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When I was a high school student during the late 1940s, the first so-called "wonder drugs"—initially penicillin and then the broad-spectrum antibiotics such as tetracycline—were entering the U.S. market. From their profitable experience developing the broad-spectrum antibiotics, the leading pharmaceutical companies of America and Europe acquired a strong research orientation that led to a cascade of new therapeutic entities, including additional anti-infectives, vaccines, diuretics, and then other agents to reduce heart attack risks, tranquilizers, antidepressants, birth control pills, anti-fungal agents, immunosuppressants, cortico-steroids, AIDS inhibitors, powerful pain relief agents, and many other agents effective against specific diseases. Thanks to this pharmaceutical revolution, life spans have been prolonged, the incidence and duration of hospital stays have been reduced, and the quality of countless citizens' lives has been enhanced.[1]

The benefits of modern pharmaceutical therapy have accrued mainly to the citizens of the world's more prosperous nations. United Nations staff have estimated that average purchases per capita of modern pharmaceutical products (excluding traditional

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1. *See* FRANK R. LICHTENBERG, THE EFFECT OF PHARMACEUTICAL UTILIZATION AND INNOVATION ON HOSPITALIZATION AND MORTALITY 23, (National Bureau of Economic Research Working Paper No. w5418, 1996) (estimating that a $1 increase in pharmaceutical purchases was associated on average with a $2.65 reduction in hospitalization expenditures), *available at* http://papers.nber.org/papers/w5418.

medicines) in 1990 (calculated at prevailing exchange rates) in diverse parts of the world were as follows:[2]

North America	$123.90
European Community	102.90
Other Western Europe	85.70
Japan	276.60
South and East Asia	5.00
China	4.80
Latin America	20.30
Sub-Saharan Africa	3.30

A rough extrapolation of these figures reveals that the 73 percent of the world's 1990 population located in south and east Asia, including China, Sub-Saharan Africa, and Latin America, consumes only 16.2 percent of modern pharmaceutical output by dollar volume. One consequence of the inadequate purchasing power that limits such nations' ability to consume pharmaceuticals is a higher rate of morbidity and debility, which in turn impairs the growth of income so that pharmaceuticals can be afforded—a vicious cycle.

Nearly all of the research-oriented pharmaceutical companies responsible for innovations in drug therapy have their home bases in the United States, the European Community nations, or Japan, where demand is most intense and highly able scientists interacting with first-rate universities are at hand. Excepting those of Japan, the research-oriented pharmaceutical companies are among the most multinationally oriented enterprises in the world.

Discovering a new drug and carrying it through the tests required to obtain marketing approval from regulatory agencies in the United States and Europe costs upwards of $100 million per successful new chemical entity. Once such a large investment has been made, there are powerful incentives to obtain requisite regulatory approvals in other nations and sell the product as widely as possible. Foreign markets are served both by exporting, often from a tax haven such as Puerto Rico, Ireland, or Singapore, and through direct plant investment in consuming nations. According to United Nations estimates, pharmaceutical imports averaged 8.2 percent of domestic consumption during 1989 in developed nations and 19.8

2. *See* ROBERT BALLANCE, THE WORLD'S PHARMACEUTICAL INDUSTRIES: AN INTERNATIONAL PERSPECTIVE ON INNOVATION, COMPETITION AND POLICY 30-31 (1992).

percent in less-developed nations.[3] In 1980, approximately 27 percent of the world's demand was satisfied through local production by foreign-owned companies.[4] Since then, the extent of multinational operation has increased, in part due to numerous cross-border mergers. In 1995, members of the Pharmaceutical Research and Manufacturers of America trade association recorded prescription drug sales of $65 billion within the United States and $37 billion outside the United States.[5]

