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Food and Drug Administration
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Re: Prescription Drug Importation; Docket No. 2004N-0115, 69 Fed. Reg. 12810 (March 18, 2004)

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit comments regarding prescription drug importation to the Task Force convened by the Secretary of Health and Human Services (HHS) in accordance with section 1122 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Pub. L. No. 108-173. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. Investing more than $33 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA believes that opening the U.S. drug supply to widespread foreign importation, while politically expedient, is ill-conceived and dangerous and will put thousands of American consumers at risk. PhRMA thus opposes such efforts for the following reasons, as elaborated in the body of our comments:

- ***Importation schemes are unsafe.*** At a time when we are struggling to combat counterfeit drugs and tighten security at our borders, we should be searching for ways to close existing loopholes in the drug distribution chain, not creating new ones by opening up the borders to foreign imports. While some believe importation can be done safely, even FDA recognizes that there is no technological "magic bullet" or inspection process that can protect against adulterated or counterfeit foreign drugs. Consequently, implementing importation would jeopardize the safety of millions of American consumers.

- ***Importation would not result in cost savings.*** There is no indication that implementing a responsible importation scheme (assuming one even exists) would result in cost savings. The costs of counterfeit-resistant technologies and industry and government testing and inspections likely would run billions of dollars each year, and the costs of defending against unmeritorious product liability claims would add substantially to that number. Even if there were cost savings, the law does not require that these get passed on to consumers. If the experience in Europe is any guide, any cost savings resulting from foreign importation will be captured by the parallel traders rather than passed on to consumers.

- ***Importation is bad public policy.*** Importation of foreign drugs is nothing more than an endorsement of, and attempt to import, foreign price control practices. These have been a disaster in foreign countries, limiting patient access to new medicines and significantly restricting research and development activities in foreign countries. American patients deserve better. For individuals who lack prescription drug coverage and cannot afford their medicines, there are better and safer ways to obtain needed medications, including company patient assistance programs, discount card programs, "shopping around," and, most significantly, the new Medicare drug benefit.

SUMMARY

For several years now, public policy makers have looked for ways to address rising health care costs in the United States. Prescription drugs are the best value in health care – saving lives, reducing pain and suffering, keeping people out of hospitals and nursing homes, and reducing other forms of health care spending. Nevertheless, prescription drugs play a steadily increasing role in the maintenance of health and the treatment of illness. Spending on prescription drugs has, therefore, increased in recent years.

The growth in prescription drug spending should be placed within the larger context of health care expenditures. Notwithstanding growth in use of and spending on medicines, prescription medicines account for only a small proportion of health care spending and growth in health care spending. According to the Centers for

Medicare & Medicaid Services (CMS), of every health dollar spent in the U.S., only about 10.5 cents is spent on outpatient prescription medicines.[1] In addition, according to a report issued by the Kaiser Family Foundation, prescription drug spending increases have begun to moderate somewhat, and today hospital spending is rising faster than spending on prescription medicines.[2]

Until December, Medicare – unlike nearly all private health insurance plans – did not cover most prescription medicines used by its 40 million elderly and disabled beneficiaries, despite the growing role of medicines in maintaining health and treating illness. Other state and federal programs (like Medicaid) did cover prescription drugs, but payors (both public and private) chafed at the prospect of seemingly high short-term expenditures on medicine, even when those costs would ultimately defray longer-term costs to the health care system.

Although members of Congress – both Democrat and Republican – sought for years to enact a Medicare prescription drug benefit, that law would not take final shape until the summer of 2003. On December 8, 2003, President Bush signed into law the most ambitious reform of Medicare in the program's 38-year history. All Medicare beneficiaries are eligible this June for a Medicare-endorsed discount card that offers discounts on prescription medicines. The lowest income seniors are eligible for $600 (per individual, or $1200 per couple) this year, and again next year, to help them afford their prescription medicines until the full Medicare prescription drug benefit begins in 2006. In 2006, all Medicare beneficiaries will be able to enroll in plans that cover prescription

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1 Centers for Medicare & Medicaid Services, "National Health Expenditures," 8 January 2004, http://www.cms.gov/statistics/nhe.

2 "Trends and Indicators in the Changing Health Care Marketplace, 2004 Update," Kaiser Family Foundation (May 2004).

drugs. Plans may vary somewhat, but in general, individuals can choose a prescription drug plan and pay a premium of about $35 a month. They will pay the first $250 of their prescription drug costs, and Medicare will pay 75 percent of the costs (and individuals the remaining 25 percent) between $250 and $2,250. Once an individual has reached $3,600 in out-of-pocket spending, Medicare will pay 95 percent of the costs, and individuals will be responsible for the remaining 5 percent. Individuals with low incomes and low assets will not have to pay premiums or deductibles and will only pay a small co-payment for each prescription needed. Other people with low incomes and limited assets will get help paying the premiums and deductible, and the amount they pay for each prescription will be limited.

Negotiation of a workable prescription drug benefit took several years. In the meantime, policymakers looking for a "quick fix" to rising health care costs began to look favorably at the foreign practice of imposing price controls on medicines. The result was section 804 of the Federal Food, Drug, and Cosmetic Act (FDCA) – initially enacted in 2000 and then revised in 2003 and tacked onto the back of the Medicare law. This provision, in its current form, would allow the commercial importation of price-controlled drugs from Canada – despite a steadily increasing volume of counterfeit medicines in the global market, despite growing evidence that drugs from third world countries are shipped through Canada to the United States, and despite the danger to American patients from medicines that have been stored, shipped, and handled by third parties outside the jurisdiction of the U.S. Food and Drug Administration (FDA).

The new law does not take effect unless the Secretary of HHS determines that importation would not raise safety issues and would produce cost savings for

American consumers. These comments explain PhRMA's position that prescription drug importation is unsafe, will not lead to any significant cost savings, and would be bad public policy.

The U.S. regulatory system governing development, approval, and marketing of new drugs is the most complex and comprehensive in the world. The U.S. does not recognize any other drug approvals as equivalent to a full new drug application (NDA) approval by the FDA, and we have not entered into a working Mutual Recognition Agreement with respect to any other country's version of "good manufacturing practices." Further, foreign health agencies are neither willing nor able to ensure the safety of drugs exported from their countries to the United States. Indeed, even fully-developed countries decline to prohibit transshipment of medicines through their borders, and some – like Canada – explicitly exempt those drugs from their laws.

Even today, with our closed distribution system and "gold standard" of approval, tens of thousands of unapproved drugs – often counterfeit, sometimes ineffective and unsafe, always unapproved and outside FDA's jurisdiction – enter the United States through the mail. FDA's inability to effectively implement the Prescription Drug Marketing Act of 1987 has contributed to the problem, but FDA and U.S. Customs have also repeatedly confirmed that they lack the resources to monitor the influx of these illegal drug imports at the border. The solution therefore is to strengthen our border and law enforcement capabilities to enforce current law, not to throw up our hands and repeal the law altogether.

Despite the safety threat – which has been documented by FDA, law enforcement, and the media – proponents of legislation argue that importation can be

made both safe and cost-effective. Importation cannot, however, be made safe with creative legislative alternatives to a system of full FDA approval and oversight, compliance with Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) requirements, and completely closed borders. Among other reasons, importation directly contradicts a core principle in the FDCA: that a medicine's safety must be proven rather than assumed. Furthermore, end-product testing is contrary to the concept of GMPs, which is premised on the notion that a product's integrity can be assured only if the process by which it is manufactured, packaged, labeled, stored, and shipped is fully under control and capable of audit at any time by FDA. Counterfeit-resistant technology available today is not a "silver bullet" for preventing the distribution of counterfeit products imported from foreign nations. A closed distribution system featuring electronic "track and trace" technology will not be ready for deployment for several more years. None of these "solutions" – technology, testing, resources – addresses the fundamental problem with importation: that it provides the opportunity for the criminal, and the merely sloppy, to endanger American patients, whether intentionally or inadvertently. America's research-based pharmaceutical manufacturers have long been held to the most rigorous pre-clinical and clinical product testing requirements, manufacturing process validation requirements, and pre- and post-approval GMP requirements in the world. American patients deserve nothing less.

Further, implementing importation will not lead to lower consumer drug prices. Neither section 804 nor any of the pending importation bills requires cost savings to be passed on to consumers. Experience in the European Union, where parallel trade is legal, demonstrates that the savings from inter-country price differentials are captured by

parallel importers and not passed on to consumers. Many of the "safety" measures described by prescription drug importation advocates – such as implementation of a track and trace pedigree system or universal deployment of counterfeit-resistant technology – would have the counter-productive effect of substantially raising costs to the healthcare system in the United States. Appropriating adequate funds for FDA, U.S. Customs, and law enforcement agencies to inspect all imports and enforce the law would seriously strain the federal healthcare budget. A prescription drug importation scheme would lead to an explosion in unmeritorious tort litigation against innocent parties, while injured consumers would be challenged to find, and bring to justice, counterfeiters, foreign importers and other bad actors who truly might be at fault. This, too, would result in additional costs to the system.

Finally, prescription drug importation is bad policy. Most importantly, a decision to implement prescription drug importation is a decision to import foreign price controls. Pharmaceutical price controls inevitably deny patients access to important new medicines. They also discourage research and development of new medicines, depress and distort international trade in pharmaceuticals, and affect U.S. jobs. Foreign pharmaceutical price controls force Americans to subsidize medical research and development for the rest of the world. Importing price-controlled drugs will support and encourage the foreign practice of price-controls, undermining one of the only free markets for medicines in the world, and effectively endorse these outcomes. Importation of prescription drugs from abroad could also violate U.S. intellectual property rights, upsetting the careful balance between encouragement of innovation and ensuring patient access to new medical discoveries.

While importation is often hailed as the only solution for individuals who lack prescription drug coverage and cannot afford their medicines, in fact there are better, safer ways to ensure that patients have access to affordable medicines. As noted, all Medicare beneficiaries are eligible for a Medicare-endorsed discount card that will offer discounts on prescription medicines. Further, in 2006, all Medicare beneficiaries will be able to enroll in plans that cover prescription drugs. Patient assistance programs sponsored by pharmaceutical companies are available to all uninsured Americans who meet income eligibility requirements. Pharmaceutical company discount card programs are another way for seniors and the disabled to save money on prescription medicines. In addition, many states operate prescription assistance programs for lower income Medicare beneficiaries. Shopping around among pharmacies can also yield savings for consumers. Finally, generic drugs available in the U.S. are often considerably less expensive than foreign, non-FDA approved drugs, and they offer a solution for many who cannot afford their medicine.

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I. BACKGROUND

A. The U.S. regulatory system governing development, approval, and marketing of new drugs is the most complex and comprehensive in the world.

The United States regulatory system governing development, approval, and marketing of new drug products is nearly a century old. It has become more comprehensive and more rigorous over time. In 1938, the Federal Food, Drug, and Cosmetic Act (FDCA),[3] which remains in place today, prohibited the marketing of any drug not shown to be "safe for use under the conditions prescribed, recommended, or suggested" in its labeling.[4] Beginning in 1962, FDA gained explicit authority to demand proof that a drug is effective and to prescribe the tests that a manufacturer must perform before its product can be approved for marketing.[5] Over the last half century, numerous amendments have expanded, strengthened, and refined the regulatory scheme.[6] These amendments include the Prescription Drug Marketing Act of 1987 (PDMA), which closed the medicine supply to products that have circulated overseas, beyond the jurisdiction of FDA and outside the control of the manufacturer. FDA now regulates virtually every stage in the life of a prescription drug sold in the U.S., from pre-clinical

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3 Pub. L. No. 75-717, 52 Stat 1040 (1938).

4 21 U.S.C. § 355(d)(1).

5 Act of October 10, 1962, Pub. L No. 87-781, 76 Stat 780, codified at 21 U.S.C. § 355(d)(5).

6 *See, e.g.*, the Durham-Humphrey Act, Pub. L. No. 82-215, 65 Stat. 648 (1951) (concerning prescription requirement); the Drug Listing Act of 1972, Pub. L. No. 92-387, 86 Stat. 559 (1972); the Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (subsequently amended); the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984); the Drug Export Amendments of 1986, Pub. L. No. 99-660, 100 Stat. 3743 (1986), the Prescription Drug Marketing Act of 1987, Pub. L. No. 100-293, 102 Stat. 95 (1988) (subsequently amended); the Generic Drug Enforcement Act of 1992, Pub. L. No. 102-282, 106 Stat. 149 (1992); and the Prescription Drug User Fee Act, Pub. L. No. 102-571, 106 Stat. 4491 (1992).

testing in animals and human clinical trials before the drug can be marketed, to manufacturing, labeling, packaging, and advertising when the drug is marketed, to monitoring actual experience with the drug after its sale to consumers.

The FDCA prohibits the introduction into interstate commerce of any "new drug" (which includes virtually all prescription drugs) that is not the subject of a new drug application (NDA) or abbreviated new drug application (ANDA) that has been approved by FDA.[7] Importation of a prescription drug constitutes introduction of that drug into interstate commerce and thus is subject to the FDA approval requirement.[8] A drug product manufactured in a plant that is not listed in the NDA or ANDA or manufactured according to specifications differing from those in the approved application, even if made by the same company holding the approval, is an unapproved drug that cannot be imported or otherwise introduced into interstate commerce.[9] Foreign versions of drugs that are approved in the United States often are manufactured by companies that do not hold an approved NDA or ANDA. Even if the foreign version is made by a company with a U.S. approval, the foreign version often does not comply with the terms of the approved NDA or ANDA and thus is unapproved. For these reasons, the importation of a drug purchased in a foreign country will usually violate the statutory requirement for FDA approval.

Some drugs available overseas are manufactured in the United States and then exported. The FDCA prohibits the importation (sometimes called the "reimportation") of these drugs, even if they are manufactured in full compliance with the approved

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7 *See* 21 U.S.C. §§ 331(d), 355(a).

8 *See* 21 U.S.C. § 321(b).

9 21 U.S.C. §§ 331(d) & 355.

NDA.[10] Congress added this prohibition on reimportation to the law in the PDMA, after a series of hearings documented adulterated and counterfeit drugs entering the country. In 1984, for instance, nearly two million counterfeits of G. D. Searle's Ovulen 21 birth control pills were found to have been shipped to Miami and New York from Panama. In 1985, 1800 bottles of Eli Lilly's antibiotic Ceclor capsules entered Miami and Boston from Singapore. The products contained Eli Lilly's active ingredient, but the capsules, labels, lot numbers, and packaging were all fake. The Energy and Commerce Committee concluded that permitting reimportation of U.S.-origin goods "prevents effective control or even routine knowledge of the true sources of merchandise in a significant number of cases."[11] As a result, "pharmaceuticals which have been mislabeled, misbranded, improperly stored or shipped, have exceeded their expiration dates, or are bald counterfeits, are injected into the national distribution system for ultimate sale to consumers."[12] Further, "the very existence of the market for reimported goods provides the perfect cover for foreign counterfeits."[13] After finding that "[l]arge amounts of drugs are being reimported to the United States as American goods returned"; that "[t]hese imports are a health and safety risk to American consumers because they may have become subpotent or adulterated during foreign handling and shipping"; and that "[t]he ready market for prescription drug reimports has been the catalyst for a continuing series of frauds against American manufacturers and has provided the cover for the importation

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10 21 U.S.C. § 381(d).

11 H.R. Rep. No. 76, 100th Cong., 1st Sess. 6-7 (1987).

12 *Id.*

13 *Dangerous Medicine: The Risk to American Consumers from Prescription Drug Diversion and Counterfeiting*, 99th Cong., 2d Sess. 22 (Comm. Print 99-2 1986).

of foreign counterfeit drugs,"[14] Congress prohibited the reimportation of approved drugs that have left the United States.[15]

There is an exception to this prohibition for the original manufacturer, who is part of a closed system and subject at all times to FDA authority and oversight.[16] The manufacturer's own importation of drugs that have never been outside its control is comparable to shipments between its manufacturing plants and warehouses within the United States. It is completely different from the importation of drugs that have been

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[14] Pub. L. No. 100-293, § 2.

[15] The record supporting the PDMA was extensive and unambiguous, and the prohibition on reimportation was not controversial. In June 1985, the staff of the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce published its first report on the drug diversion problem. Staff of Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce, 99th Cong., Report on Prescription Drug Diversion and the American Consumer: What You Think You See May Not Be What You Get (Comm. Print 99-R 1985). This report discussed the Ovulen 21 incident and laid the groundwork for the PDMA provision prohibiting reimportation. The subcommittee convened the first of eight public hearings on drug diversion and counterfeiting on July 10, 1985. Over two years, the committee would hear from state and federal law enforcement officers, private investigators, state drug and narcotic agents, Customs officials, FDA officials, pharmacists, diverters, U.S. attorneys, pharmacy and pharmaceutical trade associations, pharmaceutical sales representatives, and senior enforcement officials from state regulatory agencies. Two more Subcommittee reports were released, "Dangerous Medicine: The Risk to American Consumers from Prescription Drug Diversion and Counterfeiting," 99th Cong., 2d Sess. (Comm. Print 99-2 1986), and "Uncertain Returns: The Multimillion Dollar Market in Reimported Pharmaceuticals," 99th 2nd. Cong., Sess. (Comm. Print 99-GG 1985). Final legislation passed in early 1987. As Mr. Waxman pointed out on the day it passed the House, the PDMA "is a very important public health measure. It will provide additional assurances to American consumers that drugs they purchase will always be safe and effective... The bill was developed after one of the most extensive investigations the Energy and Commerce Committee has conducted on a health-related matter.... [The Subcommittee] discovered that all the efforts of the FDA to approve drugs for safety and effectiveness could be for naught if the wholesale distribution system didn't handle drugs properly or allowed counterfeit drugs to be passed along to consumers." 133 Cong. Rec. 10962 (May 4, 1987). He added, "[t]he bill is not controversial and has enjoyed bipartisan support."

[16] 21 U.S.C. § 381(d)(1).

placed into the wholesale and retail distribution systems of foreign countries, where they are no longer subject to FDA jurisdiction.

Notwithstanding the statutory prohibition on importation of unapproved drugs, in the early 1990s FDA articulated a policy of "enforcement discretion" with respect to personal importation of certain unapproved drugs.[17] Under this policy, FDA personnel may permit the importation of a drug if: (1) it is clearly intended for personal use; (2) the intended use of the drug is clearly identified; (3) the drug is intended for treatment of a serious condition for which satisfactory treatment is not available in the U.S.; (4) the drug is not known to present a significant health risk; and (5) the drug is not approved in the U.S. FDA officials will presume commercial use, rather than personal use, if the supply exceeds what one person might take in three months. FDA guidelines direct agency personnel to look for either: (a) the inclusion of the name and address of a doctor licensed in the U.S. and responsible for the patient's treatment with the product, or (b) evidence that the product is intended for the continuation of treatment begun in the foreign country. The personal use policy does not apply to the importation of unapproved foreign versions of drugs available in the United States, or to reimportation of drugs in violation of the PDMA. It applies only to the personal importation of drugs for which there is no approved U.S. source. Importantly, importation within the four corners of this policy remains technically illegal. The policy represents a limited exercise of enforcement discretion in the interest of individual patient treatment.[18]

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[17] *See* FDA Regulatory Procedures Manual, "Coverage of Personal Importations."

[18] FDA has repeatedly expressed concerns about the safety of mail-order personal imports, and in 2001 the agency recommended that the policy be rescinded. *See* Letter from Food and Drug Administration Acting Principal Deputy Commissioner to Secretary of Health and Human Services (requesting that HHS Secretary revoke the personal

B. Responding to constituent pressure stemming largely from the lack of Medicare coverage for prescription drugs, Congress in 2000 enacted – and in 2003 revised – legislation permitting commercial reimportation of prescription drugs that have been outside the control of the manufacturer and beyond the oversight of FDA.

In 2000, Congress authorized an additional exception to the prohibition on reimportation. The Medicine Equity and Drug Safety Act (MEDS Act) added a new section 804 to the FDCA under which pharmacists and wholesalers would be permitted to import drugs from a list of designated countries, including Canada and the countries of the European Union.[19] During the debate on the MEDS Act, however, concerns were voiced that section 804 would be ineffective (at reducing consumer prices) and unsafe (by allowing the influx of counterfeit and adulterated products). Congress responded to these concerns in part by delaying implementation until the Secretary of HHS could "demonstrate" that the law would pose no additional risk to public health and safety and that it would result in a significant reduction in the cost of covered products. Secretary Donna Shalala concluded on December 26, 2000, that it was "impossible . . . to demonstrate that [importation] is safe and cost effective."[20] Similarly, Secretary Tommy Thompson, citing an analysis by FDA on the safety issues and an analysis by his planning

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importation mail policy) (May 24, 2001); *see also* Examining Prescription Drug Importation: A Review of a Proposal to Allow Third Parties to Reimport Prescription Drugs, Hearing before the Subcommittee on Health of the Committee on Energy and Commerce of the U.S. House of Representatives, 10th Cong. 2d Sess. 40 (July 25, 2002) ("[W]e stand by that recommendation and believe that we should work with the Congress to develop legislation that would indeed give FDA the ability to screen these drugs and turn them back.") (William K. Hubbard, Senior Associate Commissioner); Continuing Concerns over Imported Pharmaceuticals, Hearing before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce of the U.S. House of Representatives, 107th Cong. 1st Sess. 48, 62, 72, 76 (June 7, 2001) (Hubbard).

