

Pharmaceutical Arbitrage: balancing access and innovation in international prescription drug markets

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Introduction

Expensive prescription drugs lie at the heart of two major public health issues: the global AIDS epidemic; and US patients obtaining less expensive drugs from Canada over the internet. Both situations call for reducing financial barriers to innovative drugs while maintaining incentives to promote innovation. For better or for worse, the WTO TRIPS Agreement on intellectual property (IP) is the global nexus for these issues.¹

Health care policymakers frequently grapple with providing access at reasonable cost while improving quality. Cost, quality, and access figure prominently in debates over pharmaceutical pricing. Prices are high, economists say, because pharmaceutical innovation is expensive. The research and development (R&D) enterprise must be nurtured, creating the next generation of break-through therapies.

Other voices counter that without financial access, innovation is a cruel taunt. New wonder drugs won't improve health unless patients actually get them. Pharmaceuticals, it is argued, are not normal market goods to be distributed primarily to the wealthy. Advocates claim special status for health care goods and services, frequently bolstered with appeals to human rights. Innovation and quality must be balanced with access and cost.

Differential pricing is the pharmaceutical industry's preferred response to the tension between innovation and access. Differential pricing permits AIDS drugs to be sold cheaply in low-income countries, while maintaining high prices in markets like the

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¹ Agreement on Trade-Related Aspects of Intellectual Property Rights, Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, Apr. 15, 1994, 1869 U.N.T.S. 299, art. 1, § 1 [hereinafter TRIPS or TRIPS Agreement]. The US implemented the WTO agreements in the Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994).

United States.² High prices in rich countries support innovation; lower prices in poor countries improve access.

Pharmaceutical arbitrage is affected by the legal institutions in each country, such as IP laws, drug regulations, and pharmaceutical reimbursement systems. As a result, patented drugs are cheaper in Canada than in the US, and cheaper still in Australia. These pricing gaps create the demand for cross-border pharmaceutical arbitrage, as Americans turn to Canada and other countries for cheaper patented drugs. If unchecked, it is feared that arbitrage will erode price discrimination, undermining the AIDS initiative.

This article explores the key functions of pharmaceutical arbitrage, its impact on access and innovation, and implications for the TRIPS Agreement and related government interventions. Part One establishes a theoretical framework for understanding pharmaceutical markets and innovation, exploring pharmaceutical arbitrage with the heuristic device of *optimal patent rents*. Part Two applies this framework in two situations: pricing of AIDS drugs in sub-Saharan Africa and Canadian-US pharmaceutical arbitrage.

The primary conclusions are striking:

- IP law has delayed access to essential medications, both in Africa and the US, contrary to some suggestions by Attaran and others. The modern defense of IP law is innovation, not that it ‘doesn’t matter.’
- The Doha Declaration at the WTO Ministerial Conference,³ and the subsequent Cancun modifications to TRIPS⁴ did not hinder innovation. Optimal incentives for innovation can be maintained while providing greatly expanded essential medicines access to the poor.
- These programs need not be limited to a small group of the world’s poorest countries, and can be expanded beyond AIDS, malaria and tuberculosis to all categories of global diseases such as cancer and heart disease, without damaging innovation. Non-rival use in non-commercial markets will not undermine innovation, but will dramatically improve human health.
- Voluntary differential pricing should be supported by an expanded and streamlined compulsory licensure process. Preventing pharmaceutical arbitrage

² See World Health Organization, Report of the Workshop on Differential Pricing and Financing of Essential Drugs: A WHO/WTO Secretariat Workshop (2001) available at <http://whqlibdoc.who.int/hq/2001/a73725.pdf> (the WHO WHOLIS library); see generally Brigitte Granville, ed., *The Economics of Essential Medicines* (2002) [hereinafter Granville (2002)].

³ World Trade Organization, Doha Declaration on the TRIPS Agreement and Public Health, WT/MIN(01)/Dec/2 (Nov. 20, 2001) [hereinafter Doha Declaration].

⁴ World Trade Organization, Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health, WT/L/540 (Decision of the General Council of 30 August 2003) [hereinafter Cancun Provisional Waiver].

from low-income markets into high-income markets is generally viewed as the linchpin to this analysis, but the most dangerous threat comes from counterfeits, not arbitrage. Resources now being expended to limit diversion in donor programs could be more profitably reallocated to anti-counterfeiting initiatives within the OECD. A prime example of misdirected effort is PEPFAR's plan to establish its own supply chain.

- Other forms of pharmaceutical arbitrage should be encouraged, as they deliver lower prices to consumers. Arbitrage within and between high-income countries, such as the Canadian internet sales to the US, will not harm innovation if patent rents are supra-optimal. PhRMA industry claims of sub-optimality must be backed with full transparency on pricing and profitability data worldwide. Proposals for Ramsey Optimal Pricing are best understood as an extreme form of price discrimination.
- Lanjouw and other commentators have argued that strong IP rights in developing countries are required in order to stimulate development of neglected disease drugs. This claim is refuted, with implications for TRIPS. In particular, a virtual IP rights regime is proposed, which may be combined with existing proposals concerning binding purchase commitments by donors.
- Access and innovation are both supported when unnecessary costs are removed from the system. Suggestions in this vein include abandoning PEPFAR in favor of the Global Fund, streamlining national drug regulatory agencies through a voluntary 'virtual licensure' process, and improving designs for subsidies and price controls. Collective preferences on risk tolerance and social issues should be respected by international donors, rather than imposing FDA or ICH standards upon local situations.
- Some pharmaceutical innovations are exhaustible and require special IP analysis. Antibiotics are a paradigm case: by the time the patent expires, the antibiotic may be worthless due to bacterial resistance. While Kades has argued for longer or perpetual patent terms for exhaustible patented pharmaceuticals, this proposal is incompatible with differential pricing for the poor. Another solution is proposed here, involving a binding purchase commitment by a donor followed by management through evidence-based medicine.
- Finally, a now-familiar story is told on the limits of neo-classical economic theory and the importance of institutions and human behavior in evaluating actual outcomes.

PART ONE. THE THEORY OF PHARMACEUTICAL ARBITRAGE

I. The Innovation Theory of IP Law

From ancient times, law and social conventions have supported the right to exclude, enforcing rights to what we call personal property.⁵ Persons investing in producing goods are able to reap a reward for their effort because the law creates a property right in the good produced. This property right is generally exclusive, meaning that other persons cannot take the property without consent or due process. With the abolition of slavery, the same can now be said of the provision of personal services. In the language of economics, goods and services are ‘appropriable.’

At common law, knowledge was not considered personal property,⁶ perhaps because the use of information is subject to (at least) two peculiar characteristics. First, it is generally more difficult to exclude other persons from using information, the condition of *inappropriability* (IP is *nonexcludible*).⁷ Second, while physical goods like corn or wheat are exhausted when used, knowledge may be used without exhaustion, the condition of *inexhaustibility* (IP is *nonrival*).⁸ The twin conditions of inappropriability and inexhaustibility permit the widest possible dissemination of knowledge without creating shortages, a potential boon for humanity.⁹

⁵ See, e.g., *Exodus* 20:15 (NRSV) (“You shall not steal”). The right to exclude from real property developed much later, and is not yet fully ascendant in some traditional communities.

⁶ *Wheaton v. Peters*, 33 U.S. (8 Pet.) 591, 657 (1834). The first English copyright statute was the Statute of Anne, 8 Ann., c. 19 (1710) and the first English “patent” statute was the Statute of Monopolies, 21 Jac. 1, c. 3 (1624). See also Carle Hesse, *The Rise of Intellectual Property, 700 B.C. – A.D. 2000: An Idea In The Balance*, *Daedalus* 26-45 (Spring 2002) (tracing the epistemological foundations of intellectual property). The innovation theory is not the sole justification for patent law, but it is the dominant one in Anglo-American jurisprudence. Another possible ground for patent law is the contract or disclosure theory, which posits that patents are socially preferable over trade secrets due to the socially useful disclosure function. Vincenzo Denicolo & Luigi Alberto Franzoni, *The Contract Theory of Patents*, 23 *Int’l Rev. of L. & Econ.* 365, 366-68 (2004). In pharmaceuticals, the marketing approval process requires disclosure in any event, making the contract theory less applicable.

⁷ Empirical research challenges the conclusion that inappropriability requires patent protection. In a survey of US manufacturing firm responses to inappropriability, patents were found to be less important than secrecy, lead time advantages, and the use of complementary marketing and manufacturing capabilities. Wesley M. Cohen, Richard R. Nelson & John P. Walsh, *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent* 2, 24-25 (Nat’l Bureau of Econ. Research Working Paper No. W7552, Feb. 2000).

⁸ While knowledge is not destroyed through use, it may lose value. Market-moving financial information loses its value quickly, particularly as market participants act on the information. From a societal perspective, however, knowledge does not lose value through use, but adds to the public domain.

⁹ This point is occasionally overlooked in this context. In his critique of the essential medicine agenda in TRIPS, Alan Sykes underemphasizes the nonrival nature of pharmaceutical patents by analogizing compulsory licensure to physical expropriation. Alan O. Sykes, *TRIPs, Pharmaceuticals, Developing Countries, and the Doha “Solution,”* 3 *Ch. J. Int’l L.* 47, 56 (2002). [re-read Sykes] William Landes and Richard Posner argue that some forms of IP are rival, particularly trademarks and personal likenesses. William M. Landes & Richard A. Posner, *Indefinitely Renewable Copyright*, 70 *U. Chi. L. Rev.* 471, 484-86 (2003). Trademarks and personal likenesses indicate origin rather than being knowledge *per se*. Other forms of IP are nonrival in the classic sense, although nonrival use will certainly undercut monopoly pricing and affect *ex ante* innovation incentives.

Unfortunately, if *homo econimus* understands that the fruits of research will be nonexcludible, then the market offers no financial incentive to innovate. Others will gladly use it without compensating the innovator. The innovator cannot capture the positive externality (or consumer surplus), undermining the incentive to innovate.

The economic model is overly pessimistic. Knowledge expanded in the centuries prior to the adoption of patent law. Important books were written before the Statute of Anne. Partial explanations include research for non-economic motives, such as curiosity. The open source movement in science is built upon such factors. The economic model also overreaches to say that knowledge is fully inappropriable. In both historic and contemporary times, transmission of knowledge has never been immediate and barrier free, as any student or professor can attest. The law of trade secrets also mitigates inappropriability.¹⁰

Nevertheless, pharmaceutical research (PhRMA) companies strongly embrace the neo-classical innovation model. PhRMA companies¹¹ spend many millions of dollars over a number of years to bring a newly patented product to market. The industry is characterized by high fixed costs and low variable costs. The first mover (a PhRMA company) incurs all research costs (including failed programs), while free riders (subsequent movers such as generic drug companies) may have limited barriers to entry and a significantly lower cost structure. (These assumptions are openly challenged in many industries. For most industries, it appears that patents play a relatively modest role in making invention non-appropriable by free riders.)¹²

¹⁰ William D. Nordhaus, *Invention, Growth, and Welfare: A Theoretical Treatment of Technological Change* 38 (1969) ("It should be noted here that there is nothing inevitable about the inappropriability of invention. Legislation involving patents and trade secrets considerably enlarges the ability of firms to appropriate their inventive output; in other words, patent laws internalize the externality").

¹¹ Pharmaceutical companies have traditionally been categorized as either research companies (Pfizer, Merck) or generic companies without significant research programs (Cipla Ltd.). The United States trade association of research pharmaceutical companies is the Pharmaceutical Research and Manufacturers of America (PhRMA), www.phrma.org. The international trade association of PhRMA company associations is the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), www.ifpma.org. Generic drug companies have their own trade associations. In recent years, these distinctions have blurred as research companies have invested in generic subsidiaries and as generic companies have begun substantial research programs. It may be more accurate to describe research or generic lines of business, rather than companies *per se*.

¹² Ashish Arora, Marco Ceccagnoli & Wesley M. Cohen, *R&D and the Patent Premium* 4, 34-35 (Nat'l Bureau of Econ. Research Working Paper No. 9431, Jan. 2003) ("Empirical work also suggests that the inducement provided by patents for innovation is small"); Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)*, at 2, 24-25 (Nat'l Bureau of Econ. Research, Working Paper No. 7552, 2000) (40 years of empirical data demonstrates that patents don't improve innovation, with exceptions in pharmaceuticals; study concludes that patents are not the most significant mechanisms for appropriating returns to innovation in most industries, with secrecy, lead time and complimentary capabilities leading); Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, in 3 *Brookings Papers on Economic Activity* 783 (Martin Neil Baily & Clifford Winston eds., 1987); Richard C. Levin, *A New Look at the Patent System*, 76 *Amer. Econ. Rev.* 199, 200-01 (1986); Edwin J. Mansfield, *Patents and Innovation: An Empirical Study*, 32 *Mgmt. Sci.* 173 (1986). In pharmaceuticals, secrecy is not an option with the public

IP law offers an allegedly second-best solution to this impasse,¹³ “promot[ing] the progress of science and useful arts, by securing for limited times, to authors and inventors the exclusive right to their respective writings and discoveries.”¹⁴ Patents are the Constitution’s favorite monopoly.¹⁵ For patents, the period of exclusivity is not less than 20 years after filing, under US federal law and the TRIPS Agreement.¹⁶ Innovator companies also command many other non-patent tools to enhance appropriation, particularly incumbent companies with strong market positions.¹⁷

The costs of patent protection for pharmaceuticals are three-fold. The cumulative effect of patent law and non-patent support for appropriation allows the innovator to charge a higher price under monopolistic conditions. Jamie Love estimates the deadweight cost at \$400 billion per year.¹⁸ Higher prices hinder access, keeping people from medicines, as demonstrated in Section VI.A below. Patents also may hinder cumulative innovation and delay the entry of knowledge into the public domain.¹⁹

The tension between the development and dissemination of knowledge permeates the most compelling issues in pharmaceutical IP policy. Patent doctrines such as scope,²⁰

drug application process and the evidence is stronger of a linkage between patents and innovation. Arora, et al., *supra*, at 4-5, 35. Arora’s study found a significant patent premium (ie., a positive return on investment), particularly in biotechnology, medical instruments and drugs. *Id.* at 30, 34-35.

¹³ See, e.g., Tomas J. Philipson & Stéphane Mechoulan, Intellectual Property & External Consumption Effects: Generalizations from Pharmaceutical Markets 3, 8, 14-15 (Nat’l Bureau of Econ. Research, Working Paper No. 9598, April 2003) (“In the private case, it is well-understood that efficient competition ex-post leads to insufficient R&D incentives ex-ante, which is of course the common second-best rationale for patents”) (at 3).

¹⁴ U.S. Const. art. I, § 8, cl. 8 (“To promote the progress of science and useful arts, by securing for limited times, to authors and inventors the exclusive right to their respective writings and discoveries”).

¹⁵ A bare patent does not grant market power if the invention is unimportant or easily substitutable. Kenneth W. Dam, *The Economic Underpinnings of Patent Law*, 23 J. Legal Studies 247-51 (1994). Pharmaceutical patents of blockbuster drugs are a strong case of patents creating market power, and may be more appropriately denominated as a monopoly. The pharmaceutical industry eschews the monopoly label, but nevertheless defends the patent system as essential to encourage R&D. One cannot have it both ways.

¹⁶ TRIPS, *supra* note 2, at art. 33. TRIPS permitted many developing countries to implement on a delayed basis. TRIPS, *supra* note 2, at arts. 65 & 66. After extensions, most developing countries must implement the TRIPS Agreement by January 1, 2005, but the 30 ‘least developed countries’ may defer full implementation for pharmaceutical products until 2016, Doha Declaration, *supra* note 3, at ¶ 7. Despite these concessions, all but 3 of African LDCs have already adopted patent laws for pharmaceuticals. Phil Thorpe, *Study on the Implementation of the TRIPS Agreement by Developing Countries*, at 1 (Study Paper 7 for the Commission on Intellectual Property Rights, (undated, cir. 2004). TRIPS merely sets minimum periods of patent protection; the US could still unilaterally extend patent protection, and has done so with copyright. WTO Members are also free to negotiate TRIPS + agreements with additional provisions in excess of the TRIPS minimum standards.

¹⁷ See Jonathan M. Barnett, *Private Protection of Patentable Goods*, 25 Cardozo L. Rev. 1251 (2004).

¹⁸ James Love, Statement of Essential Inventions, Inc. to the Commission on Intellectual Property Rights, Innovation and Public Health, at 2, April 5, 2004.

¹⁹ See notes 175 to 177 above and text accompanying.

²⁰ Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 Colum. L. Rev. 839 (1990) *passim* (examining the potential role of patent breadth in fine tuning the efficiency of the patent system). Many economic studies examine elements of this question. See, e.g., Nordhaus, *supra* note 10, at

experimental use,²¹ and fair use²² are also battlegrounds in the struggle between innovation and the public domain.²³ Too many restrictions on inappropriability (i.e., excessive IP rights), needlessly raises cost and restricts access to important pharmaceuticals.²⁴ Too few might throttle the R&D enterprise, and society will forgo valuable qualitative improvements. It is far from clear that current policy strikes an appropriate balance.²⁵ James Boyle expresses his doubts in the nearby field of copyright law:

The economic definition of chutzpah is the industry that demands a legalized monopoly, and then, once given it even though the evidence was weak, insists on the state's aid in price discrimination, the better to wring every last cent of consumer surplus out of their customers.²⁶

II. Differential Pricing and Pharmaceutical Arbitrage

A. Differential Pricing

In the neoclassical economic model, goods are sold at a single market-clearing price. Clever selling firms realize that some customers will pay more than the market-clearing

70-90; F.M. Scherer, *Nordhaus' Theory of Optimal Patent Life: A Geometric Reinterpretation*, 62 Am. Econ. Rev. 422-27 (1972) [hereinafter Scherer, *Optimal Patent Life*]; William D. Nordhaus, *The Optimum Life of a Patent: Reply*, 62 Am. Econ. Rev. 428 (1972) [hereinafter Nordhaus, *The Optimum Life of a Patent*]. For a recent example, see Philipson & Mechoulan, *supra* note 13, at 8-13.

²¹ Rebecca Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. Chi. L. Rev. 1017 (1989) [hereinafter Eisenberg, *Patents and the Progress of Science*]; Rebecca Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 Yale L.J. 177 (1987). [hereinafter Eisenberg, *Proprietary Rights*].

²² Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 Colum. L. Rev. 1177 (2000).

²³ Dam, *supra* note 61, at 261-68. See also notes 176 to 177 *infra*.

²⁴ This point assumes that increased consumption of patented pharmaceuticals creates net positive externalities, i.e. that society would benefit from increased access and consumption of the drug. Philipson & Mechoulan, *supra* note 13, at 9. This assumption will be challenged in the discussion of exhaustible drugs in Section IV.C *infra*.

²⁵ At the celebration of the 10th anniversary of the TRIPS Agreement, Pascal Lamy noted:

IPRs are justified by their societal purpose: they constitute a public policy tool to encourage innovation and creativity. These are the ends, and the patents and copyrights granted to innovators and creators are the means to achieve it. But the hierarchy of ends and means does not end here. Indeed, the encouragement of innovation and creativity is itself serving higher purposes: economic, social and cultural development that should benefit all.

So, international intellectual property policy is a question of striking the right balance between private interests, their public policy objective (access to knowledge) and other public goods. Should this public/private bargain be struck in the same way in all WTO Members? Not necessarily. Here the level of development and the national public policy objectives come into play.

http://europa.eu.int/comm/commissioners/lamy/speeches_articles/spla233_en.htm (visited June 15, 2004).

²⁶ James Boyle, *Cruel, Mean, or Lavish? Economic Analysis, Price Discrimination and Digital Intellectual Property*, 53 Vand. L. Rev. 2007, 2037 (2000).

price. The selling firm increases its profit by selling each item at the highest price each particular buyer will pay. The economic literature identifies this process as *price discrimination*, which is synonymous with differential pricing for our purposes.²⁷

Differential pricing is common. The same product is frequently sold at different net prices to various buyers.²⁸ The seller segments the markets for its product, and charges what each market segment will bear. The airline industry provides a common example. On almost every flight, passengers will have paid many different prices for the same service. The market has been segmented into multiple buyer groups, including business travelers, vacation travelers, frequent flyers, and last minute purchasers.²⁹

A selling firm might attempt to differentiate its prices on an individual sale basis, a pure form of differential pricing which Pigou labeled *first-degree price discrimination*.³⁰ First-degree price discrimination is also known as *perfect price discrimination*, since it fully extracts all consumer surplus for the benefit of the producer,³¹ providing cash flow for pharmaceutical innovation but impairing access through higher consumer cost.

Transaction costs almost always make first-degree differential pricing untenable: the seller's marginal costs of collecting and understanding all of the relevant factors for each buyer usually outweigh the gains in marginal revenue.³² If the number of market segments is kept relatively small, however, the marginal revenue may exceed the marginal cost, resulting in *second- or third-degree price discrimination*.³³ In second-degree price discrimination, purchasers segment themselves into price levels. For example, railroad passengers choose either first, second or third class seats and coupon clippers segment themselves into distinct markets. In third-degree price discrimination, the producer segments the market, generally using monopolistic power to distinguish the different prices customers are willing to pay. Global sales of patented pharmaceuticals offer examples of both second- and third-degree price discrimination.³⁴ The focus of this

²⁷ *Price discrimination* is the term generally utilized in the economic literature, but should not be confused with price discrimination under the Robinson-Patman Act, 15 U.S.C. §§13-13b, 21a (2004). This article follows the usage most common in the essential medicines literature, *differential pricing*. Tiered pricing and price segmentation are other terms occasionally used for pharmaceutical differential pricing. See, e.g., DG Trade, European Union, Tiered Pricing for Medicines Exported to Developing Countries, Measures to Prevent Their Re-Importation into the EC Market and Tariffs in Developing Countries (EU Working Document, Apr. 22, 2002).

²⁸ This particular definition is found in Louis Philips, *The Economics of Price Discrimination* 6, 17 (1983).

²⁹ Louis Philips argues that the airline example is not technically an example of price discrimination, concluding that reserving a seat weeks in advance and buying a last minute ticket are different services. Philips, *supra* note 28, at 9. Nevertheless, the example is ubiquitous and easily grasped. See, e.g., Ernst R. Berndt, American Enterprise Institute for Public Policy Research, *Uniform Pharmaceutical Pricing: An Economic Analysis* 5-6, 9-10 (1994).

³⁰ The classic description of first-, second-, and third-degree price discrimination is found in Pigou, *The Economics of Welfare* ch. 17 (4th ed. 1920). A helpful summary of Pigouvian price discrimination may be found in Philips, *supra* note 28, at 11-14.

³¹ Perfect from the perspective of the selling firm, rather than the consumer. Philips, *supra* note 28, at 158.

³² Pigou, *supra* note 30, at 280.

³³ See Pigou, *supra* note 30; and Philips, *supra* note 28, at 12-13.

³⁴ Examples of second-degree price discrimination include consumer selection of branded or unbranded drugs, and the opportunity to apply for patient assistance programs.

article is third-degree price discrimination, but the more general term *differential pricing* will be used, following the established usage in the essential medicines literature.³⁵

Differential pricing is endemic to pharmaceutical markets.³⁶ Pharmaceutical companies segment markets for differential pricing purposes, generally along efficient boundaries such as political borders or payor classes, with the support of legal institutions. Pharmaceutical differential pricing exists among different countries (such as Canada, US, and South Africa) and among different buyers or payor classes within countries (examples in the US include Medicare, Medicaid, Veterans Affairs, federal employees, private health plans, and individuals).

B. Pharmaceutical Arbitrage

Arbitrage is the nemesis of differential pricing.³⁷ Differential pricing assumes that the first purchaser is the ultimate user. Delta Air Lines is willing to sell some seats cheaply to vacationers so long as it is certain that only the vacation buyers are being satisfied at rock-bottom prices. The Saturday night stay requirement is commonly imposed to distinguish between business and vacation travelers for differential pricing purposes.

Arbitrage occurs when buyers in a lower-priced market re-sell the product to consumers in a higher-priced market. Pharmaceuticals sold for \$5 in India may be identical to products sold for \$1000 in the United States, creating the opportunity for arbitrage. When arbitrage involves IP and crosses an international border, it is called *parallel trade*.³⁸ Absent other constraints, neo-classical economic theory predicts that arbitrage will erode price-differentiated markets, moving all sales towards an equilibrium price. As a result, arbitrage redirects consumer surplus away from the producer, and into the hands of the consumer,³⁹ improving access through lower cost, but potentially harming innovation through reduced cash flow to pharmaceutical companies. As will be seen

³⁵ See *supra* note 27.

³⁶ See Sections VI and VII below. But at least one Wall Street Journal editor is calling on PhRMA companies to abandon price discrimination for a single price in all developed countries. Holman W. Jenkins, Jr., *Two CEOs, Two Trials*, Wall St. J., July 14, 2004, at A15 ("A better idea would be for Pfizer and fellow drug makers to publish and stick to a single price at which each drug will be sold to customers in the developed countries. Price discrimination may be socially beneficial; It may allow more people to benefit from a new drug than would be possible if each had to pay an equal share of research costs. Politically, however, price discrimination has become an albatross around the industry's neck, because other developed nations use price controls to force R&D costs back onto American consumers.")

³⁷ For a classic account of the interplay between arbitrage and differential pricing, see Philips, *supra* note 28, at 14-16.

³⁸ Parallel trade, "also called grey-market trade, is the act of taking goods placed into circulation in one market, where they are protected by a trademark, patent or copyright, and shipping them to a second market without the authorization of the local owner of the intellectual property right." Keith E. Maskus & Mattias Ganslandt, *Parallel Trade in Pharmaceutical Products: Implications for Procuring Medicines for Poor Countries*, in *The Economics of Essential Medicines* 57 (Brigitte Granville, ed., 2002). The practice is not necessarily illegal, depending upon the country's laws concerning exhaustion of IP rights. See *infra* Section III.C.1.

³⁹ Philips, *supra* note 28, at 18.

later, the empirical reality of pharmaceutical arbitrage departs from the neo-classical model in significant ways.

III. Legal Institutions Affect Pharmaceutical Arbitrage

Successful pharmaceutical price discrimination requires market segmentation and must minimize arbitrage by customers. Several tools may be employed, including contract, product differentiation, and regulatory structures. Each of these institutions affect the empirical results in pharmaceutical markets.

A. Contract

Private ordering may support differential pricing. The contract between buyer and seller may forbid arbitrage. Airlines generally forbid the transfer of tickets. Firms may contractually prohibit parallel trade of their products. Some firms refuse to sell equipment, but only lease it with sub-leasing forbidden.⁴⁰ If the customer breaches the agreement, the seller can pursue contractual remedies to punish arbitrage. These contracts are often contracts of adhesion. This is the path taken with clickwrap and shrinkwrap licenses for software.⁴¹

The effectiveness of contractual remedies will in many cases depend upon whether the seller has privity with every arbitrageur, and in the monitoring costs required to ensure compliance. In pharmaceutical markets, multiple layers of pharmaceutical distributors and retailers lack privity with manufacturers and shrinkwrap licensing is impractical. Contractual approaches may also run afoul of competition law. The European Court of Justice is generally skeptical of contractual provisions preventing intra-European arbitrage.⁴²

B. Product Differentiation Through Marketing and Transaction Costs

Arbitrage requires a substitutable product. If the product is fungible and easily transferable, then the consumer can collapse the price discriminating market segments.⁴³ Producers rarely concede strict fungibility: marketing and transaction costs are deployed to support differential pricing.

Aspirin might be considered a fungible commodity. The active ingredient is well known and unprotected by patents. And yet the aspirin market is filled with differentiated products. Some aspirins are marketed with brand names as proxies for safety and reliability. Others are compounded with other ingredients such as caffeine or buffering

⁴⁰ The famous example of leased Xerox equipment is described in Philips, *supra* note 28, at 151-153. A more recent example is the software industry's widespread use of non-transferable licenses.

⁴¹ J.H. Reichman & Jonathan A. Franklin, *Privately Legislated Intellectual Property Rights: Reconciling Freedom of Contract With Public Good Uses of Information*, 147 U. Pa. L. Rev. 875 (1999).

⁴² Case C-306/96, *Javico International and Javico AG v. Yves Saint Laurent Parfums SA*, 1998 E.C.R. I-1983, [1998] 5 C.M.L.R. 172 (1998).

⁴³ Berndt, *supra* note 29, at 8-10. Philips, *supra* note 28, at ch. 1.

agents. Aspirin may be purchased in particular sizes, shapes and delivery methods such as pills, capsules, or gel caps. Despite this product differentiation, at some level all aspirins are subject to substitution. If the preferred brand or form of aspirin is unavailable, or priced too high, some consumers will substitute another form of aspirin, or may even substitute with another class of analgesic such as ibuprofen or acetaminophen.

Transaction costs influence the ease of substitution. If transaction costs are low, products may be easily compared and substituted. Conversely, high transaction costs inhibit substitution. Differential pricing is easier to sustain to the extent the product is less substitutable and to the degree that transaction costs are relatively high. If PhRMA companies can raise transaction costs, they can hinder pharmaceutical arbitrage.

C. Government Regulation of Pharmaceutical Markets

Pharmaceutical regulation influences substitution, transaction costs, and arbitrage. Two major legal categories are particularly relevant to pharmaceutical arbitrage: IP laws and national drug regulatory agencies (NDRAs).

1. Intellectual Property (IP) Laws

IP laws support pharmaceutical differential pricing by creating legally enforceable rights such as patents, trademarks and copyrights. Pharmaceutical patents prevent substitution during the patent period by identical compounds. Trademarks support brand identification and differentiation of products to consumers, preventing consumer confusion or unintended substitution.⁴⁴ The government may also seize counterfeit or improperly diverted drugs.⁴⁵ All of these efforts support differential pricing.

In many countries, the first sale of a patented product exhausts the public law rights of the patent holder for that item.⁴⁶ The exhaustion rule is a necessary condition⁴⁷ to legal domestic arbitrage, as it permits domestic resale by the purchaser without the permission of the patent holder.⁴⁸ Exhaustion may be applied on a domestic or an international

⁴⁴ Timothy H. Hiebert, *Parallel Importation in U.S. Trademark law 151-57* (1994) (discussing the consumer confusion theory underlying the exclusion of parallel imports under trademark law); Warwick A. Rothnie, *Parallel Imports 101-05* (1993) (discussing the role of distinct domestic goodwill to successfully exclude parallel goods under trademark law).

⁴⁵ For an interesting story on the diversion of Serostim within the US, see Christopher Windham, *Cracking Down on Illicit Use of AIDS Drugs*, Wall St. J., Jan. 19, 2004, at B1.

⁴⁶ Rothnie, *supra* note 44, at 125-42 (Anglo-Commonwealth patent law), 143-150 (US patent law).

⁴⁷ Necessary but not sufficient. Significant price differentials and low transaction costs are also required. The power of other factors is demonstrated by the persistence of pharmaceutical pricing differentials within the EU, despite a strong internal exhaustion rule and EU firms specializing in pharmaceutical arbitrage. Rothnie, *supra* note 44, at 477, 494-97; see generally DG Trade, *supra* note 27, at § 3.

⁴⁸ Domestic parallel trade in pharmaceuticals is legal within the EU and the US. See, e.g., Case 187/80, *Merck v. Stephar and Exler*, 1981 E.C.R. 2063, [1981] 3 C.M.L.R. 463 (parallel drug trade is legal in the EU); Donald S. Chisum, *Chisum on Patents §16.03[2]* (2003) (the US domestic exhaustion rule); but see Case T-41/96, *Bayer A.G. v. E.C. Commission*, [2001] 4 C.M.L.R. 4 (unilateral acts by pharmaceutical company to choke off supply of drugs to parallel exporters is not actionable under EU law).

basis. The domestic exhaustion rule renders parallel imports illegal while the international exhaustion rule removes patent law barriers to international parallel trade.⁴⁹ US law only recently rejected the international patent exhaustion rule,⁵⁰ and the extent of the rejection may not yet be clear,⁵¹ although the recent Free Trade Agreement with Australia commits both parties to the domestic exhaustion rule.⁵²

Even if the US follows the domestic exhaustion rule for pharmaceutical patents, drugs sold in the US, exported to Canada, and then re-imported back into the US arguably qualify for domestic exhaustion.⁵³ However, the Prescription Drug Marketing Act of

⁴⁹ DG Trade, *supra* note 27, at §3.1 (“A country providing for international exhaustion effectively makes parallel imports legal, while a country (or regional group) that provides for national (or regional) exhaustion enables rightholders to act against such imports”). TRIPS does not commit to a position on exhaustion, specifically reserving the issue to domestic law. TRIPS, *supra* note 1, art. 6. Some commentators writing on the economics of essential medicines mention in passing that US patent law rejects the international exhaustion rule. *See, e.g.*, Jean O. Lanjouw, Intellectual Property and the Availability of Pharmaceuticals in Poor Countries 19-20, n.29 (Center for Global Development, Working Paper No. 5, April 2002) *reprinted in* Innovation Policy and the Economy [hereinafter Lanjouw, Intellectual Property]; and John H. Barton, Differentiated Pricing of Patented Products (WHO, Commission on Macroeconomics and Health Working Paper No. 2, 2001). *See* note 51 *infra* and text accompanying for a critique of the current US patent exhaustion rule.

