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Foreword: Globe-Hopping Pharmaceuticals

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Each spring the incoming editorial staff at the American Journal of Law and Medicine chooses the focus for the following year's Symposium Issue, and well-known scholars in the field are asked to contribute to its publication. Since these authors are already experts in the area, we give them free rein to explore whatever aspect of the overall topic interests them most. We thought that this year's subject, GLOBALIZATION OF PHARMACEUTICALS: INTERNATIONAL REGULATORY ISSUES, might produce papers exploring high-profile international controversies related to direct-to-patient advertising,[1] pharmacovigilance[2] or the regulation of dietary supplements increasingly consumed all over the globe.[3] We also expected articles dealing with regional and international efforts to achieve greater regulatory harmonization, such as those involving the European Medicines Agency,[4] the nascent Trans-Tasman Pharmaceutical Products Regulatory Authority,[5] or the International Committee on Harmonisation.[6] Two of our authors chose to examine one of those latter predicted subjects tangentially, but only one focused squarely on achieving more regulatory congruence on an international scale.

This symposium topic drew forth a series of nine articles from our twelve experts that fell—somewhat surprisingly—into four seemingly disparate categories;

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[1] Margaret Gilhooley, *Heal the Damage: Prescription Drug Consumer Advertisements and Relative Choice,* 38 J. OF HEALTH LAW 1 (2005); Caroline L. Nadal, *The Societal Value of Prescription Drug Advertisements in the New Millenium: Targeted Consumers Become The Learned*, 9 J.L. & POLY 451 (2001); American Medical Association, *Direct-to-Consumer Advertising of Prescription Drugs,* 55 FOOD & DRUG L.J. 119 (2000); Tamar Terzian, *Direct-to-Consumer Prescription Drug Advertising,* 25 AM. J.L. & MED. 149 (91999); Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141 (1997).

[2] World Health Organization, *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Product*s (2002), *available at* http://whqlibdoc.who.int/hq/2002/a75646.pdf; Phil B. Fontanarosa et. al., *Postmarketing Surveillance—Lack of Vigilance, Lack of Trust*, 292 JAMA 2647 (2004).

[3] *See generally*, Symposium, *The Dietary Supplement Health And Education Act: Regulation at a Crossroads*, 31 AM. J.L. & MED. 147 (2005).

[4] European Medicines Agency, http://www.emea.eu.int/.

[5] Australian New Zealand Therapeutic Products Authority, http://www.anztpa.org/index.htm.

[6] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, http://www.ich.org/cache/compo/276-254-1.html.

intellectual property dilemmas affecting global pharmaceuticals, parallel trade of licit drugs between the US and Canada, the increasing threat presented by counterfeit pharmaceuticals, and the inadequate regulation of manufacturer conflicts of interest likely to compromise human subject and patient safety.

These categories encompass a wide range of subjects, but on close examination the articles share a common subtext. The increasing globalization of pharmaceutical markets—trade in pharmaceuticals now constitutes approximately 3% of total world commerce[7]—means that no single nation can hope to resolve the countless dilemmas related to drug development, safety, efficacy, access, and pricing alone. Moreover, no one-size-fits-all regulatory or market solution to these global problems exists. Instead, the articles that follow attempt to grapple with second-best remedies from distinctive points of view, offering a mix of regulatory and market solutions to these complex issues.

INTELLECTUAL PROPERTY DILEMMAS

The first article in this collection offers Kevin Outterson's innovative approach for delivering essential medicines at low cost to the developing world—where most of the global disease burden lies—without depriving manufacturers of their expected return on investment in patented pharmaceuticals.[8] He proposes patent buy-outs of these drugs followed by marginal cost pricing in middle and low-income nations (which he defines broadly as the non-OECD countries). Treatments for chronic and infectious diseases would then be available to *all* residents of the targeted countries, rather than just the few who could afford to pay the patented price. His win/win proposal would compensate manufacturers in the amount of their expected patent rents from product sales in underdeveloped countries, in exchange for licenses to make generic versions of the drugs available to their citizens at marginal cost. Outterson acknowledges that this scheme would over-include beneficiaries in some non-OECD countries with larger middle class populations (China, India, and Brazil, for example). He nonetheless posits that his solution would help to relieve the disease burden in developing countries, while adequately preserving innovation incentives for manufacturers.