[19] Pub. L. No. 106-387, 114 Stat. 1549, 1549A-35 (2000).

[20] Letter from Secretary Donna Shalala to the Hon. William J. Clinton (December 26, 2000).

office on the cost issues, decided not to "sacrifice public safety for uncertain and speculative cost savings."[21]

In the recently enacted Medicare drug benefit legislation, Congress replaced the MEDS Act with a new section 804. Reimportation language was included in the drug benefit legislation – despite enactment of a prescription drug benefit for Medicare beneficiaries – primarily because proponents of importation were working separately from the Medicare conferees to address access issues. As explained below (page 98), the new Medicare discount card, fully operational on June 1, and the drug benefit that will be available on January 1, 2006, provide safe and effective ways for low-income Americans to access affordable medicines. Company and state patient assistant programs, as well, are available to help the uninsured. These options are all safer than the importation of foreign products.

The new language, in section 1121 of the MMA, would permit reimportation only from Canada, and it would not permit the reimportation of controlled substances, biological products, infused drugs (including peritoneal dialysis solutions), intravenously injected drugs, drugs inhaled during surgery, or parenteral drugs that the Secretary finds pose a threat to public safety.[22] Under the new provisions, reimported drugs must still comply with sections 501, 502, and 505 of the FDCA. That is, they must not be adulterated, misbranded, or unapproved new drugs.[23]

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[21] Letter from Secretary Tommy G. Thompson to Senator James Jeffords (July 9, 2001).

[22] 21 U.S.C. § 384(a)(3).

[23] 21 U.S.C. § 384(c).

The MMA permits reimportation by pharmacists and wholesalers that register with FDA and provide the name of a registered agent.[24] For each shipment, the importer must submit information and documentation to FDA. Besides basic information such as the quantity of drug shipped, the date shipped, and the origin and destination of the shipment, the importer must document the lot number and source of the drug and establish the drug's chain of custody. The importer must also test samples of the drug for authenticity and degradation.[25] The importer must certify that the drug is approved for U.S. marketing and is not adulterated or misbranded, and must provide records from a qualified laboratory showing the drug complies with established specifications and standards.[26]

Congress again included a requirement that the Secretary determine importation would be safe. Thus none of these provisions takes effect, and no new imports are authorized, unless and until the Secretary certifies that importation will not raise safety issues and will lead to savings for consumers. In order to make any such certification, the Secretary must conduct a careful and thorough factual investigation.[27] The contours of this factual investigation will necessarily overlap those of the study

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[24] 21 U.S.C. § 384(a)(1) & (f).

[25] 21 U.S.C. § 384(d)(1)(J)(III)(aa). Somewhat more lenient sampling rules apply where the import is shipped directly from the first foreign recipient of the drug. In contrast, much more lenient pedigree (chain-of-custody) rules apply where the import is not shipped from the first foreign recipient. In other words, when a product has been shipped through multiple foreign locales, the law substitutes slightly more rigorous testing (testing of a statistically valid sample from each batch in all shipments, rather than testing a statistically valid sample of the shipments themselves), but it abandons any pretence of documenting a chain of custody.

[26] 21 U.S.C. § 384(d)(1).

[27] FDA has been unambiguous and unwavering in its position that importation is unsafe. A complete list of FDA statements to this effect since 2000 can be found in the Appendix. Any certification under the MMA that importation can be done safely would need to explain the basis for a complete reversal in position.

required under section 1122 of the MMA, which directs the Secretary to "conduct a study on the importation of drugs into the United States pursuant to section 804 of the Federal Food, Drug, and Cosmetic Act (as added by section 1121 of this Act)."

The Conference Report issued on November 21, 2003, elaborates eleven topics that should be addressed in the study report.[28] Those are:

1. the limitations, including limitations in resources and in current legal authorities that may inhibit the Secretary's ability to certify the safety of imported drugs (addressed on pages 23-39 and 59-68 of these comments);

2. the pharmaceutical distribution chain and the need for, and feasibility of, modifications in order to assure the safety of imported products (addressed on pages 23-39 of these comments);

3. whether anti-counterfeiting technologies could improve the safety of products in the domestic market as well as products that may be imported (addressed on pages 23-29, 39-50 and 59-68 of these comments);

4. the costs borne by entities within the distribution chain to use anti-counterfeiting technologies that may be required to provide import security (addressed on pages 42-44 of these comments);

5. the scope, volume and safety of unapproved drugs, including controlled substances, entering the United States via mail shipment (addressed on pages 10-16 of these comments);

6. the extent to which foreign health agencies are willing and able to ensure the safety of drugs being exported from their countries to the United States (addressed on pages 50-59 of these comments);

7. the potential short- and long-term impacts on drug prices and prices for consumers associated with importing drugs from other countries (addressed on pages 76-97 of these comments);

8. the impact on drug research and development, and the associated impact on consumers and patients, if importation were permitted (addressed on pages 81-97 of these comments);

9. the agency resources, including additional field personnel, needed to adequately inspect the current amount of pharmaceuticals entering the country (addressed on pages 16-23 of these comments);

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[28] *See* H. Rep. No. 108-391, at 833-834.

10. the liability protections, if any, that should be in place if importation is permitted for entities within the pharmaceutical distribution chain (addressed on pages 68-75 of these comments); and

11. ways in which importation could violate U.S. and international intellectual property rights and additional legal protections and agency resources that would be needed to protect those rights (addressed on pages 81-97 of these comments).

The Department of HHS convened a Task Force on Drug Importation to compile information and assist in responding to the eleven issues. As part of this effort, HHS has opened a public docket and is requesting public comment. PhRMA's comments follow. For each section of our comments, we indicate the issue in the House Report on which we are offering comment.

II. COMMENTS

A. Implementing importation would jeopardize the safety of millions of American consumers.

1. Even today, with our closed distribution system, tens of thousands of unapproved drugs – often counterfeit, sometimes ineffective and unsafe, always unapproved – enter the United States through the mail.[29]

According to testimony provided in June 2003 by Elizabeth Durant, Executive Director of Trade Compliance and Facilitation at the U.S. Bureau of Customs and Border Protection, "[m]illions of packages come through mail and express courier facilities each year. Thousands of packages, particularly in the mail, are found to contain illegal and unapproved pharmaceuticals."[30] Further, Customs estimates that "10 million

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[29] This section of our comments responds to item 5 on page 9 (the request for information about the scope, volume, and safety of unapproved drugs, including controlled substances, entering the United States via mail shipment).

[30] Testimony of Elizabeth Durant, Executive Director of Trade Compliance and Facilitation at the Bureau of Customs and Border Protection, before the House Energy and Commerce Subcommittee on Oversight and Investigations (June 24, 2003).

people cross the land border annually carrying the same unapproved products."[31] Other publicly-available data corroborate these estimates. For example, according to Juniper Research, a business and market research company in Darien, Connecticut, U.S. consumers spent $700 million in 2002 on prescription drugs from foreign online pharmacies, and were estimated to spend approximately $1.4 billion in 2003.[32] According to IMS Health Consulting, a pharmaceutical information company, Americans spent $695 million on prescription drugs from Canada in 2003, compared with $414 million in 2002.[33] A poll conducted in June 2002 identified over 1 million U.S. consumers using the Internet as a means to access prescription medicines from Canadian pharmacies.[34] This figure was also reported by the *Kansas City Star* and the *Toronto Star* in July 2003.[35]

These illegal prescription medicine imports come from all over the world. In the first of two series of "blitz" exams conducted by FDA and Customs in 2003, 1153 imported drug products were examined.[36] The overwhelming majority of these products

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31 *Id.*

32 Jodi S. Cohen, "Defiant Stores Offer Rx for Rising Cost of Drugs; Businesses Help Seniors Buy Cheaper Medicine from Canada; U.S. Suit Says the Drugs Aren't Safe," *Chicago Tribune* (September 12, 2003).

33 Bob Tedeshi, "Looking to Canadian Web Pharmacies for Savings," *New York Times* (March 8, 2004).

34 Testimony of Elizabeth A. Wennar, M.P.H., D.H.A, President and CEO, United Health Alliance Bennington, Vermont, and Principle, HealthInova, Manchester, Vermont, before the House Government Reform Subcommittee on Human Rights and Wellness (April 3, 2003).

35 *See* David Olive, "Big Pharma Blames Canada," *The Toronto Star* (July 17, 2003); Matt Sterns, "Demand Pushes Drugs via Canada; Illegal or Not, Sales to U.S. Thriving," *Kansas City Star* (July 30, 2003).

36 The first blitz exams were conducted in the Miami and New York (JFK) mail facilities from July 29-31, 2003, and in the San Francisco and Carson, California mail facilities from August 5-7, 2003. The second blitz exams were conducted in the Buffalo,

– 1019 or 88 percent – were illegal unapproved drugs.[37] Of the drugs examined, 15.8 percent (161) entered the U.S. from Canada; 14.3 percent (146) from India; 13.8 percent (141) from Thailand; and 8.0 percent (83) from the Philippines. The remaining drugs came from other countries. In a second series of blitz exams, FDA and Customs examined 1006 packages. FDA determined that 80 percent had been exported from Canada, 16 percent from Mexico, and 4 percent from Japan, the Netherlands, Taiwan, Thailand and the United Kingdom.[38] Further, as explained below (page 55), many of the drugs shipped from Canada clearly originated in a third country.

The prescription medicines entering the United States via illegal importation include dangerous, unapproved, and counterfeit medicines. For example, they include:

- ***Drugs that are improperly labeled.*** Many of the drugs that were examined by FDA and Customs during the import blitzes did not contain adequate labeling or instructions for proper and safe use. Some products contained foreign labeling, some contained dual labeling (labeling in English and another foreign language), and several contained no labeling whatsoever and were offered in loose plastic bags or tissue paper. Others were shipped in containers that appeared to be intended for pharmacists, without U.S.-approved patient labels.

- ***Controlled substances.*** Examiners discovered over 25 different controlled substances, including: Ratio-Lenoltec with codeine, codeine, Valium (diazepam), Ativan (lorazepam), Tylenol 3 (containing codeine), Xanax, anabolic steroids, and clonazepam, all of which are controlled substances with potential for abuse and all of which can be dangerous if taken inappropriately or without a doctor's supervision. These controlled substances came from Canada, Costa Rica, Guatemala, Malaysia, New

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Chicago, Dallas and Seattle mail facilities and the Memphis and Cincinnati courier hubs, in November 2003.

[37] "FDA/U.S. Customs Import Blitz Exams Reveal Hundreds of Potentially Dangerous Imported Drug Shipments," Press Release, U.S. Food and Drug Administration, P03-73 (September 29, 2003).

[38] *See* FDA Press Release, January 27, 2004.

Zealand, Peru, the Philippines, Taiwan, Thailand, and the United Kingdom.

- ***Potentially-recalled drugs***. Blitz exam results revealed that American consumers were sent Serevent Diskus and Flovent Diskus from Canada. Both medicines are used to treat asthma and chronic obstructive pulmonary disease (COPD). Flovent Diskus is approved, but not currently marketed, in the United States. Shortly after the second series of blitz exams, certain lots of the Canadian versions of these medicines were recalled in Canada because there were concerns that their delivery systems might not function properly and might deliver too little of the drugs, or none at all. The FDA-approved version of Serevent Diskus, sold in the U.S. through legitimate marketing channels, did not have the delivery system problem and was not subject to the recall. In the United States, FDA issued a consumer alert about the illegally-imported Canadian products, but it is possible that American consumers never learned of the recall.

- ***Unapproved foreign versions of FDA-approved drugs***. Every aspect of an FDA-approved drug has been reviewed by FDA. Drugs approved by foreign regulators are different from U.S. drugs, and the differences can be significant. Due to foreign regulatory requirements, a foreign version may contain different excipients, for example, or different coloring. Foreign variations from the U.S. standards in potency and purity may raise concerns relating to both safety and effectiveness. Sometimes use of the FDA-approved version will require the supervision of a health care professional. Examples of the foreign versions found by FDA and Customs in the blitzes include:

  - APO-Tamox – an unapproved, foreign version of the anti-cancer drug Tamoxifen.

  - APO-Warfarin – an unapproved, foreign version of the blood thinner Warfarin. According to the FDA, the potency of warfarin may vary depending on how it is manufactured, and the drug must be carefully administered and monitored by a health professional in order to prevent serious bleeding complications.

  - APO-Carbamazapine – an unapproved, foreign version of the anti-convulsant drug carbamazapine, which requires initial screening and monthly monitoring of blood and platelet counts to ensure its safe use.

  - APO-Allopurinal – an unapproved, foreign version of a drug used in the management of various types of cancer. This drug requires periodic monitoring of kidney function during the first few months of treatment and can cause kidney failure with underlying renal disease.

- Alti-azathioprine – an unapproved, foreign version of an immunosuppressant drug. This drug can cause severe bone marrow depression and can be associated with increased risk of infection and cancer development. The FDA-approved version of this drug requires close monitoring of blood counts.

- Human growth hormone -- a widely-used drug indicated for a number of conditions in both children and adults. It can have serious side effects (for example, it can unmask or worsen diabetes and cause elevation of pressure in the brain) if used inappropriately or in excessive doses.

- ***Drugs requiring risk management and/or restricted distribution programs.*** Canadian-manufactured isotretinoin, a drug used to treat severe acne, was shipped without any assurance that its use would be monitored by a physician. In the U.S., isotretinoin is subject to a stringent risk management plan, under which providers are required to screen, educate, and monitor patients to avoid serious risks, such as birth defects that may occur following its use. U.S. prescribers are also expected to attest, prior to prescribing the drug, that pregnancy testing has been done to confirm the patient is not pregnant.

- ***Drugs that require initial screening or periodic monitoring of patients.*** Some that were discovered during the import blitzes include:

  - Casodex, used for the treatment of prostate cancer. A medical professional must rule out baseline liver disease prior to treatment initiation and must monitor liver function tests periodically during treatment.

  - Warfarin, an anticoagulant that requires initial and periodic monitoring of blood parameters to avoid bleeding problems.

  - Clomid, used to treat ovulatory dysfunction. A medical professional must rule out liver, thyroid, and adrenal dysfunction and should also perform monitoring during treatment to avoid ovarian hyper-stimulation.

  - Metformin, an oral hypoglycemic that requires regular monitoring of blood parameters, as well as ongoing assessments of kidney function to reduce the risk of lactic acidosis.

  - Tamoxifen, a drug for which a medical professional must rule out uterine malignancy prior to and regularly during treatment.

  - Elavil (amitriptyline), an anti-depressant for which cardiovascular disorders must be ruled out before treatment begins.

- Lithium carbonate, an anti-psychotic used to treat manic depression. Individualized dosing and careful monitoring of serum levels are required to avoid life-threatening toxicity.

- ***Drugs with clinically-significant drug-drug interactions.*** Unapproved versions of Zocor (simvastatin), imipramine, ketoconazole, Viagra (sildenafil citrate), and tramadol were discovered during the import blitzes. These medicines are associated with clinically-significant interactions with other drugs that a purchaser may be taking.

- ***Biological products that should be administered by a health care professional and that are not licensed by FDA.*** Influenza Virus Vaccine is approved in Canada but not licensed by FDA. This vaccine was discovered during one of the blitzes.

- ***Animal drugs not approved for human use.*** Clenbuterol, a drug approved for the treatment of airway disease in horses, was shipped from Costa Rica and China. This drug, which is used illicitly by athletes as a performance-enhancing drug, has not been approved for human use by the FDA and has been banned by the International Olympic Committee.

- ***Drugs withdrawn from the market.*** Consumers also import drugs that have been withdrawn from the U.S. market. For example, FDA and Customs found a shipment of Buscapina from Mexico. This appeared to be a foreign version of the drug Dipyrone, which was removed from the U.S. market in 1977 after reports that U.S. patients had developed severe blood disorders, some fatal.

In testimony before the House Government Reform Subcommittee on Human Rights and Wellness, and later before the House Government Reform Committee, FDA's Associate Commissioner for Policy and Planning has provided additional descriptions of the medicines that are illegally imported.

- ***Drugs that should be dispensed only in small amounts.*** Mr. Hubbard said, "A second example I will give, this is an anti-depressant drug. It should only be dispensed in very small amounts, about 30. This is several hundred. This drug is prescribed for a relatively high-risk population for overdose. This drug should not be given in large amounts to patients. The Canadian pharmacy sent this individual about ten months worth of that drug." He added a second example: "The next individual apparently had epilepsy and bought a drug called Gabapentin, which is usually dispensed in 30-day increments. This is what the Canadian pharmacy sent this gentleman. This is about four years worth of the drug. These drugs start

expiring in six weeks. So most of the time this patient takes these drugs, they will have been expired and ineffective."[39]

- ***Drugs that require refrigeration.*** Hubbard also noted "drugs for osteoporosis, for glaucoma, and insulin for diabetics." He explained "[t]hey are required to be refrigerated. If they're not refrigerated, they're very complex proteins that break down and become ineffective . . . . I'll even note that in the case of one pharmacy, the place where it says, 'keep refrigerated' is where they put their label. So that is a dangerously ineffective drug. In all three cases, those came from Canada ordered over an Internet site, we believe."[40]

- ***Counterfeit products lacking active ingredient.*** On February 4, 2004, FDA issued a warning to the public about a foreign Internet site selling counterfeit contraceptive patches. These counterfeit patches contained no active ingredient and therefore provided no protection against pregnancy. The Internet site, www.rxpharmacy.ws, apparently was operated by American Style Products of New Delhi, India.[41]

2. FDA and U.S. Customs have repeatedly confirmed that they lack the resources effectively to monitor the influx of illegal drug imports.[42]

While proponents of importation have argued that importation can be done safely, regulators have stated time and time again that resource constraints hamper their ability effectively to enforce current law and to handle the increasing stream of drugs

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[39] Testimony of William K. Hubbard, Associate Commissioner for Policy and Planning, U.S. Food and Drug Administration, House Government Reform Committee (June 12, 2003).

[40] *Id.*

[41] Testimony of William K. Hubbard, Associate Commissioner for Policy and Planning, U.S. Food and Drug Administration, House Government Reform Committee Hearing (March 18, 2004). On February 12, the FDA took action against three additional Internet sites associated with the sale of counterfeit contraceptive patches (www.usarxstore.com, www.europeanrxpharmacy.com, and www.generic.com). The counterfeit contraceptive patches were purported to be an FDA-approved product. Instead, customers received packages of patches without the active ingredient necessary to make the patches effective. The counterfeits were sent in plastic zip-lock bags without identifying materials, lot numbers, expiration dates, or any other labeling information.

[42] This section of our comments responds to item 9 on page 9 (the request for information about "the agency resources, including additional field personnel, needed to adequately inspect the current amount of pharmaceuticals entering the country").

being illegally imported into the U.S. If they cannot adequately enforce current law, they clearly could not protect the public safety if importation were legalized.

In March 2004, for example, Secretary Thompson told Senator Cochran that FDA is "strapped" and that it does not have enough resources to ensure that imported drugs are safe:

> Senator Cochran: Mr. Secretary, we've had some debates and votes on amendments here in the Senate relating to importation of pharmaceutical products from other countries. Are there sufficient funds in this budget request to deal with the problem of counterfeit or unsafe pharmaceutical products that may enter the United States from other countries?
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> Secretary Thompson: I don't think so, Senator. I think it's a growing problem, and we are doing the best job possible. As you know, I requested of this Congress early on when I came on to get enough inspectors to deal with some things, with food. We have increased it, but overall, I still think that there's a good chance of having counterfeit drugs. And we see that every time we stop. We had, as you know, some inspections at the border not too long ago, one in July and in September and October of this year. And about 87 percent of the drugs that came in were either mislabeled or mispackaged. Some were counterfeit, some were not certified by FDA or approved by FDA. So there are a lot of drugs that still are coming into America that are not regulated by FDA.
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> Sen. Cochran: Are we making an effort to bring this to the attention of our friends around the world and try to get help there in those countries?
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> Secretary Thompson: We are. We have a very strong, aggressive outreach program to other countries, especially to Canada. But Canada has pretty much indicated that it's not their problem, and it's our problem and that we should address it ourselves. We have started hearings. Last Friday was the first hearing. I set up a commission, headed up by Surgeon General Carmona, to take a look at reimportation, importation, as well as ways in which we can develop. We've also set up a task force on counterfeit drugs. And we announced that a couple of weeks ago. We're working with the Federal Trade Commission and the Department of

> Justice in regards to that. We are quite aggressive. But your question was: Is there enough resources? I don't think there is, because FDA is very strapped with all of its demands. And this is a huge problem, and if, in fact, we are going to have reimportation, we're going to have to have more resources in order to make sure that those [sic] reimportation of drugs are [sic] safe.[43]

Earlier the same month, the Commissioner of FDA (now the Administrator of CMS and a member of this Task Force), Dr. Mark McClellan, testified before the Senate Committee on Commerce, Science, and Transportation that FDA and Customs face competing priorities and are "unable to visually examine many of the parcels containing prescription drug products that arrive through the mail and private courier services each day."[44] He added that although FDA "works hard to inspect many legitimate manufacturing facilities selling drugs to Americans through legitimate FDA-regulated channels, including facilities located in the United States and abroad," the agency has "neither the legal authority nor the resources to assure the safety of drugs from outside the federal and state system of regulating drugs."[45] Administrator McClellan made similar comments in 2003 in a letter to Representative Tauzin regarding one of the importation bills introduced that year. In this letter, he wrote that the "sheer volume of importation that could result from enactment of this bill would easily overwhelm our already heavily burdened regulatory system."[46]

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[43] Testimony of Tommy G. Thompson, Secretary of Health and Human Services, Senate Appropriations Committee, Subcommittee on Labor, Health and Human Services and Education (March 25, 2004).