⁵⁰ One distinguished commentator states, without discussion, that the 1994 amendments reject international exhaustion for US patents. Chisum, *supra* note 48, at § 16.05[3]. The legislative history is less sanguine. The amendment was included as part of the Uruguay Round Agreements Act by which the US joined the WTO. Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994) (§ 533 of the Uruguay Round Agreements Act amended 35 U.S.C. §271(a) to expand the definition of infringement to include importation into the US of a patented product). The legislative history of this provision is obscure. The House Reports on the Uruguay Round Agreements Act do not include an analysis of Section 533, and the only mention in the summary description is: “amends the definition of infringing activity to include offers for sale and importation of a patented good.” H.R. Rep. No. 826(I), at 8. The unofficial summary by the Congressional Research Service merely states: “(Sec. 533) Deems offering to sell or import a patented invention into the United States to be patent infringement.” Congressional Research Service, Bill Summary & Status, H.R. 5110 (Pub. L. No. 103-465), 103rd Cong., 2nd Sess. (summary dated Sept., 27, 1994).

⁵¹ Four points are important. First, prior to the 1994 amendments, US patent law was leaning in favor of the international exhaustion rule, a trend which resulted in the 1995 US Supreme Court case, *K Mart Corp. v. Cartier, Inc.*, 486 U.S. 281 (1988). *See also* Rothnie, *supra* note 44, at 183; Chisum, *supra* note 48, at §16.05[3]; Second, it is not clear at all that Congress intended to overturn the international exhaustion exception by the enactment of § 533. One may declare importation an act of infringement, and yet retain the narrower exception for authorized sales abroad being imported legally under international exhaustion. But *see* Chisum, *supra* note 48, at §16.05[3]. Third, the provision, enacted as part of the Uruguay Round Agreements, was not required, as WTO Members retain domestic flexibility to choose any exhaustion rule. Finally, the heuristic of optimality (discussed in Section V *infra*) suggests that any provision which strengthens drug patent rights will enhance beneficial innovation only if patent rents were sub-optimal. This issue was not demonstrated to Congress in the legislative history to the 1994 amendment.

⁵² In 2004, the US-Australia Free Trade Agreement committed both parties to the domestic exhaustion rule for patents. US-Australia Free Trade Agreement, § 17.9.4 (2004).

⁵³ *See* Rebecca S. Eisenberg, The Shifting Functional Balance of Patents and Drug Regulation, 19 Health Affairs 119, 129-32 (Sept./Oct. 2001) [hereinafter Eisenberg, *Patents and Drug Regulation*]. Re-imported patented drugs are produced in the US under proper authority, legally exported to a second country (such as Canada) and then re-imported by a third party, arguably exhausting US patent rights over the pills themselves. There is no evidence that the 1994 modifications to 35 U.S.C. § 271(a) were intended to waive the domestic exhaustion rule on re-imported goods. *See* notes 50 and 51 above.

1987 blocks re-importation by anyone other than the manufacturer, preventing this form of arbitrage.⁵⁴

2. National Drug Regulatory Agencies (NDRAs)

The TRIPS Agreement generally leaves the drug approval process to individual countries.⁵⁵ In the United States, the national drug regulatory agency (NDRA) is the Food and Drug Administration (FDA).⁵⁶ The global diversity of regulatory actors creates the possibility that each country will have a unique drug regulatory environment, with different approaches to issues such as generic substitution, drug approval and reimbursement, parallel trade, advertising and pharmaceutical arbitrage. In addition, each country's market will differ due to other significant factors such as economic development and demand elasticity. The net result is that law assists in the creation of unique market characteristics in each country.

Several examples illustrate the point. In 1997, the FDA modified its regulations to permit direct to consumer (DTC) advertising for pharmaceutical drugs.⁵⁷ Virtually no other countries permit the practice.⁵⁸ The modification of the DTC rule by the FDA thus creates opportunities for substitution and arbitrage, by modifying information costs and resistance to substitution.⁵⁹ DTC campaigns also build consumer demand, encouraging the patient to ask for a prescription by name. Advertising shifts the demand curve for prescription drugs to the right.⁶⁰ In 2000, the most heavily advertised drugs accounted for 47.8% of the \$20.8 billion increase in US retail spending on prescription drugs.⁶¹

Drug companies also spend billions of dollars to employ product representatives, who meet with doctors in various venues. These efforts encourage particular prescribing

⁵⁴ Prescription Drug Marketing Act of 1987, 21 U.S.C. §§ 331(t), 381(d) (2004).

⁵⁵ TRIPS, *supra* note 1, at art. 1, § 1.

⁵⁶ 21 U.S.C. § 355 (2004).

⁵⁷ The regulations are now found at 21 C.F.R. § 202.1 (2004).

⁵⁸ In recent years, only the US and New Zealand permit DTC broadcast ads. NIHCM Foundation, Prescription Drugs and Mass Media Advertising 16 (2000). In 2002, Canada permitted restricted DTC advertising, and is affected by spillover from American media. Canadian Institute for Health Information, Drug Expenditure in Canada: 1985-2002 41 (2003). In the 2004 US-Australia Free Trade Agreement, web-based DTC advertising is permitted. US-Australia Free Trade Agreement, Annex 2-C, ¶ 5 (2004).

⁵⁹ Philips, *supra* note 28, at ch. 12. Spending for DTC advertising grew at an annual rate of 44.9% from 1995 to 2000, and is now growing at an annual rate of 9.4% thereafter. Stephen Heffler, et al., *Health Spending Projections For 2002-2012*, Health Affairs (Web Exclusive, Feb. 7, 2003) available at <http://www.healthaffairs.org>, at nn. 24-26 and text accompanying. Product shift, increased unit prices, and increased volumes each account for about a third of the growth in prescription drug spending. C. Daniel Mullins, et al., *The Impact of Pipeline Drugs On Drug Spending Growth*, 20 Health Affairs 210, 213 (Sept./Oct. 2001).

⁶⁰ NIHCM Foundation, *supra* note 58, at 2 (DTC advertising increases consumer sales of patented pharmaceuticals); Congressional Budget Office, How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry 20 (July 1998) [hereinafter CBO, Increased Competition].

⁶¹ NIHCM Foundation, *supra* note 58, at 2.

habits⁶² and shift demand between drugs through substitution.⁶³ In 2000, US promotional spending on prescription drugs totaled \$15.7 billion.⁶⁴

Other government agencies also influence pharmaceutical marketing. The US Department of Health and Human Services applies Medicare fraud and abuse laws to the practices of drug representatives, forbidding remuneration to encourage particular prescribing practices within federal programs.⁶⁵ Marketing and substitution are also affected by the \$7.9 billion of free samples given to doctors in 2000, the \$1.9 billion of educational conferences given to doctors,⁶⁶ and industry practices in suppressing negative research.⁶⁷ Federal law prohibits the sale of a drug sample⁶⁸ or the domestic resale of deeply-discounted drugs sold to certain hospitals,⁶⁹ hindering arbitrage of these products and thus supporting their provision at differential prices.

International arbitrage may also be proscribed by NDRA's. Under the Food, Drug and Cosmetics Act, drugs cannot be imported unless approved by the FDA,⁷⁰ creating a non-tariff barrier to international trade. Some drugs are produced in the US and exported to countries with price controls such as Canada.⁷¹ Since the drugs are produced in the US, they arguably comply with FDA rules, and could be re-imported back into the US by arbitrageurs. The US Prescription Drug Marketing Act of 1987 prohibits the re-importation of a prescription drug by anyone other than the manufacturer.⁷² The law was

⁶² In 2000, the industry employed 83,000 drug representatives at a cost of \$4 billion. NIHCM Foundation, *supra* note 58, at 5.

⁶³ NIHCM Foundation, *supra* note 58, at 7.

⁶⁴ NIHCM Foundation, *supra* note 58, at fig. 3. Approximately one third related to one-on-one meetings with doctors, visits to hospitals, or conferences, and only a portion of that could be considered educational. The largest marketing expense is for free drug samples (\$7.9 billion in 2000). *Id.* at 5. In 2000, US unit sales of the 50 most heavily advertised drugs rose at six times the rate of other drugs. *Id.* at 7 (by number of prescriptions).

⁶⁵ Andy Schneider, Taxpayers Against Fraud Education Fund, Reducing Medicare and Medicaid Fraud by Drug Manufacturers: The Role of the False Claims Act 26-36 (Nov. 2003) (review of False Claim Act litigation against drug companies, particularly involving marketing related fraud); Department of Health and Human Services, Compliance Program Guidance for Pharmaceutical Manufacturers, 68 Fed. Reg. 23731, 23733-39 (May 5, 2003).

⁶⁶ NIHCM Foundation, *supra* note 58, at 5 (spending figures); Schneider, *supra* note 65, at 26-36 (fraud cases); Department of Health and Human Services, Compliance Program Guidance for Pharmaceutical Manufacturers, 68 Fed. Reg. 23731, 23735-38 (May 5, 2003).

⁶⁷ Marcia Angell, *The Truth About Drug Companies*, 51:12 New York Rev. of Books (July 15, 2004); National Institutes of Health. Report of the National Institutes of Health Blue Ribbon Panel on Conflict of Interest Policies 2004 May 5 (draft), at 1-5.

⁶⁸ 21 U.S.C. §§ 331(t), 353(d).

⁶⁹ Prescription Drug Marketing Act of 1987, 21 U.S.C. § 353(c)(3) (2004).

⁷⁰ 21 U.S.C. §§ 360(i), 381(a) (2004).

⁷¹ For the PhRMA view on price controls, *see, e.g.*, Schneider, *supra* note 65, at 47 ("Pharmaceutical manufacturers have long maintained that government price controls will thwart the development of vital new drugs with the potential to cure diseases and relieve human suffering. The desired alternative, they argue, is a vigorous free market, with prices set through negotiations between buyers and sellers. For this market to work effectively, manufacturers contend, they must retain the right to keep their prices confidential from competitors"). Price controls are discussed in Section V.C.6 *infra*.

⁷² Prescription Drug Marketing Act of 1987, 21 U.S.C. §§ 331(t), 381(d) (2004).

ostensibly intended to address safety concerns for the US pharmaceutical supply chain,⁷³ but its effect is to prevent international pharmaceutical arbitrage or parallel trade.

PhRMA companies do not enjoy unconstrained monopoly power to set prices on patented drugs. In each major market, regulatory systems and buyer monopsony power may create countervailing pricing power. In some countries, the government sets pharmaceutical prices by regulatory process, including reference pricing⁷⁴ and rate setting.⁷⁵ In others, price regulation occurs when the government enters the market as a purchaser and acts with monopsony power.⁷⁶ Private payors (health plans or their agents such as pharmacy benefit managers) may either mimic the government prices, or utilize their own market power to negotiate prices. In the US, the uninsured or others without market power often pay the highest prices.⁷⁷

Most third-party payors have pharmaceutical substitution agendas of their own which are subject to government regulation. Many health plans now require prescriptions to be filled with generic equivalents whenever medically appropriate. US state and federal laws generally support these efforts,⁷⁸ while pharmacy laws abroad may restrict generic substitution.⁷⁹

Finally, regulatory postures can dramatically alter transaction costs. The current global standard for quality pharmaceutical manufacturing is Standards of Good Manufacturing Practice (GMP). PhRMA companies are now cooperating with the US FDA to develop a higher standard worldwide, now known as the International Conference on Harmonization or ICH.⁸⁰ Imposition of ICH would discourage substitution of drugs manufactured by less-expensive non-OECD pharmaceutical companies, the current practice of the US AIDS program, PEPFAR.⁸¹ This effort could be viewed as rent-seeking behavior through technical standards. Likewise, donor agencies often face

⁷³ H.R. Rep. No. 100-76, at 7 (1987).

⁷⁴ Patricia Danzon and Johathan D. Ketcham, Reference Pricing of Pharmaceuticals for Medicare: Evidence from Germany, the Netherlands and New Zealand (Nat'l Bureau of Econ. Research Working Paper No. W10007, Oct. 2003) (reference price systems in Germany, The Netherlands, and New Zealand).

⁷⁵ House of Commons, Examination of Witnesses (Jan. 23, 2002) (examination of Dr. John Patterson) ("Prices almost never go up on medicines in this country [England], as you saw from the report to Parliament in December. In brief, the PPRS is a scheme which caps profits and profitability in our industry at a level equivalent to the average return on capital of the FT 100.") The US effectively sets rates for government purchase of services from physicians and hospitals, but generally not for pharmaceuticals.

⁷⁶ In the US, the recently-enacted Medicare Act disabled federal monopsony power in the purchase of outpatient prescription drugs under Medicare. Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, § 301, 42 U.S.C. §1395 et seq. [§ 1808(c)(1)(C) of the SSA] (2004). [search act herein]

⁷⁷ CBO, Increased Competition, *supra* note 60 at xi.

⁷⁸ See, e.g., W. Va. Stat. § 30-5-12 (2004) (allowing pharmacists to substitute generic medicines for brand name medicines without approval from the prescriber) and W. Va. Stat. §23-4-3 (2004) (requiring generic substitution within the Workers' Compensation program).

⁷⁹ Danzon & Ketcham, *supra* note 74 at 7 (Germany restricts generic substitution).

⁸⁰ Graham Dukes, Interim Report of Task Force 5 Working Group on Access to Essential Medicines 32 (UN Millennium Project, Feb. 1, 2004).

⁸¹ See *infra* Section VI.F.

substitution choices during the procurement process, which may be subject to regulation or political intervention.⁸²

Each NDRA may take different positions on these and other issues, resulting in many different types of markets and price levels. These pricing differentials attract pharmaceutical arbitrage across political boundaries.

3. The Hatch-Waxman Act⁸³

Traditionally, patent law regulates the economic incentives of innovation while NDRA law controls efficacy and safety. Under the Hatch-Waxman Act, IP laws and NDRA laws are joined at the hip. Hatch-Waxman regulates generic entry following patent expiration, directly addressing the balance between innovation and access.

When examining the incentives for pharmaceutical innovation, the important period is not the length of the patent (20 years), but the length of the *exclusive marketing period*.⁸⁴ In the late 1990's, the US pharmaceutical exclusive marketing period was approximately fourteen years.⁸⁵ The FDA approval process is largely responsible for the six-year difference.

In 1984, Congress modified patent and FDA law in an attempt to strike a different balance between pharmaceutical innovation (quality) and affordable medications (access and cost).⁸⁶ The Hatch-Waxman Act brought generic drugs to the market more quickly while strengthening innovation incentives through extended patent terms and exclusive

⁸² The US unilateral effort on AIDS recently chose to ignore the WHO prequalification process, as well as all recipient country drug regulatory agencies, and now imposes a supplementary FDA approval process for AIDS drug procurement. This decision, ostensibly made on quality grounds, also supports the product line of PhRMA companies by imposing additional regulatory requirements on their generic competitors located in India, South Africa, Thailand and Brazil. [wsj article June 29 2004?]

⁸³ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 28 and 35 U.S.C.) [hereinafter Hatch-Waxman Act]. Under the Hatch-Waxman Act, the FDA also influences the patent process, since Hatch-Waxman extends the patent for half of the period that a drug is undergoing clinical trials, plus the full amount of time spent in the FDA approval process. 35 U.S.C. §§ 155, 155A and 156 (2004). In addition, the FDA is authorized to grant non-patent "exclusive marketing" periods to certain drugs, whether patented or not. 21 U.S.C. §§ 355a(a) (pediatric studies of drugs), 360aa (orphan drugs) (2004).

⁸⁴ The term *exclusive marketing period* means the actual period during which a pharmaceutical company sells a FDA-approved drug in the United States without direct competition. The legal sources of this period include patent law, non-patent "exclusive marketing" rights granted by the FDA under Hatch-Waxman, the use of litigation and agreements to forestall competitive entry, and the ever-greening of patents through filings for new uses and formulations.

⁸⁵ CBO, Increased Competition, *supra* note 60, at 45-48. If someone undertakes to update this figure, care should be taken to account for all of the factors affecting effective exclusive rights.

⁸⁶ See, e.g., Elizabeth Stotland Weiswasser & Scott D. Danzis, *The Hatch-Waxman Act: History, Structure, and Legacy*, 71 Antitrust L. J. 585 (2003). Philipson and Mechoulan describe this balance in the language of economics: "Appropriate policy must *simultaneously* solve the externality problem ex-post and the R&D problem ex-ante". Philipson & Mechoulan, *supra* note 13, at 12 (emphasis in original).

marketing periods. Approval of generic drugs soared following Hatch-Waxman, but the net exclusive marketing period remained relatively unchanged.⁸⁷

The patent system is not the only source of exclusive marketing periods. The FDA may grant additional exclusive marketing periods for first-mover generic drugs,⁸⁸ certain orphan drugs,⁸⁹ and for compliance with social goals such as testing drugs for efficacy and safety on children.⁹⁰ PhRMA companies are maximizing their opportunities under these provisions.⁹¹

After a patent or exclusive marketing period expires, competition by generic drugs is not automatic. Generic drugs must receive FDA approval as well, albeit under an abbreviated process. The generic entry process can take some time, particularly if existing data on safety and efficacy cannot be used, or if the manufacturing processes are complex. PhRMA companies have resorted to strategic litigation and collusive agreements to lengthen effective exclusive marketing periods.⁹² These abuses prompted amendments to Hatch-Waxman in 2003.⁹³ PhRMA companies are already responding with new tactics keep generic drugs off the market by denying the generic companies an adequate financial return for the expensive generic approval process.⁹⁴

⁸⁷ CBO, Increased Competition, *supra* note 60, at viii-ix, 38 (Hatch-Waxman's "decline of roughly three years in the average time before generic entry is almost exactly offset by the average increase in patent terms from Hatch-Waxman extensions.")

⁸⁸ 21 U.S.C. § 355(j) (2004).

⁸⁹ 21 U.S.C. §§ 360aa-360ee (2004).

⁹⁰ 21 U.S.C. § 355a (2004).

⁹¹ For example, the number of putative orphan drugs qualifying for tax credits and extended exclusive marketing periods have soared as companies have narrowly defined markets to remain under the 200,000 person threshold. Steven R. Salbu, *AIDS and Drug Policy: In Search of a Policy*, 71 Wash. Univ. L. Q. 691, 692, 704-06 (1993) (FDA designated AZT as an orphan drug in 1987; more than half of AIDS drugs as of August 31, 1991 were designated orphans); John J. Flynn, *The Orphan Drug Act: An Unconstitutional Exercise of the Patent Power*, 1992 Utah L. Rev. 389, 389-403 (FDA designated early AIDS drugs such as AZT, and other best-selling drugs such as EPO and Taxol as orphan drugs). The tax expenditure on the Orphan Drug Act is now \$200 million per year, not including the cost of the grant of market exclusivity. Joint Committee on Taxation, *Estimates of Federal Tax Expenditures for FYs 2004-2008* (Joint Committee Print, Dec. 22, 2003). Public Citizen notes the inefficiency of the incentive mechanism: pediatric tests cost only \$3.9 million per drug on average, but the six-month patent extension can result in huge financial rewards exceeding \$1 billion. Public Citizen, *The Other Drug War II: Drug Companies Use and Army of 623 Lobbyists to Keep Profits Up 4* (Public Citizen's Congress Watch, June 12, 2002). The FDA estimates the total cost of the pediatric testing initiative from 2001 to 2021 to be \$14 billion, approximately equal to the proposed 5 year AIDS program. U.S. Food and Drug Administration, *The Pediatric Exclusivity Provision: Status Report to Congress* (Jan. 2001).

⁹² Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study 13-23* (July 2002).

⁹³ Prescription Drug and Medicare Improvement Act of 2003, 21 U.S.C. § 355(j) and tit. IX (uncodified, Pub. L. No. 108-173), 117 Stat. 2448 (2004). The Congressional Research Service prepared a summary of the Act on June 13, 2003 which provides some guidance on Congress's intent in amending Hatch-Waxman. See Congressional Research Service, *Prescription Drug and Medicare Improvement Act of 2003* (Bill Summary and Status, S.1, 108th Cong.) (June 13, 2003) available at www.thomas.loc.gov.

⁹⁴ Leila Abboud, *Drug Makers Use New Tactic to Ding Generics*, Wall St. J., Jan. 27, 2004, at B1.

Hatch-Waxman is an unwieldy tool if the goal is to achieve an optimal balance between innovation and access. Congress requires many years to reach consensus on these issues and the results have generally reified the status quo, without regard for the globally optimal level of pharmaceutical R&D.⁹⁵ Hatch-Waxman fails to distinguish between truly innovative drugs addressing urgent global needs and ‘me-too’⁹⁶ drugs targeting the relatively minor nuisances of Western affluence. Hatch-Waxman also ignores the global nature of pharmaceutical markets. This oversight has resulted in the US paying the highest patented drug prices in the world, as the largest market without significant price controls.

IV. Pharmaceutical Market Failures⁹⁷

Pharmaceutical markets are characterized by many difficulties in accommodating low-income countries and patients. While resource constraints always create economic and moral conflicts, pharmaceuticals are uniquely situated because their IP can be made available to the poor on a nonrival basis. The operative limitation here is “can be” and the global failure to provide nonrival access gives rise to the specific market failures described in the following sections: drugs for diseases which are neglected, global or develop resistance.

A. Drugs for Neglected Diseases⁹⁸

Orphan drugs treat conditions suffered by a relatively small number of patients, frequently too few to provide a revenue stream sufficient to recover R&D costs.⁹⁹ PhRMA companies are said to be unlikely to undertake R&D for potential annual markets under \$250 million (presumably for the 14 years of effective exclusive marketing).¹⁰⁰ The US addresses this market failure domestically through tax credits for

⁹⁵ CBO, Increased Competition, *supra* note 60, at 48.

⁹⁶ In recent years, Health Canada has designated only 7% of drugs approved in Canada as Category 2 breakthrough drugs. Maria Barrados, et al., 1998 Report of the Auditor General of Canada, ch. 17, ¶17.93 (Sept. 1999) available at <http://www.oag-bvg.gc.ca>.

⁹⁷ The following discussion is certainly not an exhaustive list of pharmaceutical market failures, but focuses on major innovation issues.

⁹⁸ Other alternative terms in the literature include *tropical diseases*, *developing world diseases*, *Southern diseases*, and *diseases of the poor*. The phrase tropical diseases may be misleading since some neglected conditions are not caused by tropical microbes or parasites. In this article, the terms *neglected diseases* will be used, unless the cited author intended a more specific term.

⁹⁹ A drug may be designated as an orphan under US tax law for conditions which exceed the 200,000 numerical limit, so long as “there is no reasonable expectation that the cost [R&D]...will be recovered from sales in the United States of such drug.” 26 U.S.C. § 45C(d)(1)(B); *see also* 21 U.S.C. § 360bb(2).

¹⁰⁰ Michael Kremer, *Creating Markets for New Vaccines: Part I: Rationale & Part II: Design Issues*, in Innovation Policy and the Economy (Adam B. Jaffe, et al, eds., 2001) 35, 73, 76; Jason C. Hsu & Eduardo S. Schwartz, A Model of R&D Valuation and the Design of Research Incentives 29 (Nat’l Bureau of Econ. Research Working Paper No. 10041, Oct. 2003); Michael Kremer, *Patent Buyouts: A Mechanism for Encouraging Innovation*, 113 Quarterly J. Econ. 1137-1167 (Nov. 1998). Grabowski estimates a need for peak sales of roughly \$500 million a year. H. Grabowski, J. Vernon & J.A. DiMasi, *Returns on Research and Development for 1990s New Drug Introductions*, 20 (Suppl. 3) *PharmacoEconomics* 11-29 (2002).

domestic orphan drug research and longer exclusive marketing periods under Hatch-Waxman.¹⁰¹

Neglected diseases are quite different: the patients are not few in number, but merely impoverished and primarily located in low-income countries.¹⁰² Lacking an *OECD market*¹⁰³ for these drugs or vaccines, PhRMA companies do not invest the necessary R&D, despite pressing global health needs.¹⁰⁴ The global R&D output of new drugs to treat tropical diseases over the past quarter century has been exceedingly modest, less than 1%.¹⁰⁵

The profit motive does not fully explain this dearth, since the majority of global health research funding is provided by governments or private non-profit foundations,¹⁰⁶ who are not constrained by the pricing signals of the marketplace and could conceivably respond to priority global health needs instead.¹⁰⁷

In the past decade, many global public health groups are attempting to re-orient public and non-profit spending to address the misallocation of R&D away from the needs of developing countries, such as the “10/90 Gap” project by the Global Forum for Health Research; Dr. Bernard Pécoul’s Drugs for Neglected Diseases Initiative; the Institute for OneWorld Health; and other non-profit R&D projects funded by private foundations, international organizations and several governments.¹⁰⁸ These large non-profit projects enjoy sufficient resources to recruit some leading researchers from the for-profit sector, such as the January 2004 relocation of Emilio Emini from Merck to the International

¹⁰¹ Orphan Drug Act of 1983, Pub. L. 97-414, 96 Stat. 2049 (codified in 21 U.S.C. §§ 360aa-360ee and scattered sections of 26 U.S.C.) [hereinafter *Orphan Drug Act*].

¹⁰² Jean Lanjouw has compiled a list of the 20 most important tropical diseases (the term she uses), with at least 99% of their disease burden in low-income countries. Jean O. Lanjouw, A Patent Policy Proposal for Global Diseases tab. 1 (June 11, 2001) (on file with author) [hereinafter, Lanjouw, Global Diseases]. See also Keith E. Maskus, *Ensuring Access to Essential Medicines: Some Economic Considerations*, 20 Wisc. Int’l L. J. 563, 568-70 (2002) [hereinafter Maskus, *Essential Medicines*] (public incentives are needed to stimulate demand for tropical diseases); and Philipson & Mechoulan, *supra* note 13, at 21.

¹⁰³ Herein, *OECD market* means the residents of the richer, developed markets of the world. Residence in an OECD member country is a reasonable proxy for this group. In low- and medium-income countries, wealthy elites and Western expatriates should also be included in the term OECD market.

¹⁰⁴ Pécoul, et al., *Access to Essential Drugs in Poor Countries: A Lost Battle?*, 281 J. Am. Med. Ass’n 361, 364 (1999) (“It appears that pharmaceutical R&D is abandoning tropical diseases”).

¹⁰⁵ Pécoul, et al., *supra* note 104, at 364-65 (1975-1997 data). Of the few introductions, two were derived from veterinary R&D. *Id.* at 365 (Table 2).

¹⁰⁶ With 1998 data, global health R&D funding from private for-profit sources was estimated at \$30.5 billion or approximately 42% of the global total. Global Forum for Health Research, *Monitoring Financial Flows for Health Research 2001* at 7 (GFHR/WHO 2001).

¹⁰⁷ While not subject to the market directly, government funding (such as NIH) are certainly susceptible to political influences which might skew R&D towards OECD conditions. Market pressures may influence university researchers through the Bayh-Dole Act. Only private foundations appear to be largely immune to the market’s price signals.

¹⁰⁸ The Bill and Melinda Gates Foundation has been especially prominent in this effort. WHO, *New Generation of Non-Profit Initiatives Tackles World’s “Neglected” Diseases*, Apr. 29, 2004, available at <http://www.who.int/bulletin/volumes/82/5/feature0504/en/>.

AIDS Vaccine Initiative¹⁰⁹ or for-profit VaxGen's loss of three top officers to a new non-profit AIDS vaccine foundation.¹¹⁰ PhRMA companies have recently transferred some R&D programs in neglected diseases to non-profits.¹¹¹

In addition to donor-funded R&D, several researchers have proposed market-based solutions to the problem of neglected diseases. IP rights and the TRIPS Agreement figure prominently in these proposals, which are examined in the next section.

1. IP Law Plays A Modest Role in Making a Market for Neglected Diseases

Jean Lanjouw and Alan Sykes support the enactment of IP laws in low-income countries to encourage the development of local markets for treating neglected diseases.¹¹² Lanjouw cites empirical results from India suggesting that implementation of TRIPS is encouraging the largest Indian pharmaceutical companies to invest in R&D for new chemical entities (NCEs),¹¹³ but those NCEs are either me-too generics or target global diseases.¹¹⁴ Sykes himself critiques Scherer on the question of the net value of IP laws for developing countries, placing his trust upon the huge disease burden in the developing world, which should stimulate markets if patents were available. Sykes thus looks to use IP laws to extract a greater portion of consumer surplus from the developing poor, in order to strengthen the incentives to innovate.¹¹⁵ Surely this is a last-ditch burden to impose on the world's poorest people, to be accepted only if all other solutions prove unworkable.

¹⁰⁹ Ed Silverman, *Merck Vaccine Chief Leaves for AIDS Research Group*, The Star Ledger, Jan. 13, 2004.

¹¹⁰ Reuters, *Top Brass Leave VaxGen to Start Nonprofit*, Reuters.com, Jan. 20, 2004.

¹¹¹ Paul Elias, *Nonprofits Work With Drug Firms to Treat Diseases in Third World*, Los Angeles Times, Feb. 9, 2004, at C5. Similarly, Digene Corporation and the non-profit group PATH are working to develop a cervical cancer test for use in the developing world. Michael Barbaro, *Digene to Adapt Cancer Test For Use in Developing World*, Wash. Post, Feb. 18, 2004, at E05.

¹¹² Lanjouw, *Global Diseases*, *supra* note 102, at 4; Sykes, *supra* note 9, at 58-62.

¹¹³ Jean O. Lanjouw, *The Introduction of Pharmaceutical Product Patents in India: 'Heartless Exploitation of the Poor and Suffering?'* (Nat'l Bureau of Econ. Research Working Paper No. 6366, Jan. 1998).

¹¹⁴ Hannah E. Kettler & Rajiv Modi, *Building Local Research and Development Capacity for the Prevention and Cure of Neglected Diseases: The Case of India*, 79 Bull. World Health Org. 742, 744-45 (2001) (Indian companies are likely to target the largest markets, ie. for global diseases rather than neglected diseases). A decade after the signing of TRIPS, a leading Indian pharmaceutical company reports that indeed its R&D budgets are growing rapidly, from 2.7% of sales in 2000 to 7.6% in 2003 and a projected 10% in 2004, but the primary output are generic pharmaceuticals. Adam Levitt, *Dr. Reddy's Laboratories: Driving Growth 17-25* (Bear Stearns Healthcare Conference, Sept. 8, 2003) (on file with author) [hereinafter Levitt, Dr. Reddy's Laboratories]. The primary NDA filed by the company is amlodipine maleate, which is the salt version of an innovative drug, Norvasc. The NDA is being opposed in federal court by the innovator company. *Id.* at 20. Of the eight NCEs in the company's pipeline, seven will treat global diseases such as diabetes, cancer, metabolic disorders and cardiovascular disease. The eighth is an anti-infective drug, also for global diseases, but with more applicability in developing countries. *Id.* at 27. These are hardly the type of innovations that Lanjouw hoped for, and in fact this activity could hurt global innovation by reducing expected patent rents to innovator companies through early generic entry by aggressive Indian companies.

¹¹⁵ Sykes, *supra* note 9, at 61-62.

