharmacist. She said to me, "This is going to be very expensive, but since you are a rich American, you may not mind." The price, converted to dollars, was approximately $5 for a month's supply. The label read "made in India."

32. See "Selling Cheap 'Generic" Drugs, India's Copycats Irk Industry," New York Times, December 1, 2000, pp. 1 and A12. The article includes a photo of Yusuf Hamied, chairman of Cipla and a key participant in the efforts to involve Indian generic suppliers in world supply networks.

Compulsory Patent Licensing

The TRIPS treaty requirement that recalcitrant nations begin offering patents on pharmaceutical products and other previously excluded subject matter, immediately for so-called developed nations and with delays for less-developed nations, was not the sole determinant as to whether generic competition could emerge. The original TRIPS agreement included language permitting national governments to "march in" and negate otherwise binding patent rights through so-called compulsory licensing decrees under certain specified circumstances. Under Article 31, compulsory licensing was permitted when a would-be patent user is unsuccessful within a reasonable period of time in obtaining from a patent holder the right (i.e., a license) to supply competitively a patented invention "on reasonable commercial terms and conditions" -- e.g., with the payment of what are called (but hard to quantify) "reasonable royalties." The failed negotiations condition could be waived in cases of national emergency or extreme urgency or for non-commercial public use.[33] Subparagraph 31(k) also allowed compulsory licensing to correct "anti-competitive practices," which were spelled out more fully in Article 40. The combination of subparagraph 31(k) and Article 40 appears to track in a general way the history of the United States, where, especially between 1939 and 1956 and more sporadically later, tens of thousands of U.S. patents were subjected to compulsory licensing in full or partial settlement of antitrust complaints.[34]

The exact legal procedures through which compulsory licenses can be issued under TRIPS were left unspecified, and no formal system for reporting the issuance of compulsory licensing exists. Therefore, information on the TRIPS provisions' use is at best sporadic. It is known that licenses were issued on at least seven pharmaceutical patents by Thailand, one by Brazil (with other threats settled by voluntary licensing), and one by India. The more important function of Article 31 may be to induce price reductions or the issue of voluntary patent licenses without the formal declaration of a compulsory license. In 2001, for example, both the United States and Canada threatened compulsory licensing of Bayer AG's patent on Ciproflaxin when, it was feared, terrorist activity might trigger an epidemic of otherwise untreatable anthrax. In that case, however, substantial price reductions were forthcoming and formal licensing was averted.

South Africa, with some of the most severe AIDS incidence, implicitly used the provisions of Articles 31 and 40 (plus its own competition laws) to secure licenses without carrying the action all the way to a formal declaration. By 2003, it had become known that a so-called "triple therapy," including three different anti-retroviral drugs, was the most effective way to treat AIDS. Three-drug therapy was more effective in

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33. Under United States law, the U.S. government was since at least 1952 permitted to infringe valid patents for government use. In the early 1960s, the U.S. Department of Defense was procuring patented tetracycline from Italian generic suppliers. The practice was prohibited by a special act of Congress.

34. See Marcus A. Hollabaugh and Robert Wright, Compulsory Licensing under Antitrust Judgments, staff report of the Subcommittee on Patents, Trademarks, and Copyrights, U.S. Senate Committee on the Judiciary (1960).

abetting the frequent mutations that could render individual therapeutic molecules impotent, and combining three molecules in one twice-daily pill was a superior way to ensure daily compliance, again reducing the danger of mutation. But patents covering one of the drugs (AZT) were held by GlaxoSmithKline (successor to Burroughs-Wellcome) and those for two other key ingredients were held by the German firm Boehringer-Ingelheim. The two firms declined to cross-license each other, so no single-pill therapy was available. An action by the South African Competition Commission aided by CPTECH, an offspring of Ralph Nader's U.S. consumer advocacy organization, induced the firms to offer compulsory licenses, first to a South African generic supplier, Aspen Pharmacare, and then to foreign (e.g. Indian) suppliers.[35] New triple therapies became available at unprecedentedly low prices.