Most of the R&D outlays incurred by pharmaceutical companies are made to discover therapeutically interesting molecules and prove their efficacy and safety through extensive human trials—i.e., to create knowledge that approximates what economists call a pure public good. Absent legal barriers to copying, once a drug has been found to be safe and effective, another firm might come up with a generic equivalent by spending roughly a million dollars on production process methods and formulation and begin to compete with the pioneering firm. If such generic imitation were widespread and rapid, surplus revenues that repay pioneers' initial R&D outlays and make them worthwhile would be severely eroded, undermining incentives to invest in research and product testing. Because of the huge disparity between drug finding and imitation costs, multi-industry surveys show, pharmaceutical manufacturers attach unusually high importance to the patent system, which in effect grants them 20 years of exclusive rights to their invention from the time a patent application is filed, as a means of recouping their R&D expenditures.[6]

The combination of multinationality and heavy stress on patent protection set the stage for a conflict between the pharmaceutical manufacturers and the world's developing nations. Under the Paris Convention to which most of the nations with patent systems adhered, nations were free to structure their patent laws however they desired, as long as they did not discriminate between local and foreign inventors. Many nations excluded drug products from patentability because they considered drugs (and for analogous reasons, food products) to be of such great importance to the national welfare. Even Switzerland, home to three of the world's leading pharmaceutical companies, abstained until 1977 from

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3. *See id.* at 52.
4. *See id.* at 68-69.
5. *See* PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, 1998 INDUSTRY PROFILE 100 (1998).
6. *See* Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, 3 BROOKINGS PAPERS ON ECONOMIC ACTIVITY 783, 807-12 (1987).

granting drug product patents. Most less-developed countries ("LDCs") followed that pattern and tended more generally to provide weaker patent protection than the most industrialized nations—actions perfectly compatible with the Paris Convention.

For the multinational pharmaceutical companies, the inability to obtain universal patent protection for their new products was seen as a constraint on their world wide sales and profits, limited though the potential in LDCs might be due to consumers' meager purchasing power. An attempt to alter the situation at a World Intellectual Property Organization conference in Kenya during the 1970s proved unsuccessful. The drug makers then sought other fora to pursue their quest. Led by Edward Pratt, CEO of Pfizer Inc. and a member of President Reagan's business advisory committee on international trade, the U.S. pharmaceutical companies commenced a superbly orchestrated campaign to bring the U.S. government into the dispute.[7] They fanned out to enlist the support of motion picture, music recording, and software industry leaders who were equally unhappy about the copyright protection they received abroad. The U.S. pharmaceutical makers in turn enlisted the lobbying support of their European counterparts through the so-called Dolder Group (named after a Swiss hotel at which pharmaceutical executives met regularly) and also Japanese companies. An astute public relations campaign succeeded in making "piracy" the accepted term to describe the imitation of drug or software products in nations with permissive intellectual property laws, even though "knock-off" production was quite legal under accepted international conventions. Lobbying efforts at the U.S. Congress led to amendments in Section 301 of the U.S. international trade code, defining other nations' failure to grant full patent or copyright protection for U.S. products as an unfair trade practice and charging the President's Trade Representative Office with monitoring foreign intellectual property practices and identifying for unilaterally imposed trade sanctions the most egregious perceived offenders.[8] Faced with increased tariffs, loss of most-favored-nation status, or the threat of such sanctions on the products they sought to export to the United

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7. *See* M.P. RYAN, KNOWLEDGE DIPLOMACY: GLOBAL COMPETITION AND THE POLITICS OF INTELLECTUAL PROPERTY 67-69 (1998); LYNN SHARP PAINE & MICHAEL SANTORO, PFIZER: PROTECTING INTELLECTUAL PROPERTY IN A GLOBAL MARKETPLACE (Harvard Business School case study N9-392-072 1995), *available at* http://www.hbsp.harvard.edu.

8. *See generally* AGGRESSIVE UNILATERALISM: AMERICA'S 301 TRADE POLICY AND THE WORLD TRADING SYSTEM (Jagdish Bhagwati & Hugh Patrick eds., 1990) (detailing and evaluating section 301).

States, some nations such as Korea, Thailand, and Brazil strengthened their patent and copyright laws and began enforcing them assiduously.

Prodded by industrial lobbies, the governments of the United States, European Union member nations, and Japan insisted that harmonization of national intellectual property laws be made a key agenda item in the Uruguay Round of international trade negotiations, initiated in 1986. That effort pitted the leading industrialized nations working en bloc against the less-developed countries.