Strong IP laws in low-income countries are not sufficient to create new markets for neglected disease drugs. If most patients in such countries are unable to purchase neglected disease drugs in commercial quantities and prices, the offer of patent protection will not stimulate R&D.¹¹⁶ An exclusive offer to sell drugs at a loss is not valuable.¹¹⁷ Profit-maximizing Indian drug companies will focus on their best economic opportunities;¹¹⁸ neglected disease drugs are not be at the top of that list.¹¹⁹ The leading Indian drug companies derive most of their profits from sales in the US and other OECD markets.¹²⁰

Nor are strong IP laws important to develop indigenous manufacturing capacity. The absence of pharmaceutical patents in India was the proximate cause of India's vibrant generic pharmaceutical sector. Implementation of TRIPS, and restrictions on PEPFAR procurement will hinder this path of development.¹²¹

Nevertheless, Lanjouw and Syke's focus on creating and encouraging markets is helpful, and requires a qualification of my previous definition of neglected disease drugs: a

¹¹⁶ The relative size of the commercial and non-commercial markets is important here. The growth of India and China's middle and upper classes one day will be sufficient to support commercial pricing of innovative drugs for conditions endemic only to the developing world. PhRMA companies do recognize a growing middle class market in these nations. Merck & Co, Inc., Form 10-k (filed with the SEC on Mar. 10, 2004) at 14 ("In recent years, the Company has been expanding its operations in countries located in Latin America, the Middle East, Africa, Eastern Europe and Asia Pacific where changes in government policies and economic conditions are making it possible for the Company to earn fair returns. Business in these developing areas, while sometimes less stable, offers important opportunities for growth over time."). At that point, the condition becomes a *global disease* in my lexicon, as analyzed in Section IV.B *infra*. For a discussion of the domestic arbitrage issues in these situations, *see infra* Section VI.D.

¹¹⁷ Maskus, *Essential Medicines*, *supra* note 102, at 574 (casting doubt on the efficacy of patents to improve R&D on neglected drugs); Kettler & Modi, *supra* note 114, at 742 (Indian pharmaceutical companies will still require financial incentives to research and develop drugs for neglected diseases). A recent study of neglected vaccine projects found patent incentives to be completely ineffective. Hsu and Schwartz, *supra* note 100, at 37, 43-45.

¹¹⁸ Kettler & Modi, *supra* note 114, at 745. For the leading Indian pharmaceutical company, in early 2004 only a negligible percentage of sales were of New Chemical Entities (NCEs). Most sales were either active pharmaceutical ingredients (APIs, i.e. intermediate ingredients for drugs) to the US and Europe or branded (generic) formulations sold in India and other similar markets. Levitt, Dr. Reddy's Laboratories, *supra* note 114, at 9-10.

¹¹⁹ Jean O. Lanjouw and Iain Cockburn, *New Pills for Poor People?: Empirical Evidence After GATT*, 29 World Development 265-89 (2001) (their survey of Indian drug firms in 1998 found only 16% of their R&D targeted developing country markets). In fiscal year 2002-2003, Cipla's major innovative introduction was TIOVA, a long-acting bronchodilator for Chronic Obstructive Pulmonary Disease (COPD), a global disease. Cipla also launched a new generic ARV Fixed Dose Combination (FDC). Cipla Sixty-Seventh Annual Report 2002-2003 5 (available from the company and on file with author) [hereinafter Cipla 2002-2003 Annual Report].

¹²⁰ *See, e.g.,* Rasul Bailay, *Cipla May Find Right Rx for Success: Indian Drug Firm Partners With Peers in U.S. to Crack No. 1 Market for Generics*, Wall St. J., Oct. 20, 2003, at A15; Cipla 2002-2003 Annual Report, *supra* note 119, at 7 ("During the year, Cipla's strategic alliances with leading generic companies in the USA and Europe were expanded to include additional products and projects. Currently, there are nearly 50 such projects in various stages of development in the USA alone."). For Dr. Reddy's Laboratories, the US market accounted for 57% of 2003 gross margin. Levitt, Dr. Reddy's Laboratories, *supra* note 114, at 11.

¹²¹ On PEPFAR procurement, *see* Section VI.F below.

market of \$250 million per year is necessary to incentivize R&D *at current OECD cost structures*. Non-OECD PhRMA companies may have significantly lower cost structures, enabling R&D on disease markets below the \$250 million threshold. Cipla, Ltd. and other Indian pharmaceutical companies pay their India-based chemists and investigators a fraction of the prevailing OECD pharmaceutical company research wages. These companies may also be better poised to understand and respond to the developing market and less likely to discount the actual market size due to unfamiliarity. Network effects and sunk costs are also present in pharmaceutical sales and marketing: while OECD companies have invested in marketing systems in OECD countries, emerging companies may invest in regional markets heretofore overlooked by OECD companies,¹²² and invest in process developments to lower production costs.¹²³ Nor are lower cost structures limited to non-OECD companies. Japanese companies are potential lower cost drug developers.¹²⁴ In the US, some firms specialize in scavenging cast-off R&D programs from larger companies, achieving drug development at a reduced cost.¹²⁵

Most neglected disease conditions lack a market not because of the absence of IP rights in low-income countries, but because of the poverty of the patients. Perhaps the best description of a neglected disease drug is that market-based innovation is unlikely because the target population will require the drug or vaccine to be distributed below the lowest possible amortized cost. Any such drug will require non-market funding for innovation and distribution, with or without IP regimes.

2. Neglected Disease Innovation in the Absence of a Commercial Market: Donor Purchase Commitments

In the absence of commercial markets for neglected disease drugs, some other mechanism must be found to support innovation. Michael Kremer's model of a donor purchase commitment is a prominent example,¹²⁶ attracting many commentators on the proper design of such a prize.¹²⁷ If the market threshold for R&D is truly a market of \$250 million per year for 14 years, a donor such as the Global Fund or a major

¹²² India, Russia, China, Brazil, Mexico, Africa and other markets are major markets for Indian companies such as Dr. Reddy's Laboratories. Levitt, Dr. Reddy's Laboratories, *supra* note 114, *passim*. See also Kettler & Modi, *supra* note 114, at 743 (describing the Indian pharmaceutical industry).

¹²³ Kettler & Modi, *supra* note 114, at 743-45 (but Kettler and Modi do not assume an Indian comparative advantage in cost).

¹²⁴ Japanese PhRMA companies have recently proven very successful in drug innovation through relatively low-cost research methods. Peter Landers, *Back to Basics: With Dry Pipelines, Big Drug Makers Stock up in Japan; Shunning High-Tech Gizmos, the Asian Scientists Score with Traditional Lab Work*, Wall St. J., Nov. 24, 2003, at A1.

¹²⁵ Kristen Kresge, *On the Fringe of Big Pharma*, amfAR Treatment Insider, June 2004, available at www.amfar.org (describing companies such as CombinatoRx).

¹²⁶ Michael Kremer has thoughtfully analyzed and articulated the donor purchase commitment model. Kremer, *supra* note 100, at 35-109.

¹²⁷ See, e.g., Aidan Hollis, *An Efficient Reward System for Pharmaceutical Innovation*, (draft paper dated July 2, 2004) (prizes based upon therapeutic value); Michael Abramowicz, *Perfecting Patent Prizes*, 56 Vand. L. Rev. 115 (2003); Steven Shavell & Tanguy Van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & Econ. 525 (2001) (optional reward systems are superior to IP rights systems).

foundation such as the Gates Foundation could make binding purchase commitments for a safe and effective neglected disease drug or vaccine.

While this present paper does not wade deeply into these waters, two quick comments are appropriately articulated here: (1) The offer must be binding and credible, akin to a property right. Incentives will be maximized if companies do not discount the financial reward *ex ante* for counterparty risk of breach; and (2) The prize must be held open for decades to account for long time lags in pharmaceutical R&D.

3. Virtual IP Regimes: Innovation Sans TRIPS

It is also worthwhile to note what a donor purchase commitment does not entail. First, the offer need not be winner-take-all or rent-dissipating.¹²⁸ In normal pharmaceutical markets, multiple companies develop drugs for a particular condition, well aware of the competing research efforts. While the first to market with a patented product enjoys certain advantages, within short periods rival drugs are marketed, under different patents. The system need only distinguish between a free-rider generic (should not participate), a near-simultaneous innovator (participates on a nearly equal basis),¹²⁹ and a me-too innovator (participates on a diminished basis).

This leads to my primary addition to the prizes literature: distinguishing between these categories requires the donor to reference the patent law of some country (such as the US), but it does not require the target populations to have any IP laws at all. Strong IP laws under TRIPS are simply not required for this purpose. More broadly, any donor purchase commitment system does not require IP laws covering the target populations. The appropriate incentives are in place so long as the donor is bound to a credible commitment to acts *as if* they are bound by the IP laws of a reference country such as the US. This process creates a 'reference' or 'virtual' IP regime.

This is a significant point, not well developed by supporters of TRIPS implementation in low-income countries. Virtual IP regimes will achieve all of the claimed advantages of TRIPS implementation in low-income countries for prizes, without the access-blocking effect of local IP laws. However, a more complex picture emerges when the scope is broadened from neglected diseases to global diseases such as AIDS.

¹²⁸ The classic works on the socially wasteful effects of patent races include Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J. L. & Econ. 265, 265-67 (1977) and Mark F. Grady & Jay I. Alexander, *Patent Law and Rent Dissipation*, 78 Va. L. Rev. 305, 305-10 (1992). In the context of drug prizes, it might be socially beneficial to have companies collectively spend more than the prize, as it would leverage the innovation effect of the prize. A \$1 billion prize for an AIDS vaccine might stimulate \$2 billion of R&D. This would be socially beneficial so long as the social benefits of an AIDS vaccine exceeded \$2 billion.

¹²⁹ Ron Winslow & David P. Hamilton, *Two Colorectal-Cancer Drugs are Near Approval*, Wall St. J., Feb. 12, 2004, at D5 (two innovative treatments for colorectal cancer are expected to receive FDA approval within 7 weeks of each other). It is unfair to label either drug as a me-too.

B. Drugs for Global Diseases¹³⁰

1. Global Diseases Include AIDS, Cardiovascular Disease, & Cancer

The neglected disease debate tends to overlook the fact that the chronic conditions of the high-income and low-income worlds are converging: cancer and cardiovascular disease are the second and third largest causes of death in developing countries.¹³¹ Non-communicable disease accounts for 47% of the global burden of disease.¹³² A *global disease* is a condition which affects patients in both rich and poor countries. AIDS is a global disease, bridging both worlds,¹³³ as are cardiovascular diseases and cancer.¹³⁴

As an example of crossover potential of global diseases, consider the WHO Prequalification Project. The WHO has requested prequalification dossiers on four

¹³⁰ Herein, the term *global disease* refers to conditions for which a therapeutic market exists in the OECD, and the condition is also endemic to the developing world. The definition of global disease is not static. Malaria was once a global disease, but is now largely eradicated in the OECD, rendering it neglected. Tuberculosis is following the same path. Diseases may also move in the opposite direction. Increased international mobility is likely to further blur the epidemiological effect of political borders, causing neglected diseases to migrate into the global disease category. The eastward expansion of the EU is “importing” additional infectious disease threats into the EU, requiring enhanced public health responses to tuberculosis and AIDS. Richard J. Coker, Rifat A. Atun, & Martin McKee, *Health-care System Frailties and Public Health Control of Communicable Disease on the European Union’s New Eastern Border*, 363 *Lancet* 1389-92 (Apr. 24, 2004).

¹³¹ World Health Organization, World Health Report 2003. Stephen Leeder, et al., *A Race Against Time: The Challenge of Cardiovascular Disease in Developing Economies* 12-15 (2004) (“In 1998, non-communicable diseases were responsible for 59% of total global mortality and 43% of the global burden of disease. Importantly, 78% of [non-communicable disease] deaths were borne by low- and middle-income countries, as was 85% of the NCD burden of disease...nearly 50% of deaths worldwide were due to CVD, diabetes, cancer and chronic lung disease.”). PhRMA agrees with this position when it argues that the current ‘Western oriented’ R&D program actually includes diseases endemic to the entire world, such as cancer and CVD. Dukes, *supra* note 80, App. 2, at 7-8 (Response of the Research-Based Pharmaceutical Industry to the Interim Report of the Task Force on Access to Essential Medicines) (Feb. 1, 2004).

¹³² 57th World Health Assembly, WHO Global Strategy on Diet, Physical Activity and Health, May 22, 2004.

¹³³ North America and Western Europe account for less than 2 million of the 34 to 46 million people living with HIV/AIDS in 2003. UNAIDS/WHO, *AIDS Epidemic Update* 37 (2003) [hereinafter UNAIDS/WHO, *AIDS Epidemic Update*]. While AIDS is a global disease, at least three global orphan drug market failures plague public health. One strain of AIDS (Type A) is largely confined to the developing world, and thus received less initial research attention. Pediatric AIDS is also primarily a developing country issue, including the debates over the use of Nevirapine and the absence of pediatric formulations of most AIDS drugs. *Medecins sans Frontieres, Untangling the Web of Price Reductions: A Pricing Guide for the Purchase of ARVs for Developing Countries* 5 (4th ed., 2003) [hereinafter MSF, *Untangling the Web*] (“Children living with HIV/AIDS are one of the most neglected populations: paediatric formulations are lacking and/or formulations do not meet children’s and caregivers’ needs (unpleasant tasting syrup, tablets too big to swallow, need to refrigerate some products, unbreakable tablets, lack of fixed dose combinations, and non-adapted dosages. For example there are currently no combinations for paediatric use”).

¹³⁴ Carlos Correa interprets the Doha Declaration to include global diseases such as asthma and cancer. Carlos M. Correa, *Implications of the Doha Declaration on the TRIPS Agreement and Public Health*, at 5 (WHO, Health Economics and Drugs, EDM Series No. 12, June 2002) [hereinafter Correa, *Implications of Doha*]. Others ask why diseases such as cancer and diabetes are not covered by Doha. Julian Fleet, *U.N. Approach to Access to Essential AIDS Medications, Intellectual Property Law and the WTO TRIPS Agreement*, 17 *Emory Int’l L. J.* 451, 465 (2003).

cancer drugs (vinblastine, etoposide, bleomycin and vincristine)¹³⁵ and two have been prequalified.¹³⁶ These drugs are all related to treatment of AIDS and are off-patent in the US.¹³⁷ For the treatment of TB, the WHO prequalified non-licensed generic forms of patented ciprofloxacin from India and Spain.¹³⁸ But these drugs may be used to treat conditions other than TB and AIDS related cancers.¹³⁹ To the industry, extending preferential treatment to global disease drugs outside of AIDS, malaria and TB is Pandora's Box. The following section demonstrates that the WHO prequalification process should not be limited to these three diseases, but should be extended to any global disease, on the basis of global disease burden and public health need. Furthermore, this extension will not adversely affect innovation.

2. The Global Disease Opportunity: Nonrival Use Without Harming Innovation

The most important proposition about global diseases is that a robust level of innovation is assured by OECD markets alone. A few hundred thousand early AIDS cases in the US (and government funding) were sufficient to encourage successful research programs.¹⁴⁰ Likewise, aggressive research programs are underway in most or all of the chronic conditions endemic in the OECD.

The second proposition about global diseases is that the therapeutic IP is nonrival, and can be offered to the poor without detriment. With innovation assured, IP law can stand aside and permit marginal-cost distribution for the poor.

Together, these propositions suggest a new approach to the innovation-access conundrum, calling for a radical re-evaluation of the role of TRIPS and IP for nonrival goods destined for low-income markets. Provision of pharmaceuticals to non-commercial markets on a non-rival basis will substantially improve global public health.

3. Lanjouw's Patent Option Proposal

Jean Lanjouw has proposed an option concerning pharmaceutical patents: requiring the innovator to choose patent protection in either rich countries, or poor countries, but not both.¹⁴¹ If the condition is endemic in both rich and poor countries (or in just rich

¹³⁵ WHO, *Access to HIV/AIDS Drugs and Diagnostics of Acceptable Quality, Procurement Quality and Sourcing Projec*, 15th ed., May 27, 2004, available at <http://mednet3.who.int/prequal/> (last visited July 7, 2004) [hereinafter, WHO HIV/AIDS Prequalification, 15th Ed.].

¹³⁶ Vinblastine and vincristine. WHO HIV/AIDS Prequalification, 15th Ed., *supra* note 135.

¹³⁷ FDA Orange Book (visited July 7, 2004).

¹³⁸ WHO HIV/AIDS Prequalification, 15th Ed., *supra* note 135.

¹³⁹ According to the FDA label, vincristine is indicated in acute leukemia, Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor. Ciprofloxacin is a widely used antibiotic.

¹⁴⁰ Indeed, many early AIDS drugs qualified for orphan drug status in the US, when the expected US market was fewer than 200,000 persons. Salbu, *supra* note 91, at 703-707.

¹⁴¹ Lanjouw, *Global Diseases*, *supra* note 102, at 5. Philipson and Mechoulan have criticized Lanjouw's proposal as providing an inadequate incentive for goods with strong positive externalities. Philipson &

countries), the innovator will likely choose protection in rich countries. If the condition is unique to poor countries, her proposal would allow patent protection in that market. Restating her proposal in my framework: (1) neglected disease innovations should be patented only in low-income countries; and (2) global disease innovations should be patented only in OECD countries.

The first proposition was critiqued in the section on neglected diseases immediately above.¹⁴² Patents in Malawi are unlikely to incentive significant neglected disease R&D programs, and even if they did, innovation should not require extracting additional consumer surplus for the world's poorest people.

The second proposition completely upends US policy on TRIPS, and returns most of the developing world to the pre-TRIPS environment. Indeed, the proposal can be reconciled with TRIPS only by greatly expanding the Doha and Cancun exceptions to include all global diseases. The developing world and essential medicine advocates would celebrate this result, but the US is likely to resist. Politics aside, PhRMA's concern about the second proposal will be preventing the TRIPS-exempted low-income countries from exporting global disease generic medications to OECD countries, the process of pharmaceutical arbitrage.¹⁴³

Lanjouw's work articulates the different markets which exist for pharmaceuticals in rich and poor countries, and affirms that global disease innovation does not require IP laws in low-income countries. Her proposal on global diseases converges with my own, as I suggest that pharmaceutical innovation does not require IP laws in low-income countries, but I base my conclusion on the nonrival nature of the information.

C. Exhaustible Drugs

Once global disease patents expire, drug formulations enter the public domain.¹⁴⁴ After about fourteen years, all of the wonders of pharmaceutical innovation become freely available for world public health.¹⁴⁵ Perhaps a fourteen-year lag is a reasonable balance between innovation and access, particularly in global disease categories such as cancer, cardiovascular disease and other chronic conditions. Rich consumers pay for and receive

Mechoulan, *supra* note 13, at 19-20. This critique is misplaced, even if one assumes that global patent rents are sub-optimal at present. *See infra* Section IV.A

¹⁴² Section IV.A *supra*.

¹⁴³ Politics will again intrude on Lanjouw's proposal when the time comes to create the list of countries deemed poor enough to qualify for the exception. If the list is short (such as the 30 poorest countries permitted by the TRIPS Council to delay implementation), then generic AIDS ARVs would never reach South Africans or Brazilians. If the list is longer, then the assumption that the lost markets would be small may be false and R&D incentives may be weakened.

¹⁴⁴ The patent holder must first disclose the invention in a public filing.

¹⁴⁵ Meaning available at marginal manufacturing cost, without the need for research cost recovery or royalty. This dynamic does not resolve the market failure of neglected drugs, which will never be developed absent adequate non-market incentives.

the latest innovations (2004 medicine) while the poor might well be satisfied with the (slightly) less effective, but much less expensive, 1990 pharmacopoeia.¹⁴⁶

This model might suffice for many conditions, but it breaks down in the face of significant therapeutic advances. It may be acceptable to give the poor a slightly less effective but vastly cheaper generic drug. It is much more problematic to offer a grossly inferior treatment, or no treatment whatsoever. For example, the American Enterprise Institute alleges that ineffective off-patent malaria drugs are routinely provided to developing countries by global donors, while a patented effective drug is underutilized.¹⁴⁷

Many diseases mutate in response to treatment. Antibiotics lose effectiveness as bacteria develop resistance.¹⁴⁸ Resistant strains of tuberculosis and malaria are increasingly evident.¹⁴⁹ Even cancer may mutate in response to certain therapies.¹⁵⁰ Resistance is related to both usage and compliance. To delay resistance to ARVs, the WHO recommends first-line combination therapy of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-NRTI (NNRTI).¹⁵¹ Resistance proceeds more quickly the more a drug is utilized and the less compliant patients are with the regime.¹⁵² Fixed Dose Combination (FDC) drugs are easier to comply with and therefore more effective in delaying the onset of treatment failure.¹⁵³ There is also some evidence that use of

¹⁴⁶ The Earth Institute's 2004 report adopts this position for cardio vascular medications because "multiple, cheap medications are now available. Pharmaceuticals in nearly every class of drug used for CVD are now off patent. There is no need to wait for a global trade agreement." Leeder et al., *supra* note 131, at 73-74. Lipitor would be a prominent counter-example. The report also highlights the marginal cost-effectiveness of some newer pharmaceuticals in resource-constrained settings. *Id.* At 74.

¹⁴⁷ Malarial resistance to chloroquine runs to 80% in some locations; an alternative drug, Artemisinin, is more expensive and underutilized, especially in combination therapy. AEI, Giving the Poor Drugs that Don't Work, (Dec. 2, 2003) available at www.aei.org. But see Jack C. Chow, M.D., Letter to the Editor, *WHO, Global Fund Get Best Medicine Available*, Wall. St. J., Jan. 26, 2004, at A15 (responding to the Jan. 21, 2004 editorial and the underlying article from *Lancet*).

¹⁴⁸ A new class of antibiotics – fluoroquinolones – works well with drug resistant strains, but are expensive, leaving the poor with worn-out classes of antibiotics. Oxfam, *Fatal Side Effects: Medicine Patents Under the Microscope*, in Brigitte Granville, ed., *The Economics of Essential Medicines* 81, 93 (2002).

¹⁴⁹ Pécoul, et al., *supra* note 104, at 363-65 (specific examples of resistant strains in tropical diseases); AEI, Giving the Poor Drugs that Don't Work, (Dec. 2, 2003), available at www.aei.org.

¹⁵⁰ [cancer cite]

¹⁵¹ WHO, Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for a Public Health Approach – 2003 revision, available at www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf. S. Pujari, et al., *Safety and Long-Term Effectiveness of Generic Fixed-Dose Formulations of Nevirapine-Based HAART Amongst Antiretroviral-Naïve HIV-Infected Patients in India* (background document for WHO meeting on Fixed Dose Combinations for HIV/AIDS, Tuberculosis, and Malaria) (Nov. 18, 2003).

¹⁵² Usage does not result in resistance in a linear fashion, but many factors are involved, including compliance with management protocols and the use of combination therapies. Disparities in compliance with treatment regimes may have many causes, including inadequate health care infrastructure, socio-economic factors, and cultural approaches to health. The primary point is that widespread, global use of an exhaustible drug will probably advance the onset of resistance, particularly in a single drug format when FDCs are preferred.

¹⁵³ Christian Laurent, et al., *Effectiveness and Safety of a Generic Fixed-Dose Combination of Nevirapine, Stavudine, and Lamivudine in HIV-1-Infected Adults in Cameroon: Open-Label Multicentre Trial*, 364 *The Lancet* 29 (July 3, 2004); Gregory K. Robbins, et al., *Comparison of Sequential Three-Drug Regimens as*

nevirapine in a single dose to reduce mother-to-child-transmission (MTCT) increases the risk of resistance for the mother.¹⁵⁴ After failure of first-line therapy, protease inhibitors are required, currently at ten times the cost and requiring refrigerated supply chains.¹⁵⁵

One result of the biology of resistance is that certain pharmaceutical innovations lack the characteristic of inexhaustibility.¹⁵⁶ By the time the patent expires, the drug may be well on its way to ineffectiveness. In these cases, the public domain receives little of value. The poor get an ineffective drug, and perhaps nothing is in the pipeline to replace it if the condition no longer threatens OECD patients. The 'IP contract' has been breached. This calls for a major re-evaluation of pharmaceutical IP policy in this sub-field, treating some innovations as exhaustible resources which should be managed to optimize global public health.¹⁵⁷

Erik Kades has made a major step in that direction, suggesting that optimal management of antibiotics may require giving innovators much longer, or even perpetual patents.¹⁵⁸ Most of the literature on optimal patent length focuses on the innovation side of the equation; Kades' work redirects attention to the potential role of patents and NNDRA law in rationalizing the utilization of exhaustible innovations. Establishing longer or perpetual patents for antibiotics would be a complete reversal of pre-Hatch-Waxman policy, which previously restricted special generic entry only to antibiotics.¹⁵⁹

While Kades' suggested patent extension might resolve some of the issues created by exhaustibility, it has major implications for differential pricing and access for the poor. With an exhaustible resource, use should be 'managed' to maximize the social welfare. If the market is chosen as the mechanism, and control given to the patent holder through

Initial Therapy for HIV-1 Infection, 349 N. Eng. J. Med. 2293 (Dec. 11, 2003); and Robert W. Shafer, et al., *Comparison of Four-Drug Regimens and Pairs of Sequential Three-Drug Regimens as Initial Therapy for HIV-1 Infection*, 349 N. Eng. J. Med. 2304 (Dec. 11, 2003). The US government agrees: Joint Principles Statement Issued Regarding Principles for Fixed-Dose Combination Drug Products (Apr. 8, 2004) available at www.hhs.gov/news/press/2004pres/20040408b.html (visited July 8, 2004).

¹⁵⁴ Laurent, et al., *supra* note 153, at n.28.

¹⁵⁵ N. Kumarasamy, *Comment: Generic Antiretroviral Drugs – Will They Be The Answer to HIV in the Developing World?*, 364 *The Lancet* (July 3, 2004).

¹⁵⁶ See Section I *supra* for a discussion of inexhaustibility.

¹⁵⁷ The economics of pricing exhaustible resources is discussed by Louis Philips, Philips, *supra* note 28, at ch. 7, including his interesting modification to Coase, *id.* at 125-29.

¹⁵⁸ Kades' argument is that public health would be maximized by granting long-term or perpetual patents for drugs which lose effectiveness with use, such as antibiotics. A patent holder rationally maximizes sales during the exclusive marketing period, even for uses which are medically marginal. From a public health perspective, this practice speeds the development of resistant strains of bacteria or viruses. Global public health would be maximized by extending the exclusive marketing period indefinitely, and encouraging judicious use of the drug in the most compelling cases. Eric A. Kades, *Plagues and Patents* (William & Mary Law School Working Paper No. 2003-Kades-1, Mar. 11, 2003) available at www.ssrn.com (No. 387241). Philipson and Mechoulan make a similar point when they conclude that the optimal patent life is infinite if the good creates negative externalities, giving antibiotic resistance as one example. Philipson & Mechoulan, *supra* note 13, at 9, 13-14.

¹⁵⁹ 21 U.S.C. § 357 (1996) (prior to amendment by Pub. L. No. 105-115, § 125(b)(1), 111 Stat. 2325 (1997)). While the Hatch-Waxman Act expanded the generic entry process to other drugs, 21 U.S.C. § 355(j) (2004), the special generic entry process for antibiotics was not repealed until 1997.

an unlimited patent, exhaustible drugs will be rationed to the people most able to afford the increased price. Differential pricing for the poor is incompatible with the market allocation of exhaustible drugs.

One potential escape from this quandary is to choose a non-market method of allocation. For exhaustible drugs requiring management, public ownership or management could ration the demand queue with evidence-based medicine, preventing premature exhaustion. The likelihood of public intervention will dampen the business case for innovation of exhaustible drugs, requiring recourse to non-market incentives similar to neglected diseases. While Kades focuses on domestic management of the resource, the biology of resistance necessitates global management. Globalization makes the management of exhaustible drugs a global issue.

The proposal for perpetual patents also misses the negative effect that patents can have on optimal resistance management. The WHO first-line treatment (two NRTIs and one NNRTI) is currently not available in a FDC form from PhRMA companies. No single company holds the patents (or a license) to the correct combination of drugs to create a single FDC, despite abundant evidence that a FDC would improve compliance. The only FDC treatments available in July 2004 which comply with WHO guidelines are unlicensed generic FDC (nevirapine, stavudine, and lamivudine) produced by two Indian companies, Cipla Ltd. and Ranbaxy Laboratories Ltd. The only other triple-drug FDC prequalified by the WHO is GlaxoSmithKline's combination of lamivudine, zidovudine and abacavir, all of which are NRTIs.¹⁶⁰

V. The Heuristic of Globally Optimal Patent Rents

Assume that for the pharmaceutical industry there is a *globally optimal patent rent*.¹⁶¹ The globally optimal patent rent must be sufficient to fund the socially optimal level of R&D. Optimization must balance concerns of cost, quality and access, looking for the greatest net gain to global public welfare.

¹⁶⁰ WHO HIV/AIDS Prequalification, 15th Ed., *supra* note 136

¹⁶¹ The economic analysis of socially optimal patents has been undertaken by Nordhaus and Scherer. Scherer, *Optimal Patent Life*, *supra* note 20, at 422; Nordhaus, *The Optimum Life of a Patent*, *supra* note 20, at 428; Nordhaus, *supra* note 10, at ch. 5. Scherer argues that shortening patent life will reduce R&D only for the most marginal inventions, particularly in industries with nonpatent barriers to entry and post innovation pricing discipline. Scherer, *Optimal Patent Life*, *supra*, at 426. The pharmaceutical research industry contains both conditions. Nordhaus concluded that a fixed patent life was not optimal, but given that requirement, the length of the life should err to a longer rather than a shorter period. Nordhaus, *The Optimum Life of a Patent*, *supra* at 428. Philipson and Mechoulan cover the same territory when they argue that “[a]ppropriate policy must *simultaneously* solve the externality problem ex-post and the R&D problem ex-ante.” Philipson & Mechoulan, *supra* note 13, at 12-15. Recently, Christopher Yoo undertook a nuanced review of copyright law which covers some of the same terrain as my approach, but with assumptions of copyright market entry and substitutability which do not apply to pharmaceutical patents. See Christopher S. Yoo, *Copyright and Product Differentiation*, 79 N.Y.U.L. Rev. 212 (2004).

Maximizing R&D at all costs should not be our objective. Resources devoted to R&D are not available for other uses.¹⁶² Uwe Reinhardt puts it this way: “Year after year, the last dollar spent on drug research and development (R&D) should yield society as much benefit as it would have yielded if it had been spent to produce other goods or services.”¹⁶³

We should avoid the assumption that all R&D targets are equally valuable. Some innovations are more valuable than others. Companies allocate research funds in response to price signals from commercial pharmaceutical markets, which are largely unresponsive to the pervasive market failures described in Section IV above.¹⁶⁴ Americans now have a third drug for erectile dysfunction,¹⁶⁵ and funds for neglected disease innovation are literally going to the dogs,¹⁶⁶ but a malaria vaccine is not available.¹⁶⁷

We can safely assume that the status quo rarely results in globally optimal patent rents or the globally optimal level of R&D. You get the sense that the participants in the essential medicines debate do not engage on this issue. For example, James Love estimates the static global deadweight loss on pharmaceutical patents at over \$400 billion per year,¹⁶⁸ while Joseph DiMasi and Henry Grabowski assume that the “dynamic benefits created by patents on pharmaceuticals can, and almost surely do, swamp in significance their short-run inefficiencies.”¹⁶⁹

¹⁶² Currently the US spends more than 15% of its GDP on health care. Stephen Heffler, et al., *Health Spending Projections Through 2013*, Health Affairs ex. 1 (Web Exclusive, Feb. 11, 2004) available at www.healthaffairs.org. Perhaps we can agree that increasing pharmaceutical R&D to 20% or 50% of GDP would be excessive.

¹⁶³ Uwe E. Reinhardt, *An Information Infrastructure For the Pharmaceutical Market*, 23:1 Health Affairs 107 (Jan/Feb 2004).

¹⁶⁴ Philipson and Mechoulan make a similar point in the language of economics: “Under external effects in consumption, rewards to innovation should not be guided by potential *consumer* surplus, as under private goods, but the entire *social* surplus that includes benefits to non-consumers as well as consumers...” Philipson & Méchoulan, *supra* note 13, at 2.

¹⁶⁵ Viagra (sildenafil) was approved by the FDA in 1998, Levitra (vardenafil) in August 2003, and Cialis (tadalafil) in November 2003. See FDA Talk Paper, *FDA Approves Third Drug to Treat Erectile Dysfunction* (Nov. 21, 2003) available at <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01265.html>; FDA Talk Paper, *FDA Approves New Drug for Treatment of Erectile Dysfunction in Men* (Aug. 19, 2003) available at <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01249.html>; and *First Oral Therapy for Erectile Dysfunction*, 28 FDA Medical Bull. 1 (Summer 1998) available at <http://www.fda.gov/medbull/summer98/erectile.html>.