The original text of TRIPS Article 31 specified that the compulsory licenses it authorized had to be "predominantly for the supply of the domestic market."[36] This posed a difficulty. Many less-developed nations lack the technological capability to produce advanced organic pharmaceutical molecules. A license issued only domestically for them would be of little use. For a supplier in India, on the other hand, the "domestic market" language could be a bar to licensing and then exporting in majority quantities to other needy markets. This issue was addressed at the 2001 World Trade Organization conference in Doha, leading to a declaration that:[37]

> We recognize that WTO members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement.

A definitive solution was postponed, but in 2003 the WTO formally declared that border-hopping licenses could be issued "in good faith to protect public health."[38] The earlier 2001 Doha declaration also stated that "Each Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted" and that:[39]

> Each member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that

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35. See Competition Commission of South Africa, "GSK and BI Issue Anti-retroviral Licenses," Competition News, March 2004, pp. 1-2; and "Agreement Expands Generic Drugs in South Africa to Fight AIDS," New York Times, December 11, 2003, p. A24.

36. "Predominantly" was apparently interpreted informally to mean that a majority of sales were domestic.

37. World Trade Organization, "Declaration on the TRIPS Agreement and Public Health," WT/MIN(01)/Dec/W/2.

38. Decision of the WTO General Counsel, August 30, 2003 (WT/L/540), aamended in WT/L/641; and "WTO to let poor nations import generic drugs," Philadelphia Inquirer, August 31, 2003. In 2005 the compromise was adopted as a permanent amendment to TRIPS.

39. Supra note 37.

public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

Many of the most advanced pharmaceuticals originate not in company laboratories but through basic research pursued by university scientists. Since universities lack the capabilities needed to manage large-scale clinical tests, manufacture new drugs, and distribute them to users, universities in the United States since at least passage of the Bayh-Dole Act[40] in 1980 have granted typically exclusive licenses for relevant new drug entity patents to commercial firms. The practice attracted public scrutiny in 2001. Yale University licensed a patent on the anti-retroviral molecule stavudine (d4T) to Bristol-Myers-Squibb, whose high prices on third world sales of its branded product Zerit stimulated student protests. Yale officials thereupon brought pressure to bear on Bristol-Myers to reduce its third world prices drastically and to allow other companies to enter into competitive manufacturing overseas. This experience in turn led to a multi-university concord encouraging patent licensing strategies that "make affordable versions [of drugs, vaccines, and medical diagnostic tools] available in resource-limited countries."[41]

Consequences for Research and Development

Dramatic changes have occurred in the supply of advanced pharmaceutical products since the TRIPS agreement was adopted in 1995. Nations that once chose not to do so are gradually being required to issue pharmaceutical product patents for bona fide technological achievements. Numerous national and international organizations have been reoriented or formed de novo to bargain for low prices in procuring patented pharmaceuticals for low-income nations when suppliers were disinclined for diverse reasons not to engage in differential pricing voluntarily. The TRIPS agreement initially carved out exceptions to its strong pro-patent requirements in compulsory license clauses and then adopted further extensions. All this has led to huge decreases in the prices paid for life-saving drugs (if payment has been required at all) to the world's least advantaged citizens.

The key remaining question is, how has downward pressure on third-world pharmaceutical product prices affected company incentives to invest in research and the development of new drugs? As a first approximation, measures that limit the profits obtainable through pharmaceutical innovations also reduce incentives to invest in bringing new drugs onto the market (although the arrival of generic competition to already-marketed drugs also spurs R&D on more advanced replacements). Difficult tradeoffs must be faced. For drugs targeted toward diseases at least as prevalent if not more prevalent in rich nations, providing weaker patent protection and facilitating tougher competition in low-income nations undoubtedly has a small, even if not vanishing, negative impact. A deeper analysis of the tradeoff suggests the following

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40. 94 Stat. 3019 (1980).