LDCs were opposed to granting stronger intellectual property rights because such grants seemed so clearly against their national interests. If they allowed patents on drug products, the multi-national enterprises ("MNE") would have stronger monopoly positions in selling their products to the limited array of domestic consumers able and willing to pay, so prices would be elevated relative to those charged by local drug makers able to "knock off" the most advanced products invented elsewhere and sell them at more competitive prices. Higher prices mean smaller quantities demanded and hence lower health benefits from the newest therapies. If imports were the vehicle through which the MNEs sold their newest drugs, and probably also if the drugs were produced by local branch plants, the profits realized would be repatriated to the MNEs' home countries, imposing a drain on scarce hard-currency reserves. To be sure, higher sales and profits for the multinationals would mean stronger incentives to invest in R&D (conducted almost entirely in highly industrialized nations) and hence the emergence of more new products. A theoretical analysis of less-developed nations' incentives reveals that to compensate for the loss of domestic surplus (assuming linear demand functions) as a result of high drug prices for existing patented products, a threefold increase in the number of equivalent new products reaching the LDCs would be required.[9] Such a large increase in new products driven solely by the modest sales increase attributable to newly-authorized patenting in low-income nations seemed highly improbable.

The tradeoff might become more favorable for less-developed countries if granting patent protection on new drug products strengthened the incentives of indigenous pharmaceutical compa-

9. *See* F. M. SCHERER, INDUSTRY STRUCTURE, STRATEGY, AND PUBLIC POLICY 363-65 (1996). Viewing the situation from the perspective of the world as a whole rather than that of a single LDC, an increase of less than one-third in the number of equivalent new products will compensate for the loss of consumers' surplus as a result of monopolized, as compared to competitive, pricing of the new products that would reach the market without patent protection.

nies so much that those firms began developing innovative drugs, selling them at home and perhaps exporting them too. The benefits from granting product patents would also be enhanced if multinational companies were spurred to develop new drugs explicitly targeted toward diseases prevalent mainly in low-income nations.

Evidence on the first of these possibilities is provided by the experience of Italy. During the 1950s and 1960s, Italy did not grant drug product patents. A thriving "knock-off" drug industry emerged, selling drugs at bargain prices in the home market and becoming the world's leading exporter of new drugs to other nations that also denied patent protection to drug products.[10] During the 1970s, however, multinational enterprises challenged the Italian law, and in 1978, the Italian Supreme Court ruled that the law denying drug product patents was unconstitutional. It ordered that the law be amended and that the Italian authorities begin accepting drug patent applications immediately. Analyses of events during the decade that followed yield three principal conclusions: (1) no significant increase in Italian drug R&D expenditures relative to world trends; (2) no significant increase in the number of new drug entities introduced by Italian firms; and (3) a sharp deterioration of the Italian trade balance in drugs into the negative realm as export sales faltered and multinational firms imported many of their products into Italy from elsewhere in Europe. In addition, numerous Italian drug manufacturers were acquired by multinational firms seeking to strengthen their foothold in the Italian market. It is unclear why Italy failed to make the transition from drug imitator to drug innovator. It may be that a decade is too short a time to do so, or price controls may have impaired domestic market incentives for the development of pioneering drugs. Also, Italy lacked the university research infrastructure and cooperative university-industry relationships needed to nourish drug innovation. What is clear is that leadership in the production and export of knock-off drugs to nations lacking product patent protection shifted to India.

There is little evidence on the second possibility—an increase in the targeting of drug development efforts toward low-income nations' health problems by multinational drug companies. An early investigation of this possibility and also the hypothesis that the anticipation of domestic future product patent protection

10. Indeed, in the late 1950s, frustrated by the high prices charged for tetracycline by licensees to the patent held by Pfizer, the U.S. armed forces invoked their statutory right to infringe domestic patents and purchased tetracycline from Italian firms.

stimulated Indian manufacturers' new drug discovery efforts up to 1997 yielded equivocal findings.[11]