John A. Vernon, Joseph H. Golec and W. Keener Hughen's paper elaborates on the pricing/regulation interplay by exploring "the links between prices, profits and R&D," from the viewpoint of economists rather than policy analysts.[9] Because (generally higher) U.S. drug prices are determined primarily by market mechanisms, while almost all other developed countries regulate (usually lower) prescription drug prices, some social scientists have advocated price regulation and parallel trade to reduce the disparity for American consumers. Vernon and his co-authors consider the reasoning of these policy analysts flawed, and develop an empirical model simulating the impact of price regulation on pharmaceutical R&D to illustrate its destructive effects. Their results indicate that a policy shift toward increased price regulation may well "have a significant impact on future innovation," rather than

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[7] World Trade Organization, *World Trade Report: Exploring the Links Between Trade, Standards and the WTO*, at xxiv (2005), *available at* http://www.wto.org/english/res_e/booksp_e/anrep_e/world_trade_report05_e.pdf. Textiles, iron and steel, for example, have smaller shares of global trade. *Id.*

[8] Kevin Outterson, *Patent Buy-Outs for Global Disease Innovations for Low and Middle-Income Countries*, 32 AM. J.L. & MED. 159 (2006).

[9] John A. Vernon et. al., *The Economics of Pharmaceutical Price Regulation and Importation: Refocusing the Debate*, 32 AM. J.L. & MED. 175 (2006).

merely reallocating a portion of allegedly excess pharmaceutical profits to patients, as other approaches have theorized.

PARALLEL TRADE IN PHARMACEUTICALS

Parallel trade in pharmaceuticals refers to cross-border commerce in branded drugs that occurs outside of the manufacturers' usual distribution channels—one might label it the unauthorized, but putatively legal, international distribution of medicines. Parallel trade usually takes place only when cross-border pricing disparities generate profits sufficient to attract those arbitrageurs willing to incur the necessary transaction costs. As the articles in this symposium illustrate, once pharmaceuticals move beyond the relative safety of manufacturer-sanctioned international distribution channels they become vulnerable to adulteration stemming from many sources; careless handling by middlemen and deliberate manipulation by hardened criminal elements are but two examples. Indeed, as Bryan Liang points out in his article,[10] organized crime has increasingly turned from trafficking in illegal drugs to peddling legitimate ones, because the penalties for breaking the law are so much more lenient for the latter than the former.[11]

In the first of the articles on parallel trade,[12] Aidan Hollis and Peter Ibbott dissect the vogue for U.S. imports of Canadian drugs, and demonstrate why neither country should be beating the drums for parallel trade in pharmaceuticals. They acknowledge the obvious; that the Canadian government's price regulation creates the cost disparity that initially makes Canadian drugs attractive to American buyers. But they also point to exchange rate fluctuations and manufacturer price discrimination schemes as important pieces of the current arbitrage lure. They show, however, that parallel trade—primarily through internet pharmacies—has the long-run tendency to escalate Canadian prices and to foster price discrimination there, and could well foment drug shortages in that country. On the U.S. side of the equation, the threat that internet pharmacies will flood American markets with counterfeit drugs is real. Hollis and Ibbot show why we might want to think again before undermining manufacturers' global and domestic price discrimination strategies in the US.

The second parallel trade article, by Mary Ellen Fleck Kleiman,[13] explores the Constitutional implications of state initiatives to import "cheaper Canadian (and other) drugs" for their citizens. She identifies the provisions of the Food, Drug and Cosmetic Act that prohibit U.S. re-importation of prescription drugs by both individuals and organizations, and illuminates the serious safety and other concerns that justify the ban. Describing efforts in six states to circumvent the prohibition through various legislative enactments, Fleck Kleiman takes the position that the FDCA both expressly and impliedly pre-empts most state initiatives to exploit the pricing differential available from Canadian pharmacies. She concludes that U.S. public safety requires that these efforts be blocked on Constitutional grounds.

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[10] Bryan A. Liang, *Fade to Black: Importation and Counterfeit Drugs*, 32 AM. J.L. & MED. 279 (2006).

[11] *Id.* at 291-92.

[12] Aidan Hollis & Peter Ibbott, *How Parallel Trade Affects Drug Policies and Prices in Canada and the United* States, 32 AM. J.L. & MED. 193 (2006).

[13] Mary Ellen Fleck Kleiman, *State Regulation of Canadian Pharmacies: A Prescription to Violate the Supremacy Clause*, 32 AM. J.L. & MED. 219 (2006).

In the third of the Canadian parallel trade articles,[14] Daniel Gilman reiterates the point that "parallel trade is dangerous"[15] unless we are prepared to commit significant administrative resources to ensuring the safety of distribution channels—an unlikely scenario in the current political climate that would soon swallow up any short-term financial gain to U.S. consumers. Canada and the U.S. may have more regulatory convergence regarding pharmaceuticals than is found between and amongst most other countries, but Gilman shows that the European experience with harmonization through the European Medicines Agency has hardly proved a model for facilitating cross-border drug purchases. He also underscores a little-known fact—more prescriptions are already written in the U.S. for cheaper generics than for branded drugs,[16] and that number will only rise as many of today's best-selling drugs go off-patent over the next few years. Moreover, the number of U.S. patients who now "pay retail" for drugs, as opposed to those who have some form of insurance covering pharmaceuticals, is not as large as most people assume.