[44] Testimony of Dr. Mark B. McClellan, Commissioner of Food and Drugs, Hearing before the Committee on Commerce, Science and Transportation, United States Senate (March 11, 2004).

[45] *Id.*

[46] Letter from Mark B. McClellan, M.D., Ph.D., Commissioner, Food and Drug Administration to the Honorable W.J. "Billy" Tauzin (July 18, 2003) (re H.R. 2427).

Other FDA officials have made the same point. In November 2003, for example, the Associate Commissioner for Regulatory Affairs, John Taylor, told the Senate Committee on Commerce, Science, and Transportation that the agency was "doing its best to stop the increasing flow of violative drugs into this country," but that the task was "daunting."[47] He added that "[e]ach day thousands of packages containing prescription drugs are imported illegally into the United States" and noted that "while the volume of imported drugs has increased enormously, FDA has not received additional resources or authority to address these shipments, in contrast to the case for food security at the border."[48] Further, FDA's risk-based enforcement strategy is "overwhelmed by the number of incoming packages that must be evaluated" which "presents a significant ongoing challenge for the Agency."[49] The volume of importation that could result from enactment of a bill to legalize importation "could easily overwhelm our already heavily burdened regulatory system."[50]

In June 2003, Mr. Taylor told a subcommittee of the House Energy and Commerce Committee that "[w]ith the available resources and competing priorities facing the agency, experience shows that we are unable to visually examine the large volume of parcels containing prescription drugs that arrive in the mail and courier

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47 Testimony of John M. Taylor, III, Associate Commissioner for Regulatory Affairs, Food and Drug Administration, before the Committee on Commerce, Science and Transportation, United States Senate (November 20, 2003).

48 *Id.*

49 *Id.*

50 *Id.*

services each day."[51] When asked by Representative Davis about the solution, he expressed doubt whether any amount of increase in resources would ever be sufficient:

> Mr. Davis: What exactly would you suggest that Congress needs to do to be a part of the solution here? We are spending most of the day talking about the problem so far, and it is easy to sit here and criticize you, but what we are entitled to and what the public is entitled to, [sic] for you to be painfully direct for us as to exactly what Congress needs to do to be part of the solution here because, if you are not part of the solution on this, you are part of the problem.
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> Mr. Taylor: I, quite frankly – I guess as a starting point, looking at some comprehensive solution that just doesn't focus at providing additional resources because, as I stated earlier, providing us additional investigators doesn't seem to be the answers, and no matter how many investigators you provide us, it seems that based on the numbers, we would still struggle to look at all these packages and prevent their entry into the United States.
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> Mr. Davis: Mr. Chairman, if I could just finish this last question, and I will stop there. What else besides resources?
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> Mr. Taylor: Well, I guess what I am saying is that resources aren't the answer. It is some type of comprehensive solution that focuses on why people are purchasing these products and importing them into the United States seems to be the answer.[52]

The agency's Senior Associate Commissioner for Policy and Planning, William Hubbard, told the same committee that simply providing FDA more resources would not fix the fundamental safety problem. Chairman Greenwood asked, "if you use this current system that you have in place, the number of personnel that you would need to really have a pretty foolproof system would be unrealistic. . . . So isn't it the case that

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51 Testimony of John M. Taylor, III, Associate Commissioner for Regulatory Affairs, Food and Drug Administration, before the House Energy and Commerce, Subcommittee on Oversight and Investigations (June 24, 2003).

52 *Id.*

we really need to change the system that we use to approach this problem rather than simply call for more resources?" Mr. Hubbard responded, "I think that is correct. . . . I have 537 investigational FTEs devoted to this task, and those bodies don't just handle pharmaceutical products. They handle foods, biologics. They are involved in preventing the spread of BSE to this country. They are involved in taking steps to prevent the monkeypox outbreak from growing. They are involved in homeland security and food safety. So those 500-some-odd people are vested with a large job, and it is simply not one that the resources – increasing the resources will not really cause a big dent. We really need to change the system."[53] In 2001, Mr. Hubbard commented in a letter to Representative Tauzin on an amendment offered by Representative Gutknecht to allow personal importation: "[t]he increased volume of potentially dangerous imported drugs would place an additional strain on an already compromised U.S. regulatory approach to protecting consumers from unsafe personal importations."[54] And in a hearing before the Oversight and Investigations Subcommittee of the House Commerce Committee in 2001, he commented that FDA does not have the resources to look at "small packages."[55]

Representatives of U.S. Customs agree that the task of monitoring imported drugs is already overwhelming. One official commented at the same hearing in 2001 that "[d]etecting prohibited pharmaceuticals among the tens of millions of parcels

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[53] Testimony of William Hubbard, Associate Commissioner for Policy and Planning, Food and Drug Administration, before the House Energy and Commerce, Subcommittee on Oversight and Investigations (June 24, 2003).

[54] Letter from William Hubbard, Senior Associate Commissioner for Policy, Planning and Legislation to The Honorable W.J. "Billy" Tauzin, Chairman, House Energy and Commerce Committee and The Honorable John Dingell, Ranking Member, House Energy and Commerce Committee (July 17, 2001).

[55] Testimony of William Hubbard, Senior Associate Commissioner for Policy and Planning, before the House Committee on Commerce, Subcommittee on Oversight and Investigations (June 7, 2001).

passing through our mail facilities each year presents a massive challenge."[56] She explained, "[o]ur limited resources require a risk management approach with which we utilize advance intelligence, records of past seizures, and other factors to locate packages that present the most significant threat."[57] The government's inability to inspect imports was amplified in an exchange with Representative Dingell:

> Mr. Dingell: Ms. Durant, two questions. A simple yes or no answer I think will suffice. In your Carson City project, in 4 or 5 weeks Customs inspectors could have stopped approximately 16,000 parcels containing pharmaceuticals or something that appeared to be a pharmaceutical. Is that correct?
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> Ms. Durant: That is correct.
>
> Mr. Dingell: It is also true that FDA could process only a tiny fraction of these, approximately 30 a day? Is that right?
>
> Ms. Durant: That is also correct.
>
> Mr. Dingell: So they could only then have reviewed a minute portion of this?
>
> Ms. Durant: That is correct.

If FDA and Customs lack the resources now to inspect the millions of packages that cross the border annually, when drug importation is illegal, they would surely be helpless if ten or twenty times that volume crossed the borders under a legalized drug importation scheme. Further, paradoxically, as Congress builds more and more so-called safety provisions into an importation scheme, the crushing burden on FDA and Customs will increase. If biologics are to be excluded, for example, and if unapproved

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[56] Testimony of Betsy Durant, Office of Trade Programs, United States Customs Service, Before the House Committee on Commerce, Subcommittee on Oversight and Investigations (June 7, 2001).

[57] *Id. See also* Testimony of Betsy Durant, Office of Trade Programs, United States Customs Service, Before the House Committee on Commerce, Subcommittee on Oversight and Investigations (May 25, 2000).

and misbranded drugs are to be excluded, then someone must check each of the millions of packages crossing the border. Cost-savings and safety, in a sense, may be flip-sides of the same coin. Just as the Secretary needs to determine whether importation can be done in a way that will guarantee the safety of the patient, he will also need to consider the fiscal impact of increasing the FDA and Customs budgets by several orders of magnitude in order to implement "safety" provisions.

3. Congress and HHS should tighten the pharmaceutical distribution chain in the United States rather than open the borders to foreign products.[58]

a) FDA's inability to fully implement the PDMA has contributed to the domestic diversion and counterfeiting problem that endangers American consumers.

One basic tool for helping to preserve the safety of our country's drug supply is the maintenance of a closed distribution system. This objective is not always met, but where there are deviations, safety issues inevitably arise, and the integrity of the drug supply is compromised. In a closed distribution system, the manufacturer ships drug product to a distributor, who in turn ships to the pharmacy for dispensing to the patient. Multiple distributors may become involved, but the key is that each transaction in the supply chain is documented and tracked, so that the pedigree of the product involved can be traced and verified by lot at any point in the chain of distribution.

The drug distribution chain in U.S. commerce is not entirely closed, in part due to limitations in the law. Counterfeit and tainted products surface from time to

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[58] This section of our comments responds to the items 1, 2, and 3 on page 9 (the limitations in resources and in current legal authorities that may inhibit the Secretary's ability to certify the safety of imported drugs; the pharmaceutical distribution chain and the need for, and feasibility of, modifications in order to assure the safety of imported products; and whether anti-counterfeiting technologies could improve the safety of products in the domestic market as well as products that may be imported).

time, and the public health is put at risk. Domestic challenges thus remain great. These challenges would, however, be multiplied significantly by the added complexities and burdens of an expanded international supply of drugs from various wholesalers and pharmacies.

The PDMA and the Prescription Drug Amendments of 1992[59] amended the FDCA to establish requirements for the distribution of prescription drugs that are designed to promote integrity in the pharmaceutical distribution system. These provisions require secondary wholesale drug distributors to provide purchasers a statement, also called a "pedigree," that identifies each prior sale, purchase, or trade of the drug.[60]

FDA published regulations that would require that the pedigree also include the proprietary and established names of the drug, its dosage, the container size, the number of containers, lot or control numbers of the drug being distributed, the business name and address of all parties to each prior transaction involving the drug (starting with the manufacturer), and the date of each previous transaction.[61] However, FDA has repeatedly stayed these regulations and refused to implement the pedigree requirements of the PDMA, due to concerns that it would not be feasible for secondary wholesalers to obtain the information necessary to provide the required pedigrees. Most recently, FDA stayed the regulations until December 1, 2006, in order to permit industry

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59 Pub. L. No. 102-353, 106 Stat. 941 (1992).

60 21 U.S.C. § 353(e)(1)(A).

61 21 C.F.R. § 208.50. The requirement that the pedigree include the names and addresses of all parties involved in each prior transaction comes directly from section 503(e)(1)(A) of the FDCA.

to develop and implement a track-and-trace system that it is hoped will "accomplish and surpass the goals of PDMA."[62]

Pending development and adoption of new technology to track drug sales and other transfers through the distribution chain, the absence of an established paper pedigree is a serious weakness in current law that would be greatly exacerbated by new drug imports. No easy fix is in sight. FDA's inability to put the full pedigree requirements of the PDMA into effect is part of the problem.[63] However, the PDMA itself has critical limitations. In particular, the PDMA does not require that authorized distributors of record provide the information to secondary wholesalers needed to create a complete pedigree for each drug. In a 2001 Report to Congress, FDA noted that in order to enable secondary wholesalers to achieve full compliance with the PDMA's pedigree requirement, Congress would have to amend section 503(e) of the PDMA to enable secondary wholesalers to obtain pedigree information from all prior purchasers, including authorized distributors.[64] Although Congress has considered the issue, it has not yet acted on FDA's recommendation to amend the PDMA.

Without a pedigree from secondary wholesalers, there is no legally-required document that ensures traceability back to the drug manufacturer and guards against drugs that are counterfeit or that are stored in an inappropriate manner. This creates a major obstacle to full traceability, and it may permit unscrupulous parties to

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62 69 Fed. Reg. 8105, 8107 (February 23, 2004).

63 *See, e.g.*, First Interim Report of the Seventeenth Statewide Grand Jury, No. SC02-2645 (Fla. 2003) (http://myfloridalegal.com/grandjury17.pdf) ("[W]e conclude that both FDA and [Florida] DOH have failed to aggressively enforce their respective paper pedigree laws. We believe that strict enforcement of our pedigree paper law is essential to protecting the public from drug counterfeiters.").

64 The Prescription Drug Marketing Act: Report to Congress, June 2001, at 22-23.

"launder" counterfeit or diverted drug products through unknowing distributors and break the recorded chain of custody. This loophole in the PDMA, exacerbated by FDA's inability to implement its regulations, already creates a weakness in the strong protections afforded American consumers. This weakness would be greatly compounded if the pharmaceutical distribution chain were expanded to accommodate legal imports of prescription drugs.

b) Congress should impose tougher penalties for counterfeiting and other violations.

The inadequate penalties available for violations of the PDMA and statutes prohibiting counterfeiting drug products present another obstacle to protection of the public from unsafe imports. The maximum penalty for a felony drug counterfeiting violation is three years imprisonment and/or a $10,000 fine. That penalty can be imposed only upon a finding that the counterfeiter acted with intent to defraud or mislead.[65] Compare the far more stringent penalty for counterfeiting another product, such as currency, and the penalties for distributing illicit drugs.[66]

This disparity underscores the leniency in the prescription drug counterfeiting laws, and weakens the ability of the law to deter wrongdoers. In addition, the statutory scheme does not adequately punish those who have some indication that they are receiving counterfeit drug products and deliberately fail to act upon that knowledge, for example by failing to conduct basic due diligence to ensure the product's

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[65] 21 U.S.C. § 333(a)(2). The fine may be subject to enhancement pursuant to 18 U.S.C. § 3571.

[66] *See* 18 U.S.C. § 485 (providing for fine and/or up to 15-year term of imprisonment for the act of counterfeiting U.S. currency); 21 U.S.C. § 841 (establishing terms of imprisonment for distribution of controlled substances, ranging up to life in prison for serious violations).

pedigree is accurate, or by overlooking obvious red flags such as deeply discounted prices or suspicious packaging.

In short, the statutory scheme does not permit FDA to seek adequate penalties for parties that counterfeit pharmaceutical products or that otherwise knowingly undermine the safety of the U.S. drug distribution system. Because the penalties are imposed by statute, FDA and prosecutors may not unilaterally impose greater fines or seek a longer prison term for violators, although in some circumstances prosecutors can allege additional legal violations, such as mail fraud and conspiracy. The net result is inadequate deterrence, and a further limitation on the ability of current legal authorities to ensure the safety of drug imports.

c) Congress should impose stricter wholesaler licensing requirements.

Drug wholesalers are subject to a variety of state laws with differing standards of enforcement, permitting unscrupulous wholesalers to establish operations where they will face the least regulation. All 50 states require wholesale drug distributors to be licensed, and some states – notably Florida and Nevada – have instituted stricter regulatory oversight. Typically, states require background checks of wholesalers for felony convictions before issuing a license, establish drug storage and handling requirements, and require record keeping. Requirements vary, however, and wholesalers have an incentive to locate their operations in the states with the least stringent rules.

FDA has published Guidelines for State Licensing of Wholesale Prescription Drug Dealers, set forth in 21 C.F.R. part 205. FDA's regulations establish minimum standards for state licensing authorities, ensuring at least a basic level of regulatory consistency across the 50 states. FDA has not, however, audited each state's

regulations and related enforcement operations to ensure that they actually comply with FDA standards. FDA can begin to close the loopholes in the distribution system by drafting stronger minimum standards for licensing and oversight of wholesale operations, and by ensuring that states implement the tighter standards. This would be one step toward raising the level of state oversight of wholesale distributors across the country. However, until FDA has addressed the issue of inconsistent, often lax, state licensure and regulation of wholesale operations, this will remain a major weakness in the distribution chain. The result is a diminished ability to ensure that tainted imports will not flow over the borders, into the wholesaler distribution system, and to patients, without appropriate regulatory control and oversight.

d) Congress should more strictly regulate repackaging.

Drug repackaging operations may also create an opportunity for subpotent, adulterated, or otherwise problematic drug products to enter the market. Drug products are routinely repackaged after shipment from the manufacturing facility. Certain repackaging is performed, for example, when health maintenance organizations (HMOs) or hospitals repackage drugs for internal distribution; such practices rarely create the opportunity for distribution of counterfeit or diverted drugs. However, repackaging is also undertaken by other entities in the distribution chain and may pose a threat to public health.

For example, an unscrupulous repackager may dilute the drug before packaging it in new containers, to give the appearance of greater quantity, or drugs may be adulterated during the repackaging process. Drugs may also be repackaged using inferior or substandard materials, which may result in product quality deterioration. Repackaging interferes with tamper-resistant features and counterfeit-resistant

technologies that manufacturers build into original product packaging, thereby undermining the effectiveness of such innovations.

Implementation of the PDMA pedigree requirement is the best means of limiting repackaging operations. The threat to the system posed by repackaging can also be addressed by increased FDA surveillance over relevant entities in the drug distribution chain, including frequent inspections of repackaging facilities to ensure compliance with GMPs and record keeping requirements. However, until the pedigree requirement is in place and FDA has increased its facility inspections, the practice of drug repackaging will remain a significant weakness in the distribution chain and will continue to pose a threat to public safety. This threat would grow if an expanded volume of imports were to begin to flow to repackagers for further distribution.

B. Importation cannot be "made safe" with creative legislative alternatives to the current gold-standard system, with full FDA approval and oversight, GMP and GDP compliance, and completely closed borders.

1. Importation directly contradicts a core principle in the FDCA: that a medicine's safety must be proven rather than assumed.[67]

Inherent in the federal regulatory scheme governing development, approval, and marketing of new drug products is the requirement that a manufacturer prove to FDA that its drug is safe and effective. The burden of proof falls on the manufacturer, and the process of developing the data to meet this burden takes many years. In the pre-clinical testing stage, for example, a manufacturer conducts laboratory and animal tests to evaluate the safety of its new compound. In the second stage, before performing any clinical trials in humans, the manufacturer submits an investigational new

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[67] This section of our comments responds to item 1 on page 9 (limitations that may inhibit the Secretary's ability to certify the safety of imported drugs).

drug application (IND) to FDA.[68] Every IND must contain sufficient pharmacological and toxicological data to show that it would be reasonably safe to conduct clinical trials in humans.[69] An IND must also detail the drug's chemical composition, structural formula, proposed dosage form, and proposed route of administration; the investigative plan and proposed clinical trial protocols; any prior human experience (including foreign data); and prior withdrawals from investigation or marketing.[70] If FDA is satisfied that the pre-clinical animal data do not demonstrate an unacceptable safety risk to humans, the drug sponsor may begin clinical studies in humans.[71]

During the clinical program, the sponsor tests the drug for safety and efficacy in small doses and multiple doses, in healthy volunteers and patients, and in varying demographic groups. Following the clinical trials, the drug sponsor prepares and submits an NDA, seeking FDA's permission to manufacture, distribute, and market the drug in the United States. Among other things, the NDA must include the preclinical data, such as laboratory and animal studies, evaluating the drug's pharmacology and toxicology;[72] data on the manner in which the drug is absorbed, distributed, metabolized, and excreted in humans (pharmacokinetic and bioavailability data);[73] clinical data obtained from administering the drug to humans, including data demonstrating the drug is safe under the proposed conditions of use;[74] a description of the proposed methods by

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68 21 C.F.R. § 312.40.

69 21 C.F.R. § 312.23(a)(8).

70 21 C.F.R. § 312.23.

71 21 C.F.R. § 312.21, 312.40.

72 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d)(2).

73 21 C.F.R. § 314.50(d)(3).

74 21 U.S.C. § 355(d)(5); 21 C.F.R. § 314.50(d)(5).

which the drug will be manufactured, processed, and packed;[75] a detailed chemical description of the drug and its active ingredient;[76] a list of each patent claiming the drug, drug product, or method of use, or a statement that there are no relevant patents making such claims;[77] and the drug's proposed labeling.[78]

In order to permit marketing, FDA reviewers must find that the drug satisfies two fundamental requirements of the FDCA – that it is "effective" and "safe." The sponsor must have "substantial evidence" that the drug will have the effect it purports to have, under the indicated conditions of use.[79] "Substantial evidence" means evidence from adequate and well-controlled clinical studies.[80] The drug also may not be approved unless there are "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof."[81] Approval of an NDA can take anywhere from six months to three years.[82]

In short, the FDCA creates a system where a drug must be proven safe before it may enter the drug supply. Importation would flip this system on its head. The World Health Organization (WHO) has found, and FDA has repeatedly told Congress

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75 21 U.S.C. § 355(b)(1)(D); 21 C.F.R. § 314.50(d)(1)(i)-(iii).

76 21 U.S.C. § 355(b)(1)(B)-(C); 21 C.F.R. § 314.50(d)(1)(i)-(iii).

77 21 C.F.R. § 314.50(h)-(i).

78 21 U.S.C. § 355(b)(1)(F), 21 C.F.R. § 314.50(e).

79 21 U.S.C. § 355(d), 21 C.F.R. § 314.105(c).