¹⁶⁶ In 1999, the FDA approved two drugs to treat canine Cognitive Dysfunction Syndrome, also known as separation anxiety in dogs. FDA Talk Paper, *FDA Approves First Behavioral Drugs for Dogs* (Jan. 5, 1999) available at <http://www.fda.gov/bbs/topics/answers/ans00934.html>. Perhaps soon a drug will be developed for erectile dysfunction in dogs.

¹⁶⁷ For an introduction to donor efforts (led by the Bill & Melinda Gates Foundation) to stimulate development of a malaria vaccine, see <http://www.malariavaccine.org>.

¹⁶⁸ James Love, Statement of Essential Inventions, Inc. to the Commission on Intellectual Property Rights, Innovation and Public Health, at 2, April 5, 2004.

¹⁶⁹ Joseph A. DiMasi & Henry G. Grabowski, *Patents and R&D Incentives: Comments on the Hubbard and Love Trade Framework for Financing Pharmaceutical R&D*, at 2 (presentation, June 25, 2004).

In a major recent study, the Congressional Budget Office conceded that no one knew whether current levels of pharmaceutical R&D were optimal.¹⁷⁰ And yet this is a pressing question.

A. Globally Sub-Optimal Patent Rents

Globally sub-optimal patent rents would stifle the production of innovative drugs, creating a generational equity issue. The present group of patients may benefit from sub-optimal patent rents because innovative treatments are cheaper and more available, but future quality will be compromised. Profit maximizing companies will not continue to cross-subsidize sub-optimal drugs with the profits from supra-optimal drugs: rather, sub-optimal drugs will not be developed and profits from supra-optimal drugs will inure to shareholders and management. This is the nightmare scenario portrayed by PhRMA companies when they articulate the fear that innovation may be squelched.

B. Globally Supra-Optimal Patent Rents

Globally supra-optimal patent rents are rarely recognized as a problem by PhRMA companies. By definition, supra-optimal patent rents are not required to fund innovation. Supra-optimal patent rents harm consumers by raising prices and restricting access without the counterbalancing benefits of future innovation.

1. Are Supra-Optimal Patent Rents Possible?

One economist reviewer suggested that patent rents cannot be supra-optimal because PhRMA companies have not fully appropriated all consumer surplus associated with their products. This is another way of saying that PhRMA companies have not yet achieved first degree differential pricing (or Ramsey Optimal Pricing). Ramsey Optimal Pricing would maximize the sales and profits of PhRMA companies, but it does not respond to the distributional balance between innovation and access. Nor does it address the quality of research undertaken with the surplus so completely extracted from consumers. In a market beset with profound agency problems and information disparities, it is absurd to assume that consumers will purchase pharmaceuticals at the cost-effective price. Given what we know about pharmaceutical markets, it is at least equally likely that PhRMA companies will stimulate demand which varies from optimal therapeutic need, while neglecting less lucrative markets.

My economist friend also fails to account for important negative externalities. PhRMA companies have failed to get the right pills to the right people at the right price. If another regime would result in greater global welfare (improved therapeutic outcomes)

DiMasi and Grabowski cite the 2003 study by Philipson and Mechoulan, but that study assumes sub-optimality rather than proves it. See Philipson & Mechoulan, *supra* note 13.

¹⁷⁰ The 1998 study by the Congressional Budget Office states: “No one knows whether that amount of investment in R&D is over or under the optimal level.” CBO, Increased Competition, *supra* note 60, at 48.

without damage to dynamic innovation incentives, then it should be preferred even if it reduces patent rents slightly. This article intends to make that case.

Consider the vast global gains in welfare which would result if non-rival use of pharmaceuticals could be accomplished without diminishing the incentive to innovate. The opportunity cost of failing to provide non-rival use of pharmaceuticals such as AIDS drugs is staggering. The net gains to global social welfare would be very significant, even if these access gains came at the cost of a modest slice of innovation. It is in this sense that patent rents may be supra-optimal.

2. Are Patent Rents Supra-Optimal?

Some limited empirical evidence suggests that PhRMA companies earn above market rates of return, one possible indicator of supra-optimal patent rents.¹⁷¹ The industry's long-term profits are four times the rate of the Fortune 500.¹⁷² Analysis of IRS data from 1990 to 1996 demonstrates that the drug industry's after-tax profits are more than triple the rate for all industries.¹⁷³

Optimal patent rents must account for other sources of public funding for R&D, such as government grants, direct government expenditures, foundation donors and tax incentives. These public sources account for over a third of global R&D in the sector. The industry also receives substantial tax incentives, resulting in an effective US federal income tax rate of 16.2%, compared with 27.3% generally.¹⁷⁴

Supra-optimality may be indicated in the way PhRMA companies spend their cash flow. The pharmaceutical industry currently spends more on sales and marketing than R&D.¹⁷⁵ Large marketing expenses are not proof that pharmaceutical patent rents are supra-

¹⁷¹ The barriers to this calculation are both empirical and theoretical. On the empirical front, internal company data are not generally available to researchers. Studies by DiMasi, Hansen and Grabowski rely on self-reported company data rather than a truly objective data set. Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. of Health Economics 151 (2003). IRS data shows extraordinary profits and low taxation, Gary Guenther, Congressional Research Service, *Federal Taxation of the Drug Industry from 1990 to 1996* (Dec. 13, 1999), but is protected against public disclosure by the Internal Revenue Code. Accurate pricing data is unavailable outside of the companies. CBO, *Increased Competition*, *supra* note 60, at 20. On the theoretical front, useful questions are posed by Reinhardt, *supra* note 163; and William S. Comanor, *Political Economy of the Pharmaceutical Industry*, 24 J. Econ. Lit. 1178, 1182-86 (1986).

¹⁷² David H. Kreling, et al., The Kaiser Family Foundation, *Prescription Drug Trends: A Chartbook Update* ex. 32 (Nov. 2001). The judgment of the equity markets is significant, even under a weak form of the efficient capital markets hypothesis.

¹⁷³ Guenther, *supra* note 137.

¹⁷⁴ Guenther, *supra* note 137.

¹⁷⁵ Kreling, et al., *supra* note 172 at ex. 30 (top 10 major pharmaceutical manufactures in 2000 spent 34.4% of revenues on "marketing, general and administrative" and 13.7% on "research and development;" *but see* Uwe E. Reinhardt, *Perspectives on the Pharmaceutical Industry*, 20 Health Affairs 136 (2001) (not all SG&A expenses are truly marketing). With deference to Reinhardt, the differential is large enough to suggest that R&D receives less than marketing, absent more specific and verifiable data.

optimal, but merely indicate that the industry believes the return on investment in marketing is greater than alternative investments such as R&D.

Some scholars, including the anti-commons movement,¹⁷⁶ suggest that the neo-classical link between patents and innovation is overstated, particularly for industries marked by cumulative innovation¹⁷⁷ such as genetics.¹⁷⁸ If so, the optimal patent rent may be less than previously expected.

The most important data required to resolve this question are in the hands of the industry and are not available in a reliable form to independent researchers.¹⁷⁹ This fact alone is a compelling reason to demand transparency. It certainly seems plausible to presume that supra-optimal patent rents are currently being collected. The burden of coming forward with contrary evidence could be placed on the parties controlling the relevant information, the PhRMA companies.

C. Implications of Global Optimality

Pending the resolution of the empirical issue, the concept of globally optimal patent rents is useful as a heuristic tool. The following sections outline several implications which follow from applying to the tool to pharmaceutical markets.

1. Differential Pricing

Patented pharmaceuticals can be delivered at marginal cost of production to the poor without harming innovation. The majority of AIDS patients in developing countries are quite poor and are not part of the global market for patented drugs. Supplying their needs is a humanitarian response, with no markets actually lost to the pharmaceutical

¹⁷⁶ The classic article is Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 Science 698 (1998). For a recent study on the importance of maintaining a scientific commons, see J.H. Reichman & Paul F. Uhlir, *A Contractually Reconstructed Research Commons For Scientific Data In A Highly Protectionist Intellectual Property Environment*, 66 Law & Contemp. Probs. 315 (Winter/Spring 2003).

¹⁷⁷ Oren Bar-Gill & Gideon Parchomovsky, *The Value of Giving Away Secrets*, 89 Va. L. Rev. 1857 (2003). While Bar-Gill and Parchomovsky list “pharmacology” as one such industry, they do not make that case convincingly in the article. If PhRMA companies are eager to publish and forego patents, it is a nascent trend.

¹⁷⁸ The work of Tim Hubbard is particularly interesting in this regard. See, e.g., Tim Hubbard & James Love, *Medicines Without Barriers: From the Human Genome Project to Open Development Models for Medical R&D*, New Scientist, June 14, 2003.

¹⁷⁹ See *supra* note 171. Pharmaceutical pricing and profitability data is notoriously opaque and misleading. Schneider, *supra* note 65; Gardiner Harris, *Drug Companies Settle 7 Suits for \$1.6 Billion*, N.Y. Times, Nov. 6, 2003 (“Drug companies have paid a total of \$1.6 billion since 2001 to settle seven suits brought by whistle-blowers that accused them of marketing fraud and overbilling Medicare and Medicaid”). Some researchers suggest that increased pricing opacity is necessary to sustain differential pricing for low-income countries. Patricia M. Danzon & Adrian Towse, *Differential Pricing for Pharmaceuticals: Reconciling Access, R&D and Patents* 16-20 (AEI-Brookings Joint Center for Regulatory Studies, Working Paper 03-7, July 2003).

companies. These non-market patients could receive unlicensed or royalty-free drugs without impacting the cash flow of PhRMA companies.¹⁸⁰

If global patent rents are sub-optimal, royalty-free production should still be allowed so long as it did not replace any commercial market, and thus did no financial harm to the patent owner.¹⁸¹ Monitoring costs would be borne by third parties in order to prevent additional expense to the innovator.

If global patent rents are supra-optimal, PhRMA companies could bear the expenses of monitoring and enforcing differential pricing without harming innovation. Supra-optimality also permits expansion of differential pricing programs to middle-income markets, even with some displacement of commercial markets. The magnitude of expense and market loss that could be tolerated would depend on the amount by which patent rents were supra-optimal.

2. Compulsory Licensing

For developing countries, compulsory licensing may be required. Compulsory licensing creates a credible threat on the part of low- and medium-income countries, pressuring PhRMA companies to undertake the hazards of differential pricing. US threats of compulsory licensing of ciprofloxacin were instrumental in securing a lower price from Bayer,¹⁸² and compulsory licensing remains an important remedy in litigation.¹⁸³ Brazilian compulsory licenses permitted the distribution of free ARVs to any Brazilian with AIDS.¹⁸⁴ Medicines Sans Frontieres and others consider the threat and use of compulsory licenses to have been essential in convincing companies to establish

¹⁸⁰ This topic is explored in depth in Section VI *infra*.

¹⁸¹ Philipson and Mechoulan criticize this position, but their stance is undermined if global patent rents are supra-optimal. Philipson & Mechoulan, *supra* note 13, at 19-20. Even if one assumes sub-optimality, differential pricing for ARVs does not reduce R&D incentives if cash flows to the innovators are untouched. Philipson and Mechoulan's argument thus collapses to a complaint that differential pricing does not improve upon status quo R&D incentives. If the effect in innovation is positive or neutral, the health gains (positive externalities) from increased access should drive policy.

¹⁸² Jill Carroll & Ron Winslow, *Bayer Agrees to Slash Prices for Cipro Drug*, Wall Street Journal, Oct. 25, 2001 ("The agreement comes after a high-stakes threat by Tommy Thompson, HHS secretary, to break Bayer's patent for Cipro if he didn't get the price he wanted."). The US compulsory license statutes are 7 U.S.C. § 2404 (patents necessary for the nation's food supply), 17 U.S.C. § 115 (2004) (copyrights to certain musical works), 28 U.S.C. § 1498 (2004) (patents); 35 U.S.C. § 203 (patents developed through the use of government research funding under the Bayh-Dole Act); and 42 U.S.C. § 2183 (atomic energy). The US compulsory license statutes do not contain the restrictions required by Article 31 of TRIPS. See TRIPS Agreement, *supra* note 1, at art. 31. In May 2004, the US held a Bayh-Dole hearing on the compulsory licensure of an AIDS drug. [cite to Fed Reg].

¹⁸³ Makan Delrahim, Deputy Assistant Attorney General, Antitrust Division, *Forcing Firms To Share the Sandbox: Compulsory Licensing of Intellectual Property Rights and Antitrust*, Presentation at the British Institute of International and Comparative Law, May 10, 2004.

¹⁸⁴ Jorge Bermudez, *Expanding Access to Essential Medicines in Brazil: Recent Economic Regulation, Policy-Making and Lessons Learnt*, in Brigitte Granville, *The Economics of Essential Medicines* 193 (2002); see also Judy Rein, *International Governance Through Trade Agreements: Patent Protection for Essential Medicines*, 21 *Northwestern J. Int'l L. & Bus.* 379, 394-404 (2001) (resistance by Brazil, South Africa and Thailand).

meaningful differential pricing programs,¹⁸⁵ as well as voluntary no-royalty licenses such as Merck's recent grant to South African-Indian company Thembalami Pharmaceuticals.¹⁸⁶

Voluntary programs to reduce prices have not been successful. A Nexis search over the past 5 years will reveal many announcements of dramatic price cuts or voluntary programs, but all of these announcements combined have not resulted in much actual treatment in 2004.

Compulsory licenses for non-commercial markets will not harm innovation if dysfunctional arbitrage is blocked. Royalty-free production by a third party does not add any marginal cost to the innovator, and thus will not harm innovation in this case.¹⁸⁷ If global patent rents are supra-optimal, then royalty levels on compulsory licenses may be zero without loss of innovation incentives. The burden of proof of sub-optimality should be on the innovator companies seeking a higher royalty, and the royalty rate in conditions of sub-optimality should balance innovation and access goals.

A free rider problem emerges if compulsory licensure decisions are evaluated solely at the national level. Each country may rationally choose to shirk its share of R&D costs, the same free rider problem afflicting innovation generally. The decision to compel a license requires some form of global coordination to internalize the negative externality. The TRIPS modifications at Doha and Cancun are prominent intermediate steps, limiting compulsory licensure to those situations with sufficient need, and attempting to limit the negative externalities which might flow from pharmaceutical arbitrage of these products.

3. Dysfunctional Pharmaceutical Arbitrage

The most dangerous form of pharmaceutical arbitrage is diversion from charitable non-commercial markets into OECD markets.¹⁸⁸ *Dysfunctional* arbitrage undermines

¹⁸⁵ World Health Organization, *Surmounting Challenges: Procurement of Antiretroviral Medicines in Low- and Middle-Income Countries: The Experience of Medecins Sans Frontieres 7* (pre-publication draft, 2003) [hereinafter WHO, *Surmounting Challenges*]; Marleen Boelaert, et al., *Letter to the Editor*, 287 J. Am. Medical Ass'n 840-41 (2002) ("This impressive discount offered by the companies to developing countries was not merely due to public outcry, but mostly as a response to competition by generic drugs").

¹⁸⁶ Press Release, *Merck & Co., Inc. Grants License for HIV/AIDS Drug Efavirenz to South African Company, Thembalami Pharmaceuticals*, July 14, 2004, available at www.pressmethod.com/releasestorage/5003645.htm.

¹⁸⁷ Assuming that production for compulsory licensure is limited to non-commercial markets. This result holds without regard for whether patent rents are currently super- or sub-optimal. Critiques of compulsory licenses by Merges and others are not applicable here because the goal is not the initiation of efficient bargaining around a rule, but the provision of essential medicines at marginal cost without harming innovation. See Robert P. Merges, *Contracting into Liability Rules: Intellectual Property Rights and Collective Rights Organizations*, 84 Calif. L. Rev. 1293 (1996) (arguing that compulsory licenses in digital media are less efficient than private contractual efforts).

¹⁸⁸ Parallel trade from poor countries to rich countries is incompatible with differential pricing of essential medicines. See Danzon & Towse, *supra* note 179 (parallel trade defeats the objectives of differential pricing); and David A. Malueg & Marius Schwartz, *Parallel Imports, Demand Dispersion, and International Price Discrimination*, 37 J. Int'l Economics 167, 193 (1994).

differential pricing and compulsory licenses for the poor, particularly if global patent rents are sub-optimal. The EU recognizes that its attempts to support differential pricing for essential medicines depend in part upon blocking arbitrage into the OECD.¹⁸⁹

It is important to note the limited scope of the case against dysfunctional pharmaceutical arbitrage. It does not apply to generic drugs because protecting the generic company's profits will not incentivize innovative R&D, and thus arbitrage restrictions on generic drugs are not supportable on innovation grounds.¹⁹⁰

Restrictions are also inappropriate between and to low-income markets, so long as commercial markets are not replaced. TRIPS flexibility for trade between and to low-income countries would not harm innovation and could leave these decisions to local governments. Arbitrage restrictions could be lifted on sales to and within the poorest countries.

Some level of arbitrage to recent immigrants to the OECD might be tolerable. Very little money is at stake for PhRMA companies¹⁹¹ and the likely OECD consumers of smuggled African drugs might well be at the margins of the country's health care system. These patients may not be market participants either, despite their physical location in an OECD nation. The well publicized confiscation of 6,000 packages of 'African' AIDS medications in The Netherlands in October 2002 might fit this profile.¹⁹² Even if they are market participants, receiving familiar medications from home, in their native language, might well be the best medical practice. Uniform use of English labels in multicultural world is not a culturally competent practice for recent immigrants lacking good English skills.

Arbitrage controls may also unnecessary between and within OECD countries if patent rents are supra-optimal. Put another way, parallel trade in patented pharmaceuticals within the OECD may be permitted. Pharmaceutical arbitrage within the OECD is the subject of Section VII below on Canadian-US pharmaceutical arbitrage. If patent rents are sub-optimal, the domestic exhaustion rule could apply in OECD markets, forbidding parallel imports into OECD countries and raising patent rents. Otherwise, the international exhaustion rule should apply to sales between OECD markets since consumers will benefit while innovation incentives remain intact. Outside of OECD markets, the international exhaustion rule should always be applied, as there is no innovation-based warrant for denying access to the poor.

4. Optimizing Subsidies

¹⁸⁹ DG Trade, *supra* note 27, at §1.

¹⁹⁰ Restrictions might be appropriate on other grounds, such as safety. If a generic drug has not been approved in a market, importing it would not be arbitrage. For unpatented or generic products, no innovation-based case for banning parallel trade can be offered.

¹⁹¹ See Section [] below for how little money is derived from ARV sales outside of the OECD.

¹⁹² Dukes, *supra* note 80, at 50, n.1.

Another form of optimization creates subsidies to achieve particular goals. Push subsidies include tax credits for R&D, general research grants such as the US National Institutes of Health, and the orphan drug tax credit. Pull subsidies include the patent system, exclusive marketing periods for orphan and pediatric drugs, and donor purchase commitments for development of a specific pharmaceutical, such as an AIDS or malaria vaccine¹⁹³ or antidotes to bioterrorism.¹⁹⁴

The heuristic suggests three implications: (1) For drugs or conditions with sub-optimal patent rents, government intervention should increase patent rents towards optimal levels. For example, subsidies are essential for neglected diseases, where the target population cannot afford any commercial price for therapy; (2) Subsidies can be limited to drugs with sub-optimal patent rents without harming innovation. Scarce subsidies should not be directed to drugs with strong commercial potential, but should be reserved for neglected diseases; and (3) For patented drugs with supra-optimal patent rents, the government may intervene to achieve other goals, such as improved financial access, without undermining R&D innovation.

Applying these implications to recent policy proposals is instructive. Scherer and Watal have proposed expanding US tax incentives for donating pharmaceuticals to poor countries,¹⁹⁵ but this additional push subsidy is warranted only if patent rents are sub-optimal. The current donor focus on supporting R&D for neglected diseases is strongly reinforced. Proposals for indiscriminate tax credits (such as the US R&D tax credit or the possessions tax credit) are unsupported absent evidence of sub-optimality of global patent rents.

5. National Drug Regulation and WHO Prequalification

National regimes for testing the safety and efficacy of patented drugs are inefficient, duplicating scientific work and wasting resources unnecessarily. Each New Chemical Entity (NCE) requires clearance by the FDA in the US and parallel regulatory authorities throughout the OECD,¹⁹⁶ as well as by the NDRA in every country where the drug will be sold. Prior to the establishment of the EMEA, some estimates put the cost of duplicative NDRA processes within the EU alone at £500 million per year.¹⁹⁷ NDRA

¹⁹³ Michael Kremer, *Pharmaceuticals and the Developing World*, 16 J. of Econ. Persp. 67, 82-85 (2002); Kremer, *supra* note 100. For a recent example, see Institute for OneWorld Health, *Institute for OneWorld Health Receives Gates Foundation Grant to Fund Development of Malaria Vaccine*, July 13, 2004, available at www.oneworldhealth.org.

¹⁹⁴ The Congressional Research Service indicates that “guaranteeing a market through contract authority” is an aspect of President Bush’s Project BioShield to develop bioterror countermeasures. Frank Gottron, Project Bioshield (CRS Report for Congress, RS21507) (July 23, 2003). The proposed size of the pull subsidy for bioterror countermeasures is \$5.593 billion through FY 2013. *Id.*

¹⁹⁵ Frederick M. Scherer & Jayashree Watal, *Post-TRIPS Options For Access to Patented Medicines for Developing Countries* (WHO Commission on Macroeconomics and Health, 2001) [hereinafter Scherer & Watal, *Post-TRIPS Options*].

¹⁹⁶ One attempt at coordination is the European Agency for the Evaluation of Medicinal Products (EMEA). Council Regulation 2309/93, O.J. (L 214) as amended by Commission Regulation 649/98 O.J. (L 88) 7.

¹⁹⁷ Rothnie, *supra* note 44, at 493-94 and sources cited therein.

rules also delay the launch of innovative drugs in many countries.¹⁹⁸ A ‘reference’ approval process would reduce duplicative costs and speed market entry of pharmaceuticals.¹⁹⁹

A reference approval system requires at least four provisions: (1) Safety and efficacy testing would be referenced against approval in certain flagship countries. For example, if a compound was approved as safe and efficacious by either the US FDA or the EU’s EMEA, then it would automatically be deemed to meet standards in the target country; (2) WHO prequalification (or a similar process) would be deemed to satisfy other domestic NDRA requirements such as bioequivalence and good manufacturing practices; (3) IP rights and drug marketing approvals should be de-linked. IP rights would still be enforceable under domestic law and TRIPS, but NDRA approval should proceed apace; and (4) In categories of strong local collective preference (such as RU-486), the NDRA may retain a veto.

The US opposes the first three of these elements, without an innovation warrant. Expansion of the WHO prequalification process is a clear example. WHO Prequalification is urgently needed in regions such as Asia, with many different companies producing unlicensed ARVs under unknown conditions.²⁰⁰ In the 2004 World Health Assembly, the US pushed to remove the word “strengthening” from the WHO HIV/AIDS Resolution concerning prequalification.²⁰¹ The word was retained in the final document,²⁰² but the US continues to marginalize the prequalification process.²⁰³

The US also opposed permitting reference approvals in various free trade agreements, on the grounds that the rights of data exclusivity must be protected. The recent Free Trade Agreement with Australia requires linkage between drug approval and patent status for the first time.²⁰⁴

¹⁹⁸ See Patricia M. Danzon, Y. Richard Wang & Liang Wang, *Impact of Price Regulation on the Launch Delay of New Drugs: Evidence From Twenty-Five Major Markets in the 1990s* (Nat’l Bureau of Econ. Research, Working Paper No. 9874, July 2003). This study collects data on launch delay, and concludes that in addition to difficulties with the drug approval process, many companies delay applications to enter some smaller markets due to fears of pharmaceutical arbitrage. If global patent rents are supra-optimal, this industry practice is reprehensible, as it voluntarily withholds important drugs from patients.

¹⁹⁹ Many NDRAs practice a form of reference approval when they require, as a condition of application for marketing approval, prior marketing approval in either the US, the EU, or Japan. My suggestion is that NDRAs could consider extending the practice for all of the biological aspects of the marketing approval process, retaining only the right to veto based on a collective preference, as well as approval of the labeling.

²⁰⁰ amfAR, TREAT Asia Special Report: Expanded Availability of HIV/AIDS Drugs in Asia Creates Urgent Need for Trained Doctors, at 4, July 2004, *available at* www.amfAR.org.

²⁰¹ *Cmp.* World Health Organization, A57/A/Conf.Paper No. 3 Rev. 1, 20 May 2004 *with* Rev.2 (May 21, 2004).

²⁰² WHO, Fifty-Seventh World Health Assembly, Scaling up Treatment and Care Within a Coordinated and Comprehensive Response to HIV/AIDS, WHA57.14 (May 22, 2004) at 3(3).

²⁰³ Marilyn Chase, *Generic AIDS Pill Gets Acceptance*, Wall St. J., July 2, 2004, at B3.

²⁰⁴ [Oxfam on FTAs; Outterson; Henry]

Resources are also wasted in the generic entry process. NDRA should not require generic applicants to repeat any clinical studies without a clear benefit to public health.²⁰⁵ Generic companies also expend resources to reverse engineer patented drugs. Reverse engineering in this case is a wasteful effort and needlessly delays launch in low-income countries by several years.²⁰⁶ US TRIPS + proposals to extend data exclusivity to 5 or 10 years²⁰⁷ will increase the cost of generic entry.

Taking unnecessary costs out of the NDRA system makes R&D more productive, lowers the threshold for cost-effective innovation, and delivers innovative drugs to patients more quickly.

6. Price Controls

This article is agnostic on the question of the desirability of pharmaceutical price controls generally. The purpose of this section is to describe what form price controls should (or should not) take if policy makers choose to adopt them.

The heuristic suggests five conclusions about pharmaceutical price controls. It confirms three relative uncontroversial points: (1) Price controls should exclude generic products; (2) Developing country prices should not be used in OECD external reference pricing systems; and (3) Price controls should be stable over long periods of time, giving companies accurate *ex ante* innovation incentives. The last two conclusions are likely to meet more controversy: (4) Optimization is preferred over price-fixing and reference pricing; and (5) PhRMA company data should be more transparent on a global basis.

First, generic pharmaceutical products must be excluded from price controls. The special case for government intervention in pharmaceutical prices derives from the monopoly market power granted by the state for patented drugs. Generic products do not generate monopoly rents, and thus should be exempt.²⁰⁸

Second, differential pricing for the poor requires blocking actual arbitrage from low- and medium-income countries into OECD markets. Likewise, virtual forms of this arbitrage must be prevented.²⁰⁹ OECD markets should not utilize developing country prices as an

²⁰⁵ PhRMA companies withhold much of this data as trade secrets, but when a patent is set to expire, there is no innovation warrant to delay generic entry, unless all generic entry is premature.

²⁰⁶ Watal reports a lag of about two years for unlicensed pharmaceuticals reverse-engineered in India. Jayashree Watal, *Pharmaceutical Patents, Prices and Welfare Losses: A Simulation Study of Policy Options for India under the WTO TRIPS Agreement*, 23 *The World Economy* 733-52 (2000).

²⁰⁷ [Oxfam on FTAs].

²⁰⁸ Internal reference pricing systems should refer to generic prices within the therapeutic class, but generics themselves should not be reimbursed under an internal reference pricing system. Inclusion is not warranted, and may actually keep the generic prices artificially high. No pro-innovation goal is served by artificially high generic prices, other than a very indirect and inefficient subsidy of the innovator companies.

²⁰⁹ See Section V.C.3 *supra* and Section VII.A.3 *infra*.

external reference price within the OECD.²¹⁰ At present, this is not a realistic problem, as it appears that no OECD country uses donor prices in its reference pricing system.

Third, price controls must be stable over long periods of time. Pharmaceutical research requires long lead times before marketing. Companies should receive accurate *ex ante* pricing signals that are reliable. Otherwise, companies will discount the current price signals from an expected market for the political risk of more onerous price controls, increasing the scope of the market failures discussed in Section IV *supra*.

Fourth, the heuristic prefers optimization over price-fixing and reference pricing. The term *optimization* is used very broadly here, not limited to the model of utility rate-setting. In this context, it is a governmental process for balancing the needs of innovation and access. The Hatch-Waxman Act may be considered an example, balancing the goals of innovation and low-cost access to generics. Modifications to the doctrine of patent breadth, or modifying effective patent length would have similar effect, if the goal was to optimize the balance between cost, quality and access.²¹¹

By contrast, price-fixing implies a price level without special regard to innovation. Likewise, reference pricing schemes typically proceed without considering issues of optimizing innovation. Canada epitomizes the latter approach; New Zealand the former. By contrast, the reimbursement systems in Australia and the United Kingdom illustrate two different optimization approaches which support innovation.

Australia's Pharmaceutical Benefits Scheme (PBS), each new drug must be approved under an economic evaluation process if governmental reimbursement is desired. The company must submit a dossier to the Pharmaceutical Benefits Advisory Committee (PBAC) proposing a price for the drug and supporting the economic efficiency of that price, given the drug's clinical advantages of existing therapies. In other words, Australia pays for value: highly innovative drugs receive a much higher price; me-too drugs are priced with the lowest-cost equivalent. The incentives are obvious.

The United Kingdom's National Institute of Clinical Effectiveness (NICE) also performs economic evaluation of drugs, but targets a drug company's UK return on investment for its drug portfolio to the FTSE 100 London stock market index. One can argue about

²¹⁰ F.M. Scherer & Jayashree Watal, *The Economics of TRIPS Options for Access to Medicines*, in Brigitte Granville, ed., *The Economics of Essential Medicines*, 32, 48-49 (2002) (arguing for a ban on external reference pricing which uses prices in low-income nations). Just as physical arbitrage, this practice should be restricted only when it flows from poor to rich nations. External reference pricing within the OECD, or within low- and middle-income countries does not undermine differential pricing for the poor. *But see* Scherer & Watal, *supra*, at 49 (also suggesting preventing parallel exports from any price-controlled country). Danzon and Towse address the external reference pricing problem by suggesting increased pricing obscurity and opacity so that the rock-bottom prices are not "directly observable." Danzon & Towse, *supra* note 179, at 6, 16-17. Their solution is vigorously rejected by Medicins Sans Frontieres, which has been very active in negotiations price discounts and distributing ARVs in sub-Saharan Africa. MSF, *Untangling the Web*, *supra* note 133; WHO, *Surmounting Challenges*, *supra* note 185, at 7.

²¹¹ *See* Merges & Nelson, *supra* note 20.

transfer pricing games and whether the FTSE 100 is an appropriate target, but the overall structure of the program is designed to support innovation at a reasonable price.

Finally, greater transparency is warranted. Human biology is relatively similar worldwide, and yet many NDRA accept confidentiality restrictions on data submitted for marketing approval and reimbursement, needlessly reinventing the wheel each time. The economic evaluation studies submitted to the Australian PBAC would be very helpful in formulary and reimbursement decisions worldwide. Conflicts of interest are created when researchers and policymakers receive undisclosed funds from drug companies. The National Institutes of Health is currently embroiled in a major controversy as we are just beginning to understand how profoundly PhRMA influences research.²¹² Transparency would mitigate these conflicts. Finally, if certain forms of price controls are adopted, optimizing patent rents will require accurate global data on pharmaceutical pricing, profitability, and innovation. This information is not currently available to independent researchers, forcing policy makers to rely on the DiMasi study of secret industry data.²¹³ It strains credulity to base important pharmaceutical policy decisions on secret industry data, unavailable for study by other researchers.

7. Free Riders

The heuristic has additional implications for the free rider problem in pharmaceutical innovation. If the free rider is a low-income country (or person), we can consider the situation either a gift or harmless non-rival use. Free riding by OECD markets is a more complicated problem.

In the post-Bismark world, most OECD countries have created direct or indirect governmental reimbursement of prescription drugs. One cannot expect governments to passively accept differential pricing directed by the drug companies. Nor should governments accept Ramsey Optimal Pricing based upon the government's ability to pay. Governmental resources are too scarce to completely neglect the monopsony power, with the possible (temporary) exception of the United States.²¹⁴

Acting solely in the national interest, governments may negotiate for the lowest possible prices, unconcerned about the possible negative global effects on innovation. PhRMA companies may respond by raising prices in uncontrolled markets. The US is the largest such market.²¹⁵ Put another way, OECD countries with price controls are said to be free riders on American innovation.

²¹² National Institutes of Health. Report of the National Institutes of Health Blue Ribbon Panel on Conflict of Interest Policies 2004 May 5 (draft), at 1-5 available at http://www.nih.gov/about/ethics_COI_panelreport.htm.