COUNTERFEIT DRUGS

Bryan Liang's article tackles the issue of counterfeit drugs head-on, citing sources who estimate that "approximately 10-15% of all drugs sold in the world are counterfeit,"[17] warning too that the gray market (i.e. parallel trade) is the supply chain's "soft underbelly."[18] Laing's article goes into chilling detail about the ease with which counterfeit drugs can be made, packaged and slipped into legitimate streams of commerce, facilitated by bifurcated pharmaceutical regulation at the state and federal levels. He also outlines why detection is so difficult; causal connections are difficult to make, drug-ingesting patients are often sick to begin with so any deterioration in their condition is usually attributed to their underlying disease, and packaging that might reveal fabrication is often thrown away. By the time you read his conclusion arguing for an international regulatory solution to the counterfeiting problem you may be thinking twice about what's sitting in your medicine cabinet, even if you didn't purchase it on the gray market.

Donald deKeiffer's contribution looks at the problem of counterfeit and mislabeled drugs in "legitimate" markets, specifically eschewing discussion of internet pharmacies and direct importation from Canada and elsewhere.[19] Using the Carlow Medicaid fraud case from Florida as his springboard, deKeiffer sets forth chapter and verse on the many routes by which counterfeit drugs "piggyback . . . on . . . 'legitimate' gray market" pharmaceutical shipments to infiltrate the U.S. distribution pipeline, and on the variety of schemes criminals have hatched for accomplishing that end. His proposed solution relies on currently available technology as well as regulatory reform. It includes such simple measures as requiring drugs to be dispensed in the same blister pack unit dose packaging that is used in the European Union, mandating Radio Frequency Identification to track drug inventories, and employing more tamper-resistant packaging and coding to foil counterfeiters.

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[14] Daniel Gilman, *Oy Canada! Trade's Non-Solution to "*the *Problem" of U.S. Drug Prices*, 32 AM. J.L. & MED. 274 (2006).

[15] *Id.* at 252.

[16] *Id.* at 259.

[17] Liang, *supra* note 10 at 281.

[18] *Id.* at 294.

[19] Donald deKeiffer, *Trojan Drugs: Counterfeit and Mislabeled Pharmaceuticals in the Legitimate Market*, 32 AM. J.L. & MED. 325 (2006).

INADEQUATE REGULATION OF CONFLICTS OF INTEREST

Rob Gatter's paper on the conflicts of interest that undermine the protection of research subjects all over the world draws attention to the way that the pressure to get new drugs to market quickly compromises the safety of participants in international clinical trials.[20] Echoing the point made in Kevin Outterson's article—that industrialized countries constitute the primary market for pharmaceutical companies even when they may not constitute the locus of greatest medical need—Gatter points out that the clinical research on human subjects necessary to serve manufacturers' objective of speed often takes place globally. International standards governing conflicts of interest are woefully inadequate, and he raises the possibility that "the international community may be deliberately choosing to provide less protection" for research subjects in order to promote the commercial interests of the drug industry.[21] He advocates tightening those standards, and sees the FDA as the prime candidate to push for reform on an international scale.

Finally, W. John Thomas speculates on whether the "Vioxx Story" would have had the same troubled outcome had the controversial drug been introduced first through the European Union's regulatory structures, rather than undergoing the "process corruption" that marked its journey through the FDA approval system and beyond.[22] Thomas asserts that the U.S. drug licensure system is subject to political influence (swayed by manufacturer campaign contributions) and "compromised by conflict of interest," but concludes that the pharmaceutical industry has at least equal regulatory clout in Europe. Notwithstanding the centralization of drug approval through the European Medicines Agency, since member-states retain their own approval processes for many drugs, manufacturers can forum-shop the most attractive (i.e. manufacturer-friendly) national venues for getting to market. Thereafter they can rely on mutual recognition procedures to obtain "side door" marketing permission in other EU countries.

The thought provoking contributions to this symposium remind us yet again that technology never delivers unmixed blessings, no less so when it comes to pharmaceuticals circulating in global markets. Globe-hopping pharmaceuticals increase the complexity of our world while they deliver their benefits to broader populations. The troubles they spawn ensure that the search for even second-best remedies will be a never ending quest. Our authors lay to rest the myth of simple solutions to multi-national "legitimate drug" dilemmas, and delve beneath the surface to propose a variety of sophisticated approaches for dealing with them without hindering the distribution of medications to places that need them most. Last February, these experts brought new perspectives to the discussions of globalizing pharmaceutical regulation at Boston University School of Law's workshop for symposium participants. We are proud to be a part of moving those ideas to a wider audience through this publication.

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[20] Robert Gatter, *Conflicts of Interest in International Human Drug Research and the Insufficiency of International Protections*, 32 AM. J.L. & MED. 351 (2006).

[21] *Id.* at 361.

[22] W. John Thomas, *The Vioxx Story: Would it Have Ended Differently in the European Union?* 32 AM. J.L. & MED. 381 (2006).