What some multinational drug companies have done is to *donate* already developed drugs such as Zithromax (effective against trachoma blindness), Ivermectin (effective against river blindness), and Albendazole (effective against lymphatic filariasis parasites) to especially poor nations with a high incidence of such diseases.[12] Four pharmaceutical companies led the list of U.S. corporations, ranked by the total amount of money devoted to philanthropic giving in 1998.[13] Presumably, the market value of the drugs donated in this way could be claimed as tax deductions by the donor corporations. Since the marginal cost of a typical still-patented drug tends to be on the order of 20 percent of the U.S. wholesale price, and since for most corporations (but perhaps, because of tax credits on Puerto Rican production, not the drug makers) the marginal corporate income tax rate is 34 percent, it is conceivable that the drug companies' charity actually increased the donors' after-tax profits. If this conjecture is correct, the donation programs may in fact be a subtle form of foreign aid subsidized by the U.S. Treasury.

As the Uruguay Round negotiations culminated in 1993, the industrialized nation coalition demanding patent law unification held firm, and the final draft included a strong Trade-Related Intellectual Property Rights ("TRIPS") chapter. Less-developed nations were presented with hard choices. On the one hand, they could agree to strengthen their intellectual property laws and accept the consequences outlined above. On the other hand, they could opt out and lose the benefits of World Trade Organization ("WTO") membership, including gradual relaxation of industrialized nation import restraints against agricultural products and phase-out of the Multi-Fibre Agreement limiting the export of textiles and apparel—fields in which many LDCs had found comparative advantage. The best the LDCs could do was to negotiate compromise clauses in the final draft—notably, allowing LDCs ten years from January 1995 to implement full drug patent rights and providing exceptions under which national governments could abridge the rights granted. Exceptions can occur when monopolistic abuses of patent rights are proven, or non-exclusive compulsory licensing of

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11. *See* JEAN O. LANJOUW & IAIN COCKBURN, *Do Patents Matter?: Empirical Evidence After GATT* 1-4, (National Bureau of Econ. Research Working Paper No. 7495, 2000), *available at* http://www.nber.org/papers/w7495.pdf.

12. *See id.* at 22-23.

13. *The List: Corporate Giving*, BUS. WK., Jan. 24, 1990, at 8.

patents with "adequate remuneration" is permitted when a proposed patent licensor has been unable within a reasonable period of time to "obtain authorization [for domestic use] from the right holder on reasonable commercial terms and conditions." Exactly what these loopholes mean is at best unclear; the provisions are likely to be contested in future proceedings before the WTO.[14] Meanwhile, the Uruguay Round treaty requires that less-developed nation signatories accept interim patent applications in a so-called letter box, granting to the patent applicant exclusive marketing rights for five years beginning not later than the year 2000 for new drugs covered by pending applications.

Some nations, such as Brazil, have complied fully with the TRIPS mandates. In other nations compliance remains bitterly disputed and the subject of U.S. complaints to the WTO. In Argentina, for example, implementing legislation proposed by President Menem was at first rejected by the Parliament and then passed in a weakened form that, according to U.S. trade officials, fails to comply with the Uruguay Round treaty language. As of 1999, India had not passed implementing legislation or delineated procedures for accepting letter box applications. In April 1999, the United States government launched a special review threatening trade sanctions against South Africa for its efforts to import drugs at bargain prices from nations with no drug product patent protection and to issue compulsory licenses permitting domestic manufacture of Taxol (effective against certain forms of cancer) and drugs that could help combat an AIDS epidemic. A contemplated complaint to the World Trade Organization concerning South Africa's policies was apparently headed off when AIDS activists threatened to make the U.S. policies a contested issue in Al Gore's campaign to win the U.S. presidency.[15] Had the Seattle round of international trade negotiations not collapsed in debacle during December 1999, it was likely that less-developed nations would have sought reconsideration and weakening of the Uruguay Round TRIPS agreements.

The debate over drug product patent extension into the Third World is a classic problem of federalism, questioning whether

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14. Exploitation of the loopholes is encouraged in a World Health Organization staff report, to which the U.S. pharmaceutical company trade association and the U.S. Food and Drug Administration have taken pointed exception. *See* World Health Organization Staff Report, *Globalization and Access to Drugs: Implications of the WTO/TRIPS Agreement* 32-36 (1998), *available at* http://whqlihdoc.who.int/hq/1998/WHO_DAP_98.9_revised.pdf.