²¹³ Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. of Health Economics 151 (2003). See note 179 *supra*.

²¹⁴ The federal government is prohibited from exercising monopsony powers in the new Medicare Part D drug benefit. Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, § 301 (codified at § 1808(c)(1)(C) of the Social Security Act).

²¹⁵ The United States did not adopt price controls on pharmaceuticals in the recently-enacted Medicare drug benefit. Prescription Drug and Medicare Improvement Act of 2003, Pub. L. No. 108-173, § 301, 42

Whether the free rider thesis is true empirically is an open question. Perhaps the crusade against the scourge of low-priced drugs is misplaced. Perhaps American prices are supra-optimal and Canadian prices are optimal.²¹⁶ Other countries may make up for their lower prices with higher volumes, eliminating the free rider problem. In many EU countries, drug prices are lower but account for a higher percentage of health expenditure than in the US. It may be unfair to label such countries as free riders. Empirical doubts are also raised when the US tolerates significant domestic free riders without apparent harm. Canadian prices are similar to the Federal Supply Schedule. Some Medicaid rebates and the US Public Health Service's 340b program get better deals than Australia or Canada. Before one picks up stones to cast, check the glazing at home. PhRMA acts as if the empirical question is beyond doubt, proceeding apace to the solution phase. To answer these questions properly requires transparent research access to confidential company data, as discussed in Section V.C.6 above. In any event, free riding is an innovation problem only if global patent rents are sub-optimal.

The current PhRMA solution is to use US free trade agreements to raise drug prices outside of the US.²¹⁷ To this end, USTR recently created the post of Assistant United States Trade Representative for Pharmaceutical Policy.²¹⁸ Bilateral treaties are an awkward solution to this global coordination problem. USTR may succeed in raising drug prices in the least appropriate places. The greatest success will be found in the poorest countries, or other smaller countries desperately seeking preferential access to the

U.S.C. §§ 1395 et seq. [§ 1808(c)(1)(C) of the SSA] (2004). However, the United States is not entirely immune to rate-setting inclinations in health care. Almost every other major health care good or service purchased by Medicare or Medicaid is subject to rate-setting, including the services of physicians, hospitals, ambulatory surgical centers, and home health agencies. For a discussion of Medicare and Medicaid pharmaceutical pricing options, see Schneider, *supra* note 65, at 20-22, 45-48.

²¹⁶ The free rider hypothesis assumes a joint sunk cost, but another possibility is that lower-priced countries such as Canada are efficiently avoiding waste.

²¹⁷ Elizabeth Becker & Robert Pear, *Trade Pact May Undercut Inexpensive Drug Imports*, N.Y. Times, July 12, 2004; Peter Drahos & David Henry, *The free trade agreement between Australia and the United States: Undermines Australian public health and protects US interests in pharmaceuticals*. 328 Brit. Med. J. 1271-1272 (May 29, 2004) available at <http://bmj.bmjournals.com/>; M.W. Serafini, Drug Prices: A New Tack, 36:16 National Journal (Apr. 17, 2004) ("So [House Speaker] Hastert and [Senator] Kyl championed the novel idea that the key to lowering U.S. prescription drug prices is to persuade foreign governments to raise their prices...The idea of trying to level the international playing field on prescription drug pricing originated with the U.S. pharmaceutical industry. But Hastert and Kyl played significant roles last fall in persuading the Bush administration to embrace this strategy...The result was the United States' first free-trade agreement that included modest concessions on pharmaceutical price controls."); M.W. Serafini, *The Other Drug War*, 36:12 National Journal (Mar. 20, 2004). Elizabeth Becker, *Drug Industry Seeks to Sway Prices Overseas*, N.Y. Times, Nov. 27, 2003; Mark B. McClellan, Speech Before the First International Colloquium on Generic Medicine (Sept. 25, 2003) www.fda.gov/oc/speeches/2003/genericdrug0925.html. McClellan's speech was widely reported. See, e.g., C. Bowe & G. Dyer, *Americans Lured By Lower Prices*, Financial Times 17 (May 5, 2004) ("The rhetoric intensified in September when Mark McClellan, then head of the FDA, attacked European drug price controls and said other rich nations should pay more of the development cost for drugs.").

²¹⁸ A clear outline of the Bush Administration's pharmaceutical trade agenda can be found in the testimony of Grant D. Aldonas, Under Secretary of Commerce for International Trade, to the US Senate Finance Committee on April 27, 2004.

US market.²¹⁹ Because these markets are small and generally poor, they can make very little contribution to the global fight against free riders. The US stance should be the opposite: low-income markets are the best targets for the gift of non-rival use.

If USTR's solution is to be significant for innovation, it must involve the EU and Japan, but PhRMA will find these countries better positioned to resist bilateral US pressure to modify sensitive domestic policy. Nor is there any guarantee that increased prices abroad would result in lower US prices. A strategy which depends upon offending America's best trading partners should be preceded by proof that innovation and access will be improved. The ultimate free riders are counterfeiters, not governments, and any strategy to increase global pharmaceutical prices will increase the opportunity for counterfeits.²²⁰

Other forms of global coordination should be considered, such as Jamie Love and Tim Hubbard's Global R&D Treaty,²²¹ or a multilateral approach through the TRIPS Council. The R&D Treaty would permit prices to decline to marginal manufacturing costs since R&D would no longer be recovered through the price mechanism. At lower price levels, access is greatly improved and the opportunity for counterfeits diminished.

* * * *

In Part Two of this article, the theory of pharmaceutical arbitrage will be placed in two contexts: the AIDS crisis in sub-Saharan Africa, and prescription drug importation from Canada to the US. In both cases, pharmaceutical arbitrage plays a central role.

For AIDS drugs, certain forms of arbitrage are inappropriate, specifically diversion from sub-Saharan countries to the OECD of differentially priced ARVs. Other forms of arbitrage do not hinder innovation. Unfortunately, both TRIPS and the US government are attempting to impose far greater restrictions in the name of innovation, with serious public health implications.

The desirability of Canadian-US pharmaceutical arbitrage hinges on whether global patent rents are supra-optimal or not, and whether one credits the fears on safety of Canadian sourced drugs. If global patent rents are supra-optimal and safety concerns overblown, then US consumers are needlessly overcharged for patented drugs, and many suffer negative health outcomes from restricted access.

PART TWO. THE PRAXIS OF PHARMACEUTICAL ARBITRAGE

²¹⁹ Witness the TRIPS + provisions in negotiated or pending FTAs with Morocco, Singapore, Jordan, Australia, Israel, CAFTA and FTAA.

²²⁰ Adian Hollis may well be the first to make this connection to counterfeiting explicit. Hollis, *supra* note 127.

²²¹ Tim Hubbard, *Alternatives to the Price System*, (Presentation at Columbia University, Dec. 4, 2003); James Love, *A New Trade Framework for Global Healthcare R&D*, (Presentation at Columbia University, Dec. 4, 2003); James Love, *From TRIPS to RIPS: A Better Trade Framework to Support Innovation in Medical Technologies*, (Workshop on Economic Issues Related to Access to HIV/AIDS Care in Developing Countries) (May 27, 2003).

VI. Pharmaceutical Arbitrage of AIDS Drugs in Sub-Saharan Africa

PhRMA companies have been reluctant to make patented ARV drugs available on an affordable basis. Fear of pharmaceutical arbitrage and the general weakening of IP laws are the root causes of this reluctance. Applying the theory of pharmaceutical arbitrage to AIDS may transcend the competing goals of innovation and access, by improving access while supporting optimal R&D.

A. Financial Constraints Limit Access to AIDS Drugs in Sub-Saharan Africa

Globally, AIDS is not under control, with approximately 40 million persons living with HIV/AIDS worldwide.²²² Ninety-five percent live outside of North America and Western Europe. Two thirds of infected persons, new infections and deaths are in sub-Saharan Africa.²²³ An estimated 5.5 million people in developing countries need ARV treatment for HIV/AIDS, but only 5% of those currently receive it; in sub-Saharan Africa in 2003, only 1% of the people who need ARV therapy actually receive it.²²⁴ Large scale roll-out of ARV therapy in low-income countries is now the global health goal.²²⁵

Purchasing AIDS drugs at US prices is not an option for the vast majority of these people. The per capita annual cost of a popular ARV in the US is \$6894,²²⁶ and the recently introduced Fuzeon (enfuvirtide) costs \$20,000 per year.²²⁷ The annual per capita health expenditures in sub-Saharan Africa averages \$29.30²²⁸ and range from \$12

²²² UNAIDS/WHO, AIDS Epidemic Update, *supra* note 133, at 2. While much progress has been made, AIDS is not fully under control in the OECD. In 2003, 66,000 to 94,000 persons were newly infected with HIV in North America and Western Europe. *Id.* at 38. But these numbers are quite small when compared to sub-Saharan Africa, and the health and longevity of the US patients have improved. *Id.* at 28-30 (“AIDS mortality continues to drop, thanks to the widespread availability of antiretroviral treatment”).

²²³ UNAIDS/WHO, AIDS Epidemic Update, *supra* note 133, at 38; Robert Greener, UNAIDS, *HIV/AIDS and Absorptive Capacity* (Kaiser Family Foundation HealthCast, Jan. 29, 2004) (2003 data) available at http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=1066 [hereinafter Greener, UNAIDS].

²²⁴ In sub-Saharan Africa, less than 1% currently receive ARV treatment. WHO, *Surmounting Challenges*, *supra* note 185, at 2, 5. Reuters, *UN to Seek \$6 Billion to Fight AIDS in Third World*, Nov. 6, 2003.

²²⁵ Institute of Medicine, *Scaling Up Treatment for the Global AIDS Pandemic: Challenges and Opportunities*, July 2004; 57th World Health Assembly, *Scaling Up Treatment and Care Within a Coordinated and Comprehensive Response to HIV/AIDS*, WHA57.14, May 22, 2004.

²²⁶ In the US, the annual cost for Combivir is \$6894, as described in Section VI.C.1 below.

²²⁷ Vanessa Fuhrmans, *Medical Dilemma: Costly New Drug for AIDS Means Some Go Without; Programs for the Uninsured are Facing Tough Choices With Advent of Fuzeon*, Wall St. J., Jan. 13, 2004. Fuzeon is the first fusion inhibitor treatment for HIV, developed at Duke University. Ironically, high cost has forced the North Carolina AIDS assistance project to strictly ration the number of residents who can receive the treatment. U-Wire, *Duke University: North Carolina Firm's New AIDS Drug Development On Hold*, 2004 WL 59460572 (Jan. 22, 2004) (“Steve Sherman, director of North Carolina’s ADAP, said the program set a cap for 25 state residents to be eligible for Fuzeon treatment at any one time, creating a system of rationing medical care.”) Other states such as Alabama have decided the cost is too high to cover the drug at all, despite its effectiveness. Fuhrmans, *supra*.

²²⁸ World Bank, 2004 World Development Indicators (2001 data).

(Malawi) to \$253 (South Africa).²²⁹ Reducing the price of AIDS medications for the poor is thus a necessary condition to extending ARV treatments to millions of afflicted persons worldwide.²³⁰ Indeed, for many patients, the drugs must be free. Recognizing the important public health issues, Brazil,²³¹ India,²³² South Africa,²³³ and China²³⁴ produce unlicensed ARVs for the poor, provoking conflicts between human rights and IP rights.

1. PhRMA's Response: Differential Pricing of ARVs

The European Commission has embraced “tiered [differential] pricing as the principal means of rendering essential medicines affordable ... to the poorest populations.”²³⁵ Differential pricing is possible because of relatively low marginal costs of production. Most patented drugs can be produced relatively cheaply, absent research cost recovery. The primary variable expenses are direct manufacturing costs, which are a small fraction of the retail prices of patented ARVs. A high ratio of retail prices to direct manufacturing costs enables a company to sell at highly differentiated prices without selling below marginal cost.²³⁶

While the public does not know the true marginal manufacturing costs of most patented drugs, differential pricing is a useful proxy. Differential pricing ratios currently exceed 30:1 in ARV drugs. For example, in November 2003, a daily dose of GlaxoSmithKline's best selling combination ARV drug Combivir²³⁷ costs about \$19.76 per day or \$7215 per

²²⁹ World Bank, 2004 World Development Indicators (2001 data); *see also* Markus Haacker, *Providing Health Care to HIV Patients in Southern Africa*, in Brigitte Granville, ed., *The Economics of Essential Medicines*, 242, 244 (2002). After adjustments for purchasing power parity, Haacker's figures rise to \$44.8 (Malawi) and \$552.3 (South Africa).

²³⁰ Funds for ARVs and drugs to treat opportunistic infections are scarce. UNAIDS estimates these needs at approximately 37% of the total \$10.7 billion which should be spent on HIV/AIDS in 2005 for a comprehensive response. Total unmet financial need in 2005 is projected at approximately \$5 billion. Greener, UNAIDS, *supra* note 223. If these drugs were available at a much lower cost, resources could be redeployed to prevention and other unmet priorities.

²³¹ Ellen 't Hoen, *TRIPS, Pharmaceutical Patents, and Access to Essential Medicines: A Long Way from Seattle to Doha*, 3 Chi. J. Int'l L. 27, 32-33 (2002) [hereinafter 't Hoen, *TRIPS*].

²³² Mark Schoofs, *Clinton Program Would Help Poor Nations Get AIDS Drugs*, Wall St. J., Oct. 23, 2003, at B1 (Indian and South African drug companies); Cipla 2002-2003 Annual Report, *supra* note 106, at 7 (“In HIV/AIDS care, the Company continued its pioneering role in making available a range of antiretroviral drugs including unique combination products. These were made available at reasonable prices not only in India but also in other parts of the world”).

²³³ Schoofs, *supra* note 232, at B1 (Indian and South African drug companies); 't Hoen, *TRIPS*, *supra* note 231, at 30-31 (describing South Africa's efforts to provide royalty-free ARVs to its population and the legal and political challenges to those actions by the United States and PhRMA companies).

²³⁴ Jim Yardley, *China Begins Giving Free H.I.V./AIDS Drugs to the Poor*, N.Y. Times, Nov. 8, 2003 available at www.nytimes.com.

²³⁵ DG Trade, *supra* note 27, at §2.2. Low-income countries targeted for essential medications by the EU had a per capita income of less than \$765 in 2000.

²³⁶ Alan Sager & Deborah Socolar, *Do Drug Makers Lose Money on Canadian Imports?* 7 (Boston University Health Reform Program, Data Brief No. 6, Apr. 15, 2004) (roughly estimating marginal US manufacturing and distribution costs for prescription drugs to be 9.9%).

²³⁷ Combivir is a fixed dose combination (FDC) of 300 mg zidovudine (ZDV or AZT) and 150 mg of lamivudine (3TC). MSF, *Untangling the Web*, *supra* note 113, at 13. The best clinical FDC also adds a

year by mail order in the United States.²³⁸ In sub-Saharan Africa in 2003, GlaxoSmithKline sells Combivir to health agencies at 90 cents per day or \$329 per year,²³⁹ and has announced a new non-profit price of 65 cents per day.²⁴⁰ Even this low price may not reflect GlaxoSmithKline's marginal cost, because Aurobindo of Hyderabad, India sells an unlicensed generic form of Combivir to governments and nonprofit agencies at 56 cents per day or \$204 per year.²⁴¹ The differential pricing ratio for Combivir is approximately 35:1.²⁴² This ratio is likely to increase. Medecins sans Frontieres (MSF) targets an annual per patient cost of \$50 to \$100 in the near future.²⁴³ Achieving the lowest possible price is an urgent necessity: "If you have the option of spending \$200 per person per year or \$600 per person per year, and you're electing to spend \$600, that means you're treating one person when you could be treating three."²⁴⁴

Triomune is Cipla's brand name for the most important triple-drug therapy FDC for sub-Saharan Africa, containing nevirapine, stavudine and lamivudine. Triomune is produced as an unlicensed generic by Cipla Ltd and sold in Cameroon for about \$20 per month.²⁴⁵ As of July 2004, Triomune is not available in a licensed form, a rare inversion in which a generic is a sole-source supplier. The patents for nevirapine, stavudine and lamivudine are held by different companies, and they are apparently unable to conclude a cross-licensing agreement.²⁴⁶ Triomune's components, taken as 6 separate pills per day, cost about \$35 per month in Cameroon.²⁴⁷ In the US, the total retail cost of the patented components is \$936 per month, a ratio exceeding 46:1.²⁴⁸

NNRTI such as efavirenz (EFV). Gregory K. Robbins, et al., *Comparison of Sequential Three-Drug Regimens as Initial Therapy for HIV-1 Infection*, 349 N. Eng. J. Med. 2293 (Dec. 11, 2003) and Robert W. Shafer, et al., *Comparison of Four-Drug Regimens and Pairs of Sequential Three-Drug Regimens as Initial Therapy for HIV-1 Infection*, 349 N. Eng. J. Med. 2304 (Dec. 11, 2003).

²³⁸ Calculation of the US price comes from drugstore.com (60 tablets of Combivir for \$592.99, taken twice per day), available at www.drugstore.com (visited July 8, 2004).

²³⁹ t Hoen, *TRIPS*, *supra*, note 231, at 32-33.

²³⁹ MSF, *Untangling the Web*, *supra* note 133, at 13.

²⁴⁰ GlaxoSmithKline plc 2003 Annual Report, Form 20-F, at 4 available at <http://www.sec.gov/edgar/searchedgar/companysearch.html>.

²⁴¹ GSK itself also issued a voluntary license to Aspen Pharmacare for production of generic Combivir. GlaxoSmithKline plc 2003 Annual Report, Form 20-F, at 29 available at <http://www.sec.gov/edgar/searchedgar/companysearch.html>.

²⁴² The numerator is \$7215 and the denominator is \$204.

²⁴³ WHO, *Surmounting Challenges*, *supra* note 185, at 9. As of 2004, the WHO 3 x 5 program estimates the per person per year cost for first-line drugs at US\$304. World Health Organization, *The World Health Report 2004: Changing History* 30 (2004).

²⁴⁴ Ellen Nakashima & David Brown, *U.S. Rule on AIDS Drugs Criticized: Ban on Using Aid to Buy Foreign Generics Hinders Treatment, Experts Say*, Wash. Post, July 14, 2004, at A12 (quoting Rachel Cohen of MSF).

²⁴⁵ Laurent, et al., *supra* note 153.

²⁴⁶ [cite]

²⁴⁷ Laurent, et al., *supra* note 153.

²⁴⁸ Epivir (lamivudine) costs about \$9 per day or \$270 per month; Zerit (stavudine) costs about \$10.51 per day or \$316 per month; Viramune (nevirapine) costs about \$11.67 per day or \$350 per month. All data in US \$, taken from www.drugstore.com, visited July 8, 2004. The ratio numerator is \$936 and the denominator is \$20.

High differential pricing ratios are not limited to ARVs. Ciprofloxacin is available in unlicensed generic form in Africa at \$0.0189 per 500 mg tablet,²⁴⁹ in the US retail market it sells for about \$5 a pill,²⁵⁰ a ratio of 264:1.

2. The Activists' Response: The 'Health and Human Rights' Exception to Global IP Laws

The AIDS crisis has fueled claims for a 'health and human rights'²⁵¹ exception to global IP laws, permitting the expropriation of drug patents in the face of vast human suffering, akin to a starving child taking a loaf of bread. Many world religions require charity in these circumstances. Jesus expected His disciples to treat the poor fairly,²⁵² as did King Solomon and the Prophet Isaiah.²⁵³ Proponents also ground their claims in humanitarian traditions and various UN instruments and treaties.²⁵⁴

The health and human rights approach suffers from illimitability. While the current debate is largely about AIDS, the health and human rights community will not be limited only to AIDS advocacy.²⁵⁵ If a health and human rights exception to IP law is established for AIDS, then it may prove impossible to resist extensions to tuberculosis, malaria, cancer, or indeed any condition. The TRIPS Agreement limited the "public health" exception to "measures necessary to protect public health...provided that such measures are consistent with this Agreement."²⁵⁶ The Doha Declaration interpreting TRIPS covers "public health problems afflicting many developing and least-developed countries, especially those resulting from HIV/AIDS, tuberculosis, malaria and other epidemics."²⁵⁷ The change was not accidental. The United States argued against expansion, but ultimately conceded the point under pressure.²⁵⁸ The Cancun Provisional

²⁴⁹ WHO International Drug Price Indicator Guide, available at <http://erc.msh.org/dmpguide/> (visited July 8, 2004).

²⁵⁰ www.drugstore.com (visited July 8, 2004).

²⁵¹ See generally any volume of *Health and Human Rights: An International Journal*, published by the Francois-Xavier Bagnoud Center for Health and Human Rights at Harvard University.

²⁵² *Luke* 12:33 ("Sell your possessions and give to the poor. Provide purses for yourselves that will not wear out, a treasure in heaven that will not be exhausted, where no thief comes near and no moth destroys") (NIV).

²⁵³ See, e.g., *Proverbs* 28:27 ("He who gives to the poor will lack nothing, but he who closes his eyes to them receives many curses") (NIV); *Isaiah* 11:4 ("but with righteousness he will judge the needy, with justice he will give decisions for the poor of the earth. He will strike the earth with the rod of his mouth; with the breath of his lips he will slay the wicked") (NIV).

²⁵⁴ See, e.g., U.N. Charter, art. 55 ("the United Nations shall promote: ... solutions of international economic, social, health, and related problems"); International Covenant on Economic, Social and Cultural Rights, art. 12, ¶ 1 ("the right of everyone to the enjoyment of the highest attainable standard of physical and mental health").

²⁵⁵ See, e.g., Jonathan M. Mann et al., eds., *Health and Human Rights: A Reader* (1999). Nor will it remain limited to AIDS in sub-Saharan Africa, a limit found in many access programs sponsored by PhRMA companies. MSF, *Untangling the Web*, *supra* note 133, at table 2.

²⁵⁶ TRIPS Agreement, *supra* note 1, at arts. 8.1, 27.2.

²⁵⁷ Doha Declaration, *supra* note 3, at ¶ 1.

²⁵⁸ During the negotiations leading up to the Doha Declaration of June 2001, PhRMA, the United States, Japan, Switzerland, Australia and Canada argued for limiting the Declaration to "public health crises such

Waiver²⁵⁹ and the recent Canadian compulsory licensure legislation²⁶⁰ also are not limited to AIDS, malaria and tuberculosis. Advocates will encourage expansion to cover all of the ailments of the poor.²⁶¹ The near-poor will be next in line, followed by the middle class.²⁶² Each step shrinks the market segments which pay patent rents. At some point, patent rents may become sub-optimal.

It may also prove impossible to limit the exception to health care. While the TRIPS exception relates to public health, the human rights community does not rely upon TRIPS as its foundational text. If human rights are violated by human suffering, claims may be asserted against the wealth of the OECD to alleviate global poverty. The exception is also not greatly limited by restricting it to ‘opportunity goods’ such as health, education, shelter and nutrition. The cost to fulfill these items alone would swallow the rule of private property. While the Bible requires charity and hospitality, it also supports private property: the Eighth Commandment states: “You shall not steal” and the Tenth Commandment promotes respect for private property.²⁶³

None of this should be taken as an indictment of the health and human rights movement. Recent achievements are impressive: the Doha Declaration, the Cancun Provisional Waiver, the Global Fund, NGO provision of health care to millions, a \$15 billion commitment from President Bush, and many others. The movement has focused world attention and resources on pressing global health problems. But dogmatic appeals to ‘rights’ -- whether human or IP -- should not be taken too seriously. The rhetoric of rights may take the form of absolutes, but the task at hand is to prioritize rights, to balance the competing needs of access (human rights) with innovation (IP rights). The

as HIV/AIDS and other pandemics.” ‘t Hoen, *TRIPS*, *supra* note 231, at 38-41. The text proposed by developing countries simply stated: “Nothing in the TRIPS Agreement shall prevent Members from taking measures to protect public health.” *Id.* at 39. The final compromise text was closer to the developing countries position. *Id.* at 40. Essential medicine advocates have declared victory over this ambiguous text. Correa, *Implications of Doha*, *supra* note 134, at 5.

²⁵⁹ Two weeks before the September 2003 Cancun meeting of the WTO, a provisional waiver of TRIPS was agreed to by the Members, permitting cross-border shipments of drugs produced under the Doha Declaration. Cancun Provisional Waiver, *supra* note 4; EU Strongly Welcomes WTO Deal On Generic Medicines, IP/03/1189 (Sept. 1, 2003) [hereinafter EU, Cancun] (The EU uses the phrase “Perez Motta text” to describe the Cancun Provisional Waiver). Under the Cancun Provisional Waiver, developing and least-developed WTO Members may import pharmaceuticals produced under compulsory license if the importing country lacks the relevant pharmaceutical production capacity. While the Cancun Provisional Waiver contains no limitation to AIDS, tuberculosis or malaria, its definition of ‘pharmaceutical product’ refers back to paragraph 1 of the Doha Declaration. Cancun Provisional Waiver, *supra* note 4, at ¶ 1(a).

²⁶⁰ The Jean Chretien Pledge to Africa Act, House of Commons, 3rd Sess., 37th Parliament, 52-53 Eliz. II, 2004 (Bill C-9) (received Royal Assent on 14 May 2004); Steven Chase, *Chretien sets sights on drug legislation for legacy*, *Globe and Mail*, Nov. 5, 2003 available at www.theglobeandmail.com (“Senior officials vow that the bill will not restrict diseases treated”). [add July 2004 USTR –CAN joint stmt]

²⁶¹ Correa, *Implications of Doha*, *supra* note 134, at 5 (Doha ‘covers any “public health problem”, including those that may be derived from diseases that affect the population in developing as well as developed countries, such as asthma or cancer”).

²⁶² A similar process is underway as the Global Fund expands its programs from the poorest sub-Saharan nations to include middle-income countries such as Honduras. WHO, *Surmounting Challenges*, *supra* note 185, at 25.

²⁶³ *Exodus* 20:15, 17 (NSRV).

International Covenant on Economic, Social, and Cultural Rights (and its progeny such as the South African Constitution) acknowledge the need to balance when the State's obligation qualified as "reasonable...within its available resources" while moving towards the "progressive realisation" of the right in question.²⁶⁴ The task of this article is to reach many of the same goals as the health and human rights community, but to take a path which is not open to charges of being anti-innovation.

3. Achieving Both Access and Innovation

The next few pages present my proposals for maximizing public health while promoting innovation. Differential pricing is embraced, together with compulsory licensure to keep PhRMA honest. Dysfunctional pharmaceutical arbitrage from low-income markets to OECD markets is forbidden, but is not found to be a significant empirical problem. Much more troubling is the threat of counterfeit drugs. All other forms of pharmaceutical arbitrage are encouraged as a means to lower consumer prices. Finally, a series of recommendations are made for modifications to TRIPS and PEPFAR. In TRIPS, the Doha Declaration did not harm innovation, permitting simplification and expansion of the compulsory licensure process. PEPFAR is criticized as a duplicative supply chain, following procurement policies uninformed by the theory of pharmaceutical arbitrage or best medical practice, and without due respect for collective preferences of recipients.

B. Encourage Differential Pricing With Compulsory Licensure

1. TRIPS Hinders Delivery of ARVs

The interlocking web of IP and NDRA laws significantly hinder distribution of low-cost medicines for the poor.²⁶⁵ PhRMA companies did not voluntarily embrace differential pricing of ARVs at a 30:1 ratio. The companies strongly resisted both significant price reductions as well as unlicensed ARV drugs, citing both TRIPS and domestic IP legislation.²⁶⁶

In response to the high cost of ARVs in low-income countries, Medecins sans Frontieres and other NGOs flouted IP law and prescribed unlicensed ARVs produced by Cipla Ltd. and others.²⁶⁷ South Africa passed a compulsory licensing law,²⁶⁸ and was promptly sued by PhRMA companies. The US government suspended bilateral economic assistance to

²⁶⁴ The quotes are from the South African Constitution, Section 27(2), but similar conditions can be found throughout the ICESCR. Note however that the right to health in ICESCR is less qualified: "...the right of everyone to the enjoyment of the highest attainable standard of physical and mental health." ICESCR, Art. 12.1.

²⁶⁵ MSF, *Untangling the Web*, *supra* note 133; WHO, *Surmounting Challenges*, *supra* note 185.

²⁶⁶ WHO, *Surmounting Challenges*, *supra* note 185; 't Hoen, *TRIPS*, *supra* note 231, at 30-33; Susan K. Sell, *TRIPS and the Access to Medicines Campaign*, 20 *Wisc. Int'l L. J.* 481, at 491-96 (2002) [hereinafter Sell, *TRIPS*]; Rein, *supra* note 184, at 394-404.

²⁶⁷ WHO, *Surmounting Challenges*, *supra* note 185, at 9, 42 (allowing companies set their own differential pricing does not work well in Ukraine for MSF).

²⁶⁸ Medicines and Related Substances Control Amendment Act No. 90 of 1997 (Republic of South Africa).

South Africa as punishment for defending the suit.²⁶⁹ The US government and PhRMA companies relented under great pressure in April 2001, shortly before the Fourth WTO Ministerial Conference in Doha.²⁷⁰

Brazil has implemented a highly effective (and free) ARV therapy program. Brazil produced ARVs domestically under compulsory licenses, sparking an outcry from PhRMA companies and the US.²⁷¹ In January 2001, the United States requested a WTO panel against Brazil to prevent Brazilian exports of unlicensed AIDS drugs to Africa.²⁷² Under international pressure, the US withdrew the panel request on June 25, 2001, in the months leading up to Doha.²⁷³

In a widely-cited 2001 study, Attaran and Gillespie-White demonstrated the relative paucity of ARV patents in many sub-Saharan countries.²⁷⁴ This article has been widely

²⁶⁹ Omnibus Consolidated and Emergency Supplemental Appropriations Act, 1999, 112 Stat. 2681-153 (1999) (suspending appropriation of all bilateral economic assistance to South Africa, including AIDS/HIV programs, until steps are taken to repeal section 15(c) of South Africa's Medicines and Related Substances Control Amendment Act No. 90 of 1997). Many commentators have written about the case and the US trade pressure exerted upon South Africa. See, e.g., 't Hoen, *TRIPS*, *supra* note 231, at 30-31; Lissett Ferreira, *Access to Affordable HIV/AIDS Drugs: The Human Rights Obligations of Multinational Pharmaceutical Corporations*, 71 *Fordham L. Rev.* 1133, 1155 (2002); Rein, *supra* note 184, at 400-402. Doha paragraph 4 discourages Members from exerting bilateral pressure which hinders the exercise of TRIPS and Doha rights. Correa, *Implications of Doha*, *supra* note 134, at 12.

²⁷⁰ Editorial, *South Africa's Moral Victory*, 357 *Lancet* 1303 (Apr. 28, 2001); John R. Thomas, CRS Report for Congress, *HIV/AIDS Drugs, Patents and the TRIPS Agreement: Issues and Options* 16 (July 27, 2001) [hereinafter Thomas, CRS Report].

²⁷¹ Bermudez, *supra* note 184, at 191-94.

²⁷² World Trade Organization, Request for the Establishment of a Panel by the United States, Brazil Measures Affecting Patent Protection, WT/DS199/3 (Jan. 9, 2001). Executive Order 13155 had specifically reserved to the United States the right to seek such a panel. Exec. Order No. 13155, 65 Fed. Reg. 30521, 30522 (May 10, 2000) ("this order does not prohibit the United States Government from invoking the dispute settlement procedures of the World Trade Organization to examine whether any such law or policy is consistent with" TRIPS). For an overview of the Brazilian and South African situations by the Congressional Research Service, see Thomas, CRS Report, *supra* note 270, at 13-17.

²⁷³ 't Hoen, *TRIPS*, *supra* note 231, at 38-47; Thomas, CRS Report, *supra* note 270, at 15; Correa, *Implications of Doha*, *supra* note 134, at 2, n.6.