80 21 U.S.C. § 355(d).

81 21 U.S.C. § 355(d)(1).

82 "NDA Approval Rates for NDAs Received FY 1993-2002 and Approved within 36 Months" < www.fda.gov/cder/present/MedianAPtime/LifeTables/ NLifeTable2NDA.htm> (visited February 18, 2004).

and the public, that the drug supply circulating in commerce outside the United States contains a high percentage of counterfeits and cannot be assumed safe. The rising volume of counterfeit and adulterated medicines have been described in the press and documented by FDA.[83] And still, proponents of importation would open the borders. A "show us the bodies" approach to the U.S. borders is fundamentally inconsistent with the

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[83] *See, e.g.*, "Counterfeit Drugs Becoming a Big and Dangerous Business," *CBN NEWS* (April 16, 2004); "Online Drugs Raise Warning," *Seattle Post* (April 15, 2004); "Pharmacy Boss Jailed, Fined For Smuggling In Bogus Viagra," *The Straits Times* (April 14, 2004); "Scramble Is On To Fight Fake Drug Market," *Associate Press Newswires* (April 12, 2004); "Health Experts Warn About Growing Danger of Counterfeit Drugs," *The Partnership for Safe Medicines* (April 8, 2004); "Drug Firms Decry Importation," *Los Angeles Times* (April 6, 2004); Joyce Primo-Carpenter, "A Matrix of Drug Quality Reports on USAID-Assisted Countries by the U.S. Pharmacopeia Drug Quality and Information (USP DQI) Program," USP Global Assistant Initiatives (March 30, 2004); "The menace of fake drugs in Nigeria," *Healthyskepticism.org* (March 22, 2004); "16-year old receives counterfeit Epogen," *Fox 5 News* (March 1, 2004); "Drug regulators study global treaty to tackle counterfeit drugs," *The British Medical Journal* (February 28, 2004); FDA, "Combating Counterfeit Drugs" (February 18, 2004); "Counterfeit drugs and the danger to Westchester," *The Journal News.com* (February 16, 2004); "Fake drugs, real threat: Seizures of counterfeit prescription medicines and arrests are on the rise, causing new concerns. The FDA insists the country's supply of pharmaceuticals is safe," *Los Angeles Times* (February 9, 2004); "Rx Drugs: Rising Arrests Over Counterfeits Examined," *American Health Line* (February 9, 2004); "FDA Deems Some Birth Control Patches Fake," *The Associated Press* (February 4, 2004); "Despite U.S. Crackdown, Cities Still Offer Imported Meds," *Connecticut Post* (January 30, 2004); FDA NEWS, "Recent FDA/U.S. Customs Import Blitz Exams Continue to Reveal Potentially Dangerous Illegally Imported Drug Shipments" (January 27, 2004); "On the trail of the world-wide web of fake lifestyle drugs," *Independent on Sunday* (January 18, 2004); "Exposé of company selling bogus Viagra forces British-owned website to close," *Independent on Sunday* (January 18, 2004); "Anti-Counterfeit Steps by Drugmakers Sought; Legislators' Goal Is to Halt Illegal Sales," *The Washington Post* (January 17, 2004); "U.S. panel probes way to fight fake medicines," *Reuters* (January 16, 2004); "The growing problem of counterfeit prescription drugs," *NBC Nightly News* (January 11, 2004); "Exposed – the fake Viagra racket," *Independent on Sunday* (January 11, 2004); "Drug Wholesalers Face State Efforts To Tighten Rules," *The Wall Street Journal* (January 8, 2004); "Business & Innovation Life Sciences: Pharmaceuticals; Feeling Lucky? That Drug You're Counting on May Not Be What It Appears. As Counterfeiters Become More Sophisticated at Copying Drugs Like Viagra, Above, The Industry Is Scrambling For Ways To Protect Its Wares," *The Boston Globe* (January 5, 2004). These are just the examples from the first four months of 2004.

premise of the FDCA that a medicine must be affirmatively proven safe before FDA will permit it to be sold to consumers.[84]

2. Safety and quality cannot be "tested into" a product.[85]

a) End-product, or terminal, testing is contrary to the concept of GMP embodied in the FDCA.

FDA's GMP regulations are based on the fundamental quality assurance principle that quality, safety, and effectiveness "cannot be inspected or tested into a finished product," but instead must be designed and built into a product.[86] FDA has reiterated this bedrock principle on numerous occasions, most recently in connection with its 2003 initiative to modernize the GMP regulations.[87]

GMP is a systems approach that requires a company to build quality directly into the entire manufacturing operation, in order to ensure that the process itself

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[84] The requirement that a medicine be proven safe was crafted by Congress in response to a tragic incident involving an unproven product. In September 1937, more than 100 people – many of them children – died after taking a product called "Elixir Sulfanilamide," a sulfa-based product used to treat infections like strep throat. The manufacturer had used diethylene glycol (now known as antifreeze) as a solvent, without performing safety testing. Congress responded in 1938 by requiring "premarket notification" for new drugs. Before a new drug could be marketed, it was required to be tested on humans in accordance with investigational new drug (IND) regulations promulgated by FDA. When sufficient data were obtained under the IND to demonstrate the safety of the drug, the manufacturer was required to submit a new drug application (NDA) for the drug to FDA. If FDA did not disapprove the NDA within sixty days after filing, the NDA became effective and the drug could be marketed. FDA now serves as a gatekeeper, ensuring that any drug sold to American patients has been proven safe. If the supporters of importation prevail, however, Congress will essentially turn back the clock to 1937, when products were marketed until proven dangerous, and public health measures came only after tragedy struck.

[85] This section of our comments responds to item 1 on page 9 (limitations that may inhibit the Secretary's ability to certify the safety of imported drugs).

[86] 61 Fed. Reg. 20104, 20105 (May 3, 1996).

[87] *See* Draft Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance (August 2003); *see also* Guideline on General Principles of Process Validation (May 1987).

is under control and therefore will consistently produce a drug product that meets designated specifications. The GMP regulations impose strict controls on every aspect of the manufacturing process, including: (1) the qualifications and responsibilities of employees and consultants; (2) the design and maintenance of manufacturing facilities; (3) the design, construction, cleaning, and maintenance of manufacturing equipment; (4) the receipt, storage, testing, and acceptance of pharmaceutical raw materials and components, including containers and closure systems; (5) the manufacturing process itself, including reprocessing procedures; (6) the packaging and labeling of finished drug products; (7) the storage and distribution of final products; (8) required laboratory testing procedures; and (9) recordkeeping requirements.[88] Failure to satisfy any of these GMP requirements renders the affected drug product "adulterated" and thus illegal in the United States – even if testing fails to reveal any obvious deficiencies in the product.[89]

The GMP requirement of the FDCA – which is part of the approval process and continues to apply when a drug is marketed – embodies the theory that a product's integrity can be assured only if the process by which it is manufactured, packaged, labeled, stored, and shipped is fully under control and capable of audit at any time by FDA. Importation – which would permit an unapproved drug to enter the medicine supply upon end-product testing (not even necessarily of the drug, perhaps merely of a sampling from each lot) at the point of entry – flips this theory on its end.

As the GMP regulations suggest, end-product testing is inherently limited and cannot be relied upon to ensure the quality and safety of drug products. Many end-product tests have limited sensitivity and may fail to detect substances, such as impurities

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88 *See* 21 C.F.R. Part 211.

89 21 U.S.C. § 351(a)(2)(B).

or degradants, that are present in a drug product at low levels.[90] If these substances are dangerous at low levels or have an adverse effect on product quality (e.g., they accelerate degradation of active ingredient), the end-stage testing will fail to reveal that the drug product may be unsafe, unstable, or ineffective. In essence, such testing would yield an unacceptably high rate of "false negatives," i.e., finding no quality or safety problems when such problems actually exist.

Also, drug products often are extremely complex, and end-product testing does not reveal all variations that may affect safety and effectiveness. Even seemingly minor changes in manufacturing process or storage conditions may introduce variations in the product, such as new impurities, that cannot be predicted or easily tested. These variations can have a significant impact on safety and effectiveness. For example, testing might be conducted to demonstrate that a drug product contains the proper strength of a specific active ingredient; however, such testing would not detect other variations in the product caused by manufacturing changes, such as increased pill hardness or contamination with cleaning chemicals, that could have a significant impact on safety and effectiveness. While dissolution and impurity testing might be added to the battery of tests conducted on the drug product, such testing still would not detect meaningful variations in the drug product, such as new or different impurities or changes in the drug's stability profile. Because of the complexity of drug products, end-product testing simply cannot measure all of the possible variations that could affect safety and effectiveness.

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[90] *See* Guideline on General Principles of Process Validation, supra note 87, at 3.

Because of these significant limitations, FDA does not rely upon terminal testing alone to assure the safety and quality of drug products. Instead, through the GMP regulations and guidance documents, which implement the GMP requirement in the FDCA, FDA seeks to minimize the variability in the manufacturing process itself. Safety and quality cannot be inspected or tested "into" a drug product; they must be built into the product through rigorous approval requirements and strict controls over the conditions under which drugs are manufactured and distributed.

b) There are technological and practical impediments to the use of end-product testing to assure the authenticity, safety, and quality of imported prescription drugs.

End-product testing is inadequate to assure the authenticity of imported drugs. While random sampling and inspection may be helpful in the manufacturing context, it will never be sufficient to detect counterfeit drugs entering the U.S. from abroad. This is because "counterfeits can easily be commingled with authentic product, either by the case, by the bottle, or by the pill."[91] Therefore, as FDA concludes, "[n]o random sampling plan will be able to detect and protect against such criminal conduct since the threat does not depend upon the nature of the reimported product, but upon the integrity of those handling it."[92] It follows that, in order to identify counterfeit imports, an inspection and testing program would need to authenticate all drug products offered for importation. This would be cumbersome and prohibitively expensive. Large shipments would need to be removed from shipping containers and broken down into individual units, and each individual unit would need to be inspected or analyzed

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91 Letter from Lester M. Crawford, D.V.M., Ph.D., Deputy Commissioner of FDA, to the Honorable Thad Cochran (July 17, 2002).

92 *Id.*

separately before being repackaged. Not surprisingly, therefore, in its final report detailing new strategies for keeping counterfeit drug products out of the U.S. drug supply, FDA did not cite end-product testing as a sufficient, or even significant, weapon in the fight against counterfeiting.[93]

Even if a 100 percent inspection program (whether visual inspection or chemical testing) were economically feasible, it would not be sufficient to ensure the authenticity of imported products. Visual inspection of drug packaging and labeling, for example, is not a workable means of identifying counterfeits. Drug packaging and labeling – and the overt counterfeit-resistant features incorporated therein (color-shifting inks, for example, and holograms) – are too varied and numerous to permit real-time verification of drug products. It is not realistic to expect inspectors (let alone pharmacies and patients) to be familiar with the wide variety of overt features used on the thousands of different drug products likely to be imported. This problem will be exacerbated by the need to rotate overt features on a regular basis to stay one step ahead of counterfeiters. Further, even counterfeit-resistant technologies can be themselves counterfeited, often within 18 to 24 months.[94] Finally, visual inspection is of little or no value when a drug product has been repackaged. Repackaging removes or destroys a drug's original packaging and labeling, as well as any counterfeit-resistant technologies incorporated by the manufacturer. Virtually all drugs that are imported will have been repackaged to

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[93] Combating Counterfeit Drugs: A Report of the Food and Drug Administration, at www.fda.gov/oc/initiatives/counterfeit/report 02_04.html (February 18, 2004) ("Final Counterfeit Report").

[94] In one situation, counterfeiters replicated the Pfizer logo, blister card, foil backing on the pill pack, and hologram of Pfizer's product. In another situation, counterfeiters offered a purported Lilly product over the internet even though the drug had not yet been approved in the United States or anywhere else in the world.

substitute U.S. packaging and labeling for foreign packaging and labeling. A visual inspection after repackaging would be pointless. Visual inspections therefore can not be expected to reliably detect counterfeit products destined for import.

Examinations of products for covert features, and chemical analysis of products, are more accurate ways to authenticate imported drug products, but they too have limitations. First, they do not allow real-time verification of a drug's authenticity. Authentication by means of covert features and chemical taggants typically requires specialized equipment and testing methods. These tests often cannot be performed onsite. Tests for taggants, in particular, may take several days to conclude. Second, as noted above, random sampling methods cannot be used to eliminate the presence of counterfeit drugs; chemical analysis would therefore need to be performed on every drug product offered for importation. This would be prohibitively expensive. It would also be counterproductive, because it likely would destroy the very products being tested. Further, covert features, chemical taggants, and authentication testing methods are – for good reason – secrets closely held by the manufacturers. Authenticity testing would need to be performed by the manufacturer, or by a third party to whom the manufacturer has disclosed this sensitive information. While there are significant legal impediments to requiring such disclosure, there are also practical ones: sensitive information could fall into the wrong hands. Finally, not every drug product includes chemical taggants and covert features. As to these drugs, no laboratory test would verify authenticity.

Safety testing of imported pharmaceuticals suffers from many of the same limitations as does authenticity testing, and it has some additional limitations. Visual inspections for safety issues, for example, would be even less effective at identifying

safety problems than at identifying counterfeits. Most safety problems leave no visual clues. Visual inspection would not detect dangerous impurities in a drug product, stability problems caused by improper storage conditions, or degradation of the active ingredient, to give a few examples. It is likely to reveal only the most obvious safety problems, such as opened or water-damaged products. Chemical testing for safety issues has significant limitations because of the complexity of many drug products and the lack of sensitivity of many tests. Just as in the manufacturing context, end-product testing in the importation context cannot measure all of the possible variations in a product that could affect its safety and effectiveness. Moreover, this testing would be extremely expensive and, like authenticity testing, would in many cases require the manufacturer to divulge trade secrets.

3. Counterfeit-resistant technology available today cannot, by itself, prevent the distribution of counterfeit products imported from foreign nations.[95]

a) Although a number of counterfeit-resistant technologies are available today to detect and deter counterfeiting, these technologies are inherently limited.

Counterfeit-resistant technologies available to detect and deter counterfeiting include overt and covert features incorporated into the packaging and/or labeling of a product, as well as chemical taggants incorporated into the drug product. Overt features include holographic images, special stickers, inks of gradated colors, and threads in the container label, all of which can be used to verify that a container is authentic. Covert features include special inks, threads, and materials that are known

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[95] This section of our comments responds to items 3 and 4 on page 9 (whether anti-counterfeiting technologies could improve the safety of products in the domestic market as well as products that may be imported).

only to the manufacturer and require special equipment (for example, a UV light source) to identify. Covert features also include small amounts of a chemical taggant incorporated into the pharmaceutical preparation. Chemicals can be part of the bulk formulation of the active ingredient or can be incorporated into the gel capsule or film coating of the pill. A company can also use the known analytical composition of the formulation for authentication purposes. For example, defined impurity profiles and/or amounts of different inactive ingredients as well as dissolution patterns can be tested to determine a drug's authenticity. These technologies are all limited, however, as explained in the paragraphs that follow.

First, these technologies are merely resistant to counterfeiting; they are not counterfeit-proof. Experts believe that counterfeit-resistant features must be changed regularly, as counterfeiters will reliably duplicate them.[96] The experience of the Bureau of Printing and Engraving, with respect to U.S. currency, demonstrates the point. The U.S. government uses a number of different counterfeit-resistant technologies in its bank notes, including color-shifting inks, embedded threads, and micro-printing. At the same time, in order to stay ahead of counterfeiters, the government redesigns the notes and, specifically, the counterfeit-resistant features, every seven to ten years. Despite this, new U.S. currency is counterfeited quickly. The government recently introduced the third new $20 bill in ten years – complete with a watermark image engrained into the paper, an embedded vertical plastic strip, and color-shifting ink (the appearance of which changes in hue from copper to green as the bill is tilted) – and three weeks later, the press reported

[96] FDA Counterfeit Drug Task Force, Interim Report, U.S. Department of Health and Human Services, Food and Drug Administration (October 2003), at 17.

that "a bunch of computer-generated phonies have turned up."[97] According to an October 2003 CNN report, counterfeit bills were found in and around Brockton, Massachusetts, and Elkhart, Indiana.[98]

Moreover, as technology improves, counterfeiting gets easier. According to a report to Congress prepared by the Secretary of the Treasury, "the Secret Service suspects that the counterfeiting of U.S. currency may become progressively easier as the generally available technology improves and the cost of computer equipment (including printers and scanners) decreases."[99] For example, "[c]ounterfeiting with laser color printers is likely to increase with the affordability of the printers. Similarly, the growing use of the Internet is expected to aid counterfeiting."[100] "Once a currency note is scanned and the resulting electronic image is enhanced," the report explains, "the image can be transmitted electronically, including over the Internet, and printed in batches of any size by individuals who would be unable to make the image themselves."[101] Criminals who counterfeit labeling and packaging for prescription medicines rely on similar computer and laser print technology.

Second, as explained earlier, counterfeit-resistant technologies do not provide real time verification of a drug's authenticity. Covert features will require off-site testing and time. It is not realistic to expect Customs inspectors, distributors, pharmacists, and patients to be familiar with the wide variety of overt features used on

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97 "New $20 Not So Counterfeit-Proof," *MSNBC Report* (October 30, 2003).

98 "Bogus Bills: Counterfeit New $20 Bills Starting to Appear," *CNN Daybreak* (October 31, 2003).

99 Report to the Congress by the Secretary of the Treasury, "The Use and Counterfeiting of United States Currency Abroad, Part 2" (March 2003).

100 *Id.*

101 *Id.*

the thousand of drug products available.[102] Furthermore, unless every foreign country simultaneously approved the use of identical overt and covert counterfeit-resistant features – which is unlikely – some imported drugs will always be unprotected.[103]

Third, as explained earlier, counterfeit-resistant technologies are rendered useless if a drug product is repackaged. Repackaging is common in the industry and – because foreign versions of drugs approved in the United States will have foreign packaging and labeling – may be an inevitable part of a drug importation scheme.[104] The practice is subject to only minimal oversight, and it has been implicated in recent counterfeiting incidents, including one that led to a recall of 200,000 bottles of counterfeit Lipitor in early 2003.[105]

Fourth, effective counterfeit-resistant technology would be prohibitively expensive. Estimates from FDA and the Congressional Budget Office (CBO) suggest a counterfeit-resistant technology mandate could substantially increase the cost of any importation scheme. For example, after initial discussions with the Bureau of Printing

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102 It is not clear whether it would be appropriate or feasible to establish a centralized electronic database to solve this problem. Since using such a database would be time consuming, pharmacists probably would not use it on a routine basis for authentication purposes. In addition, it is not clear who would maintain this database, have access to it, or update it. Because counterfeit-resistant features will need to be changed regularly, the database would need multiple entries for the same package, significantly complicating efforts to authenticate particular drug products. If the database were publicly available, counterfeiters would have easy access to all of the measures currently being used. A centralized database could thus serve as a more valuable resource for counterfeiters than for pharmacists and patients.

103 If some foreign regulatory authorities required counterfeit-resistant packaging for their domestic markets to deviate, even in some minor way, from the packaging approved by FDA, the number of legitimate counterfeit-resistant presentations would exponentially increase, leading to even more pharmacist and consumer confusion.

104 Both the Grassley bill (S. 2307) and the Dorgan bill (S. 2328) contemplate the importation of unapproved foreign versions of U.S.-approved drugs.

105 *See* David Schwab, "Clamping Down on Counterfeits – Fed Report to Outline Ways to Control Fake Medicines," *The Star-Ledger* (September 25, 2003).

and Engraving, FDA estimated the counterfeit-resistant technology mandate in the Pharmaceutical Market Access Act of 2003 (H.R. 2427) could "raise the cost of prescription drugs by as much as $2 billion in the first year."[106] In a cost estimate of the same bill, CBO stated that the cost of the provision mandating the use of anti-counterfeiting technology would be "significant."[107] According to CBO, "the cost of this requirement to the affected entities would exceed the annual threshold specified in UMRA [Unfunded Mandates Reform Act] ($120 million in 2003, adjusted annually for inflation) in each of the first five years for which the mandate would be effective."[108] Further, "the requirements for counterfeit-resistant packaging would increase the cost of producing prescription drugs, and some or all of those costs would be passed through to the consumer."[109]

The high cost of counterfeit-resistant technologies could ultimately undermine the very purpose of any foreign drug importation scheme. In its analysis comparing the prescription drug importation provisions of H.R. 2427, the Medicare reform bills (H.R. 1 and S.1 as they entered conference), and prior importation law (with the MEDS Act not implemented), the Congressional Research Service (CRS) noted that the pharmaceutical industry would face the cost of the development, manufacture, and ongoing maintenance of the packaging technologies to deter tamper and counterfeiting. According to CRS, the "U.S. consumer will likely end up bearing a significant portion of

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106 Letter from FDA Commissioner Mark McClellan, M.D., Ph.D. to Chairman W.J. "Billy" Tauzin (July 18, 2003).

107 CBO, Cost Estimate, H.R. 2427, The Pharmaceutical Market Access Act of 2003 (November 19, 2003).

108 *Id.*

109 *Id.*

all of these costs through taxes and increased prices."[110] The Secretary's evaluation of the supposed cost-savings associated with importation must take this cost into account.

b) Unit-of-use packaging will not eliminate the counterfeiting problem.