15. *See* Kathy Chenault, *Will the AIDS Plague Change U.S. Trade Policy?* BUS. WK., Sept. 13, 1999, at 58.

economic policy choices should be made locally or by a supervening governmental entity. Usually decentralization is favored on allocative efficiency grounds while the possibilities of redistributive equity pull toward centralization. However, in the TRIPS debate, the opposite is true. Decentralization of patent policies allows poor nations to address their health problems despite limited resources by free-riding on wealthy nations' inventions, while the suppression of free-riding under a centralized policy improves the allocation of world R&D resources. Curiously, while the TRIPS debate was proceeding, the U.S. Supreme Court handed down a patent law decision logically inconsistent with the U.S. position on drug product patents in international fora.

The U.S. Patent Code includes provisions allowing the federal government to infringe valid patents when infringement serves the national interest and reasonable compensation is paid.[16] The requirements for reasonable compensation have been interpreted historically to imply much lower payments than the foregone monopoly profits standard imposed in private patent infringement damages cases. In *Florida Prepaid Postsecondary Education Expense Board v. College Savings Bank*, a majority of the Supreme Court ruled (over the strong dissent of a four-member minority) that Congress had exceeded its constitutional powers in nullifying individual states' sovereign immunity from patent infringement suits in federal courts, provided that the states maintain their own in-state legal procedures (either legislative or judicial) to ensure that the patent holders' property is not taken without due process of law.[17] Armed with that precedent, the states might in the future seek to alleviate their escalating drug cost burdens under Medicaid (and possibly in the future Medicare) by setting up patent-infringing generic drug production operations or importing drugs from no-patent jurisdictions and offering to pay "reasonable compensation" for the use of the infringed patents. Compensation substantially less than the monopoly profits foregone by the patent holders might arguably satisfy the due process requirement.[18]

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16. *See* 28 U.S.C. § 1498 (1994). For an illustration of an actual case, see *supra* note 10.

17. Florida Prepaid Postsecondary Educ. Expense Bd. V. College Sav. Bank, 527 U.S. 627 (1999).

18. An example is the position taken by the courts of Canada in implementing tbe compulsory licensing of drugs up to 1987. When Hoffmann-LaRoche requested a flat fee royalty tbat would bave amounted to 30 percent of the price of Valium *before* the emergence of generic competition, the Canadian Exchequer Court set an *ad valorem* royalty of four percent on sales *after* the emergence of generic competition. The Court provided that in setting the terms of the license and fixing the amount of royalty or other consideration payable, "the Commissioner shall have regard to the desirability of making the medicine available to the public at the lowest possible

One might argue that an analogous bargain must govern the division of powers between a supranational federalist organization such as the WTO and its member nations, especially when issues that are literally a matter of life or death are joined. Indeed, from the U.S. Senate debate that preceded U.S. ratification of the Uruguay Round treaty, it was clear that U.S. legislators were reluctant to cede such life-or-death powers to a supranational federal body. For the United States to insist that other member nations should not infringe patents issued within their home jurisdictions, paying compensation deemed reasonable under their own judicial or administrative processes, would be hypocritical, given the Supreme Court's strong states' rights position in the *Florida Prepaid Postsecondary Education* case.

What seems clear is that controversy over the Uruguay Round TRIPS mandates will continue and indeed intensify.

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price consistent with giving to the patentee due reward for the research leading to the invention." *See* Hoffmann-LaRoche Ltd. v. Frank W. Horner Ltd., (1970) C.P.R. 107-108. Four percent royalty rates became standard in subsequent drug patent licenses. *See* F. M. Scherer, *The Economic Effects of Compulsory Patent Licensing, in* MONOGRAPH SERIES IN FINANCE AND ECONOMICS 1977, at 47 (N.Y.U. Graduate Sch. Bus. Admin. Center for Study Fin. Inst. Monograph 1977-2, 1977).