²⁷⁴ Amir Attaran & Lee Gillespie-White, *Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa?*, 286 *J. Am. Medical Assn.* 1186 (2001) (after the manuscript was submitted, Merck gave a \$25,000 grant). Several critical letters to the editor were received for the next volume of the journal. Boelaert, et al., *supra* note 185, at 840-41; Eric Goemaere, et al., *Letter to the Editor*, 287 *J. Am. Medical Ass'n* 841 (2002); Michael J. Selgelid & Udo Schuklenk, *Letter to the Editor*, 287 *J. Am. Medical Ass'n* 842 (2002) ("In the world of politics the carefully qualified conclusions of Attaran and Gillespie-White are likely to be misrepresented by pharmaceutical industry lobbyists claiming that "it has been shown that patents do not matter," with the aim of blocking proposed TRIPS agreement amendments that weaken pharmaceutical patent protection in developing countries"). In their reply to these letters, Attaran and Gillespie-White do not make the broad claim that patent laws are no barrier to ARVs in sub-Saharan Africa, but merely suggest that where patents exist, other alternatives can be pursued, such as voluntary licensure or switching to another therapy. Where patents do not exist, they call for unlicensed production, ignoring the industrial infrastructure issue described above. Amir Attaran & Lee Gillespie-White, *In Reply*, 287 *J. Am. Medical Ass'n* 842-43 (2002). [add Attaran 2003 emory transcript]; see also Amir Attaran, *How Do Patents and Economic Policies Affect Access To Essential Medicines In Developing Countries?*, 23 *Health Affairs* 155 (2004).

interpreted to claim that patents do not hinder ARV access in sub-Saharan Africa.²⁷⁵ Attaran published a follow-on report in *Health Affairs* in 2004, again suggesting that patents have not been a major hindrance to ARV access. This conclusion is not warranted from their data.

Patent law ensured that ARVs were available in the OECD for many years before the developing world began to receive treatment.²⁷⁶ As recently as 2002, no person in the developing world had received ARVs through official donor support from any country or multilateral institution.²⁷⁷ When MSF and Paul Farmer independently began proof of concept ARV treatment in Thailand, South Africa, and Haiti in 2000 and 2001, some were puzzled at their attempts, due to costs per patient exceeding \$10,000 for patented drugs.²⁷⁸ Access to AIDS medications was discussed at the highest levels at the WHO as early as 1991.²⁷⁹ Thirteen years later, in 2004, the world is just beginning to scale-up towards universal provision of ARVs and it may take a long time to achieve it. Precious years were lost because the drugs were too expensive for the developing world, and they were too expensive because of patent protection and the fears of arbitrage.²⁸⁰

Attaran defends his conclusions by identifying many sub-Saharan countries wherein patents had not been filed for some ARVs. This fact is both misleading and irrelevant because the sub-Saharan countries where patents have not been filed do not possess the domestic industrial base to manufacture ARVs.²⁸¹ Only one company produces

²⁷⁵ Lanjouw, *Intellectual Property*, *supra* note 49, at 11-12 (“industry uses this fact [the Attaran & Gillespie-White study] to stress that patents in the poorest countries are not impeding access to drugs”); *see, e.g.*, Harvey E. Bale, Jr., *Patents, Patients and Developing Countries: Access, Innovation and the Political Dimensions of Trade Policy*, in *The Economics of Essential Medicines* 100, 106, n.10 (Brigitte Granville, ed.) (2002). Bale is the head of the international PhRMA company trade association.

²⁷⁶ Combination therapy was available in the US from December 1995 with the approval of the first protease inhibitors, Invirase (SQV) on December 7, 1995 and Crixivan (IDV) and Norvir (r) in early 1996. Lamivudine was approved for marketing in the US on November 17, 1995.

²⁷⁷ *African HIV/AIDS Crisis: Pursuing Both Treatment and Prevention: Hearing Before the Sen. Comm. on Foreign Relations, Subcomm. on African Affairs*, [107th Cong., 1st Sess.] (Feb. 14, 2002) (statement of Jeffrey D. Sachs).

²⁷⁸ As of December 2000, the World Bank still considered ARV treatment in poor countries to be “cost-ineffective.” *See* Barton Gellman, *An Unequal Calculus of Life and Death; As Millions Perished in Pandemic, Firms Debated Access to Drugs*, *Wash. Post.*, Dec. 27, 2000, at A1 [hereinafter Gellman, *Unequal Calculus*].

²⁷⁹ Gellman, *Unequal Calculus supra* note 278 at A1.

²⁸⁰ Joan-Ramon Borrell and Jayashree Watal, *Impact of Patents on Access to HIV/AIDS Drugs in Developing Countries*, (Center for Int’l Development, Harvard Univ., CID Working Paper No.92, May 2002) [permission to cite not yet received from authors] (Finding a significant increase in ARV uptake would have resulted absent patents; this paper is a static analysis, ignoring the innovation question, and does not model subsidized ARV markets, which might have demonstrated a much larger negative impact of patents). Barton Gellman, *A Turning Point That Left Millions Behind; Drug Discounts Benefit Few While Protecting Pharmaceutical Companies’ Profits*, *Wash. Post.*, at A1, Dec. 28, 2000 (“For a decade, makers of AIDS medications had rejected the idea of lowering prices in poor countries for fear of eroding profits in rich ones.”).

²⁸¹ Correa, *Implications of Doha*, *supra* note 134, at Annex 2.

unlicensed ARVs in Africa, Aspen Pharmacare in South Africa²⁸² (By contrast, Asia has 27 companies producing unlicensed ARVs in 8 countries.)²⁸³ Attaran finds Aspen's home market, South Africa, to be effectively covered by patent filings. Indeed, PhRMA companies sued South Africa over unlicensed production of ARVs, as discussed above.

With South Africa stymied, unlicensed ARVs would have to be imported into sub-Saharan Africa from elsewhere, such as Brazil or India. Brazil was sued to block this practice,²⁸⁴ and India has faced a US-requested WTO dispute resolution on its implementation of TRIPS for pharmaceuticals,²⁸⁵ as well as US "Special 301" threats.²⁸⁶ India must be TRIPS compliant on January 1, 2005. The USTR frequently used the Special 301 watch list to discipline countries attempting to produce generics, even if legal under domestic law or TRIPS.

The mere possibility of a patent filing acts as a deterrent to a generic new drug application in sub-Saharan Africa, since the innovator could undercut the market investment by the generic company, while tying them up in litigation. A recent study finds that all but 3 of Africa's least developed countries have implemented laws for pharmaceutical patents as of 2004, despite the flexibility granted by the Doha Declaration to delay implementation until 2016.²⁸⁷ The attacks on Brazil, South Africa, and India were prominent and the intended lessons were not lost on other developing countries.

Procurement policies by donors also undercut Attaran's argument. All of the AIDS/HIV drugs on the WHO Prequalification list are produced either in the OECD or in India.²⁸⁸ USTR and PEPFAR also hinder procurement of unlicensed ARVs by multilateral and official donors.

The patent thicket effectively covers all sources of unlicensed ARVs for Africa, forming an effective deterrent to ARV commercialization by generic companies, even in the absence of a formal patent filing in every sub-Saharan country. Treatment with unlicensed ARVs occurs only by complying with TRIPS exceptions, or by (temporary) PhRMA company forbearance.

Perhaps what Attaran and Gillespie-White meant is that patent law shouldn't be used to delay access any longer. If so, we are in agreement. But it is historical revisionism of the

²⁸² Wendell Roelf, *Aids Drugs are Available—But Are There Enough?*, Mail & Guardian, May 17, 2004. Thembalami Pharmaceuticals in South Africa is a joint venture with Indian producer Ranbaxy, importing the APIs from India.

²⁸³ amfAR, TREAT Asia Special Report: Expanded Availability of HIV/AIDS Drugs in Asia Creates Urgent Need for Trained Doctors, at 4, July 2004, available at www.amfAR.org.

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²⁸⁵ India-Patent Protection For Pharmaceutical and Agricultural Chemical Products, WT/DS50/R (Sept. 5, 1997) and WT/DS50/AB/R (Dec. 19, 1997).

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²⁸⁷ Phil Thorpe, *Study on the Implementation of the TRIPS Agreement by Developing Countries*, at 1 (Study Paper 7 for the Commission on Intellectual Property Rights, (undated, cir. 2004).

²⁸⁸ WHO, HIV/AIDS Prequalification, 15th Ed., *supra* note 135.

foulest kind to claim that patents didn't matter over the last decade for access to cheap ARV therapy in Africa.

2. The Doha Declaration and the Cancun Provisional Waiver Modified TRIPS to Address Access Issues

At the Fourth WTO Ministerial Conference in Doha, WTO members agreed to the Doha Declaration as an interpretation of TRIPS.²⁸⁹ The Doha Declaration allows WTO Members to take measures to “protect public health and, in particular, to promote access to medicines for all.”²⁹⁰ WTO Members may compel licensure to protect public health, without limitation to AIDS or any particular disease.²⁹¹

The TRIPS Agreement restricts compulsory licenses to domestic use, effectively preventing exports.²⁹² Since many countries do not have domestic pharmaceutical production capacity, the no-export rule prevents many countries from delivering low-cost ARVs to HIV/AIDS patients.²⁹³ Compulsory licenses are not useful to Malawi absent the opportunity to import from Brazil, India or South Africa. The ensuing debate was energetic, leading up to the Cancun WTO meeting in 2003.

Immediately prior to the Cancun meeting, on August 30, 2003, the US conceded the point. Under the Cancun Provisional Waiver, the WTO now permits exports of compulsory licensed drugs to poor countries.²⁹⁴ The Cancun Provisional Waiver also established a WTO notification process for cross-border compulsory licenses. The TRIPS Council must be notified, but WTO approval is not required.²⁹⁵ In May 2004, Canada amended the Canadian Patent Law to permit compulsory licenses for certain drug exports to needy nations.²⁹⁶ As of July 2004, no WTO Member has notified the TRIPS

²⁸⁹ Doha Declaration, *supra* note 3. The legal status of the Doha Declaration is discussed in James Thuo Gathii, *The Legal Status of the Doha Declaration on TRIPS and Public Health Under the Vienna Convention on the Law of Treaties*, 15 Harv. J.L. & Tech. 291 (2002) and by Correa, *Implications of Doha*, *supra* note 134, at 5. The legal status of the Cancun Provisional Waiver is a joint commitment by WTO Members to abide by its terms in good faith. EU, Cancun, *supra* note 259. Practically speaking, it would be impossible to prevail at DSB on a provision contrary to the Cancun Provisional Waiver. The legal status of both Doha and Cancun are expected to be clarified in a planned 2004 amendment to TRIPS. Cancun Provisional Waiver, *supra* note 4, at ¶ 11; Doha Declaration, *supra* note 3, at ¶ 7. In this process, WTO has demonstrated unexpected legislative flexibility.

²⁹⁰ Doha Declaration, *supra* note 3, at ¶ 4.

²⁹¹ Doha Declaration, *supra* note 3, at ¶ 5; ‘t Hoen, *TRIPS*, *supra* note 231, at 40-41. US law permits compulsory licenses by the federal government. See *supra* note 182 and text accompanying.

²⁹² TRIPS Agreement, *supra* note 1, at art. 31(f).

²⁹³ See Doha Declaration, *supra* note 3, at ¶ 6.

²⁹⁴ Cancun Provisional Waiver, *supra* note 4. EU, Cancun, *supra* note 259.

²⁹⁵ Cancun Provisional Waiver, *supra* note 4, at ¶ 2. Notice must be given to the WTO, but approval is not part of the process. EU, Cancun, *supra* note 259.

²⁹⁶ The Jean Chretien Pledge to Africa Act, House of Commons, 3rd Sess., 37th Parliament, 52-53 Eliz. II, 2004 (Bill C-9) (received Royal Assent on 14 May 2004). The law created a positive list of drugs eligible for compulsory licensure, a procedural hurdle not required by the WTO. *Id.* at Schedule 1.

Council,²⁹⁷ even though many companies are apparently exporting unlicensed generics without bothering to comply with the Cancun procedure.²⁹⁸

3. Streamline and Expand Compulsory Licensure Under TRIPS

Voluntary programs of differential pricing have been problematic. Each PhRMA company creates idiosyncratic policies specifying which countries qualify for differential pricing on any particular drug. Transaction costs are high when essential access discounts are negotiated on a case-by-case basis.²⁹⁹ Essential access policies vary by the status of the purchaser (NGO, IGO, government, private buyer). Many of these policies are limited to sub-Saharan Africa or specific low-income countries, thereby excluding AIDS crises in Asia, the former Soviet states, Latin America or most of the Caribbean.

Voluntary programs of differential pricing also fail to achieve differential pricing at the marginal cost of production, which is absolutely necessary in low-income countries. Voluntary negotiations kept ARV prices unnecessarily high for years and delayed effective treatment for millions of dying people.³⁰⁰ Sovereign threats of compulsory licenses, public pressure from NGOs, and actual competition from unlicensed generic companies persuaded PhRMA companies and the US to embrace significant ARV differential pricing for poor countries.³⁰¹ Compulsory licensure enables ex-factory pricing closer to true marginal manufacturing cost, particularly if the tender process is competitive. Generic competition pierces the pricing veil, accelerates differential pricing towards true marginal production costs, and does not rely on public disclosure of confidential financial information from the companies. Given the endemic opacity of all PhRMA data on costs, perhaps the best way to calculate marginal cost is through compulsory licensure.³⁰²

Compulsory licenses are difficult to administer under TRIPS. The procedures are time-consuming and expensive. Companies may delay utilization for many months or years, while both sides employ advocates to press their positions. This process is wasteful, particularly when duplicated in multiple countries.³⁰³ Absent the credible threat of

²⁹⁷ The WTO has established a webpage to announce notifications under Doha and Cancun, http://www.wto.org/english/tratop_e/trips_e/public_health_e.htm. None are posted as of July 20, 2004.

²⁹⁸ See notes 306 and 307 below and text accompanying.

²⁹⁹ MSF, *Untangling the Web*, *supra* note 133, at 5.

³⁰⁰ A five company group negotiated with 5 UN agencies for a year in 2000 and 2001 without tangible success. Each company ended up negotiating access deals with each individual country. Paul Blustein & Barton Gellman, *HIV Drug Prices Cut for Poorer Countries; Other Firms May Follow Merck's Lead*, Wash. Post, at A1, March 8, 2001.

³⁰¹ See the discussion in Section V.C.2 above.

³⁰² PhRMA simply asserts that "there is no guarantee that generic companies will price at marginal cost." Dukes, *supra* note 80, App. 2, at 27 (Response of the Research-Based Pharmaceutical Industry to the Interim Report of the Task Force on Access to Essential Medicines) (Feb. 1, 2004). Absent the patent monopoly, generic companies in a competitive environment will certainly price much closer to marginal cost than PhRMA companies.

³⁰³ Paul Blustein & Barton Gellman, *HIV Drug Prices Cut for Poorer Countries; Other Firms May Follow Merck's Lead*, Wash. Post, at A1, March 8, 2001.

compulsory licensure, PhRMA companies have few reasons to cooperate with differential pricing, particularly for global diseases outside of the media glare of AIDS.

Attaran is fond of saying that no compulsory license has been issued under TRIPS.³⁰⁴ Perhaps Malaysia's compulsory license to Cipla Ltd. in February 2004 is the first under TRIPS.³⁰⁵ Some delay is to be expected since the process of importing unlicensed generics from abroad was legally uncertain until the Cancun Declaration in 2003.

But the focus on formal compulsory licenses under TRIPS misses the point. Many companies are engaged in cross-border sales of unlicensed ARVs without complying with the TRIPS process. Triomune is the best triple-drug FDC first-line treatment available in sub-Saharan Africa, and it is produced without a TRIPS license. Brazil produces ARVs without license, both for domestic purposes and for aid projects to Africa. Thailand avoided a compulsory license by ruling Bristol-Myers' didanosine patent invalid on public health grounds.³⁰⁶ In response, PhRMA companies are demonstrating more flexibility in 2004, reducing the need for compulsory licensure of first-line ARVs.³⁰⁷ But the US government keeps the pressure up. India and Thailand are the major sources of FDCs for export, and both are under pressure from the USTR. Thailand is now preparing a generic FDC as a second-line therapy, containing efavirenz, lopinavir and ritonavir. The US and Thailand are negotiating a free trade agreement with TRIPS+ provisions.

Anarchy cannot be good for medical treatment.³⁰⁸ Permitting TRIPS non-compliance also sends mixed messages to developing countries on the rule of law. A better process is urgently needed. TRIPS (and USTR) should make the ARV production and export process more rational, not more difficult. This market should come in from the grey.

C. Prevent Dysfunctional Pharmaceutical Arbitrage and Counterfeits

1. ARV Arbitrage and Counterfeits

³⁰⁴ [Attaran cite]

³⁰⁵ *Cipla Gets Malaysian Nod for AIDS Drugs: In a Trailblazing Move, Malaysia Has Issued a Compulsory License*, Business Standard, Feb. 26, 2004. As of July 19, 2004, Malaysia has not posted a notification on the WTO website.

³⁰⁶ *Government Pharmaceutical Organization v. Bristol-Myers*, Thailand Central Intellectual Property Court, Oct. 2002.

³⁰⁷ See, e.g., Press Release, *Merck & Co., Inc. Grants License for HIV/AIDS Drug Efavirenz to South African Company, Thembalami Pharmaceuticals*, July 14, 2004, available at www.pressmethod.com/releasestorage/5003645.htm.

³⁰⁸ The amfAR July 2004 report notes the difficulties with 27 companies in 8 countries in Asia producing unlicensed ARVs, and only one of them (Cipla Ltd.) operating with WHO Prequalification. amfAR, *TREAT Asia Special Report: Expanded Availability of HIV/AIDS Drugs in Asia Creates Urgent Need for Trained Doctors*, at 4, July 2004, available at www.amfAR.org.

In the rhetorical battles over essential medicines, innovation advocates have not always taken great care to distinguish arbitrage from counterfeiting.³⁰⁹ Much may be learned by contrasting the two practices.

Pharmaceutical companies are at risk from international arbitrage. Combivir is GlaxoSmithKline's best selling ARV drug, and the company holds a 45% global market share in HIV/AIDS drugs,³¹⁰ totaling £1.5 billion in 2002 sales.³¹¹ PhRMA companies rely on patent rents to support innovation. If actions to improve financial access to patented drugs result in globally sub-optimal patent rents, then the research enterprise may be threatened and prospective quality will have been sacrificed in the name of present access. This is PhRMA's innovation storyline. When PhRMA companies finally agreed to significant differential pricing of ARVs in low-income countries, they insisted on strong anti-diversion protections and burden-sharing by the recipient countries.³¹²

Arbitrage certainly seems possible. The consumer retail price of a kilogram of the active ingredients in Combivir is about \$20,000 in the US, but sells for as little as \$612 in Hyderabad and sub-Saharan Africa.³¹³ The price differential is equal to about 25 times the average per capita income in the lowest-income countries. Neo-classical economic theory predicts that entrepreneurs³¹⁴ will divert these drugs from the poor and export them to wealthy countries where they will fetch higher prices. Since the great majority of the world's AIDS patients are in poorer countries, if only a small percentage was diverted, significant volumes of ARVs could flow into OECD markets.³¹⁵

³⁰⁹ In copyright and patent practice, a 'counterfeit' or 'pirated' copy was manufactured by an unlicensed source, but it might well be as functional as the genuine article. In pharmaceuticals, a counterfeit does not contain the proper active ingredient. A safe and effective pill which comes from an unauthorized manufacturer is denominated herein an *unlicensed* product.

³¹⁰ Gautam Naik, *Glaxo's HIV Drugs Come Under Pressure: Competition, Calls for Price Cuts Weakens Company's Dominance of Maturing Market*, Wall St. J., Sept. 22, 2003, at B3.

³¹¹ GlaxoSmithKline plc 2003 Annual Report, Form 20-F, at 63 (total of all HIV sales) available at <http://www.sec.gov/edgar/searchedgar/companysearch.html>.

³¹² Barton Gellman, *A Turning Point That Left Millions Behind; Drug Discounts Benefit Few While Protecting Pharmaceutical Companies' Profits*, Wash. Post, at A1, Dec. 28, 2000.

³¹³ The active ingredients in Combivir total 450 mg per tablet. A kilogram of active ingredients will create approximately 2222 tablets. The retail price of 2222 tablets of Combivir in the US retail market exceeds \$20,000. See www.drugstore.com (visited July 9, 2004).

³¹⁴ Or smugglers, depending upon your perspective. The domestic practice is frequent within the United States, even with less significant price incentives to arbitrage. Jackie Judd, Senior Fellow with the Kaiser Family Foundation Speaks with Gilbert M. Gaul and Mary Pat Flaherty, Washington Post Staff Writers on a Five-Day Special Report Called "Pharmaceutical Roulette," that Focuses on Prescription Drug Safety Issues in the United States, (Kaiser Family Foundation transcript, Oct. 24, 2003) available at www.kff.org (describing significant arbitrage diversion within the US market taking advantage of relatively modest price differentials).

³¹⁵ The United States is a likely target market. The EU may not be vulnerable to diversion because most of its citizens are covered by a third party prescription drug benefit, and are not as price sensitive. DG Trade, *supra* note 27, at §3.3. This conclusion might be true for ultimate consumers, but perhaps European intermediaries will find arbitrage earnings from this trade.

Given these facts, it would be striking if ARV arbitrage did not occur.³¹⁶ And yet reality appears to depart from the neo-classical economic model, for there is quite limited evidence of dysfunctional arbitrage.³¹⁷ Empirical evidence to date does not indicate a sizable arbitrage market in ARVs from low-income markets into the OECD.³¹⁸

One possible reason is the practice is generally regarded as immoral and illegal. The impact of these norms is significant in pharmaceutical arbitrage markets. When pharmaceutical arbitrage is unmistakably legal, it flourishes, even at low differential pricing ratios. For example, the EU adopted a ‘community exhaustion’ rule, permitting parallel trade in patented and trademarked products. Differential pricing ratios of less than 2:1 have been sufficient to create a multi-billion euro legal arbitrage market within the EU.³¹⁹ Canada provides another example. Pharmaceutical arbitrage from Canada to the US operated for years under legal ambiguity. Proponents occupied the moral high ground of enhanced consumer access. The pricing differential is less than 2:1, but the arbitrage market now probably exceeds \$600 million a year.³²⁰ So the first lesson is to prevent any legal or moral uncertainty concerning dysfunctional arbitrage: the diversion to OECD markets of drugs intended for the poor should be clearly illegal. The EU has moved in this direction.³²¹

Criminal enterprises can hardly be expected to forgo pharmaceutical arbitrage on legal or moral grounds. The pricing ratios operating in the illegal cocaine market are broadly similar to ARVs. The US wholesale price of a kilogram of cocaine ranges from \$13,000 to \$25,000,³²² comparable to the US retail value of a kilogram of the active ingredients in Combivir.³²³ The US retail price of a gram of cocaine is about \$100.³²⁴ The retail price

³¹⁶ See Section II.B above.

³¹⁷ Meaning arbitrage from low-income markets into OECD markets. See Section V.C.3 above.

³¹⁸ In October 2002, 6000 packages of HIV/AIDS medicines were found to have been diverted from West Africa to The Netherlands. Dukes, *supra* note 80 at 50, n.1. As of 2002, both the European Commission and the pharmaceutical companies acknowledged that pharmaceutical arbitrage from poor countries into the OECD was “still largely theoretical.” DG Trade, *supra* note 27, at §3.3.

³¹⁹ Peter West & James Mahon, Benefits to Payers and Patients from Parallel Trade (York Health Economics Consortium Working Paper, May 2003) (estimating direct savings of € 631 million in 2002 from legal pharmaceutical arbitrage (parallel trade) within the EU).

³²⁰ See Section VII.A below.

³²¹ At present, the EU Council Regulation only applies to “tiered price” pharmaceutical exports to 76 listed developing and least-developed countries and to “HIV/AIDS, malaria, tuberculosis and related opportunistic diseases,” (a limitation which should be amended following Cancun). The EU defines a “tiered price” pharmaceutical as being offered to the poor for either direct manufacturing cost plus no more than 15% or at less than 25% of the OECD weighted average ex-factory price. Council Regulation 953/2003 to avoid trade diversion into the European Union of certain key medicines, art. 7, 2003 O.J. (L135/6) art. 3(a).

³²² US Drug Enforcement Administration, Drug Trafficking in the United States, Sept. 2001, *available at* <http://www.usdoj.gov/dea/pubs/intel/01020/index.html> (visited July 7, 2004) (2000 data). Retail prices per gram are significantly higher, particularly for smaller quantities.

³²³ See note 313 above.

³²⁴ Office of National Drug Control Policy, Trends in Cocaine Prices (1981-2000) (price per gram for purchase of 1 to 10 grams). The UK price for a gram in similar lots is around £ 50. Independent Drug Monitoring Unit Ltd., UK Drug Prices 2002 *available at* <http://www.idmu.co.uk/prices02.htm>.

of cocaine in Columbia is about \$3 to \$5 a gram,³²⁵ yielding a ratio of about 25:1.³²⁶ Since ARV arbitrage offers potentially higher pricing ratios, one might expect criminal enterprises to enter the ARV business. But there is little evidence that they have.

Counterfeiting opportunities may explain the absence of criminal ARV arbitrage. (Counterfeit prescription drugs do not contain the active ingredients, but are packaged, labeled and sold as if they do).³²⁷ In the illegal (nonprescription) drug market, counterfeiting is a marginal practice. If users don't get high, the product doesn't sell, particularly in a game with repeat players. The business plan of the Cali drug cartel probably includes a quality assurance mechanism.³²⁸

In prescription drugs, the opportunity for counterfeiting is much greater. Patients are generally unable to tell whether a counterfeit pill contains the correct active ingredients. It may take weeks or months to notice that therapy is failing, and the cause of failure may not be linked with the counterfeits. Counterfeits may be introduced into legitimate supply chains, diluting therapy but making the counterfeiting more difficult to observe and trace. These information characteristics enable the seller of counterfeit prescription drugs to act as if the transactions were discrete, rather than repeating. Retail sales of counterfeit pharmaceuticals are not only possible, but is a growing practice empirically, growing at an alarming pace.³²⁹

While obtaining arbitrated ARVs might be possible, obtaining them in sufficient quantities would require a procurement team in the field (sub-Saharan Africa), with multiple diversions against an alerted supply chains, followed by repackaging and a reverse supply chain back to OECD markets. It would be easier still to just produce counterfeit pills in a single location, appropriately labeled and packaged, and introduce them into OECD markets directly. Counterfeiting dispenses with the need to collect the product in far-flung locations, repackage it, and transporting it back to OECD markets. Counterfeits can be produced in market at very modest cost, more cheaply perhaps than

³²⁵ From a hopelessly anecdotal source, a travel journal of an American using drugs in Columbia. David Ashley, *Cocaine in Columbia*, available at <http://www.erowid.org/experiences/exp.php?ID=1796> (visited July 9, 2004) (the website, not Columbia).

³²⁶ The numerator is \$100 per gram and the denominator is \$4 per gram.

³²⁷ Pharmaceuticals may contain sub-therapeutic doses of the active ingredients; be improperly packaged, labeled, or stored; or may contain improper contaminants. These drugs are *substandard* rather than being counterfeit.

³²⁸ See the interesting (and merely conjectural) marketing plan for the Cali Cartel by Matthew Kwan, completed during his MBA studies at the Melbourne Business School, available at www.darksided.com/au/mba/cali.html (visited July 8, 2004).

³²⁹ The FDA estimates that pharmaceutical counterfeiting has increased four fold in the past few years. See the Washington Post series of articles on counterfeit drugs which ran in Fall 2003, by Mary Pat Flaherty and Gilbert M. Gaul. See, e.g., Mary Pat Flaherty and Gilbert M. Gaul, *Anti-Counterfeit Steps Drugmakers Sought; Legislators' Goal Is to Halt Illegal Sales*, Wash. Post, Jan. 17, 2004, at A11; Mary Pat Flaherty and Gilbert M. Gaul, *Miami Man Charged With Selling Counterfeit Lipitor*, Dec. 6, 2003, at E1; Mary Pat Flaherty and Gilbert M. Gaul, *Lax System Allows Criminals To Invade the Supply Chain*, Wash. Post, Oct. 22, 2003, at A1. The Wall Street Journal has also covered the story. Anna Wilde Mathews and Heather Won Tesoriero, *Murky Channels: Bogus Medicines Put Spotlight On World of Drug Distributors*, Wall St. J., Sept. 29, 2003, at A1.

obtaining diversions in low-income countries. Finally, it is unlikely that anyone would bother to counterfeit a cheap generic drug. Expensive, patented drugs are the targets of counterfeiters; cheap generics are not.³³⁰ A criminal is unlikely to counterfeit a pill and sell it as aspirin or Triomune, when it could be sold as Lipitor or Fuzeon.

Counterfeits are the real danger to both public health and PhRMA innovation, not dysfunctional arbitrage. Counterfeiting will remain an issue so long as the actual product has a high value relative to the cost of manufacturing a plausible placebo. Taking all R&D cost recovery out of the price system will greatly reduce counterfeiting pressure, but so long as a placebo can be made for a fraction of the value of the actual pill, counterfeiting will remain an issue.

2. Hindering Dysfunctional Arbitrage

Despite my insistence that counterfeiting is the primary threat, it seems logical to make some efforts to hinder dysfunctional arbitrage, particularly if the efforts do not damage other goals.

The most common practice is to increase transaction costs for smugglers through monitoring and enforcement action. The Cancun Provisional Waiver requires importing countries to implement reasonable measures to prevent diversion and re-exportation. “Reasonable” measures must be “within their means” and “proportionate to their administrative capacities and the risk of trade diversion.”³³¹ Under Cancun, developing and least developed countries inappropriately bear these costs even if global patent rents are supra-optimal.³³²

Minor diversions at the clinic or patient level should not be an enforcement focus. Given the difficulty in setting up a source collection system, it is unlikely that small batches or individual blister packs will filter back to OECD markets in significant quantities. Hence, there is no harm to innovation. Minor local diversions are likely to remain in the region, and may well be re-sold to patients outside of the current distribution system. This is not a best-case result, but certainly is not an enforcement priority. The priority should be on weaknesses in the supply chain where large batches could be diverted in a single transaction. The risk may be greatest while the product is still outside of the recipient country.

A second option is to modify the product to resist substitutability. The pharmaceutical manufacturing process could be altered to create multiple versions of any prescription

³³⁰ The examples of counterfeits in most media and FDA reports are of expensive patented drugs such as Lipitor, Epogen, Zyprexa and Serostim. See Leila Abboud, Anna Wilde Mathews & Heather Won Tesoriero, *Fakes in the Medicine Chest; As Drug Counterfeiting Rises, FDA May Propose Changes in Sales, Distribution Network*, Wall St. J., Sept. 22, 2003, at B1.

³³¹ Cancun Provisional Waiver, *supra* note 4, at ¶ 4.

³³² If global patent rents are supra-optimal, these costs could be borne by the PhRMA companies without harming innovation. Placing the burden on countries with annual per capita health budgets of \$100 or less is exceedingly unfair.

drug, distinguished by radically different colors, shapes, names, sizes and packaging. Markets must be segmented into commercial and charitable markets, and never the twain shall meet. The Cancun Provisional Waiver addresses this issue: exporting countries must clearly identify the products through labeling or marking and through special coloring or shaping.³³³ The EU recently acted to adopt a Council Regulation designed to hinder diversion into the EU market, including alteration of appearance.³³⁴ GlaxoSmithKline and others are following this procedure, altering both the packaging and the color of the product.³³⁵

Third, OECD consumers can be persuaded to resist substitution. Advertising could be directed to commercial market consumers, warning them never to take the red pills with labels in Swahili. This should not be an implicit safety warning: “those pills may not be safe,” since Africans will be told exactly the opposite: “the red pills are safe and effective.”³³⁶ Advertising should describe diversion as a moral and legal issue: OECD patients who take pills intended for impoverished Africans are stealing from the poor.³³⁷ Under the EU Council Regulation, all covered pharmaceuticals exported from the EU will bear a special logo identifying the product as destined for the poor.³³⁸ In addition, domestic law within the OECD should criminalize the practice, as discussed in Section VI.C.1 above.

Fourth, virtual pharmaceutical arbitrage into OECD countries should be banned outright under TRIPS. Virtual pharmaceutical arbitrage occurs when an OECD market uses differential prices for the poor under its national external reference pricing scheme.³³⁹

These strategies are unlikely to be fully effective, which is why PhRMA companies were slow to embrace aggressive differential pricing. But so long as commercial markets are not replaced, the practice will not harm innovation. Modest leakage from commercial markets may reduce patent rents, but may or may not harm innovation. Most importantly, the concern over diversion should not distract us from the greater threat of counterfeit drugs.

D. Implications of Domestic Market Arbitrage

The current TRIPS approach is tied to state sovereignty, affecting legal regimes along national political boundaries. TRIPS aggregates customers into country-level markets,

³³³ Cancun Provisional Waiver, *supra* note 4, at ¶ 2(b).