41. Universities Allied for Essential Medicines, "Global Access Licensing Framework" (2007), addressed on the internet at www.essentialmedicine.org.

generalizations:[42]

1) The smaller is the ratio of attainable potential quasi-rents (roughly, profits before deduction of fixed costs) in low-income nations relative to those in wealthy nations, the stronger is the case for weak patents in low-income nations.

2) The more the marginal utility of income diminishes with increased affluence, the stronger is the case on total economic welfare grounds for weak patents in low-income nations.

3) The case for weak patents in low-income nations is stronger when R&D is a virtuous rent-seeking process, with R&D expenditures rising competitively to exhaust supra-normal profit opportunities, than when a prospect theory of R&D investment applies (i.e., when some companies hold preferred and relatively imitation-proof ex ante positions in developing a new product).[43]

4) The case for weak patents in low-income nations is strengthened when indigenous firms build their technological capabilities through imitative (i.e., generic) production that can then serve as a platform for advancing to higher levels of productivity and innovativeness (mirroring the Japanese, South Korean, and most recently, Chinese economic development histories).

A special case of condition (1) exists for so-called "tropical diseases" -- that is, diseases endemic preponderantly in low-income nations and rare in highly developed nations. Malaria and dengue fever are examples. Then nearly all of the quasi-rents attainable through successful R&D come from low-income nations. The expectation of such rents may be so meager that R&D investments will not be made even under the most favorable market conditions,[44] but in borderline cases, limiting the strength of patent rights is likely to weaken incentives even more. If so, some form of public-

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42. See F. M. Scherer, "A Note on Global Welfare in Pharmaceutical Patenting," The World Economy, July 2004, pp. 1127-1142.

43. On the prospect theory, see Edmund W. Kitch, "The Nature and Function of the Patent System," Journal of Law & Economics, October 1977, pp. 265-290; and William D. Nordhaus, Invention, Growth and Welfare (MIT Press: 1969), Chapter 5. On rent-seeking, see D. G. McFetridge and M. Rafiquzzaman, "The Scope and Duration of the Patent Right and the Nature of Research Rivalry," in Research in Law and Economics, vol. 8 (1986), pp. 91-129. For a synthesis see F. M. Scherer, "Pharmaceutical Innovation," in Bronwyn Hall and Nathan Rosenberg, eds., Handbook: Economics of Innovation (North-Holland, 2010), pp. 560-571.

44. See Medicins sans Frontieres Access to Essential Medicines Campaign, Fatal Imbalance: The Crisis in Research and Development for Neglected Diseases (Geneva: 2001), which found that among 1,393 new drug chemical entities introduced into world markets between 1975 and 1999, only 13 to 15 were for so-called "tropical" diseases.

spirited philantrophy by private organizations or governments must fill the gap. The gap-filling problem can be addressed through subsidies on either the supply side or the demand side. On the supply side, governments (or even pharmaceutical companies, in their philanthropic modes) can support research, development, and testing of therapies for diseases neglected under normal market incentives. Or on the demand side, advance commitments can be made to purchase at subsidized prices new drugs and vaccines effective against neglected tropical diseases.[45] Through such philantrophy, the conflict between technological progress and maximum consumer access to its fruits can be minimized.

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45. See Ruth Levine et al., Making Markets for Vaccines: Ideas to Action (Washington: Center for Global Development, 2005), on an "advanced market commitment" initiative targeting HIV/AIDS, malaria, and tuberculosis vaccines that was considered favorably by the G-8 government leaders at plenary meetings between 2005 and 2008 but never fully implemented.