Although some have suggested that pharmaceutical manufacturers adopt "unit-of-use" packaging to address the counterfeiting problem, there are legal, economic and practical impediments to its widespread adoption in the United States, and in any event it can still be counterfeited.

Unit-of-use packaging is "any container closure system designed to hold a specific quantity of drug product for a specific use and dispensed to a patient without any modification [by the pharmacist] except for the addition of appropriate labeling."[111] A "unit of use" can be packaged in bottles (for example, a 30-pill bottle, sold to and sold by the pharmacist as such, with nothing more than the addition of appropriate labeling) or in blister packaging (for example, a blister card of seven days worth of a particular product). Most non-solid oral dosage pharmaceutical products (e.g., ophthalmic drops, nasal sprays, inhalers, creams, and ointments) are packaged in unit of use, but very few solid oral dosage forms (e.g., tablets and capsules) are packaged in this format.

Increased use of unit-of-use packaging could help combat counterfeiting by reducing (but not eliminating) repackaging, thereby ensuring that counterfeit-resistant technologies employed by the original manufacturer remain intact throughout the

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110 CRS, CRS Report for Congress, "Importing Prescription Drugs – Comparison of the Drug Import Provisions in the Medicare Reform Bills, H.R. 2427, and Current Law" (October 8, 2003).

111 Final Counterfeit Report, supra note 93, at 4.

distribution chain all the way to the patient. There are, however, significant impediments to widespread adoption of unit-of-use packaging.

First, even with a general move to unit-of-use packaging, companies may need to continue producing a variety of package sizes. Decisions on packaging format are typically driven by market demand and vary from product to product. The dispensing system in the United States is heterogeneous, with over 80,000 dispensing sites including chain and independent pharmacies, hospital pharmacies, managed care organizations, mail order pharmacies, clinics, and doctor's offices. Each of these customers may have a different preference depending on its dispensing practice. While many pharmacies have adjusted inventory control procedures and moved to "just in time" inventory (where inventory is restocked automatically based on sales and therefore more market-responsive), this may not be universal practice. Where it is not the practice, of course, a pharmacy may need to have a variety of package sizes on hand.

A proliferation of unit-of-use packaging presentations might also be required by virtue of the product's dosing regimen and safety profile. For pills where the dosage regimen is one pill a day, it is economical to design blister packs that will hold the requisite amount. For dosing regimens of two or more per day, small bottles are a more economical packaging unit. Further, any move to unit-of-use packaging must accommodate medicines where there may be various dosing regimens. It is common for anti-infectives to have variable dosing regimens (e.g., 7, 10, 14, or 21 days; in the case of some oral antifungals, one or two pills could constitute a full dosing regimen). A proliferation of unit-of-use packaging options for each drug could take up considerable

pharmacy shelf space and cause confusion in filling prescriptions when the appropriate package unit is not available.

Second, the Consumer Products Safety Commission (CPSC) regulations implementing the Poison Prevention Packaging Act (PPPA)[112] create a disincentive for manufacturers to use unit-of-use packaging. Current regulations require testing of packaging formats. In the case of a cap or vial closure system, CPSC regulations define a clear pass/fail standard – "test failure" occurs if a child removes the cap. (Packaging is deemed child-resistant if there are no test failures in a certain percentage of tests.) In the case of unit-of-use packaging, CPSC regulations establish a subjective standard – a test failure occurs if a child "opens or gains access to the number of individual units which constitute the amount that may produce serious personal injury or serious illness."[113] Therefore, before adopting unit-of-use packaging, a sponsor must determine the amount that may cause a somewhat vaguely defined "serious personal injury or serious illness" in a child, submit toxicological data to CPSC, wait for CPSC confirmation of its conclusion as to the number of units the opening of which would constitute failure, and then test the package. If the package fails, the investment of time and money cannot be recovered. This discourages use of unit-of-use packaging. It is unclear under current law whether the CPSC will permit "type testing" for unit dose formats (a practice whereby a package type that has successfully passed protocol testing may be used for other products without

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112 15 U.S.C. § 1471 *et seq.*

113 16 C.F.R. § 1700.20(a)(2)(ii).

additional testing), and the lack of clarity compounds the disincentive to adopt this method of packaging.[114] Many manufacturers therefore opt for bottles.

In any event, from a technological standpoint, unit-of-use packaging is not difficult to counterfeit. For instance, while unit of use packaging is generally prevalent in Europe, as explained below (page 66), a number of pharmaceutical companies have discovered counterfeit packaging in EU member states. Indeed, in its final report on counterfeiting, FDA recognized that unit-of-use packaging "does not create a sufficiently high level of security to justify its use as a stand-alone anti-counterfeiting measure."[115]

c) Tamper-evident packaging will not defeat counterfeiters.

Nor will tamper-evident packaging provide the magic bullet to defeat counterfeiters. To be sure, tamper-evident packaging may provide some marginal protection against counterfeit drugs. Examples of tamper-evident packaging include: film wrappers, blister packaging, heat shrink bands or wrappers, bottle mouth inner seals, tape seals, breakable caps, and sealed tubes. Over-the-counter (OTC) medicines have been required to have tamper-evident packaging for a number of years, and many prescription drugs incorporate similar features. Like unit-of-use packaging, however,

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114 The Healthcare Compliance Packaging Council (HCPC) filed a petition with the CPSC in March 2003 requesting that the Commission permit type-testing of unit dose formats. In May, the Commission declined to docket the petition on the grounds that "current CPSC regulations implementing the PPPA do not restrict a company from relying on child resistant test data generated by the package manufacturer or from testing of similar packages for a different substance." Letter from Stephen Lumberg, Assistant General Counsel, CPSC, to Peter G. Mayberry, Executive Director, HCPC (May 27, 2003). Notwithstanding this helpful clarification, there is still considerable uncertainty about the use of type testing. The establishment of performance and design standards – for example through an established standards organization – would facilitate type testing and reduce this hurdle to unit-of-use packaging.

115 Final Counterfeit Report, supra note 93 at 4.

tamper-evident packaging is not difficult to counterfeit. And like overt counterfeit-resistant features, tamper-evident packaging is rendered useless by repackaging. Tamper-evident packaging is therefore only moderately useful as an anti-counterfeiting technology, and FDA has thus concluded that it should not be used as a "stand alone" anti-counterfeiting technology.[116]

4. A closed distribution system featuring electronic "track and trace" technology, though essential to the fight against counterfeiting and diversion, will not be ready for deployment for several more years.[117]

A closed distribution system is the best way to assure the integrity of the U.S. pharmaceutical supply. As discussed above, a closed system is one where product is shipped directly from the manufacturer to the distributor and then on to the pharmacy and finally, the patient. Each business transaction in the supply chain is recorded and a pedigree, ultimately tracing each lot back to the manufacturer, is maintained. Ideally, this pedigree would be generated and maintained electronically in order to permit the authentication of drug products in real time at any point in the distribution system. An electronic "track and trace" system – which can track drug products in real time throughout the distribution system from manufacturer to patient and provide an electronic pedigree vouching for the authenticity of distributed drug products – is critical to a truly closed distribution system.[118]

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[116] Final Counterfeit Report, supra note 93 at 5.

[117] This section of our comments responds to item 3 on page 9 (whether anti-counterfeiting technologies could improve the safety of products in the domestic market as well as products that may be imported).

[118] Simply coding packaging at the pallet or case level, as some have suggested, will not fully assure authenticity down to the individual packaging unit. In fact, it may lead to a false sense of security as countless individual packaging units coming from different

Constructing a national electronic pedigree system, however, is a daunting task that will take considerable time and resources. Before such a system can be implemented, complex technological, legal, regulatory, and financial issues need to be resolved by and among FDA and all interested stakeholders throughout the distribution chain, including manufacturers, primary wholesalers, secondary wholesalers, hospitals, and pharmacies.

Stakeholders have not yet agreed, for example, on the optimal technology for track and trace. Bar code technology has been employed for a number of years to control inventory and for product identification. Within the UCC/EAN standards system there is a Global Individual Asset Identifier that incorporates serialized identification of individual package units. This lends itself to automated track and trace. Unfortunately, bar codes require packaging to be actively scanned, and at some distribution levels this could be prohibitively labor intensive. Because Radio Frequency Identification (RFID) chips emit a signal permitting passive reading, this may be more suited to an automated system. RFID is not yet, however, a fully-validated technology. As the technology becomes more robust, it may be the better substitute for printed bar codes.

Even after a technology has been selected and validated, there remain significant hurdles to implementing a national track-and-trace system. Decisions must be made about construction, management, and ownership of the database or databases used to maintain and update the code on each drug, as it passes through the distribution chain. It is not clear, for example, whether there will be one centralized database or many manufacturer-specific databases. Ownership of the data and access to the data need to be

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cases in the same lot or different lots are bundled together and shipped. At this point, the ability to track and trace is lost.

resolved. In the case of multiple databases there will have to be a centralized routing system so that information on each product will get to the appropriate manufacturer's database. Also, each packaging unit must be labeled with a unique serial identification (whether a bar code or RFID). Each manufacturer would have to have its own assigned list of numbers with a leading prefix to assure that there are no duplicate numbers within the overall system. The National Drug Code (NDC) number is suitable to this task as it identifies both the product and the manufacturer. The remainder of the data field can be used for the serial number. Since each transaction will have to be registered, all distributors, pharmacies, and other dispensing sites will need equipment to read the serialized information. Manufacturer packaging lines will have to be modified to print serialized bar codes or incorporate RFID chips.

The full cost of constructing, validating, and implementing a track-and-trace system is unknown, but it will likely take at least five years to select a technology, validate it, resolve these legal and practical issues, and construct a system.

5. Foreign health agencies are neither willing nor able to ensure the safety of drugs exported from their countries to the United States.[119]

a) The Canadian government is neither willing nor able to ensure the safety of drugs exported from Canada to the United States.

Although some proponents of drug importation argue that importation would be safe if limited to drugs imported from Canada, the Canadian government is neither willing nor able to ensure the safety of drugs exported from Canada to the United

[119] This section of our comments responds to item 6 on page 9 (the extent to which foreign health agencies are willing and able to ensure the safety of drugs being exported from their countries to the United States).

States. Under Canadian law, drug products that are not manufactured for consumption in Canada or sold for consumption in Canada – and drugs that were, but have since been repackaged and relabeled – fall outside the scope of the Canadian Food and Drugs Act, provided they are labeled for "export" and bear an export certificate. With evidence mounting of transshipment of pharmaceuticals through Canada to American customers, the Canadian government has stated that it will not guarantee the safety and effectiveness of drugs exported from Canada to the United States.

Health Canada's Therapeutic Products Directorate regulates medicinal products under the Food and Drugs Act and its implementing regulations. The scheme generally prohibits the sale of any drug product unless the transaction falls within a listed exception. For example, one exception permits sale if – (1) the drug is the subject of a Notice of Compliance (NOC) issued by the relevant Minister, and (2) the patient presents a valid prescription to a pharmacist.[120] In addition to imposing a premarket approval requirement, Canadian law prohibits the fabrication, packaging, labeling, distribution, import, and wholesale of a drug except in accordance with an "establishment license."[121] Further, all drug establishments involved in these activities must comply with Canadian GMP regulations.[122] Finally, the Health Products and Food Branch Inspectorate regularly inspects all establishment license applicants and holders for compliance with GMP

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120 An NOC issues after the sponsor submits a New Drug Submission (NDS), which is the Canadian equivalent of an NDA. An NOC is issued pursuant to Regulation C.08.004(1)(a).

121 Regulation C.01A.004.

122 Regulation C.02.003.

regulations, and it has considerable enforcement authority over establishment license holders for violations of the Act and regulations.[123]

Health Canada regulations state that "no person shall import into Canada for sale a food or drug the sale of which in Canada would constitute a violation of the Act or these Regulations."[124] The agency interprets this to require that all imported products comply with all requirements of the Act, whether or not intended for re-export.[125] The Act neither expressly permits nor expressly prohibits the export of drug products that have been imported, manufactured, or sold for the Canadian market. Nor is there an exception from the general NOC requirement for exported products.

Notwithstanding the preceding, Section 37 of the Act provides that the Act as a whole does not apply to products for export, if the exporter notifies the Health Products and Food Branch Inspectorate and signs an export certificate, indicating that – (1) the drug products are labeled for export, (2) the drug products were not manufactured for consumption in Canada and are not sold for consumption in Canada, and (3) the drug products do not contravene any known requirement of law in the country to which they are being shipped. Section 37 thus seems to significantly limit the power of the Canadian government to regulate products purchased in a third country and transshipped through Canada for sale to Americans even if it wanted to regulate such products. According to this provision, a party who manufactures, packages, distributes, or exports these products need not obtain Canadian marketing approval, need not comply with Canada's

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123 *See, e.g.*, www.hc-sc-gc.ca/hpfb-dgpsa/inspectorate/pol_0011_tc_e.html (inspection policy).

124 Regulation A.01.040.

125 *See* www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/guide_comm_import_e.html (importation and exportation policy).

establishment licensing requirements, need not comply with Canadian good manufacturing practice requirements, and is not subject to the Canadian government's inspection or enforcement authority.

Further, if a Canadian entity obtains a product intended for the Canadian market, and repackages (or relabels) it for the American market, intending to sell the product to Americans rather than Canadians, it may invoke the same exemption. Health Canada has taken the position that the safety and quality of products exported from Canada are matters for the drug regulator in the destination country.[126] In Health Canada's view, these products fall outside its mandate and its jurisdiction. Again, then, if the exporter identifies the product as intended for export, signs an export certificate, and notifies the Inspectorate, its activities will fall outside Health Canada's jurisdiction.

In recent years, there has been an explosion in pharmaceutical transshipment through Canada. According to FDA, while 80 percent of the parcels in its second series of blitz exams (discussed above, page 11) were exported from Canada, not all of these products originated in Canada. Some had been imported into Canada and then exported into the United States. For example, FDA Commissioner (now CMS Administrator) McClellan noted that "at the Dallas, Seattle, and Buffalo mail facilities, imported drugs were encountered which were manufactured in Canada, Mexico, Costa Rica, India, Pakistan, New Zealand, Taiwan, Thailand, and a host of other countries. However, in some cases, the drugs that had obviously been manufactured in other countries were exported from Canada."[127] In testimony last year, FDA's Associate Commissioner for Policy and Planning, William Hubbard, gave an additional example.

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126 "Taking Responsibility for Drug Safety," *The Washington Post* (May 21, 2003).

127 *See* FDA Press Release, January 27, 2004.

He described an 82-year-old man who bought two drugs from a web site based in Arizona that offers to sell Canadian drugs. The patient instead received drugs "made in India." According to Hubbard, "this gentleman apparently had prostate enlargement and epilepsy, but what he received was a Tupperware container, and in that Tupperware container... were drugs for prostate enlargement with no labeling, no warnings or anything and the drug for epilepsy. But the really unique thing about this story is that it had a funny return address on it – India. And in fact, it says on the package, made in India. He was told on that web site and when he made the phone call that he was getting a U.S. produced drug, sold in Canada, and sold back to him. He got Indian drugs that are not approved, have no labeling, no information and he called the FDA and was outraged why are we letting this stuff in."[128]

Data from Industry Canada, a department of the Canadian Federal government, corroborate the evidence of transshipment found by FDA. According to Industry Canada data, between September 2002 and September 2003, there was a significant increase in Canadian imports of pharmaceuticals from countries such as Singapore, Ecuador, China, Argentina, South Africa, and Thailand, to name a few.[129] The Industry Canada data are presented in the table that follows. The majority of these countries have documented counterfeiting problems, and none has a Mutual Recognition Agreement (MRA) with Canada on good manufacturing practices (GMP) for prescription medicines. According to a recent report by Prudential Financial, which relied on the Industry Canada data, Internet drug sellers appear to be increasingly obtaining their

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128 Testimony of William K. Hubbard, Senior Associate Commissioner for Policy, Planning and Legislation, U.S. Food and Drug Administration, before the House Government Reform Subcommittee on Human Rights and Wellness (June 12, 2003).

129 Industry Canada, Trade Data Online, at <www.strategis.ic.ga.ca>.

product (for shipment into the U.S.) from countries such as Bulgaria, Singapore, Argentina, South Africa, and Pakistan.[130]

COUNTRY	2002 TO 2003 INCREASE	
Singapore	$13.8 TO $17.9 M	**30%**
Ecuador	$.74 TO $2.2 M	**198%**
China	$24.9 TO $35.5	**43%**
Iran	$.049 TO $1.41 M	**2,753%**
Argentina	$.22 TO .72 M	**221%**
South Africa	$.28 TO $.51	**84%**
Thailand	$.61 TO $.92 M	**52%**

Source: Industry Canada, Trade Data Online, <www.strategis.ic.gc.ca> (20 November 2003)

With proponents of importation pointing to Canadian exports as the solution, and with evidence of transshipment mounting, the Assistant Deputy Minister of Health Canada recently wrote to the Washington Post to state her government's position on the safety and quality of products exported from, or through, Canada to the United States.[131] She explained that Health Canada could not guarantee the safety and effectiveness of drugs exported to the United States and noted that the Canadian government had not agreed to assume any responsibility for the safety of these drugs. Importing countries, alone, are responsible for ensuring the quality, safety, and effectiveness of drugs intended for their markets.

In short, therefore, the Canadian government is neither willing nor able to ensure the safety of the rapidly increasing number of pharmaceuticals exported from, and

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130 Diane Duston and Tim Anderson, "Importation of Drugs into the U.S. Appears Difficult to Stop – Puts Low Pressure on EPS," Prudential Financial Equity Research (October 8, 2003).

131 "Taking Responsibility for Drug Safety," *The Washington Post* (May 21, 2003).

through, Canada to patients in the United States. Although the new section 804 is limited on its face to drugs imported from Canada, Canada's failure to prohibit transshipment through its borders – and its refusal to regulate those products – means that, in fact, section 804 permits importation of drugs from anywhere in the world. There is no assurance that these products will be safe, effective, or – indeed – even what they purport to be.

b) Other developed countries also do not apply the same strict regulatory standards to products shipped through their borders to the United States as to products intended for their own citizens.

Although section 804 of the FDCA nominally limits importation to drugs from Canada, its predecessor (the MEDS Act) permitted importation from the countries listed in section 802(b)(1)(A).[132] Several pending importation bills would permit importation from more countries than just Canada.[133] For this reason, and because – as

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[132] When the MEDS Act was enacted, these countries were: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Liechtenstein, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, and the United Kingdom. When section 802(b)(1)(A) was enacted, these countries were deemed – though not without controversy – to have sophisticated drug approval systems "comparable to" that of FDA. *See, e.g.*, Sen. Rep. 99-225 at 2 ("Under the bill, drugs covered by the amendments may only be exported to certain countries and under certain conditions. The drugs may be shipped to three categories or tiers of countries . . . [including] [d]eveloped countries with sophisticated drug approval systems comparable to that of the Food and Drug Administration.") Rather than listing the countries in the European Union by name, however, section 802(b)(1)(A) refers to "the European Union or a country in the European Economic Area." On May 1, 2004, the EU expanded to include the Czech Republic, Cyprus, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia.

[133] S. 2307 (Grassley) would permit importation from Canada and then, two years later, from Australia, the European Union (EU) and European Economic Area (EEA) countries, Japan, and New Zealand (i.e., unlike the MEDS Act, not Israel, Switzerland, or South Africa). The EEA includes, in addition to the EU member states, Norway, Iceland, and Liechtenstein. S. 2328 (Dorgan) would permit importation from Canada, initially,

explained in the prior section – the limitation in section 804 is illusory, the Task Force must consider whether a broader range of countries regulate exported and transshipped products as rigorously as they do products intended for their domestic markets.

The 25 countries listed in footnote 132 generally require that pharmaceutical products intended for domestic distribution be pre-authorized for marketing. They typically also require manufacturers to hold manufacturer's authorizations and distributors to hold distributor authorizations. They impose some version of "good manufacturing practices," although GMP requirements vary from country to country, and they often impose "good distribution practice" (GDP) requirements on distributors. Some require import licenses, some require export licenses, and most inspect manufacturers and sometimes also importers and exporters. Products intended solely for export, however, are usually subject to fewer regulatory requirements and less scrutiny than products intended for domestic consumption. Further, like Canada, most of these countries do not regulate products merely transshipped through their borders for another destination, such as the United States.

In nearly every one of these 25 countries, pharmaceuticals imported or manufactured domestically for a foreign market are <u>not</u> subject to the same rigorous regulatory requirements as pharmaceuticals intended for domestic distribution. Most jurisdictions do not apply the full range of their laws (marketing authorization,

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and then from Australia, Canada, members of the EU on January 1, 2003, Japan, New Zealand, and Switzerland (i.e., unlike the MEDS Act, not Switzerland, South Africa, or EA countries). It is unclear whether the restriction to countries that were member of the EU prior to its recent expansion would be enforceable, in light of the practice of parallel trade within the EU.

manufacturer's license, GMP, distributor's license, and GDP) to products that are imported or manufactured solely for export.