³³⁴ Council Regulation 953/2003 to avoid trade diversion into the European Union of certain key medicines, art. 7, 2003 O.J. (L135/5) ¶10. While the Council Regulation addresses importation in luggage for personal use, similar to the US personal importation rule, it does not address (but probably covers) internet sales. *Id.* at ¶13, art. 10. Seized product may be used for humanitarian purposes. *Id.* at ¶14.

³³⁵ GlaxoSmithKline plc, 2003 Annual Report, Form 20-F, at 29.

³³⁶ Vertical product differentiation based on quality is common in some products (regular v. premium gasoline), but is probably untenable in pharmaceuticals.

³³⁷ If the arbitrated drugs were voluntarily sold rather than stolen, then the moral claim weakens.

³³⁸ Council Regulation 953/2003 to avoid trade diversion into the European Union of certain key medicines, art. 7, 2003 O.J. (L135/7). The logo is found in Annex V of the regulation.

³³⁹ See *supra* note 188 and text accompanying in Section V.C.3 above.

reflecting both transaction costs and the political realities of sovereignty. This state-centric system is not surprising, given that only states are WTO Members, but the process suffers from both over-inclusion and under-inclusion.

1. Over-inclusion: Losing Elite Markets?

Over-inclusion occurs when an entire country is granted an exception or extension under TRIPS, even though some people within low- or middle-income countries can afford to pay market prices for the drugs.³⁴⁰ Even in the poorest countries, an elite cadre of individuals control enough wealth to afford these drugs. In middle-income countries such as India, Brazil, Chile, Mexico, South Africa and China, these markets are very significant and growing.³⁴¹ The elites in non-OECD countries are actually part of the “OECD market,” and should be expected to participate in the market on normal commercial terms.

Theory suggests that providing low-cost AIDS drugs to South Africa might make it more difficult to charge full price to wealthy or middle class South Africans, but apparently PhRMA companies effectively segment the markets,³⁴² much as they do in the US. The persistence of domestic differential pricing, even in the face of extensive donor programs,

³⁴⁰ In its 2001 submission to the United States Trade Representative, PhRMA claimed that \$260 million was lost annually due to unlicensed drug products in Argentina. Pharmaceutical Research Manufacturers of America, National Trade Estimate Report on Foreign Trade Barriers (NTE) (Dec. 17, 2001) *cited in* Sell, *TRIPS supra* note 266 at n.55. In 2003, the estimate has ballooned to \$600 million, without any apparent verification. United States Office of Trade Representative, 2003 National Trade Estimate Report on Foreign Trade Barriers 5-6 (2003) *available at* www.ustr.gov/reports/nte/2003/index.htm.

³⁴¹ Pharmaceutical companies may currently prefer to keep the small full-priced elite market in developing countries rather than risk arbitrage. Oxfam, *supra* note 148, at 93 (drug companies target elite households in Argentina, Brazil, India and China); W. Duncan Reekie, *The Development Trilemma and the South African Response*, in Brigitte Granville, ed., *The Economics of Essential Medicines* 161, 167 (2002) (The top 20% of South Africans enjoy a per capita GNP of \$27,699, comparable to OECD levels, and are therefore a significant market for drug companies); WHO-WTO, *Differential Pricing and the Financing of Essential Drugs*, in Brigitte Granville, ed., *The Economics of Essential Medicines* 209, 213, 220 (2002) (recognizing elite drug markets in developing nations); Scherer & Watal, *Post-TRIPS Options, supra* note 195; Patricia Danzon & Michael Furukawa, *Prices and Availability of Pharmaceuticals: Evidence from Nine Countries* exh. 8 (undated presentation, on file with author) *available at* <http://hc.wharton.upenn.edu/danzon/index.htm> (prices normalized by national income in Chile and Mexico are 528% and 529% of the US prices; I interpret this data to mean that drug purchasers in Chile and Mexico must have personal incomes far in excess of the national average). In their public filings with the US Securities and Exchange Commission, PhRMA companies acknowledge the growing middle class markets in the developing world. Merck & Co, Inc., Form 10-k (filed with the SEC on Mar. 10, 2004) at 14. PhRMA companies have recognized the potential of these markets for some time. Foreign Trade Practices (Part 2): Hearing Before the Subcomm. on Oversight and Investigations, and the House Comm. on Energy and Commerce, 99th Cong. 196 (1985) (statement of Gerald Mossinghoff, President, PhRMA).

³⁴² In South Africa, the NGO and public sector price for a triple therapy regime (ZDV/3TC+NVP) was US\$400 per person year while the private sector price in South Africa was US\$2007. WHO, *Surmounting Challenges, supra* note 185, at 37. A recent WHO survey found significant variations in prices of essential medications within most countries surveyed. Jeanne Madden, *Basic Results That the WHO/HAI Survey Offers Country-Level Investigators*, 33 *Essential Drug Monitor* 15 (2003). Significant domestic price variations indicate that various legal and market-based segmentation approaches were apparently functioning.

testifies to the effectiveness of market segmentation by PhRMA companies and the apparent weakness of actual pharmaceutical arbitrage pressure.³⁴³

2. Under-inclusion: Neglecting the Poor in Middle-Income Countries?

Under-inclusion occurs when a country does not qualify for TRIPS special treatment, despite the presence of a desperately needy population who cannot afford patented prescriptions. The state-centric system lays responsibility for these low-income patients on the middle- and upper-income countries in which they reside. Here we see a weakness of the TRIPS system of defining market segments by state political borders rather than actual health needs or ability to afford medicines. It also illustrates the arbitrary categories of development and the difficulties a country might face when it graduates to a higher category.

Two accommodations may be offered without damaging innovation: (1) Low-income country concessions may be extended to middle-income countries, so long as domestic price discrimination legal structures are successfully maintained. Segmenting the markets on political boundaries should not be the exclusive focus. Domestic legal institutions will affect this question as much or more than TRIPS; and (2) If global patent rents are supra-optimal, PhRMA companies could bear the loss of some elite markets without harming innovation. Some level of domestic arbitrage is tolerable during the condition of supra-optimality.

A simple estimate in the case of HIV drugs may be useful. PhRMA will not suffer much lost profit if sales of HIV products in every non-OECD country dropped to zero. GlaxoSmithKline, the largest participant in the HIV market, reports sales in three geographic regions: the US, Europe, and "International." This latter category includes OECD countries such as Japan, Canada and Australia, as well as non-OECD countries in Latin America, Asia, Africa and the Middle East. Even so, total International HIV sales in 2003 were only £155 million,³⁴⁴ in a year when gross profit was £17.2 billion and SG&A expenses were £7.5 billion. Actual profits from ARV sales in non-OECD markets are likely to be negligible to GSK's global profits, particularly if elite markets in non-OECD countries remain commercial.

E. Implications for Ongoing Modifications to TRIPS

One misapprehension about Doha and Cancun is that AIDS activists and developing countries won at the expense of global innovation. In fact, the compromise is fully supportive of global pharmaceutical innovation, as demonstrated above. The TRIPS Agreement is scheduled to be amended to incorporate both the Doha Declaration and

³⁴³ Within the US market, internal diversion is illegal in many cases. See Heather Won Tesoriero & Gary Fields, *FBI, FDA Investigates Big Drug Wholesaler*, Wall St. J., Sept. 19, 2003, at B1 (alleged diversion from discounted hospital markets to higher-priced secondary markets).

³⁴⁴ GlaxoSmithKline plc 2003 Annual Report, Form 20-F, at 61-63,

Cancun Provisional Waiver.³⁴⁵ As part of that process, five suggestions are offered to improve drug access while preserving innovation.

1. Expand the List of Countries Eligible for Differential Pricing

As of January 1, 2005, concessions under TRIPS will be largely limited to the 30 poorest members of the WTO, excluding countries such as Mexico, India, China and Brazil.³⁴⁶ Differential pricing should be extended to target populations in a larger group of countries. If patent rents are supra-optimal, loss of some elite markets will not harm innovation. Even if patent rents are sub-optimal, additional countries can receive differential pricing if they undertake serious measures to segment and protect the local elite OECD market.³⁴⁷ As the AIDS epidemic widens to Eastern Europe and Central Asia, access must be expanded in regions beyond sub-Saharan Africa.

2. Expand Differential Pricing to All Global Diseases

Doha and Cancun need not be effectively limited to AIDS, malaria and tuberculosis, but may be expanded to all global diseases without risk to innovation, so long as dysfunctional arbitrage and counterfeiting are hindered.³⁴⁸ This suggestion may not require a formal modification to TRIPS, but does require breaking out of the “AIDS/Malaria/TB” box. This single recommendation has profound implications for global public health.

3. Strengthen and Streamline the TRIPS Compulsory License

The TRIPS Council should streamline essential access procurement by joining with WHO to create a centralized alternative to ad hoc negotiations and litigation. This alternative could be a global non-exclusive compulsory license process for generic production of essential access medications.

Essential features of this TRIPS/WHO license would include: (1) A uniform process for creating and amending the list of target populations³⁴⁹ and the list of essential medicines. This list should be greatly expanded to include all safe and effective patented drugs for global disease conditions. The WHO Essential Medicines List is historically too restrictive, and until recently did not include most patented medications, under the

³⁴⁵ The WTO is expected to amend TRIPS to reflect the Doha Declaration and the Cancun Provisional Waiver. EU, Cancun, *supra* note 259; Cancun Provisional Waiver, *supra* note 4, at ¶ 11.

³⁴⁶ Only a few countries have notified the TRIPS Council of their intent to delay full TRIPS implementation until the January 1, 2005 deadline, namely Argentina, Cuba, India, Pakistan, Jordan, Uruguay, Egypt, United Arab Emirates and Turkey. All but 3 least developed countries in Africa have already adopted pharmaceutical patents, many years prior to the 2016 deadline. Phil Thorpe, *Study on the Implementation of the TRIPS Agreement by Developing Countries*, (Study Paper 7 for the Commission on Intellectual Property Rights, (undated, cir. 2004).

³⁴⁷ See Section VI.D above.

³⁴⁸ See Sections IV.A and V.C.3 above.

³⁴⁹ The term ‘populations’ is used in lieu of ‘countries,’ recognizing the inclusion issues raised in Section VI.D above.

assumption that patented medicines would be unavailable to the poor; (2) These drugs could be deemed to comply with the patent and NDRA laws of the relevant countries, a form of 'reference approval';³⁵⁰ and (3) The compulsory license royalty may vary by the drug and target population, and may be zero for low-income populations or higher amounts for middle-income populations. If patent rents are supra-optimal, the royalties may be set at zero.

4. Re-direct Enforcement Resources to the Greater Risk of Counterfeits

While TRIPS may be somewhat useful in hindering dysfunctional arbitrage, the burden of these efforts must not fall on low-income countries. The bulk of these efforts might be more efficiently deployed in OECD markets. Within OECD markets, counterfeiting should receive the lion's share of attention.³⁵¹ Many of these legal modifications can be made in the domestic laws of the OECD and need not wait for TRIPS or TRIPS + trade agreements. Arbitrage in non-OECD markets can drop far down the TRIPS agenda.

5. Enable Countries to Take Full Advantage of Existing TRIPS Flexibilities

Phil Thorpe's study on TRIPS implementation recently found that most developing countries have not taken advantage of the flexibilities and exceptions permitted under TRIPS.³⁵² He does not explore the reasons behind this failure, but two are likely. First, many countries may lack the impartial technical assistance needed to implement these provisions, including restrictions on "new use" patents, Bolar provisions, and international exhaustion rules. Second, the TRIPS+ offensive of the USTR and the 'Special 301' reports from that same office are frequently used to bluster countries into modifying domestic law to the liking of US owners of IP. WTO Members should have a realistic opportunity to implement the flexibilities bargained for in TRIPS, unhindered by unilateral US interests.

F. Implications for PEPFAR

When the Bush Administration established PEPFAR, it chose to largely bypass existing multilateral institutions such as the Global Fund. PEPFAR calls for only 6.3% of the \$15 billion to be placed with the Global Fund, with the remainder devoted to unilateral US efforts.³⁵³ This move reflects the Bush Administration's penchant for unilateralism, even in the world of AIDS.

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³⁵¹ See Section VI.C.1 *supra*.

³⁵² Phil Thorpe, *Study on the Implementation of the TRIPS Agreement by Developing Countries*, at 1 (Study Paper 7 for the Commission on Intellectual Property Rights, (undated, cir. 2004).

³⁵³ The President's Emergency Plan for AIDS Relief: U.S. Five-Year Global HIV/AIDS Strategy 16 (Feb. 23, 2004).

The Global Fund's procurement and supply management guidelines prioritize lowest price, assured quality and legal compliance.³⁵⁴ Grant recipients retain some flexibility in how they balance cost, quality and access in the local context. For example, a recipient country could choose to rely on the WHO prequalification process as the quality mechanism on ARV drugs, or it could choose to impose different standards based on local collective preferences. Similar choices may be made between licensed drugs and unlicensed generics.

One way to understand PEPFAR is that it inverts the Global Fund's ARV procurement priorities and strikes a different balance between access and innovation. PEPFAR gives first priority to legal compliance (and highest quality) rather than lowest effective cost, shunning unlicensed generics.³⁵⁵ PEPFAR requires approval by a "stringent regulatory authority" before procurement, meaning the NDRAs from the US, EU and Japan (the ICH), and possibly Canada.³⁵⁶ Critics attacked these standards as inappropriate barriers to rapid roll-out. On May 16, 2004 PEPFAR announced a new "fast track" FDA certification for generic ARVs, rather than following the WHO pre-certification process.³⁵⁷ PEPFAR will impose "all FDA standards for drug safety, efficacy, and quality,"³⁵⁸ even though existing studies have proven the efficacy of ARV treatment with unlicensed generics.³⁵⁹ PEPFAR is also creating its own supply chain management system, independent of The Global Fund.³⁶⁰ These efforts are duplicative and will inevitably raise costs and delay treatment.³⁶¹ Amazingly, the US funds both programs, and remains the largest donor to The Global Fund.³⁶²

³⁵⁴ Global Fund, Guide to the Global Fund's Policies on Procurement and Supply Management (April 2004).

³⁵⁵ From the beginning, PEPFAR guidance to its field offices prohibited acquisition of cheaper generic FDCs. GAO, U.S. AIDS Coordinator Addressing Some Key Challenges to Expanding Treatment, but Others Remain, at 37, July 2004 (GAO Report GAO-04-784). A cynic might view 'highest quality' as merely a stalking horse for 'highest price.'

³⁵⁶ GAO, U.S. AIDS Coordinator Addressing Some Key Challenges to Expanding Treatment, but Others Remain, at 19-37, July 2004 (GAO Report GAO-04-784).

³⁵⁷ Tommy G. Thompson & Randall L. Tobias, HHS Proposes Rapid Process of Fixed Dose Combination and Co-Packaged Products: Joint Statement Issued by HHS Secretary Thompson and U.S. Global AIDS Coordinator Tobias, May 16, 2004, available at www.state.gov/r/pa/prs/ps/2004/32503.htm; Gautam Naik, Mark Schoofs & Sarah Lueck, *Viral Strain: In AIDS Fight, Ambitious Goals Meet Hard Realities - Millions of Ill in Poor Nations Fail to Get Drugs as Funds, Medical Systems Fall Short*, Wall St. J. July 1, 2004, at A1; Sarah Lueck & Michael M. Phillips, *U.S. Awards Grants in AIDS Battle: Disbursement is First Part of a \$10 Billion Pledge; Generics Issue is Unresolved*, Wall St. J., Feb. 24, 2004, at D 5 (raising unresolved questions about whether the Office of the US Global AIDS Coordinator will procure generic AIDS drugs at the lowest possible price).

³⁵⁸ Ambassador Randall L. Tobias, U.S. Global AIDS Coordinator, Testimony before the U.S. Senate Committee on Appropriations, Subcommittee on Foreign Operations, May 18, 2004.

³⁵⁹ Laurent, et al., *supra* note 153; Robbins, et al., *supra* note 153; Shafer, et al., *supra* note 153; and Pujari, et al., *supra* note 151.

³⁶⁰ U.S. Agency for International Development, Draft Statement of Work Published for Comment—Supply Chain Management System for the President's Emergency Plan for AIDS Relief, June 7, 2004.

³⁶¹ See, e.g., GAO, U.S. AIDS Coordinator Addressing Some Key Challenges to Expanding Treatment, but Others Remain, July 2004 (GAO Report GAO-04-784); Mark Schoofs, *At Zimbabwe Clinic, Wait Is Long And U.S. Drug Cupboard Is Bare*, Wall St. J., July 1, 2004, at A8.

³⁶² The Global Fund Annual Report 2003.

Three PEPFAR goals require detailed comment: (1) Erecting hurdles to procurement of unlicensed generic ARVs in order to steer additional volume at higher prices to PhRMA companies; (2) Establishing a separate supply chain, permitting the US to maximize protection against diversion and arbitrage;³⁶³ and (3) Controlling quality and delaying the onset of resistance. My recommendations are as follows:

1. Permit Unlicensed Generics

The first goal is not legitimate on innovation grounds, since donor programs do not replace existing commercial markets for ARVs. PEPFAR's unilateralism is not needed for innovation, but imposes American notions of the appropriate quality-access balance upon desperately poor countries. Innovation does not require ignoring their collective preferences for low cost treatment under WHO prequalification. PEPFAR appears to operate in the mode of many bilateral aid projects, as a subsidy for domestic exports. The PEPFAR legislation requires 55% of the US appropriations to be used in treatment, and 75% of that amount (or 41.25% of the total) to be spent on ARVs for fiscal years 2006 through 2008.³⁶⁴ Blocking generic ARVs will funnel \$6.18 billion dollars in additional ARV sales to PhRMA companies,³⁶⁵ at a price much higher than generics.³⁶⁶ PEPFAR's stand also diverts those unit sales away from companies such as Cipla, another move advantageous to PhRMA companies.

2. Do Not Create Duplicate Supply Chains

The heuristic tells us that the second goal may be legitimate: avoid arbitrage from donor programs to high-income markets.³⁶⁷ But the analysis is not so simplistic. PEPFAR costs are very significant, including both duplicated program expenses and indirect costs from delayed and constrained treatment. PEPFAR is devoting special efforts to minimize drug diversion within the recipient countries.³⁶⁸ These costs should be balanced against the benefits of averted arbitrage. As demonstrated in Sections V.C.3 and VI.C above, most arbitrage is not harmful to innovation, and modest levels of dysfunctional arbitrage may be tolerable, particularly in conditions of supra-optimality.

3. Unlicensed Generic FDCs Delay Resistance

³⁶³ U.S. Agency for International Development, Draft Statement of Work Published for Comment—Supply Chain Management System for the President's Emergency Plan for AIDS Relief, June 7, 2004, at 6.

³⁶⁴ United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003, Pub. L. No. 108-25, §403 (2003).

³⁶⁵ 41.25% of \$15 billion.

³⁶⁶ GAO, U.S. AIDS Coordinator Addressing Some Key Challenges to Expanding Treatment, but Others Remain, at 20, July 2004 (GAO Report GAO-04-784); Ellen Nakashima & David Brown, *U.S. Rule on AIDS Drugs Criticized: Ban on Using Aid to Buy Foreign Generics Hinders Treatment, Experts Say*, Wash. Post, July 14, 2004, at A12 (quoting Rachel Cohen of MSF). See also Section VI.A above.

³⁶⁷ See Section VI.C above.

³⁶⁸ GAO, U.S. AIDS Coordinator Addressing Some Key Challenges to Expanding Treatment, but Others Remain, at 44, July 2004 (GAO Report GAO-04-784).

PEPFAR's final goal is quality, together with the fear of mismanagement, leading to resistance. This is an important question, as discussed in Section IV.C above on exhaustible drugs. Unfortunately, it is likely that another parallel AIDS relief system will hinder the uniform management of the disease. A parallel system further complicates treatment in the field and confuses providers. Resistance must be managed globally. Furthermore, if PEPFAR's primary goal is the avoidance of resistance, it should not erect barriers to Triomune and other FDCs, which are the first-line treatments most effective in preventing the emergence of resistant strains, but which are only available as unlicensed generic in FDC form.³⁶⁹ PEPFAR's insistence on US FDA standards will delay the procurement of FDCs. If PEPFAR requires the same standards on anti-malarial FDCs (Fixed-dose Artesunate Combination Therapy or FACT), the most effective treatment for managing resistance will be unnecessarily delayed,³⁷⁰ despite the fact that WHO has already prequalified a FACT.³⁷¹

If the purpose is to maximize global health, PEPFAR should be abandoned and all funds allocated to the Global Fund, where US Health and Human Services Secretary Thompson sits as Chair.

VII. Pharmaceutical Arbitrage from Canada

Pharmaceutical arbitrage is not just an issue in low- and middle-income countries; millions of US residents are importing cheaper patented drugs from Canada and elsewhere, the 'Boston Tea Party of the 21st Century.'³⁷² Drug imports from Canada should be a textbook example of pharmaceutical arbitrage at work, as PhRMA companies scramble to protect high-priced US markets.

For the larger essential medicines debate, the most salient conclusion from the following analysis is that pharmaceutical arbitrage will flourish, even at relatively low arbitrage ratios below 2:1. Aggressive moves by PhRMA companies and the FDA have not succeeded in stopping the arbitrage. The key factor is the legal ambiguity and moral support for the practice of importing from Canada. Institutions and human behavior matter a great deal when neo-classical economic theory is applied in the real world.

In the narrower context of US drug prices, arbitrage from Canada is unlikely to harm innovation, absent transparent access to PhRMA company data to prove the contrary.

³⁶⁹ See the discussion in Section IV.C above.

³⁷⁰ For a description of the effort to create FDCs for malaria in Africa and Latin America, see DNDi, *Malaria Patients Enter DNDi Clinical Trials*, July 2, 2004, available at www.dndi.org (visited July 18, 2004) and "FACT" Sheet, id.

³⁷¹ WHO, *Access to Artemisinin-based Combination Antimalarial Drugs of Acceptable Quality*, 2nd ed., April 26, 2004 available at <http://mednet3.who.int/prequal/> (visited July 19, 2004) (Artemether/Lumefantrine FDC manufactured by Novartis).

³⁷² Senator Joe Lieberman, Democratic Presidential Debate in Goffstown, New Hampshire, Jan. 22, 2004, available at <http://www.washingtonpost.com/wp-dyn/articles/A39875-2004Jan22.html>, quoted in Donald L. Bartlett & James B. Steele, *Why We Pay So Much for Drugs*, Time, Feb. 2, 2004, at 46

A. The Opportunity for Arbitrage

Patented drug prices in the United States are generally the highest in the world.³⁷³ Most other OECD countries have regulatory structures which significantly limit prices for patented pharmaceuticals.³⁷⁴ Canada's Patented Medicine Prices Review Board³⁷⁵ helps to keep Canadian prices significantly lower than US prices for patented drugs.³⁷⁶ This significant differential pricing invites consumer arbitrage.

The first phase of the Canadian-US arbitrage involved individuals purchasing drugs while traveling in Canada for other reasons, such as vacation or business. This arbitrage was usually limited to people who got sick while in Canada, or who unexpectedly exhausted their US prescriptions while traveling. Marginal transaction costs were negligible for those persons already in Canada.

³⁷³ US patented prescription drug prices are the highest of any major market, with the possible exception of Japan. Danzon & Furukawa, *supra* note 341, at exh. 3. Generic drugs, unprotected by patents or exclusive marketing periods, are generally priced competitively in the US. Comparisons of international drug prices should not conflate the categories. Danzon and Furukawa fault other studies for excluding generics since they represent significant volumes in the OECD. *Id.*, at 4. However, generics must be excluded when calculating patent rents or the potential for arbitrage in patented drugs. Canadian prices are 64% of US prices for patented drugs, and somewhat higher for generics, yielding a net differential of 6%. *Id.*, at exh. 4. See also Letter from William K. Hubbard, Associate Commissioner for Policy & Planning, FDA, to Ram Kamath & Scott McKibbin, Special Advocates for Prescription Drugs, State of Illinois (Nov. 6, 2003) (on file with author) [hereinafter Hubbard Letter] (generics generally cheaper in the US compared to Canada). Thus the potential for arbitrage lies in the 36% differential in patented medications, not the 6% overall figure.

³⁷⁴ Rothnie, *supra* note 44, at 491 ffg. (general, but dated, discussion of EU pharmaceutical price controls); see also Danzon, et al., *supra* note 198 (pharmaceutical companies delay launch of new drugs in EU countries with strict price controls to reduce risk of parallel trade).

³⁷⁵ Since 1988, Canada regulates patented drug prices through the Patented Medicine Prices Review Board, a quasi-judicial board which can bring proceedings against PhRMA companies which charge excessively high prices. Barrados, *supra* note 96, at ¶17.6 – 17.17; Dr. Robert G. Elgie, Canada's Patented Medicine Prices Review Board: New Approaches (Drug Industry Ass'n Washington Conference on Pharmaceutical Pricing and Reimbursement: What New Variables are at Work? 3-4 (Patented Medicine Prices Review Board, Ap. 16, 1999) available at <http://www.pmprb-cepmb.gc.ca>. The Board has effectively constrained patented drug prices in Canada. Barrados, *supra* note 96, at ¶17.25. Since the creation of the Board, patented pharmaceutical prices in Canada have increased only 1% per year on average. Elgie, *id.*, at 6. Nevertheless, Canada's system is not strictly a price control or rate setting system, but a soft reference price system with a quasi-judicial process. Barrados, *supra* note 96, at ¶17.50 – 17.56; Elgie, *id.*, at 6.

³⁷⁶ Many surveys have documented the price differential between US and Canadian patented pharmaceuticals. See, e.g., Ram Kamath & Scott McKibbin, Office of Special Advocate for Prescription Drugs, State of Illinois, Report on Feasibility of Employees and Retirees Safely and Effectively Purchasing Prescription Drugs from Canadian Pharmacies 79 (2003) (39% savings on the drugs that Illinois purchases that could be safely imported from Canada); Danzon & Furukawa, *supra* note 341, at exh. 4 (patented drugs are 36% cheaper in Canada compared with US); *Savings Immense on Canadian Drugs*, Wash. Times, Nov. 5, 2003 available at www.washtimes.com/national/20031105-112757-6536r.htm (33% to 80% cheaper for the 10 most popular drugs). If Canadian patented pharmaceuticals continue on their 1% price rise trajectory, and US drug prices continue to inflate at a greater rate, then the US – Canadian price differential will increase for the indefinite future. US retail prescription drug prices are expected to increase at 12.9% in 2004 and 12.4% in 2005. Heffler, et al., *supra* note 162, at exh. 2.

The second phase was more strategic on the part of consumers. Some US consumers noticed the price differentials when filling prescriptions in Canada. People living close to the border could make short intentional trips to fill lower-cost prescriptions, with a transaction cost of a few dollars and a modest amount of time. Bus trips were subsequently organized for people living at greater distances, specifically to stock up on patented medications. Politicians – particularly those from states near Canada - began to sponsor the trips. The transaction costs for these trips were greater – several hundred dollars and significant time – but for some consumers, the cost savings were greater still. As consumers became more accustomed to mail order pharmacies, repeat customers could avoid the transaction costs of another trip and re-order by mail from Canada. Consumer arbitrage began to erode differential pricing between US and Canadian drug prices.

These early forms of arbitrage were limited in several ways. Only drugs for outpatient non-emergency use could be easily substituted. The initial buyers were Americans who exhausted their personal drug supplies while traveling in Canada. The high transaction costs of travel to Canada limited the scope and potential expansion of this market. Information costs were also significant. Canadian pharmacies did not significantly advertise in the US during this phase of the market. Knowledge of the arbitrage opportunity was largely gained by word of mouth or opportune discovery.

1. The Internet Enables More Extensive Arbitrage

The internet dramatically altered the potential for pharmaceutical arbitrage. The transaction cost of importing a prescription from Canada dropped to a small fraction of the arbitrage savings.³⁷⁷ Many Canadian websites began to compete for the American consumer's attention. These factors multiplied the possible arbitrage market. The potential number of buyers for cross-border arbitrage jumped from several million Americans living near the Canadian border to the entire wired population of the United States. In last several years, the potential number of buyers expanded again, as US-based companies began to facilitate internet ordering of pharmaceuticals for unwired consumers, particularly the elderly. Health insurers and some government officials began to encourage consumers to acquire cheaper medicines from Canada. The media devoted increasing attention to the phenomenon from 1999, raising awareness amongst consumers that arbitrage was an option. A large and growing portion of the most valuable market for patented pharmaceutical medications is now only a click away from arbitrage.

If this process continues unchallenged, one would expect institutions such as hospitals, nursing homes, and retail pharmacies to begin to source from Canada. Payors such as health plans³⁷⁸ and governments³⁷⁹ are now following suit. The State of Illinois recently

³⁷⁷ For a patient with annual prescription costs of \$2000, a reasonable amount of search costs can be justified to save 30%.

³⁷⁸ United States-based PBMs are paying claims today from Canadian pharmacies, supporting the patient's decision to import, Kamath & McKibbin, *supra* note 376, at 13, as are some large health plans such as UnitedHealth, Thomas M. Burton, *The FDA Begins Cracking Down on Cheaper Drugs from Canada*, Wall St. J., Mar. 12, 2003, at A1, and States such as West Virginia.

recommended importing patented drugs from Canada for its employees and retirees. The State of Illinois estimates that \$250 million of its prescription drug costs could be sourced from Canada,³⁸⁰ with potential savings of \$90.7 million per year.³⁸¹ Several other states are exploring similar programs.³⁸² These state efforts are being blocked by the FDA.

The current level of arbitrage is already significant in the Canadian market. In 2004, the US retail prescription drug market is an estimated \$207.9 billion.³⁸³ In October 2003, an FDA official estimated that 3 million US prescriptions per year were being filled from Canada³⁸⁴ yielding an estimated arbitrage market size of \$600 to 700 million per year in 2003.³⁸⁵ The State of Illinois program alone could add \$250 million to this market, demonstrating the potential for growth. Canadian expenditures on prescribed pharmaceuticals in 2002 were CAN\$14.573 billion,³⁸⁶ thus the arbitrage market is already a significant part of the overall Canadian market.

Unlike ordinarily fleeting opportunities for financial arbitrage, this market is not self-correcting. Canadian prices will not increase much, given government regulation;³⁸⁷

³⁷⁹ The State of Illinois is aggressively pursuing a plan to import patented medications from Canada beginning April 1, 2004, if FDA approval is given. Kamath & McKibbin, *supra* note 376, at 3, 30.

³⁸⁰ Kamath & McKibbin, *supra* note 376, at 79-81.

³⁸¹ Kamath & McKibbin, *supra* note 376, at 19 (cost savings assumes all employees and retirees will participate).

³⁸² See, e.g., Katherine M. Skiba, *Doyle Makes Case for Buying Cheaper Drugs from Canada*, Milwaukee Sentinel-Journal, Feb. 24, 2004; Fred Frommer, *Pawlenty Tries to Win FDA over on Drug Plan*, Minneapolis Star Tribune, Jan. 16, 2004 (Minnesota Governor's attempt to win FDA approval for drug importation plan); Tony Leys, *Vilsack Offers Plan on Canadian Drugs*, Des Moines Register, Jan. 22, 2004 (Iowa's plan).

³⁸³ Heffler, *supra* note 162, at exh. 1. This number includes only retail sales of prescription drugs, excluding purchases of prescription drugs by institutions such as hospitals and nursing homes. The all-inclusive number for 2004 is closer to \$250 billion. Sager & Socolar, *supra* note 236, at 4, n. 25.

³⁸⁴ Transcript of motion for preliminary injunction at 127-28, *United States v. Rx Depot, Inc.*, No. 03-CV-0616-EA (M) (N.D. Ok. Oct. 8-9, 2003) (examination of Thomas McGinnis, Director of Pharmacy Affairs, FDA) (on file with author) [hereinafter Rx Depot Transcript].