Figure 1 a. Price Discrimination Between Markets of Differing Wealth

Wealthy Nation A

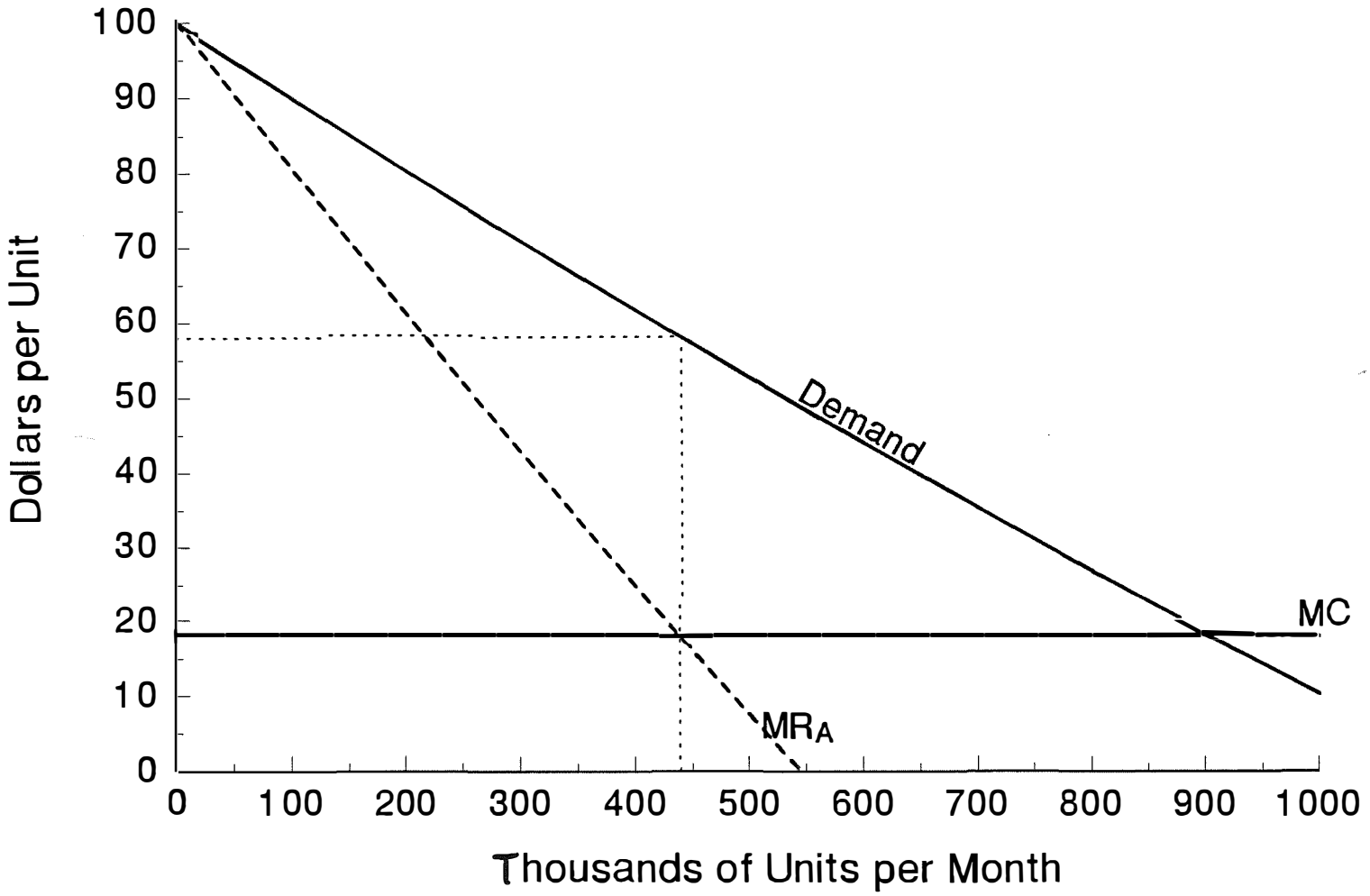

Figure 1b. Price Discrimination