With one exception (Norway), every country expressly or implicitly excludes some transshipped products from its laws. These products, which may be destined for the United States, do not have to meet the same standards as do products intended for domestic use. Some countries (like Canada) explicitly exempt transshipped products from local law. In other countries – Australia, Greece, Iceland, and the United Kingdom, for example – there is an exemption for transshipped products if certain conditions are met. For example, in Australia, transshipped products are not regulated if there is no manufacturing in the country, the goods are continuously within the control of a single person, and the goods do not clear customs. In Greece, transshipped products are not regulated if they are not subject to a "manufacturing alteration." Similarly in Iceland, transshipment is not subject to licensing or oversight unless products are subject to manufacturing. In other countries – like Luxembourg, the Netherlands, and South Africa – the exemption is available provided the products are stored in customs warehouses. (By way of contrast, Switzerland does not regulate transshipped products, but takes the position that products stored in customs warehouses have been imported and are subject to local law.) In some countries, the standards for the transshipped products are expressly lower; in Japan, for example, it is lawful to import expired medicine, repackage it as a new product, and export it to a foreign destination. The practice is prohibited only if the Japanese government deems the products "decomposed" or otherwise harmful.

In short, then, a rule that would permit importation of pharmaceuticals from the European Union and other developed countries like Japan and Australia would

not ensure the safety of imported products. Nearly every country subjects exported products to a lower level of regulation than domestic products, none prohibits transshipment, and many exempt transshipped products from their laws. This means that the importation of drugs from these countries is tantamount to the importation of drugs from anywhere in the world. There is no assurance that these products are safe, effective, or – indeed – even what they purport to be.

6. Parallel trade in Europe has raised safety issues, led to consumer confusion, and increased counterfeiting operations.[134]

Parallel trade in the EU/EEA is different from the importation contemplated by section 804 or the bills presently pending in Congress. First, the principles governing parallel trade within the EU/EEA are based on Article 28 of the European Community Treaty, which provides that goods may circulate freely between all member states.[135] This principle sets aside regulatory and intellectual property constraints that otherwise would prevent or restrict parallel trade in medicines. Second, Article 28 does not apply to imports from third countries into the EU/EEA and as a practical matter there is little parallel importation of medicines from countries outside the EEA, because regulatory and intellectual property considerations generally preclude this.

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[134] This section of our comments responds generally to the question whether importation can be done safely, as well as to items 1 and 3 on page 9 (limitations that may inhibit the Secretary's ability to certify the safety of imported drugs, and whether anti-counterfeiting technology could improve the safety of products in the domestic market as well as products that may be imported).

[135] Article 28 of the EC Treaty prohibits quantitative restrictions on imports and exports and all measures having equivalent effect between member states. A direct consequence of this principle of free movement is the classic "*Cassis de Dijon*" doctrine of the European Court of Justice that a product lawfully on the market in one member state must be able to circulate freely within the whole of the EU, subject to objectively justifiable exceptions. The same principle is contained in Article 11 of the Agreement on the European Economic Area (EEA).

Third, under EU rules, products placed anywhere on the EU/EEA market are the subject of marketing authorizations, based on harmonized data requirements, and they are manufactured and distributed in accordance with harmonized rules and standards. Regulators and consumers in the importing member state can therefore generally be confident that the rules in the exporting and intermediate member states are sufficient to ensure the safety, quality and efficacy of imported product. None of these facts would be true in the United States, if section 804 (or alternative importation legislation) were implemented.

Despite these differences, which both obviate some legal impediments to importation and moderate the safety concerns, a number of safety issues have arisen in the EU due to parallel trade. These issues should be a warning to American policymakers considering the implementation of section 804 or the enactment of alternative importation legislation. Specifically, EU member states have struggled with (1) safety issues arising from improper storage and handling, (2) safety issues arising out of repackaging and re-handling, (3) parallel import of drugs withdrawn from the market, (4) counterfeit drugs, and (5) diversion of drugs from developing countries.

First, significant health issues are associated with inappropriate storage of goods during transit. Parallel imported goods must pass through the hands of various international trading organizations, and it is not always possible for regulatory authorities to ensure sufficient physical monitoring and sampling of these products. A final WHO/WTO Workshop Paper discusses this issue.[136] The report comments that "what is

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[136] Guy Woods, Lacuna Research Limited, "Session V – Market Segmentation: techniques, actors, and incentives; Governmental Measures: Role of regulatory authorities" <http://www.wto.org/english/tratop_e/trips_e/hosbjor_presentations_e/26woods_e.pdf>.

not known, especially where parallel imported goods have passed through the hands of various international trading organisations, as they most certainly will have done, is how material has been handled whilst in transit." It points out that products pass through "countries having high temperatures and humidity – where not all warehouses are climate controlled" and that goods are exchanged "en route to local retail outlets within equatorial and tropical climates." Thus, it adds, "inevitably products will be affected by external environmental conditions and some will inevitably reach patients out of assay." For some products shipped in this manner, "it is not enough for it simply to be dispensed and consumed within its expiry date."

The report adds, "while parallel importers may themselves be required to comply locally with stringent drug wholesale regulations, there are many ways to circumvent drug regulations." For example, "[k]eeping goods in transit at the warehouse of a third party freight forwarder or courier" is one technique used "to ensure that material of marginal, or dubious, quality is physically kept well away from the licensed wholesaler and out of reach of the regulatory authorities." The report explains, "[f]rom these off site locations dealers can safely offer samples to prospective customers and can both neutralise shipments and break bulk – all without breaking national medicine control regulations." The report concludes that "regulatory authorities can really only tackle this problem by physical monitoring and sampling." This solution is limited, however; "sampling cannot be done on all products in all locations, all the time: most nations simply do not possess the border control and chemical analysis resources needed methodically to check incoming consignments."

Second, parallel trade requires both repackaging and re-labeling, which can introduce a variety of safety problems. For example, to ensure that a product is suitable for the destination market, the parallel trader will need to modify product labeling and package inserts to ensure that they conform to the linguistic requirements in the destination country. There is a risk of generating errors during translation of both the product labeling and package insert, which in turn may confuse the pharmacist or consumer. Errors in the translation of key information could result in serious injury. Further, implanting linguistic changes inevitably requires repackaging and relabeling, and hence manipulation of the product.[137] Any manipulation has the potential to result in a deterioration in quality of the product. Also, parallel traders often discard the anti-counterfeit measures that some packaging now incorporates. They can also theoretically discard temperature control printing or devices on packaging.

One member state medicines agency recently commented on a safety problem with parallel imports, which it attributed to relabeling. In its report for the years 1998-2002, the German Medicines Agency (BfArM) states:

> Events worth mentioning in connection with parallel trade:
> 2001-2002:
> Complaints from consumers and diabetics associations related to reduced activity of imported insulin preparations; Results of the investigation: insulin content of the checked products, which are to be administered by means of a pen, is in order, but possibly the functionality of the pens is affected by inappropriate relabeling of the vials; In essence products that are centrally approved in the EU are involved;

[137] Parallel traders have generally found that the use of (translated) labels affixed to the innovator's original primary and secondary packaging makes the resulting products unappealing to consumers in the destination country. Traders therefore strongly prefer to repackage products.

Consequence for parallel import approval procedure: directions for proper labeling.[138]

Parallel traders may also need to modify an imported product to conform it to presentation requirements in the destination country. For example, it is common practice for traders to repackage tablets to take into account national variations in pack sizes. They may also separate or combine blister packs to meet local requirements, which can result in the break-up or combination of product batches. It has also become common for parallel traders to cut up blister packs, where this is necessary to comply with local requirements. Not only can this practice result in the separation of product batches, but it has been known to result in the deletion of batch numbers.

In the *Paranova* case,[139] for example, the parallel trader repackaged medicines in new external packaging with a uniform appearance and in the trader's own style – albeit bearing the innovator's trademarks and the statement that the products had been manufactured respectively by "Bristol-Myers Squibb," "Boehringer Ingelheim," and "Bayer," together with the indication "imported and repackaged by Paranova." Also, in order to parallel trade the Bayer product Adalat from Greece to Denmark, Paranova repackaged the Greek product (originally sold as packages of three blister packs of 10 tablets) into 10 blister packs of 10 tablets. In order to trade in Vepesid and Vumon, the same company removed the vials and ampoules from their surrounding padding, and attached to each a new self adhesive label. The vials and ampoules were then replaced in the original padding and put in the new external packaging. In the case of Mycostatin,

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138 BfArM report on the activities for the years 1998-2002 on page 39 (See: http://www.bfarm.de/de/DasBfArM/publ/BfArM_Bericht_Bd01.pdf>).

139 Joined Cases *Bristol-Myers Squibb* v. *Paranova A/S* (C-427/93), *C. H. Boehringer Sohn, Boehringer Ingelheim KG and Boehringer Ingelheim A/S* v. *Paranova A/S* (C-429/93), and *Bayer Aktiengesellschaft and Bayer Denmark A/S* v. *Paranova A/S* (C-436/93), 1996 E.C.R. I-3457.

Atrovent, Berodual and Berotec, the importer also covered the original labels of the flasks or inhalers with its own labels. In the packaging of Mycostatin, Paranova replaced the spray in the original packaging for the inhaler with a spray from a source other than Bristol-Myers Squibb.

In the *Eurim-Pharm* case,[140] in order to import pharmaceutical products into Germany from France, Portugal, and Spain, the trader repackaged the products to comply with local German sizes. In some cases, blister packs were cut into smaller sizes. This occasionally resulted in loss of batch numbers, in which case the number was reprinted by the trader. Cutting sometimes also resulted in the loss of days from week indicators on the back of blister packs.

The European Court of Justice has found that a trademark owner may oppose repackaging when it "involve[es] a risk of the product inside the package being exposed to tampering or to influences affecting its original condition." In particular, the court considered that the condition of the product could be affected if "the external or inner packaging of the repackaged product, or a new set of user instructions or information, omits certain important information or gives inaccurate information concerning the nature, composition, effect, use or storage of the product," or if "the packaging of the repackaged product is not such as to give the product adequate protection."[141] In one case in the United Kingdom, Mr. Justice Laddie identified

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[140] Joined cases C-71/94, C-72/94 and C-73/94, *Eurim-Pharm Arzneimittel GmbH v Beiersdorf AG, Boehringer Ingelheim KG and Farmitalia Carlo Erba GmbH*, 1996 E.C.R. I-3603.

[141] *Id.* In *Paranova, supra* note 139, the Court referred also to the insertion by the parallel importer of an extra article designed for the ingestion and dosage of the product that does not comply with the method of use and the doses envisaged by the manufacturer.

instances when it would be relatively easy to show prejudice to a product's quality due to repackaging.[142] These include: damage to, or removal of product from, blister packs, or removal of pre-filled syringes from sterile packaging. Absent prejudice to product quality, he found no fault with doing whatever is necessary to commercialize a product including re-boxing and relabeling and use of an importer's own livery (e.g., use of the importer's marks and different colors). He added, however, that repackaging may lead to confusion, and that the potential exists for an increase in the mis-dispensation of products. For example, a busy pharmacist might select the wrong product for a patient owing to a change in a product's box color.

In addition to pharmacist confusion, relabeling and repackaging may result in a decrease in consumer confidence in the products. This might be true of medicines not in the language of the destination country, or medicines in re-stickered boxes. A decline in consumer confidence may have economic repercussions, but the European courts have also suggested that it could affect product efficacy.[143]

Third, in some cases, parallel trade rules in the EU have resulted in the continued availability of products in some jurisdictions despite their withdrawal by the marketing authorization holder. In the *Rhône-Poulenc Rorer* case, for example, a UK parallel importer was granted a marketing authorization to parallel trade a gel cap formulation of the Rhône-Poulenc Rorer (RPR) product *Zimovane* (INN zoplicone), a

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142 *Glaxo Group Limited and Others* v. *Dowelhurst Limited and Others* [2003], 2 C.M.L.R. 8.

143 In joined cases C-266/87 and C-267/87, *The Queen v Royal Pharmaceutical Society,* 1989 E.C.R. 1295, the ECJ suggested that, because of "psychosomatic" reasons, the use of a parallel imported product may have a negative impact on treatment.

hypnotic used for the short-term treatment of insomnia.[144] The company had withdrawn the product from the UK market when abuse of the product became common in Scotland, and had replaced it with a powder tablet formulation. Since abuse had not occurred in other member states, the gel formulation remained on sale in most continental countries. RPR sought judicial review and the matter was referred to the ECJ. Although the court conceded that formulation differences can have significant safety implications, it ruled in favor of the UK regulator's decision to maintain in force the parallel import licenses for the original gel cap formulation, despite the apparent public health concerns. Its judgment was contrary to the views of the European Commission and of the French government.

Fourth, parallel trade in Europe has also facilitated the introduction of counterfeit medicines in the destination countries. Numerous studies of parallel trade have confirmed this fact. In a survey of parallel trade in five countries – Denmark, the United Kingdom, the Netherlands, Ireland, and Germany – from 1990 to 1997, the National Economic Research Associates found that five pharmaceutical companies operating in Europe and participating in the study cited instances where the quality of their product had been compromised during the parallel import process, and three companies cited instances where counterfeit product had reached pharmacists through parallel trade.[145] A recent article noted that in 2002, Swiss customs officers uncovered evidence of possible deliveries of around 22,000 counterfeit Viagra tablets with a market value of SwFr 500,000 ($410,000). According to the article, "[t]he Swiss experience

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144 *See* Case C-94/98, *The Queen* v. *The Medicines Control Agency, ex parte Rhône-Poulenc Rorer Ltd and May & Baker Ltd.*, 1999 E.C.R. I-8789.

145 N/E/R/A, Survey of Parallel Trade (1997) (conducted for Interpharma).

with counterfeit medicines is that they are almost never passed directly to doctors or pharmacies but are smuggled through importers and wholesalers who are often unable to tell whether the medicines are counterfeit or not."[146] A blue-ribbon panel chaired by the Israeli Ministry of Health Director General Dr. Yehoshua Shemer reviewed proposed importation legislation and found that it highly probable that some of the parallel imported drugs would be unsafe. Specifically, according to the study, there was a risk of counterfeit drugs that would not meet the quality requirements of the western world. The report concluded that parallel importation of drugs to Israel would involve "potential risks to public health."[147]

Finally, although the EC treaty (and the EEA treaty) enables parallel trade only among member states, the EU/EEA have struggled with the import of pharmaceutical products from third countries. For instance, concerns about the illegal import of HIV, malaria, and tuberculosis products from developing countries into the EU have (also in the context of the Doha developments) resulted in the adoption of Council Regulation (EC) No. 953/2003.[148] This Regulation prohibits re-importation of certain listed products from designated countries and is aimed at ensuring that these products exported to developing countries at cheap prices are not re-imported by parallel traders into the Community. The Regulation requires that a permanent logo is affixed on any

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146 "EP to Consider Anti-Counterfeit Measures," *Scripp Pharma* (January 14, 2004).

147 Commission to Investigate Parallel Importation of Drugs to Israel, Final Report, Israeli Ministry of Health Director General Dr. Yehoshua Shemer (December 1997). The Government of Israel withheld the report from the legislature when the proposal was under consideration, and the legislation was adopted in early 1999. The report was finally released in the summer of 2000, when Israel's Supreme Court ordered the government to release it.

148 Council Regulation (EC) No 953/2003 of May 26, 2003 to avoid trade diversion into the European Union of certain key medicines, 2003 O.J. (L135) 5.

packaging or product and any document used in connection with the approved product sold at tiered prices. At the time the Commission proposed this Regulation, regulatory authorities were taking action against the illegal imports of HIV treatment products from third countries.

C. A prescription drug importation scheme would lead to an explosion in unmeritorious tort litigation against innocent parties, while injured consumers would lack any real recourse for their injuries.[149]

As the discussion of safety issues in Section A of these comments explained, patients could be harmed by imported drugs in a variety of ways. Harm could occur, for example, if a legitimate FDA-approved product is counterfeited, and the imported counterfeit contains the wrong amount of active ingredient, no active ingredient, or a toxic substitute. Harm could occur if a legitimate product has been stored, shipped, or handled by third parties in a way that introduced contaminants or affected its stability and purity. Harm could occur where the potency of a foreign drug is not the same as that of the FDA-approved drug for which it is intended to substitute, resulting in an over- or under-dose, or where the imported product causes side effects or drug-to-drug interactions that would not be expected with the FDA-approved version. Consumer confusion resulting from labeling differences or dosing differences between U.S. and foreign products could result in medication errors. Many of the parties associated with the drug's manufacture, import, distribution, and delivery to the patient (or, in the case of a dangerous counterfeit, with the manufacture of legitimate product) would be entirely innocent of wrongdoing and unable to prevent the injury. Nonetheless,

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[149] This section of our comments responds to item 10 on page 10 (liability protections that should be in place if importation is permitted).

in each case these parties could face the burden of defending suits alleging injury arising from the imported products.

First, parties in the distribution chain could expect negligence claims. Negligence is the failure of a responsible person to exercise the degree of care required to discharge the duty resting on him. The elements of a negligence action under state law are a legal duty of reasonable care owed by defendant to plaintiff, a breach of that duty, and injury proximately caused by that breach. A defendant is held to the standard of care that a reasonable person would exercise under similar circumstances. Whether that standard of care creates a legal duty turns on a number of considerations, including the foreseeability and likelihood of injury, the burden of guarding against injury, and the consequences of placing that burden on the defendant. Plaintiffs sometimes seek to impose a duty of care on a defendant when a product is used as intended, and sometimes when a product is used in a manner that is not intended but that is foreseeable.

Plaintiffs could try to invoke negligence against manufacturers, importers, other distributors, physicians, or pharmacies. A plaintiff might attempt to establish, for example, that given FDA's longstanding insistence that imported drugs are unsafe, injury to patients who take imported drugs is foreseeable and perhaps even likely, thus creating in the "reasonable manufacturer/importer/distributor/doctor/pharmacy" a duty of care to potential patients. Once imports are legalized, plaintiffs might allege that knowledge of the risks presented by imports creates a duty for these entities and individuals to take steps to prevent the foreseeable dangers, for example by warning the patient of the potential risks.

Plaintiffs could conceivably seek to assert additional negligence theories against importers, distributors, pharmacies, and others more directly involved in the imports. For example, a plaintiff might argue that importers and distributors negligently transported drugs into and throughout the United States, subsequently leading to patient harm. Importers and distributors are particularly susceptible to a claim that they were negligent in failing to recognize and investigate problems with the drugs at their source, such as improper handling and storage and incomplete recordkeeping practices.

Pharmacies, also, might face negligence claims. A plaintiff injured by an imported drug sold by a bricks-and-mortar pharmacy might try to attribute the harm he suffered to the pharmacy where he purchased the drug, on the ground that a pharmacy has an obligation to ensure it provides only safe drugs (i.e., unadulterated, properly labeled drugs of the correct potency). To the extent imported drugs pose a known risk to patients, a plaintiff might allege that a pharmacy was negligent if it failed to take adequate steps to ensure the quality and integrity of the drugs it dispenses. Similarly, plaintiffs might argue that pharmacies have a duty to identify any differences between the foreign import version of the drug and the version in U.S. commerce. To minimize these risks, pharmacies may have to devote significant resources to due diligence activities.

These broad and malleable negligence theories could create substantial exposure to suits from personal injury attorneys against those involved in importing drugs. Even where the linkage between legitimate sales overseas and eventual harm to a plaintiff in the U.S. is attenuated, manufacturers and other commercial entities in the distribution chain might present attractive targets and would thus be required to defend

against such claims, however speculative. The burden of mounting a defense in court against even speculative charges can be substantial.

Second, plaintiffs may bring suit under the tort theory of strict liability, or the nearly identical contract theory of breach of implied warranty of merchantability. Each theory may be premised upon an inherent defect in a product or upon the defendant's failure to warn.

Plaintiffs could seek to hold each party that plays a role in delivering pharmaceuticals to the ultimate consumer strictly liable if that consumer is injured by a defective drug. A plaintiff might argue that the dangerous conditions presented by foreign drugs, for example, were inherent in the foreign distribution and U.S. import scheme, and thus existed and were known at the time the manufacturer introduced the drugs into that scheme or a downstream party purchased the drugs for resale. Consequently, either party might at least face a strict liability lawsuit from patients injured by foreign drugs, regardless of the actual cause of the injury (e.g., improper handling by an importer that rendered the drug subpotent after it left the manufacturer's control). A plaintiff might also argue that a distributor or retail pharmacy should have recognized the safety flaws in a distribution chain that flows through foreign sources. Again, although we expect these claims ultimately would fail, innocent U.S.-based defendants could still face considerable expenses in defending against the lawsuits in the first instance.

Downstream parties in the pharmaceutical distribution chain face an even greater potential risk of liability under an implied warranty of merchantability theory, because they more neatly fit the definition of a "merchant." Pharmacies may face claims

under this theory; they are extensively regulated by governmental entities, staffed by highly qualified, licensed professionals who hold themselves out to the public as having specialized knowledge and skills, and sell drugs directly to their ultimate consumers. Even if such a claim ultimately proves unsupportable, the defendant may bear substantial expense in defending against it.