³⁸⁵ While the average size of US – Canadian prescriptions are unknown, data from the State of Illinois describes consumer co-pays of at least \$40 per prescription, Kamath & McKibbin, *supra* note 376, at 5, implying a retail price of \$200 at a 20% co-pay. One internet facilitator's data indicated an average Canadian prescription price of \$220. Private interview by author, October 2003. Recent Canadian estimates suggest a market of \$700 to \$800 million per year. Tamsin Carlisle, *Some Online Pharmacies Aren't Filling Big Orders Due to Fears of Shortages*, Wall St. J., Dec. 26, 2003, at A9; Tony Pugh, *Low-Cost Drug Sales to U.S. Should Stop, Canadian Group Says*, Philadelphia Inquirer, Nov. 16, 2003, available at www.philly.com. Other recent studies have reached similar estimates for the size of the Canadian arbitrage market. Sager & Socolar, *supra* note 236, at 4 (\$695 million in 2003, based on IMS data). The largest US retail drug store chain, CVS, estimates that US patients spend \$3 billion a year outside the USA. Pharma Marketletter (May 17, 2004). By comparison, the domestic US prescription mail order market was \$20.7 billion in 2001. NIHCM Foundation, *supra* note 58, at 9.

³⁸⁶ Canadian Institute for Health Information, *supra* note 58, at 66. Precise comparisons with US pharmaceutical sales are difficult. The Canadian figures exclude sales to non-Canadians (including cross-border internet sales) but include institutional sales (which are excluded from the comparable US statistics).

³⁸⁷ PhRMA companies recently announced small price increases permitted by the Patented Medicine Prices Review Board. Bernard Simon, *Curtailing Medicines From Canada*, N.Y. Times, Nov. 11, 2003. These price increases were targeted against drugs in the US arbitrage market. PhRMA companies are also

normal US prices will not fall unless the PhRMA companies agree to reduce their monopoly price. If the supply of patented drugs in Canada remains sufficient, a permanent arbitrage opportunity results and will persist for as long as the patent remains in force. With negligible transaction and information costs, a fungible product in abundant supply, and non-responsive pricing, one would expect a large portion of the available US market to source from Canada, limited only by the capacity of the Canadian market to handle the volume.³⁸⁸

Canadian arbitrage may destroy the differential pricing system which kept US drug prices the highest in the world. Erosion of differential pricing will shift consumer surplus from producers to consumers. American consumers will save many billions of dollars on pharmaceuticals, greatly improving financial access. The other side of the coin is that PhRMA companies may lose the lion's share of their worldwide profits.³⁸⁹ One unasked question is whether this process will result in sub-optimal patent rents. Supporters of pharmaceutical companies simply assume that drug innovation will be hindered. So long as patent rents remain supra-optimal, Canadian arbitrage improves consumer welfare without harming innovation.

2. Regulatory Arbitrage

A process similar to arbitrage also occurs between regulatory systems. Within the United States, if one particular state imposes draconian regulations upon businesses, the business owners may vote with their feet by relocating to a more attractive regulatory environment. If sufficiently important firms relocate, or credibly threaten to do so, then the state may reconsider its stance and ameliorate the harsh regulations.³⁹⁰

A variation of this process is at work in Canadian arbitrage. In the United States, pharmaceutical companies have been largely successful in blocking the adoption of price controls for its products.³⁹¹ Other nations, such as Canada, have imposed more restrictive

attempting to limit the supply of drugs provided to Canada to hinder cross-border arbitrage, encouraging shortages and retail price increases. *Id.* Both actions are designed to hinder arbitrage.

³⁸⁸ A recent CBO issue brief suggests that the net effect on US prices from Canadian arbitrage will be small. CBO, *Would Prescription Drug Importation Reduce U.S. Drug Spending?* (Apr. 29, 2004). The CBO assumed that arbitrage supplies would be successfully interdicted by PhRMA companies, capping the arbitrage at 10 to 15% of the US market, and assumed no competitive price reductions in the US. *Id.* at 4-6. Even under the CBO's pessimistic assumptions, the 10 year savings to US consumers will be \$40 billion. *Id.* at 8. Put another way, PhRMA's displaced sales from legalizing OECD arbitrage will be \$40 billion over 10 years.

³⁸⁹ Alan Sager and Deborah Socolar dispute this conclusion, claiming that Canadian arbitrage need not reduce the profits of PhRMA companies, but their conclusion requires that a high percentage of arbitrage purchases actually represent new aggregate demand. Sager & Socolar, *supra* note 236, at 1 ("We find that if new prescriptions' share of imports is 44.53 percent or more, importing actually increases drug makers' profit.) The question will turn on whether pharmaceutical demand is relatively inelastic. *Id.* At 11-13.

³⁹⁰ The classic work is Charles Tiebout, *A Pure Theory of Local Expenditures*, 64 J. Pol. Econ. 416 (1956).

³⁹¹ The industry strongly oppose price controls. Sidney Taurel, *Hands Off My Industry*, Wall St. J., Nov. 3, 2003, at A14 (Taurel is President, Chairman and CEO of Eli Lilly).

regulatory measures to reduce patent rents.³⁹² One perspective on this cross-border arbitrage is that some Americans have imported Canada's pricing regulatory system into the US for outpatient non-emergency pharmaceuticals.³⁹³ Regulatory arbitrage is at work between the US and Canada.

Regulatory arbitrage encourages domestic political reaction. Constituents' demands for pharmaceutical arbitrage has led the Congress to pass the MEDS Act, which legalizes the process once the Secretary of Health and Human Services certifies its safety and cost savings.³⁹⁴ The certification proved to be the Achilles heel, since HHS has refused to issue the certification.³⁹⁵ The Medicare Prescription Drug and Modernization Act of 2003, as passed by the House of Representatives, permitted importation from Canada without requiring the Secretary's approval.³⁹⁶ The Pharmaceutical Market Access Act of 2003, also passed by the House, permitted imports from 25 countries with effective NDRA's.³⁹⁷ The Senate version of the bill reinstated the certification requirement, effectively gutting Canadian importation under the Bush Administration.³⁹⁸ Most observers would not expect a majority of the US Congress to enact Canada's price regulatory system for the United States; nevertheless, existing federal law (if certified by HHS) would achieve a similar result, in response to consumer exploitation of arbitrage opportunities.³⁹⁹

Another example of regulatory arbitrage involves the efforts of US psychologists to obtain prescribing authority, currently denied to them under US law. Some US

³⁹² Many discussions of Canada's patented pharmaceutical pricing system wrongly assume it includes mandatory price controls. Canada's Patented Medication Prices Review Board uses a soft reference prices and quasi-judicial processes to regulate the ex-factory prices within Canada. The Board also encourages R&D at a minimum level of 10% of revenues, and grants special pricing consideration to breakthrough drugs. Barrados, *supra* note 96, at ch. 17; Elgie, *supra* note 375, at 3-4. Thus, Canada's system is one attempt to optimize patent rents, striking a balance between cost, quality and access, based upon imperfect data.

³⁹³ The American Enterprise Institute identifies this as a major weakness of proposals to permit re-importation from Canada. John E. Calfee, *The High Price of Cheap Drugs*, (Jul. 14, 2003) available at www.aei.org.

³⁹⁴ Medicine Equity and Drug Safety Act of 2000, Pub. L. 106-387, 114 Stat. 1549A-35.

³⁹⁵ Sarah Lueck, *Senate Supports Wider Importing of Canada Drugs*, Wall St. J., June 23, 2003, at A10.

³⁹⁶ Medicare Prescription Drug and Modernization Act of 2003, H.R. 1, 108th Cong. § 1121 (2003) (passed in the House on June 27, 2003). Another bill in the 108th Congress would have permitted re-importation from the EU as well. Save Our Seniors Act of 2003, H.R. 2769, 108th Cong. § 2 (2003).

³⁹⁷ Pharmaceutical Market Access Act of 2003, H.R. 2427, 108th Cong. (2003).

³⁹⁸ Medicare Prescription Drug Improvement and Modernization Act of 2003, 21 U.S.C. § 804 (2004); Sarah Lueck, *Senate Supports Wider Importing of Canada Drugs*, Wall St. J., June 23, 2003, at A10. A subsequent Administration could certify safety and cost-effectiveness and begin importation from Canada without additional Congressional legislation.

³⁹⁹ Henry J. Aaron, *Should Public Policy Seek to Control the Growth of Health Care Expenditures?*, Health Affairs W3-28 - 31 (Web Exclusive, Jan. 8, 2003) available at <http://www.healthaffairs.org>. ("The chances that we will adopt the Canadian or French health care system as a whole are about as good as those that we will join the British Commonwealth or adopt French as a second national language. Even adopting elements of foreign systems is problematic because important aspects of health care financing and delivery are mutually interrelated."). John Calfee of the American Enterprise Institute makes the point that reimportation of pharmaceuticals from Canada is equivalent to importing Canadian price controls. Calfee, *supra* note 393.

psychologists direct their patients to Canadian pharmacies, which accept prescriptions written by US psychologists.⁴⁰⁰ This practice will provide empirical evidence of the medical efficacy of prescriptions by US psychologists, a form of self-directed research.

In both cases, regulatory arbitrage focuses debate on the comparative advantages of alternative systems of regulation. This process should be encouraged, as it promotes competitive analysis of regulatory structures and allows market participants to influence the debates with diminished intermediation by interest groups.⁴⁰¹

3. Virtual Arbitrage

The closely-related concept of virtual arbitrage involves foregoing the actual importation of drugs, but using lower observed prices as an external reference price, whether by government regulation or in contract. The US employs a virtual arbitrage system in requiring certain discounts for drugs purchased under Medicaid, discounts which reference other 'best' prices.⁴⁰² West Virginia recently established a State agency which might adopt the Federal Supply Schedule or Australian PBS prices as a price cap for drug purchases by the State.⁴⁰³ If West Virginia succeeds, expect many other States to follow suit.

Virtual arbitrage is preferred in any situation where physical arbitrage is acceptable. Virtual arbitrage is more efficient than physical arbitrage, since resources are not expended in transporting products or in policing against diversion.⁴⁰⁴ Virtual arbitrage is also safer than physical arbitrage since the supply chain is not needlessly articulated through intermediaries. Just as in physical arbitrage, virtual arbitrage from low-income countries into OECD markets must be blocked if differential pricing is to be supported

⁴⁰⁰ Linda Temple, *Who Gets to Prescribe? Psychologists Send Drug Orders to Canada, Spark a Medical Debate*, USA Today, Dec. 18, 2003, at 10D.

⁴⁰¹ Alvarez and Trachtman note that regulatory arbitrage may or may not have positive effects, depending upon the condition of spillovers (negative externalities). Jose E. Alvarez & Joel P. Trachtman, *Institutional Linkage: Transcending "Trade and ..."*, 96 Am. J. Int'l L. 77, 84 (2002) citing Joel P. Trachtman, *Regulatory Competition and Regulatory Jurisdiction*, 3 J. Int'l Econ. L. 331 (2000). In the present case, pharmaceutical regulatory arbitrage is a response to the existing free rider problem of national drug price regulation. This response may well destabilize the system, and force OECD countries to re-allocate jurisdiction on drug price regulation. Efficient re-allocation of jurisdiction is the primary theme in Alvarez and Trachtman's article. Alan O. Sykes remarks that subjecting domestic regulatory systems to the pressures of global trade "need not be unfortunate. International regulatory competition may well drive out foolish and wasteful regulations rather than undermine valuable regulations." Alan O. Sykes, *International Trade and Human Rights: An Economic Perspective* 17 (Univ. of Chicago John M. Olin Law & Economics Working Paper No. 188, 2d Series, May 2003).

⁴⁰² 42 U.S.C. § 1396r-8 (2004) (using reference prices to calculate drug prices and drug rebates under Medicaid).

⁴⁰³ West Virginia Pharmaceutical Availability and Affordability Act, H.B. 4084, 2004 Reg. Sess. (W.V. 2004).

⁴⁰⁴ On the issue of the transaction costs of physical arbitrage, see the comments by Harvey E. Bale, Jr., the Director-General of the International Federation of Pharmaceutical Manufacturers Associations, in Harvey E. Bale, Jr., *The Conflicts Between Parallel Trade and Product Access and Innovation: The Case of Pharmaceuticals*, 1 J. Int'l Economic L. 637 (1998). These claims are hotly disputed by proponents of parallel trade in pharmaceuticals. West & Mahon, *supra* note 319.

for essential medicines. For this reason, several commentators have advised that OECD countries should not use low-income country differential prices as external reference prices in their domestic drug pricing regimes.⁴⁰⁵

Without clear data on patent rent optimality, no conclusion can be reached as to whether other forms of virtual arbitrage harm innovation. All arbitrage, whether virtual or not, will reduce the surplus captured by the patent holder and shift surplus to the consumer and the arbitrageur; however it begs the question to assume that arbitrage will reduce patent rents to a sub-optimal level. One should not assume that the externality is negative. It is possible that West Virginia's use of an external reference price retains supra-optimal innovation incentives while dramatically lowering the State's costs and improving access.

B. The Response to Canadian-US Arbitrage

The current efforts to hinder Canadian arbitrage include legal interdiction, increasing transaction and information costs, and selectively controlling drug supplies shipped to Canada.

1. Reducing Arbitrage Demand

a. Legal Interdiction

If transaction costs are raised significantly, at some point the arbitrage transaction will become unrewarding and the market pressure on differential pricing will abate. For consumers, the transactions must be low-risk, particularly with regard to: (1) the legality of the transaction; (2) eligibility for reimbursement from third parties; and (3) counterparty risk of fraud.⁴⁰⁶

In the first two phases of Canadian arbitrage,⁴⁰⁷ the transactions were clearly legal under US and Canadian law. The consumer physically visited a Canadian pharmacy, presented a valid prescription, and received the product. When returning to the United States, most Americans were not searched or questioned about their pharmaceuticals. Even if they had been scrutinized, the federal government allowed them to import small amounts of pharmaceuticals for personal use.⁴⁰⁸

When pharmaceutical arbitrage expanded to mail order and the internet, Canadian pharmacies and their agents emphasized the personal use exception. Prior to 2003, federal officials did not vigorously challenge this practice. Federal officials did not lack

⁴⁰⁵ See *supra* Section V.C.3.

⁴⁰⁶ Virtual arbitrage partially escapes this condition since no additional transportation costs are incurred and safety issues cannot be raised. Other transaction costs may still apply, such as the cost of observing prices and legal costs.

⁴⁰⁷ See *supra* Section VII.A.

⁴⁰⁸ The FDA's Personal Use Import Policy may be found at www.fda.gov/ora/import/pipinfo.htm.

statutory authority to block importation through the mails or package delivery services,⁴⁰⁹ but enforcement was uncommon. This lack of enforcement, coupled with the claims of legality under the personal use exception, permitted consumers to believe that the transaction was legal and the risk of government sanction was small.

Beginning in 2003, the enforcement environment changed.⁴¹⁰ Federal and state officials are currently attacking internet pharmaceutical arbitrage on multiple fronts. The FDA is aggressively enforcing against US companies involved in the trade.⁴¹¹ The Customs Department has posted clarifications of the personal use exception to discourage importation.⁴¹² Facilitators such as the Discount Prescription Center in West Virginia have been challenged by state Boards of Pharmacy as engaged in the unlicensed practice of pharmacy.⁴¹³ The FDA has sued facilitators such as Rx Depot for assisting in the importation of prescription drugs.⁴¹⁴ The FDA and state pharmacy investigators have also purchased prescription drugs in undercover operations.⁴¹⁵ Direct interdiction would include enforcement actions against consumers, but arresting grandparents for purchasing Canadian Lipitor is not politically viable.

Canadian arbitrage was born in conditions of legal uncertainty, and continues with a zone of legal protection around the consumers. In addition, the consumers occupy the moral high ground of gaining access to an important drug at market rates. These conditions allowed arbitrage to take root and grow. Citizens and governments which would never consider importing cocaine are buying Canadian drugs over the internet.

b. Raising Information and Transaction Costs

These enforcement actions, while significant, have not shut down the arbitrage trade. From the perspective of arbitrage, the more significant element is pairing enforcement action with widespread publicity to dampen consumer demand. The effect is to increase

⁴⁰⁹ See, e.g., *United States v. Ramsey*, 431 U.S. 606 (1977) (customs officials permitted to intercept mail for contraband).

⁴¹⁰ Thomas M. Burton, *The FDA Begins Cracking Down on Cheaper Drugs from Canada*, Wall St. J., Mar. 12, 2003, at A1.

⁴¹¹ Gardiner Harris and Monica Davey, *F.D.A. Begins Push to End Drug Imports*, N.Y. Times, Jan. 24, 2004; FDA News, *Recent FDA/U.S. Customs Import Blitz Exams Continue to Reveal Potentially Dangerous Illegally Imported Drug Shipments*, (Jan. 27, 2004) available at www.fda.gov; Lolita C. Baldor, *FDA: Too Costly to Legalize Drug Imports*, Las Vegas Sun, Dec. 24, 2003 (describing confiscations of illegal mail-order drugs in New York).

⁴¹² U.S. Customs and Border Protection, Medication/Drugs (undated) available at http://www.cbp.gov/xp/cgov/travel/alerts/medication_drugs.xml (visited Feb. 15, 2004).

⁴¹³ The West Virginia Circuit Court issued a preliminary injunction forbidding enforcement by the West Virginia State Board of Pharmacy against Discount Prescription Center, concluding that Discount Prescription Center was not a pharmacy and did not violate state law. *Carole Becker, d/b/a Discount Prescription Center v. West Virginia Board of Pharmacy*, No. 03-C-1237, slip op. at 11-12 (Cir. Ct. Kanawha Co. Nov. 3, 2003).

⁴¹⁴ Rx Depot was shut down by a preliminary injunction granted by District Court Judge Claire V. Eagan on November 6, 2003. *United States v. Rx Depot, Inc.*, No. 03-CV-0616-EA (M), slip op. at 2-4 (N.D. Ok. Nov. 6, 2003).

⁴¹⁵ Rx Depot Transcript, *supra* note 384, at 16-40.

consumers' transaction costs and deter arbitrage without comprehensive direct interdiction.

Raising information costs may also support product differentiation and discourage substitution.⁴¹⁶ Pharmaceutical arbitrage occurs when the consumer considers the drugs to be substitutable. These consumers are generally not trained medical specialists, and are unable to evaluate safety or efficacy.⁴¹⁷ These consumers are relying on the effectiveness of the Health Canada's Therapeutic Product Directorate (TPD), assuming that Canadian drugs are generally as safe as US drugs regulated by the FDA. If the safety or equivalence of drugs from Canadian internet pharmacies are in doubt, this assumption dissolves and risk averse consumers are less likely to arbitrage. Supporters of importation take the opposite tact. In October, 2003, the State of Illinois released a major report in support of importing patented drugs from Canada. The report concluded that the Canadian drug supply was actually more secure than the US.⁴¹⁸

A major component of the assault on pharmaceutical arbitrage has been to question safety and equivalence. The FDA has publicly announced its lack of confidence in the internet drug supply chain. Undercover operations and enforcement activities have highlighted the seizure of mislabeled, counterfeit or out of date drugs.⁴¹⁹ Questions have been raised as to whether the drugs are produced and transported under FDA standards of safety.⁴²⁰ Labeling issues, such as the Canadian label for Accutane, have been identified.⁴²¹ The actual source of arbitrated drugs has also been publicly challenged by FDA officials who muse whether the drugs actually come from Canada at all; perhaps the true source is Thailand or India.⁴²²

At one level, these accusations prove too much. Counterfeit and unsafe drugs are found in the US market generally, and are not confined to the internet supply chain.⁴²³ The FDA does not want to undermine consumer confidence in the US drug supply, but to distinguish the US domestic supply from international internet sources. Thus, the FDA opposes all international pharmaceutical arbitrage into the US.

⁴¹⁶ Philips, *supra* note 28, at ch. 12.

⁴¹⁷ Raising search costs for these consumers should hinder arbitrage and support differential pricing. See Philips, *supra* note 28, at ch. 12.

⁴¹⁸ Kamath & McKibbin, *supra* note 376, at 11-16 (finding Canadian and US systems equivalent for most aspects, but finding the Canadian system superior in preventing the introduction of counterfeit drugs and incident reporting for internal process errors).

⁴¹⁹ See, e.g., FDA News, Recent FDA/U.S. Customs Import Blitz Exams Continue to Reveal Potentially Dangerous Illegally Imported Drug Shipments (Jan. 27, 2004) available at <http://www.fda.gov>.

⁴²⁰ Rx Depot Transcript, *supra* note 384, at 16-158.

⁴²¹ Rx Depot Transcript, *supra* note 384, at 77, In. 22 (cross-examination of Melvin Frank Szymanski, consumer safety officer, FDA); Discount Prescription Center

⁴²² Hubbard Letter, *supra* note 373 (noting one instance of a Canadian website shipping an Indian drug); *Savings Immense on Canadian Drugs*, Wash. Post, Nov. 5, 2003 ("It is not an answer to this problem to say go buy drugs from Canada, which may be coming from Pakistan and India and China and all those countries we have health concerns about") (Sen. John B. Breaux, D-La).

⁴²³ Daniel Yee, *CDC: Seniors Prescribed Dangerous Drugs*, Las Vegas Sun, Feb. 9, 2004; 'Lipitor' Surfaces in Counterfeit Probe, Wall St. J., Dec. 8, 2003, at B8.

c. The Special Case of Re-importation

Questions about production safety, equivalence, and labeling are reduced for a segment of this market known as *re-importation*. As a matter of production efficiency, pharmaceutical companies do not build plants in every country of the world. Many are located in the United States, including Puerto Rico, where the US government has long encouraged pharmaceutical research and production through generous tax incentives under Section 936 of the Internal Revenue Code.⁴²⁴ Many drugs produced in these US plants are both sold into the US market as well as exported to nations like Canada. When these drugs make the return trip back to the US, the process is called *re-importation*.

Concerns about production safety, equivalence, and labeling of re-imported drugs should be carefully scrutinized. The Canadian government is fully satisfied that these drugs are safe, efficacious and properly labeled for Canadian use. The FDA worries about errors in shipping and handling from Canada to the consumer,⁴²⁵ but these questions are relevant to all mail order pharmaceuticals and are not endogenous to pharmaceutical arbitrage from Canada. The FDA correctly notes that some Canadian standards differ from FDA rules, and forbids re-importation solely on that basis.⁴²⁶ But the missing element is any showing that the Canadian drug supply is less safe. Rx Depot was one of the largest facilitators of importing prescription drugs from Canada. The FDA sued Rx Depot, demanding that importation cease. At the Rx Depot trial in October 2003, the FDA was unable to say that Canadian drugs were unsafe or had injured Americans.⁴²⁷

The most thorough recent analysis of this question concludes that the Canadian drug supply is actually safer on balance than the US. The State of Illinois report recommends a controlled importation system, with extensive safety checks, that results in a high quality drug supply at substantial savings.⁴²⁸ The EU has many years of experience with parallel trade in pharmaceuticals, without significant safety issues.⁴²⁹

2. Reducing Arbitrage Supply and Demand

Each arbitrage transaction lowers the average price. If the supply or demand of product available for arbitrage can be limited, the net financial impact on the producer will be less severe. Conversely, if supply and demand are unlimited, differential pricing will disappear, and a new equilibrium price will prevail in both markets, shifting surplus from the producer to the consumer.

a. Targeting Canadian Internet Pharmacies

⁴²⁴ 26 U.S.C. § 936 (2004) (the Puerto Rico and Possessions Tax Credit).

⁴²⁵ Rx Depot Transcript, *supra* note 384, at 29-31.

⁴²⁶ Rx Depot Transcript, *supra* note 384, at 28, 76-77.

⁴²⁷ Rx Depot Transcript, *supra* note 384, at 138-141; *but see* Hubbard Letter, *supra* note 373 (claiming that internet sales from Canada will be more open to counterfeiting).

⁴²⁸ Kamath & McKibbin, *supra* note 376, at 1-5.

⁴²⁹ West & Mahon, *supra* note 319.

Pharmaceutical companies have identified Canadian pharmacies which sell to the US market. These pharmacies have been threatened with a refusal to deal unless the cross-border sales cease.⁴³⁰ This threat not only cuts off the supply for the patented drugs being arbitrated, but it also uses the entire product line as a weapon to enforce differential pricing.

This strategy may not wholly prevent arbitrage. Some doubt the effectiveness or legality of attempts to restrict supply to Canada.⁴³¹ Members of Congress have asked the US Attorney General to investigate whether antitrust laws are being violated,⁴³² and traditional Canadian pharmacies are complaining about the impact of drug company restrictions on their domestic operations.⁴³³

Canadian pharmacies will still be able to purchase drugs for export, but will be forced to purchase through intermediaries. Expenses and marginal cost are likely to rise, but given the significant price differentials between the US and Canada, arbitrage opportunities will remain. Perverse effects should also be noted. By cutting off direct supplies to exporting pharmacies, the pharmaceutical companies force additional intermediaries into the supply chain, which increases safety and handling problems, increases inefficiencies, and increases the opportunity for spoilage and introduction of counterfeits.⁴³⁴ If the concern is truly for patient safety, supply restrictions are a crude and counterproductive tool.

b. Reducing Demand in the US With a Medicare Prescription Drug Benefit

Pharmaceutical companies also restrict demand in the US. The current market is mostly non-emergency outpatient drugs. For the Medicare population, these drugs have not

⁴³⁰ Tamsin Carlisle, *Some Online Pharmacies Aren't Filling Big Orders Due to Fears of Shortages*, Wall St. J., Dec. 26, 2003, at A9; Tony Pugh, *Low-Cost Drug Sales to U.S. Should Stop, Canadian Group Says*, Philadelphia Inquirer, Nov. 16, 2003, available at www.philly.com; John O'Connor, *Canadians Warn of Rx Shortage*, Chi. Sun-Times, Nov. 13, 2003, available at www.suntimes.com; Simon, *supra* note 275; Tamsin Carlisle, *Pfizer Pressures Canadian Sellers of Drugs to U.S.*, Wall St. J. Jan. 14, 2004, at A6. Similar restrictions have been employed for many years to hinder parallel trade in Europe, Maskus & Ganslandt, *supra* note 17, at 69-70, with limited effectiveness. West & Mahon, *supra* note 319. For the effects of the same tactic on a national level, see Danzon, et al., *supra* note 198.

⁴³¹ Kamath & McKibbin, *supra* note 376, at 22 ("we do not feel the manufacturers rhetoric to restrict supply will ever materialize either broadly or consistently, and not at all in the Canadian pharmacies that are hybrid – internet and retail for two reasons. First limiting supply to Canadians pharmacies may risk their Canadian patent protection; second, as the Minnesota Attorney General and Illinois Attorney General are currently investigating any concerted effort by the pharmaceutical companies to limit supply may violate US antitrust laws.")

⁴³² Gardiner Harris, *Some in Congress Seek Inquiry Over Drug Supply to Canada*, N.Y. Times, Nov. 1, 2003.

⁴³³ Tamsin Carlisle, *Some Online Pharmacies Aren't Filling Big Orders Due to Fears of Shortages*, Wall St. J., Dec. 26, 2003, at A9; Tony Pugh, *Low-Cost Drug Sales to U.S. Should Stop, Canadian Group Says*, Philadelphia Inquirer, Nov. 16, 2003, available at www.philly.com; John O'Connor, *Canadians Warn of Rx Shortage*, Chi. Sun-Times, Nov. 13, 2003, available at www.suntimes.com.

⁴³⁴ Kamath & McKibbin, *supra* note 376, at 11-18 (Canada's drug distribution system does not rely on intermediates to the same extent as the US system. Increasing reliance on intermediates increases the risk of counterfeit drugs.).

been covered. If Medicare provided an outpatient drug benefit, a large part of the consumer arbitrage demand would disappear. In 2003, PhRMA reversed its historic opposition to a Medicare drug benefit, and embraced a market-based third party reimbursement plan in Medicare for outpatient drugs.⁴³⁵ The new Medicare drug benefit will reduce consumer demand for arbitrage in an important population and thus support differential pricing.

C. Implications of Optimality for Canadian-US arbitrage

Mindlessly blocking pharmaceutical arbitrage within the OECD needlessly sacrifices cost and financial access on the altar of quality. Wonder drugs are useless if they are too expensive to be taken as prescribed. The government's regulatory power should not be used to force consumers into grey markets.

The US should permit functional pharmaceutical arbitrage, particularly with countries with NDRAs similar to the FDA. Regulatory resources would be devoted to coordination with these governments to ensure the integrity of the supply chain. With government support or neutrality, arbitrage would reduce US drug prices as differential pricing between OECD nations dissolved. Erosion of differential pricing would lower costs and improve financial access to important drugs.

PhRMA companies bemoan this approach as destructive of long-term research incentives. This is an overly simplistic assessment, for it assumes that patent rents would be sub-optimal at undifferentiated OECD prices. But three other conditions are possible: (1) Current Canadian⁴³⁶ prices are supra-optimal, and thus Canada is not free riding on American R&D;⁴³⁷ (2) Optimal patent rents would be achieved at prices between current US and Canadian prices; and (3) PhRMA companies will compensate for reduced unit prices by increasing volume.

If Canadian prices currently result in supra-optimal patent rents, then extending Canadian prices to the US will do no harm to innovation. This astonishing possibility would greatly reduce US pharmaceutical access issues without any decline in innovation. Price controls in Canada do not appear to have stifled innovation, as Canadian pharmaceutical R&D is robust and growing.⁴³⁸

⁴³⁵ Prescription Drug and Medicare Improvement Act of 2003, 42 U.S.C. 1395 et seq. [§§ 1860D-1860D-26 of SSA] (2004). This plan also sows the seeds of future government price controls. Once the federal government becomes the payor, price increases are directly translated into budget issues. Medicare providers such as physicians and hospitals were once paid on a fee for service market basis; after years of budgetary issues, Medicare now imposes price controls and rate setting for physician and hospital services. Pharmaceuticals may well follow the same trend line.

⁴³⁶ Or non-US OECD country.

⁴³⁷ Thanks to Professor James Friedberg for this suggestion.

⁴³⁸ Barrados, et al., *supra* note 96, at ¶ 17.11 (Canadian drug companies agreed to increase R&D to 10% of sales by the end of 1996). For current data on Canadian pharmaceutical R&D, see <http://www.canadapharma.org> (the official trade association website).

If optimality lies somewhere between US and Canadian prices, then US prices could be decreased by some amount without harming innovation. Modest levels of arbitrage and additional price transparency may achieve this result.

Finally, the Canadian experience suggests that PhRMA companies will react to reduced unit prices by stimulating demand for their products. In Canada, despite stable to declining Canadian unit prices for patented pharmaceuticals, national drug expenditure per capita is up at 10.2% annual growth rates.⁴³⁹ Companies increase their profits in declining unit price markets by increasing unit sales,⁴⁴⁰ and developing new drugs.⁴⁴¹ If profits are stable or increasing, innovation is not harmed. It may be possible to reduce prices, increase access and improve human health simultaneously – the Holy Grail of health policy.

The major barrier to empirically proving any of these three conditions is the lack of independent and reliable data on actual R&D expenditures and profits. Erosion of the OECD internal differential pricing system would put the ball in PhRMA companies' court to demonstrate whether the resulting patent rents were globally sub-optimal. For perhaps the first time, these decisions could be made on the basis of actual data, rather than imprecise estimates.

* * * * *

Conclusion

The head of the US global AIDS effort is Ambassador Randall Tobias, the former CEO of Eli Lilly & Co. When asked about the essential medicines access issue, he claimed it was “yesterday’s issue” and that “from a price point of view, there’s no longer that much difference.”⁴⁴² I beg to differ. Not only are ARVs still not widely available at marginal cost, but drug pricing remains unaffordable for other global diseases such as cancer and heart disease in low-income countries. The industry prefers to turn off the media spotlight and assume the problems were addressed at Doha and Cancun, or by PEPFAR. Meanwhile, global public health catastrophes continue to mount. For some of these conditions, we possess effective therapies which can be provided as non-rival goods, but are withheld from the poor because of IP laws.

Health care public policy should not be chained to innovation, but must also champion access, whether in Africa or Akron. The theory and praxis of pharmaceutical arbitrage suggests that pharmaceutical access may be greatly improved, at a modest cost, without damaging optimal innovation.

⁴³⁹ Canadian Institute for Health Information, *supra* note 58, at fig. 19 (stable to declining Patented Medicine Price Index since the introduction of the Patented Medicine Prices Review Board).

⁴⁴⁰ Canadian Institute for Health Information, *supra* note 58, at fig. 13 (annual growth rate of per capita prescribed drug expenditures of 10.2% 1997-2000).

⁴⁴¹ Canadian Institute for Health Information, *supra* note 58, at 33-43.

⁴⁴² Robin Wright, *A CEO to Direct the AIDS Battle: Former Eli Lilly Chief Comes Out of Retirement*, Washington Post, Feb. 13, 2004, at A25.