Between Markets of Differing Wealth

Low-Income Nation B

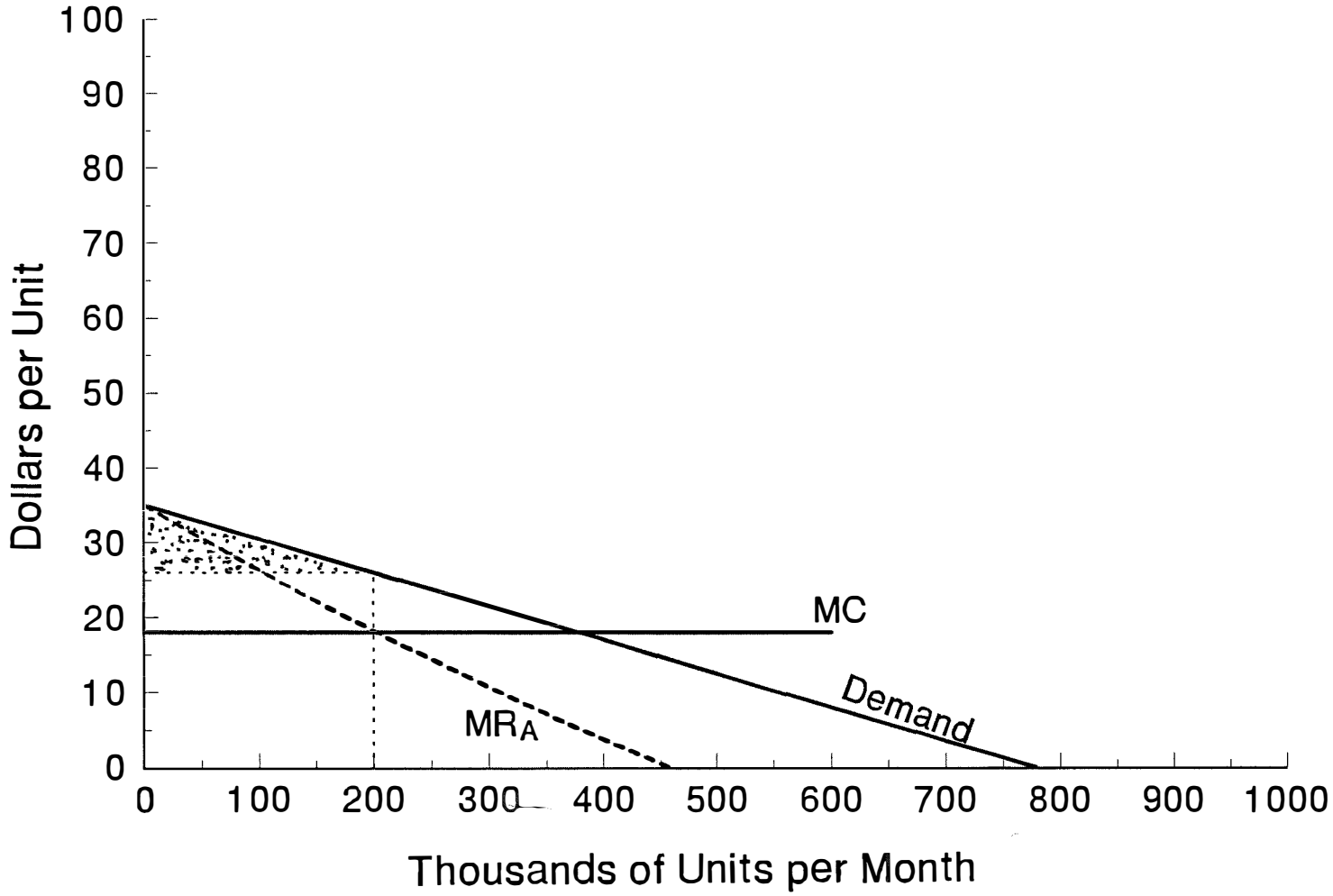

Figure 2. Market Segmentation within a National Market