Third, plaintiffs might bring suit under the tort theory of "failure to warn." The failure to warn of a product's dangerous propensities can give rise to a claim of strict liability, breach of implied warranty of merchantability, or negligence. The purpose of a warning is to apprise people coming into contact with a product of dangers of which they may be unaware so that they may take appropriate precautions to protect themselves.

Particularly with respect to imported drugs that FDA has specifically identified as potentially dangerous, plaintiffs could seek to make out an argument for failure to warn with regard to pharmacies. In general, the "learned intermediary" doctrine relieves pharmacists of the duty to warn about possible dangers of prescription drugs, for the patient's physician is deemed to be in the best position to provide any applicable warnings to the patient about the drug. However, courts in a number of states have refused to extend the protections of the learned intermediary doctrine to pharmacists who had specific knowledge of a particular danger to the patient.

Doctors and other health care professionals may similarly face liability claims. A court may conclude that a health care provider acted negligently in failing to warn patients about the dangers of filling prescriptions through non-traditional sources, including Internet pharmacies. Medical professionals are generally not held strictly liable in tort, but are expected to apply a reasonable standard of medical care under the

circumstances. Given the level of attention devoted to this issue by the federal government, media, and professional associations, a court may conclude that "ordinary care" by a doctor or other health care provider includes giving adequate warnings to patients about the potential risks of imported drugs.

A plaintiff might also argue that the manufacturer was aware of the danger posed by imported drugs and failed to respond adequately, for example by changing the labeling of foreign drugs to include a warning to eventual American purchasers about the danger of importation or by issuing a "Dear Doctor" letter to alert health care providers. Again, although we would expect these arguments ultimately to fail (in part because foreign health agencies may not permit the inclusion of warnings in English to Americans on products intended for their local market, and in part because importers are likely to repackage in any event), the burden of mounting a defense is substantial.

Fourth, although these theories would be even more attenuated than the prior claims, parties in the pharmaceutical distribution chain could conceivably face claims of common law fraud or misrepresentation or claims of violations of state unfair trade practices acts for reasons similar to those discussed above with respect to failure to warn. While the elements of these causes of action vary somewhat, they can all be fairly described as requiring a plaintiff to prove that the defendant made a false representation of a material fact with knowledge of its falsity for the purpose of inducing the plaintiff to act thereon, and that the plaintiff relied upon the representation as true and acted upon it to his damage. An omission as well as an affirmative representation may give rise to a claim of fraud, although in some states the concealment must have been done with an intent to deceive. Other states do not require an intent to deceive.

A patient might allege that a pharmacy dispensing drugs obtained from a Canadian source has committed fraud on the consumer if it fails to disclose that source and thereby give the patient the option of filling his prescription elsewhere. A distributor or wholesaler that does not fully disclose that a drug has a non-U.S. origin, or that it was transshipped through another country at some point, may face a complaint of deceptive practices.

At the same time, those who are truly responsible for consumer injuries likely would escape liability altogether because they are unknown, located in a foreign country or have forced U.S. consumers to sign a liability waiver. For the most part, foreign counterfeiters and their accomplices (e.g., unscrupulous foreign wholesalers) who are directly responsible for injecting dangerous drugs into the U.S. drug supply will be immune from suit because they either are unknown or are located in a foreign country and thus, at least as a practical matter, are beyond the reach of most injured consumers. Other responsible parties, such as the cross-border Internet pharmacies, also will have insulated themselves from liability by forcing American citizens to waive their right to the protection of the U.S. product liability laws. Indeed, this is a standard practice among many Canadian internet sellers and even among the few websites established by state governments that facilitate Canadian internet sales. Consequently, injured consumers will lack any real recourse for their injuries.

In sum, the distribution chain that supplies drugs that could be imported into the United States from foreign countries contains a wide range of parties that could be exposed to liability claims under a number of tort theories. Most such claims could be expected to fail on the merits. However, each party would face substantial litigation

risks. These suits would also burden the court system. Both would reduce the amount of any "savings" from legalized drug imports. At the same time, the truly responsible parties would avoid liability, and injured American patients would have little true recourse.

From the manufacturer's perspective, without liability protections for parties in the distribution stream, liability and litigation may depress innovation and skew drug development decisions in undesirable ways. The challenges of discovering and developing new pharmaceutical compounds have never been higher. The American public cannot afford for manufacturers to divert resources from research and development to non-productive uses such as defending frivolous lawsuits, as inevitably would happen. Further, as companies consider competing research projects, they would be required to weigh the relative risks of tort liability, and vital investment decisions might thus be adversely influenced. From the perspective of others in the distribution chain, the risk of liability will make additional insurance and contractual indemnification provisions essential. The costs of such protection will undoubtedly be passed along to patients, the ultimate consumers in this stream of commerce. Parties unable to secure adequate insurance may be forced to cease their operations, thereby reducing market competition and patient choice. The need for liability protections is therefore great. At the same time, it is difficult to imagine any protections that will be effective in practice.

D. Importation will not lead to lower consumer drug prices.[150]

1. Neither the MMA nor any of the pending importation bills requires cost savings to be passed on to consumers.

Although proponents of legalized importation argue that it will lead to lower consumer drug prices in the United States, nothing in the new section 804 of the FDCA actually requires importers to pass along their savings. This is puzzling in light of the fact that the drafters of the MMA took steps to ensure that lower prices would be passed along to Medicare beneficiaries. The new benefit will be provided by private plans that negotiate with manufacturers on behalf of patients. Negotiated prices – prices after taking into account all discounts, direct or indirect subsidies, rebates, and other price concessions – must be disclosed to beneficiaries, and beneficiaries must receive the benefit of those prices, even if actual benefits are not payable. Similarly, beneficiaries who choose to enroll in a discount card program must have access to drug prices negotiated by the card sponsor. The drafters of the MMA ensured that consumers would obtain the benefit of lower prices available to intermediaries. Importation schemes lack this assurance.

2. The savings from inter-country price differentials are captured by parallel importers, and not passed on to consumers.

Although proponents of legalized importation argue that it will lead to lower consumer drug prices in the United States, in fact, it likely will not. If importation is implemented, commercial exporters in Canada and commercial importers in the United States will be able to purchase products at artificially low prices in price-controlled jurisdictions like Canada, and then resell them at – or just below – market price in the

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150 This section of our comments responds to item 7 on page 9 (potential short- and long-term impacts on drug prices and prices for consumers associated with importing drugs from other countries).

United States. This practice would be the equivalent of parallel trade in Europe, where a supplier purchases drugs in Southern Europe (where drug prices tend to be lower) and resells them in Northern Europe (where drug prices tend to be higher). The European experience is that the parallel traders capture the benefit of this arbitrage, and consumer prices in the destination country drop very little, if at all.

Studies unequivocally establish that parallel trade has little impact on prescription drug prices in the destination countries. For example, prices in the United Kingdom have dropped by less than two percent since parallel trade began, and in Sweden they fell by only four percent.[151] A paper released in September 2002 by the German Association of Research-Based Pharmaceutical Companies (VFA) showed that importers set their prices to compete with prices in the importing country. In Germany, pharmacies are given parallel import dispensing targets to meet. The quota for 2003 was 7 percent of the pharmacy's total dispensed pharmaceuticals. Pharmacies that do not meet their quota do not receive full reimbursement from the State for the pharmaceuticals they have dispensed. Pharmacies that exceed their quota receive a credit that can be rolled over to future reporting periods. In the past, parallel imported products had to carry a price differential of at least 10 percent off the normal pharmacy sale price in order to count toward the quota. VFA found that importers increased their prices by this exact difference in price and captured any remaining difference in price as profit. Subsequent regulations eliminated the requirement that parallel imported products have a minimum price difference; any parallel imported product may now count toward a pharmacy's quota. As a result, over time, the differences in price between imported products and

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151 "E.U. Parallel Drug Trade Cited in U.S. Reimportation Debate," *Drug Industry Daily* (November 12, 2003).

original products have shrunk. In a comparison of local prices to imported prices for eight commonly-imported drugs, the maximum difference in price was six percent, but half of the products had a difference of only three percent or less. In addition, the authors noted that the increases in price by the importers "lie without exception above the increases in price by the manufacturer."[152]

In Europe, the benefit of pharmaceutical arbitrage accrues almost entirely to the parallel trader.[153] Trade normally increases economic welfare by permitting consumers in importing countries to benefit from lower prices in exporting countries. In the case of innovative pharmaceuticals, however, the lower prices in exporting countries generally reflect more aggressive regulation, not lower real production costs.[154] There is no "free trade" benefit, therefore, and parallel traders simply capture the pricing difference caused by the aggressive pricing regulation in the source country. For example, a study released in March 2001 examined the effects of parallel trade on the pharmaceutical industry by reviewing data from the Swedish market from 1995 to 1998. The Swedish market provided a natural test for the study's authors, since before 1995 Sweden prohibited parallel imports of pharmaceutical products. Sweden entered the European Union on January 1, 1995, and therefore was required to allow parallel imports. The study found that the price of goods subject to import competition, including the parallel-traded products themselves, fell only four percent in the import market. According to the authors, the data "fail to support the hypothesis that prices for products

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152 German Association of Research-based Pharmaceutical Companies (VFA), Parallel Imports and Reimportation in the Pharmaceutical Market: Misguided Health Policy (September 2002).

153 Patricia M. Danzon, The Economics of Parallel Trade, PharmacoEconomics (1998).

154 *Id.*

subject to parallel trade converge between the exporting and importing countries." Further the study results "suggest that parallel-importing firms exploit a price difference between these markets of approximately 21 percent of the original manufacturer's price in Sweden."[155] In other words, the parallel-importing firms had a margin of approximately 21 percent, and the price reduction to consumers was only 4 percent.

To give another example, in a survey of parallel trade in five countries – Denmark, the United Kingdom, the Netherlands, Ireland, and Germany – from 1990 to 1997, the National Economic Research Associates found that parallel importers took, on average, a markup of 68 percent prior to sale in the destination country, still allowing them to undercut normal route wholesalers by an average of 22 percent. The report noted that differences in retail prices between parallel import and normal route products are "much less marked," indicating a substantial portion of the gain from parallel trade accrues to the distributors, rather than the final purchasers.[156] A more recent study from the London School of Economics and Political Science reached the same conclusion: that profits from parallel trade accrue mostly to the benefit of the middlemen or parallel importers.[157] The study analyzed the impact of cross-border brand name prescription trade within the EU by taking a sample of products from six product categories (proton pump inhibitors, HMG CoA reductase inhibitors (statins), ACE I inhibitors, ACE II

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155 Mattias Ganslandt and Keith Maskus, Parallel Imports of Pharmaceutical Products in the European Union (March 2001).

156 N/E/R/A, *Survey of Parallel Trade* (1997) (conducted for Interpharma).

157 P. Kanavos et al., "The Economic Impact of Pharmaceutical Parallel Trade in European Union Member States: A Shareholder Analysis," LSE Health and Social Care, London School of Economics and Political Science, January 2004. *See also* Press Release, "New LSE Study Contradicts Accepted Benefits of EU Pharmaceutical Parallel Trade," The London School of Economics and Political Science (November 2003). The author of this study, Panos Kanavos, gave a presentation to the Task Force at the April 14 public hearing and has submitted comments to this docket.

inhibitors, serotonin selective re-uptake inhibitors, and atypical antipsychotic) across all study countries. These categories were chosen since they are used to treat a wide range of disorders and have significant impact on patient health, as well as health care budgets. The study found that parallel imports for 2002 sales to the six major destination countries within the EU accounted for only 0.3 percent to 2 percent of national medicine budgets, representing a total savings of just £43.1 million over locally-developed and manufactured products. In contrast, the parallel importers who bought these same medicines across the EU made profits of £622 million. According to the study, "[w]ith regards to patients, no clear benefits through lower prices were found." As the chart that follows indicates, the study found extremely modest direct savings to insurance organizations.

	Norway	Germany	Sweden	Denmark	UK	Netherlands
Savings to Insurance Organizations	0.7%	0.8%	2%	0.6%	0.3%	2%
Parallel Trader Markup	16%	46%	12%	38%	54%	51%

E. Importation of foreign drugs is an endorsement of, and attempt to import, foreign price control practices – which are bad for patients, harmful to innovation, and poor public policy.[158]

1. A decision to implement prescription drug importation would be tantamount to a decision to import foreign price controls.

Legislation authorizing importation of foreign prescription drugs essentially attempts to import foreign government price controls into the United States.[159] Most governments outside the United States offer some kind of national health insurance that covers the vast majority of the population. These governments dominate the health care marketplace and operate as monopsonistic purchasers of pharmaceutical products. Many of these governments take unfair advantage of this near-total control of the health

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[158] This section of our comments responds to items 7, 8, and 11 on pages 9 and 10 (potential short- and long-term impacts on drug prices and prices for consumers associated with importing drugs from other countries, the impact on drug research and development, and the associated impact on consumers associated with importing drugs from other countries, and ways in which importation could violate intellectual property rights).

[159] *See, e.g.*, John E. Calfee, "The High Price of Cheap Drugs," *The Weekly Standard* (July 21, 2003) ("Congress should dismiss all possibility of these scenarios by rejecting the drug importation legislation. It should not fall into the trap of thinking that as long as controls over U.S. prices were introduced by the government of a foreign country, we would still have a free market. We wouldn't have a free market, and we wouldn't get the benefits of one."); Doug Bandow, "Reimportation: Trojan Horse, Not Free Trade," *Institute for Policy Innovation Publication* (June 2003) ("Most important, however, reimportation, no less than attempting to equalize prices internationally by legislative fiat, would effectively apply foreign price controls on the American market. This is, in fact, the policy's objective."); James K. Lassman & John R. Lott, Jr., "The Drug World's Easy Riders," Commentary, *The Wall Street Journal* (July 23, 2003) ("In effect, reimportation of drugs would import something else to the U.S.: price controls, where the lack of such practices is the oxygen that allows pharmaceutical research to thrive. Drug price controls are pernicious. While controls on oil and other products tend to be short-lived, as voters eventually object to the resulting shortages, the effects of drug regulations are more difficult to observe, since they mainly affect medicines that haven't been invented yet."); David B. Kendall, "Don't Import Foreign Price Controls on Prescription Drugs," Progressive Policy Institute (July 21, 2003) ("Republicans have rightly opposed U.S. price controls for Medicare prescription drugs, but they are wrong to consider importing foreign price controls. The Gutknecht legislation, which has 36 Republican co-sponsors and 14 Democratic co-sponsors, runs contrary to a view held by a wide variety of members of Congress – including Democrats ranging from Sens. Edward Kennedy (MA) to John Breaux (LA) – that price controls should be kept out of the Medicare debate.").

care market to obtain drugs at below-market prices and avoid paying for the research and development costs of those drugs. Their power is only magnified in many countries by compulsory licensing laws that permit the government to abrogate a company's patent rights if it does not accede to the government's pricing demands.

Foreign government intervention in the pharmaceutical market takes a wide variety of forms. European governments, for example, employ measures that include: reference pricing systems (Belgium, Germany, Norway, Spain, and others); profit control schemes (the United Kingdom); across-the-board price cuts (Italy, Hungary, Japan, and many other countries over the last decade); price freezes (Canada); and product-by-product price controls (all European countries). Reference pricing systems vary considerably according to the countries and products to which reference is made, the calculation method used to determine the reference prices, and the reimbursement rules applicable. Some countries have formally adopted pharmacoeconomic evaluations as a mandatory step in the price-setting process (Finland and Australia) or as a prerequisite for reimbursement (Belgium and Norway). Essentially every country fixes an overall budget for public pharmaceutical spending or imposes percentage limits on growth in pharmaceutical spending. In some countries (Austria, Belgium, Italy, Germany, and France), the industry is responsible for budget overruns and forced to "rebate" or "pay back" to the government the amount of public expenditures on pharmaceuticals that exceed government targets.

Foreign countries often impose price controls through measures that discriminate against imports and favor local producers. Countries without a local pharmaceutical industry tend to rely particularly heavily on pharmaceutical price controls

to balance their health care budgets. Local interests – such as generic producers, wholesalers, and pharmacists – generally occupy a favored position within the system. For example, Italy passed a law in 2002 imposing a blanket 7 percent price decrease for all pharmaceuticals priced above a certain threshold. The impact of the price decrease fell overwhelmingly on the research-based pharmaceutical industry that produces higher-value medicines and is, not coincidentally, largely foreign-based. In Australia, the prices paid by the government's Pharmaceutical Benefits Scheme to local pharmacists are indexed for inflation and rise every year. The Australian government has adamantly opposed allowing a comparable adjustment for inflation for pharmaceutical products which, again, are largely developed abroad and imported into the country.

2. Prescription drug price controls in foreign countries have had a detrimental impact on patient access to new medicines.

Foreign price control mechanisms operate to deny patients access in the marketplace to U.S.-made pharmaceutical products. They do so first, by delaying the availability of new products, and second, by denying the availability of new products.

First, since foreign national health insurance schemes typically dominate the domestic market for pharmaceuticals, a product effectively cannot be marketed in a country until the national authorities have determined its reimbursement price. The price control bureaucracy in almost every country is opaque, and the process of obtaining a government-approved price can be lengthy. Delay can happen at any point: between the date a company submits its pricing application and the date price approval was granted, between the date the company submits an application for reimbursement and the date the company is informed about a reimbursement decision, or between the date the company

is informed of the reimbursement decision and the date that decision is published in official national reimbursement lists.[160]

Delays are a problem in many countries within the Organization for Economic Cooperation and Development (OECD). In some markets, patients must wait more than two years before they gain access to new medicines.[161] For example, European Directive 89/105 requires that applications to the competing authorities to secure a price or reimbursement for a new medicine must be decided within 90 days (or 180 days where it is necessary to agree to a price before applying for reimbursement). Nevertheless, in all EU countries with formal pricing and/or reimbursement approval systems – with the exception of Ireland, Sweden, and Denmark – the responsible regulatory bodies significantly exceed the 90-day and 180-day deadlines.[162] A 2002 survey found that in Belgium, it took an average of 671 days for the government to grant reimbursement and pricing status to new medicines.[163] In Austria, Finland, France, Greece, and Portugal, it took on average between 332 and 415 days.[164] The G10 Medicines Group of the European Commission recently concluded that the "price negotiating systems and reimbursement structures in a number of [EU] Member states

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160 The time to publication can vary from 5 days in France to 76 days in Italy to 90 days in Belgium. Cambridge Pharma Consultancy (a unit of IMS Health), "Delays in Market Access" (December 2002).

161 *Id.*

162 *Id.*

163 *Id.*

164 *Id.*

can lead to significant delays."[165] In China, the situation is even worse: not a single new product has been added to the national government reimbursement list for over 4 years.

Second, many governments use highly restrictive formularies or other policies (for example, limiting a drug to hospital use, or to use after failure of a first or second treatment) to control access to new medicines. Such an approach is bad policy and bad medicine. A patient's reaction to a medicine is highly individual, and the effects of a drug can vary across a population. Nevertheless, some governments are willing to substitute their judgments for the judgments of medical professionals, and they impose a one-size-fits-all approach with respect to medical needs by approving only one (or very few) pharmaceutical products to treat particular conditions. New Zealand, for example, has long had one of the most restrictive formulary systems in the world. The government directly controls 75 percent of the market in New Zealand and indirectly controls the rest. It typically permits very few medicines per therapeutic class. Market access for many competing products that treat the same condition is effectively and completely denied. In Europe, as a *Business Week* writer recently commented, "negotiations" between manufacturers and the national health systems over access and the deep discounts requested on price "can drag on for several years" and "[a]s a result of price controls, European consumers are heading toward second-class citizenship when it comes to access to medicines."[166]

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165 European Commission, "High Level Group on Innovation and Provision of Medicines, Recommendations for Action," G10 Medicines Report (Brussels, Belgium: European Commission, May 7, 2002).

166 Kerry Capell, "Europe Pays a High Price for Cheap Drugs," *Business Week* (February 17, 2003).

Pricing controls and restrictive formularies in Canada similarly result in reduced patient access to medicines. One recent study found that the Canadian federal new drug approval process takes 13 percent longer than the American new drug approval process. A new Canadian drug then faces more hurdles: the ten provinces. "Each province has a review committee that must approve the drug for its own formulary," the study author noted.[167] He quantified the delay: "[o]f 99 new drugs approved by the federal government in 1998 and 1999, only 25 were listed on the Ontario formulary."[168] Moreover, "the provincial approval times vary greatly from province to province. The wait time for approval in Ontario is nearly 500 days."[169]

A study conducted for the European Federation of Pharmaceutical Industries and Associations (EFPIA) in 2002 identified specific disease states as to which pricing policies and cost containment strategies in Europe have resulted in suboptimal medical care for patients:

- ***Cardiovascular disease***. In Germany, 87 percent of all patients with coronary heart disease did not receive modern lipid-lowering drugs. In Italy, 83 percent did not receive statins.
- ***Diabetes***. In Germany, 30 percent of the at least 4 million diabetes patients are not treated with drugs at all.
- ***Multiple sclerosis***. In France, less than 50 percent of patients with multiple sclerosis who are eligible for treatment with beta interferon actually receive the medicine.
- ***Schizophrenia***. In France, there are 4.4 schizophrenia sufferers per 1000 people between the ages of 31 and 50. Only 2.4, however, are treated. For the treated patients, the level of use of innovative second generation drugs continues to be at a low level.

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167 William McArthur, "Prescription Drug Costs: Has Canada Found the Answer?" National Center for Policy Analysis – Brief Analysis No. 323 (May 19, 2000).

168 *Id.*

169 *Id.*

- ***Depression.*** Across Europe, only 18 percent of patients with severe depression receive treatment with anti-depressants. In Germany, 12 percent of patients with severe depression receive treatment with antidepressants. In France, 50 to 70 percent of patients with symptomatic depression are not treated at all, whether psychotherapy or medication or both.[170]

3. Prescription drug price controls have a negative impact on research and development.

Price controls diminish the value of pharmaceutical patents. A patent right that gives the patent holder the exclusive right to sell his invention in a market, but that is limited by a requirement that the product be sold at a significantly reduced price, is of little commercial value to the right holder. A country cannot be said to adequately and effectively protect intellectual property if that country puts in place regulations that diminish the value of the patent rights granted.[171] As explained above (page 82), many countries practice reference pricing. This means that the price of a new drug is tied, by law, to the price of older and often off-patent medicines. By design, these systems are set up to compensate innovative products at the same rate as generic products and undermine the value of pharmaceutical patents in that market. The delays caused by the bureaucratic pricing process, also undermine the value of pharmaceutical intellectual property. By delaying market access, these regimes deplete potentially valuable patent

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[170] O. Schöffski, "Diffusion of Medicines in Europe," prepared for the European Federation of Pharmaceutical Industries and Associations (EFPIA) (September 2002).

[171] Because they diminish the value of intellectual property, foreign price controls are a trade issue. The United States routinely treats weak foreign patent laws as a major trade issue. Indeed, the entire rationale for the WTO TRIPS Agreement was that rampant international free-riding on innovation is a kind of trade barrier. Allowing copycat manufacturers to pirate U.S. intellectual property, whether it is embodied in software, sound recordings or medicines, undermines the export possibilities of those industries. Foreign laws that allow free-riding through other means – i.e., price controls – equally diminish the value of U.S. intellectual property rights and hurt U.S. exporters that rely on intellectual property protection.

term that cannot be recovered by the patent holder. Under Australia's system, for example, prices for new medicines are often set by reference to existing medicines in a therapeutic class, regardless of whether those other medicines are generic products. The link with these older drugs continues year after year, so that when a referenced drug goes off-patent and its price falls, the price of the newer drug that is still on patent is significantly diminished as well. The end result is that there is little reward for innovation.[172]

For most of the past century, Europe led the world in pharmaceutical innovation. In 1997, however, the United States overtook Europe for the first time both in terms of investment and in terms of the output of its innovative activity (i.e., new molecular entities).[173] The latest data on new chemical and biological entities for the period between 1998 and 2002 show that the U.S. leads all other countries in invention of new molecules. Between these years, the U.S. pharmaceutical industry led the world as the inventor of 77 new chemical and biological entities. The U.S. was followed by Europe, which had 68, and Japan, which had 29. All other countries, combined, invented just 4 new chemical and biological entities.[174] Over the past 10 years, R&D investments have doubled in Europe to reach 17 billion in 2000, but they have multiplied nearly five

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172 Various studies confirm that price controls discourage pharmaceutical innovation. *See, e.g.*, Jacob Arfwedson / CNE Health, *Parallel Trade in Pharmaceuticals* (July 2003) (warning of "significant long run harms to innovation" if parallel trade continues in Europe indefinitely); Patricia Danzon, The Economics of Parallel Trade, *Pharmacoeconomics* (March 1998) (finding that parallel trade reduces economic welfare by undermining price differentials between markets. In the long run, "even high income countries are likely to be worse off with uniform prices, because fewer drugs will be developed.")

173 European Federation of Pharmaceutical Industries and Associations, *The Pharmaceutical Industry in Figures* (Brussels, Belgium: EFPIA, 2003) ("EFPIA Figures").

174 *Id.* at 16.

times in the U.S. to reach 24 billion in 2000.[175] Further, the European share of the world pharmaceutical market has decreased from 32 percent to 22 percent over the past decade, while the U.S. share increased from 31 percent to 43 percent.[176] American companies now file over 60 percent of pharmaceutical patent applications in Europe.[177] Of the top ten worldwide products (ranked by sales volume), six originated in the U.S., while only three originated in Europe. In 1990, major European research-based companies spent 73 percent of their worldwide R&D expenditures in the EU territory, whereas in 1999, they spent only 59 percent in the EU territory. The U.S. was the main beneficiary of this transfer of R&D investment.[178]

The exodus from Europe results in part from the hospitable business climate in the U.S. – for example, the science and technology base in the U.S. and the opportunity for public-private research partnerships. The European pharmaceutical industry and the European Commission have, however, concluded that the exodus results primarily from the price control policies and cost-containment measures that lead to a lack of competition in the European market. Price controls compromise the value of patent rights, which in turn discourages innovation. EFPIA has explained that the "European pharmaceutical industry has lost its competitiveness because there is a problem of price – and innovation is not compensated."[179] EFPIA adds, "Europe lacks a climate which favours and rewards innovation. . . . Compared to the U.S., Europe is

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175 "Pfizer Leader Calls for a New Relationship Between Pharmaceutical Innovation and Europe Governments," *PR Newswire European* (February 11, 2002).

176 *Id.*

177 *Id.*

178 *Id.*

179 EFPIA Figures, supra note 173.

seen as a less attractive R&D investment location in terms of market size and incentives for the creation of new biotech companies."[180]

In a November 2000 report, the Directorate General Enterprise of the European Commission found that "the relative position of the U.S. as a locus of innovation in pharmaceuticals has increased over the past decade compared to Europe."[181] The authors noted that U.S. pharmaceutical companies are now the dominant source of innovation and innovative drugs in the world. As a result, American patients benefit greatly by getting early access to the best and newest treatments that pharmaceutical companies can offer. Not only are the newest drugs sold to Americans, but more and more of the drug development is being done by U.S.-based companies.[182] One market newsletter paraphrased analysts at SG Cowen thus: "[m]ajor drug companies are being left with little choice but to cut investments and manage the business to maintain returns. This means reduced R&D and fewer new drugs in Europe than in the U.S.A."[183]

Not surprisingly, the mere threat of price controls in the United States has had a negative impact on the market value of pharmaceutical firms. During consideration of the Heath Care Reform Act of 1993, when pharmaceutical price controls were

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180 *Id.*

181 F. Pammolli et al., "Global Competitiveness in Pharmaceuticals: A European Perspective," prepared for the Directorate General Enterprise of the European Commission (November 2000).

182 *Id.*

183 "Govt drug price controls continue to threaten Europe's pharma industry," *Pharma marketletter* (December 23, 2002).

proposed, firm market values dropped.[184] Venture capital in biotechnology similarly dropped considerably in 1994 and 1995, reflecting concern about proposed government regulation of health care spending. An analysis by Arthur D. Little of the annual growth rate in biotechnology venture capital funding from 1993 to 2000 indicated declines of 6 and 16 percent in 1994 and 1995 respectively, before expanding again in 1996.[185] A survey by the Gordon Public Policy Center of Brandeis University, conducted during the Clinton Health Care Reform debate, found that more than 70 percent of U.S. biotechnology firms feared that they would have to delay or curtail research because of the negative impact of health care reform on capital markets.[186] According to a survey conducted at that time by the trade association BIO, nearly 40 percent of biotech companies working to find treatments for HIV/AIDS, cancer, and diseases of the aging delayed or cancelled research because of capital shortfalls attributed to the health care reform debate.[187] Had the legislation actually passed, Professors Grabowski (Duke) and Vernon (Duke) hypothesize that a substantial decline in R&D and innovative activity would have occurred.[188] In short, as Professor Frank Lichtenberg of Columbia University has argued, perception of future profits greatly influences R&D spending, and "policies

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184 *See* S. Ellison and W. Mullin, "Gradual Incorporation of Information: Pharmaceutical Stocks and the Evolution of President Clinton's Health Care Reform," *Journal of Law and Economics*, Vol. XLIV (April 2001).

185 "Arthur D. Little Bio-Pharmaceutical Study Finds Significant Link Between Innovation and Market-Based Drug Pricing," Press Release, Arthur D. Little (May 9, 2002).

186 "BIO Airlifts Scientists, CEOs into D.C. for Lobbying Push," *Biotechnology Newswatch* (August 1, 1994).

187 *Id.*

188 H.G. Grabowski and J.M. Vernon, "Returns to R&D on New Drug Introductions in the 1980's," *Journal of Health Economics*, Vol. 13: 383-406.

that threaten to diminish future profits will reduce R&D investment today, even if they do not affect current profits."[189]

Real world modeling by economists has confirmed the link between price controls and reduced innovation. Professor John A. Vernon (University of Connecticut) recently demonstrated, for example, that regulation of pharmaceutical prices in the U.S. could have a "precipitous effect on pharmaceutical innovation in the long run."[190] Vernon's objective was to examine, using simulation techniques, how pharmaceutical price regulation would affect future drug innovation. Simulation experiments were run under multiple price-control scenarios to determine how these regulations would affect and alter the time path of new product innovation (relative to the baseline model without price control regulation). Professor Vernon found that under a cost-based approach to regulating the top-performing drugs (i.e., drugs in the top three deciles with respect to present value, after-tax returns), over a 50-year time horizon that was considered, total industry output would be reduced by between 30 percent and 37 percent, relative to innovative output in the absence of price regulation. Under less extreme assumptions about the effect of price regulation, the estimate was found to range between 6 percent and 24 percent.[191] Vernon pointed out that the simulation experiments provide insight into the potential consequences of a pharmaceutical price control policy in the U.S.

In another study, researchers examined aggregate data for the major pharmaceutical companies in the U.S. to study the rate of growth in pharmaceutical R&D

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189 F.R. Lichtenberg, "Probing the Link Between Gross Profitability and R&D Spending," *Health Affairs*, September/October 2001: 221-222.

190 John A. Vernon, "Simulating the Impact of Price Regulation on Pharmaceutical Innovation," *Pharm Dev Regul* (2003).

191 *Id.*

from 1952 to 2001. The paper investigated the impact of real drug prices on the R&D spending of major U.S. pharmaceutical companies. The researchers hypothesized that drug prices directly influence R&D spending. Their findings supported this expected direct effect. Specifically, the findings suggest that a 10 percent increase in real drug prices results in nearly a 6 percent increase in pharmaceutical R&D spending. Simulations based on these results indicate that the value of pharmaceutical R&D spending would have been about 30 percent lower if the federal government had limited drug prices to the same rate of growth as the general consumer price index price increases during the period 1980 to 2001. Moreover, drug price controls would have resulted in 330 to 365 fewer new drugs being brought to market during that same period of time.[192]

4. Foreign pharmaceutical price controls force Americans to subsidize medical research and development for the rest of the world.

The process of discovering and developing a new medicine is long and complex. Today, the process of bringing a drug to market takes up to 15 years.[193] As a result, the average cost to develop a new drug has grown from $138 million in 1975 to over $800 million today.[194] The risks involved in the new drug development and approval processes are also substantial. Of every 250 drugs that enter preclinical testing,

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192 C. Giaccotoo, R. Santerre, and J. Vernon, "Explaining Pharmaceutical R&D Growth Rates at the Industry Level: New Perspectives and Insights," *AEI-Brookings Joint Center for Regulatory Studies, Publication 03-31* (December 2003).

193 J.A. DiMasi, "New Drug Development in U.S. 1963-1999," *Clinical Pharmacology & Therapeutics* 69(s) (2001).

194 J.A. DiMasi, R.W. Hansen and H.G. Grabowski, "The Price of Innovation: New Estimate of Drug Development Costs," *Journal of Health Economics* 22 (2003): 151-185.

only 1 is approved by the FDA.[195] Only 3 out of 10 marketed drugs produce revenues that match or exceed average R&D costs.[196]

The pharmaceutical industry is a key component to America's high tech economy. The pharmaceutical sector contributed $229.2 billion in sales, $75.4 billion in labor income, and nearly 1.1 million employees to the U.S. economy in 1999 alone.[197] The average wage in the industry is over $18 per hour. The industry is among the top U.S. exporting industries, and ranks with the semiconductor, aerospace, and computer industry in the value of its exports.

By impeding the ability of the pharmaceutical industry to access foreign markets in a meaningful way, foreign governments effectively force U.S. consumers to bear an unfair burden of the cost of researching and developing new medicines. As former FDA Commissioner Mark McClellan recently remarked, "We cannot carry the lion's share of this burden for much longer."[198] U.S. research jobs and U.S. manufacturing jobs are at stake.

5. Importation of prescription drugs would harm consumers and undermine innovation through its impact on U.S. intellectual property rights.

Importation under section 804 would also implicate the intellectual property rights of pharmaceutical manufacturers, particularly with respect to trademarks

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195 PhRMA, Based on data from the Center for the Study of Drug Development, Tufts University, 1995.

196 H.G. Grabowski and J.M. Vernon, "Returns to R&D on New Drug Introductions in the 1980s," *Journal of Health Economics* 13 (1999).

197 Examining the Relationship between Market-Based Pricing and Bio-Pharmaceutical Innovation, study by Arthur D. Little (2002), at 24.

198 Mark McClellan, Speech before the First International Colloquium on Generic Medicine (September 25, 2003).

and patents. These intellectual property rights, which are independent of government standards, promote the public interest in distinct but equally important ways, specifically by preventing consumer deception in the case of trademarks, and promoting pharmaceutical innovation in the case of patents.

Trademark rights serve, in part, to prevent potentially confusing or deceptive uses of a mark in connection with goods that defy consumer expectations of source or quality. In today's global economy, the quality assurance function of the trademark is of paramount importance. Consumers recognize the trademark as a seal of consistent and predictable quality. Without exception, all PhRMA members have developed rigorous quality control standards to ensure that brand-name products consistently meet consumer expectations of high quality associated with American prescription drugs. These standards meet and typically exceed the FDA's regulatory requirements and encompass all phases of product testing, manufacturing, shipping, handling, storage, packaging, marketing, tracking and authentication.

As owners of registered trademarks, PhRMA's member companies have an exclusive right under federal trademark law to prevent the use of their marks in connection with unauthorized imports that fail to meet quality control standards or differ in other material respects from authorized brand-name products sold in the U.S. (such as outright counterfeits or foreign versions of a manufacturer's product that have been improperly handled by others). As a matter of trademark law, these unauthorized imports are deemed to be "non-genuine" and infringing because of the likelihood of consumer confusion and deception that arises from material differences in quality control or other characteristics.

By facilitating the importation of foreign-sourced counterfeit and adulterated drug products, Section 804 not only would pose significant safety risks but also would open the door to a large volume of infringing imports. As discussed in Section II.B below, these infringing imports would be difficult or impossible to detect. Consequently, by facilitating the use of famous trademarks in connection with infringing imports, Section 804 will dilute the valuable goodwill associated with pharmaceutical trademarks and potentially undermine consumer confidence in the integrity of U.S. brand-name pharmaceuticals.

Our system of patent rights serves the important purpose of promoting innovation. Patents provide a time-limited incentive for companies to invest in risky and expensive research and development activities, while also providing for public disclosure of novel inventions so that they add to the body of available scientific and technical knowledge. Patents are particularly critical to pharmaceutical innovation, given the enormous expense and time needed to develop safe and effective drugs. The vast majority of experimental drugs never make it to market, and even successful therapies require years of research, development and testing before meeting the FDA's rigorous approval process.

Drug importation presents patent concerns because U.S. patent rights typically are not exhausted through foreign sales. Patent rights, however, are difficult and expensive to enforce. The decision whether to bring an infringement action in the first place is made on a case-by-case basis, and even those actions that are filed present many uncertainties in terms of the availability, timing, and effectiveness of any relief. The certification of importation under section 804 would likely increase the extent of

infringing activity and thereby as a practical matter weaken the protections provided under our patent laws to encourage innovation.

Many advocates of importation have publicly acknowledged as their ultimate goal a distribution system that would totally abrogate intellectual property rights as applied to imported drugs. For example, one bill currently pending is plainly intended to override existing patent rights specifically with respect to drug importation.[199] Legislation of this type would have far-reaching effects on the pharmaceutical industry and its ability to maintain leadership in developing innovative life-saving and life-extending medicines. Such measures also raise substantial legal concerns, including under the Constitution.

III. CONCLUSION

While importation is often hailed as the only solution for individuals who lack prescription drug coverage and cannot afford their medicines, in fact there are better, safer ways to ensure that patients have access to affordable medicines.

Patient assistance programs sponsored by pharmaceutical companies are available to all uninsured Americans who meet income eligibility requirements. Roughly 65 percent of the uninsured have income levels at or below 200 percent of poverty, and these individuals are eligible for many of the patient assistance programs that provide medicines free of charge. Information on these programs can be found at www.helpingpatients.org, an interactive Web site maintained by PhRMA and 48 of its member companies. This online service, which is free and completely confidential, is

[199] Pharmaceutical Market Access and Drug Safety Act of 2004, S. 2328, 108th Cong. (2004) (proposing to amend federal patent laws to require exhaustion of patent right upon the first sale by the patentee).

designed to help individuals find patient assistance programs for which they may qualify. Last year alone, PhRMA members provided free prescription medicines to more than 6.2 million patients in the United States.

Pharmaceutical company discount card programs are another way for seniors and the disabled to save money on prescription medicines. Seniors with income levels at or below 200 percent of poverty, who lack prescription drug coverage, can access medicines made by two PhRMA member companies at a fixed monthly cost of $12 to $15. Other company discount card programs offer seniors and the disabled with income levels at or below 300 percent of poverty discounts that range from 20 to 40 percent off retail prices.

Also, this June, all Medicare beneficiaries will be eligible for a Medicare-endorsed discount card that will offer discounts on prescription medicines. The lowest income seniors will be eligible for $600 (per individual, or $1200 per couple) this year, and again next year, to help them afford their prescription medicines until the full Medicare prescription drug benefit begins in 2006. Once individuals have exhausted the $600, three PhRMA member companies have publicly stated they will offer their medicines free of charge to these individuals.

Further, in 2006, all Medicare beneficiaries will be able to enroll in plans that cover prescription drugs. Plans may vary somewhat, but in general, individuals can choose a prescription drug plan and pay a premium of about $35 a month. They will pay the first $250 of their prescription drug costs, and Medicare will pay 75 percent of the costs (and individuals the remaining 25 percent) between $250 and $2,250. Once an individual has reached $3,600 in out-of-pocket spending, Medicare will pay 95 percent of

the costs, and individuals will be responsible for the remaining 5 percent. Individuals with low incomes and low assets will not have to pay premiums or deductibles and will only pay a small co-payment for each prescription needed. Other people with low incomes and limited assets will get help paying the premiums and deductible and the amount they pay for each prescription will be limited.

In addition, many states operate prescription assistance programs for lower income Medicare beneficiaries. For instance, the State of Wisconsin offers a program for Medicare beneficiaries, which is typically a much better deal for Wisconsin seniors than any Canadian web site. According to a letter from FDA to Wisconsin Governor Doyle, a patient taking the five most commonly-prescribed drugs for seniors (Detrol, Lipitor, Accupril, Aricept, and Prevacid) for 112 days would pay only $277.50 under the Senior Care Program in Wisconsin. If that same patient bought the drugs from any of the Canadian pharmacies that the Governor of Wisconsin identified for its citizens, he would pay over six times that amount. In other words, a patient would pay $14.25 per day for the Canadian drugs, and only $2.35 for safe, FDA-regulated American drugs from his local pharmacy.[200]

Shopping around among pharmacies can also yield savings for consumers. According to John Graham, the author of a study by the Fraser Institute, Canada's leading economic think tank, "We hear about Americans who claim that they save money, some say up to 60 percent, by filling their prescriptions in Canada. That is very misleading because in some cases a consumer can save as much by bargain hunting at home as he

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[200] Letter from FDA, Associate Commissioner for Policy and Planning, William K. Hubbard to Wisconsin Governor Doyle (March 18, 2004).

can by crossing the border."[201] Numerous surveys have been done by states and cities across that country that show consumers can and do save money by shopping around. For example, a survey by the Maine Bureau of Elder and Adult Services of prescription drug prices within the State of Maine found that the retail price of 10 drugs commonly used by seniors varied by as much as 60 percent in the 100 stores across the state they surveyed.[202]

Finally, generic drugs available in the U.S. are often considerably less expensive than foreign, non-FDA approved drugs, and they offer a solution for many who cannot afford their medicine.

The solutions detailed above provide practical options for many individuals to access affordable medicines that will not risk their health and safety.

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201 Media Release, Fraser Institute, August 30, 2001, <www.fraserinstitute.ca>.

202 "State Survey Reveals Wide Range of Prescription Drug Prices," *Maine Times* (February 8, 2001).