



*A Reason for Hope*

April 26, 2004

The Amyotrophic  
Lateral Sclerosis  
Association

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852.

*Capital Office*

Re: Docket No. 2004N-0115

601 Pennsylvania Avenue, N W  
Suite 900, South Bldg.  
Washington, DC 20004

To whom it concerns:

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On behalf of the thousands of patients with Amyotrophic Lateral Sclerosis (also known as Lou Gehrig's Disease) and their families, I am submitting comments on prescription drug importation to the docket (2004N-0115) established by the Food and Drug Administration on March 18, 2004. 69 Fed. Reg. 12810 (March 18, 2004).

Stevan Gibson  
*Vice President*  
*Government Relations*  
*& Public Affairs*

These comments address the relationship between prescription drug importation and the research and development of new drugs. We have gathered studies that have been conducted on this question, and we include with the collection an overview and synthesis of their conclusions. These studies show that importation of foreign prescription drugs is tantamount to importation of foreign government price controls, and that foreign price controls have led to reduced R&D investment in those countries. Price controls have also had a negative impact on patient access to and use of new medicines.

Research, drug development, and innovation are the key for people with ALS. I want innovative companies to have the desire to apply their skills to ALS drug development and I want their business considerations to be protected so ALS drugs can be worthwhile to bring to market.

As you consider the consequences of legislation to import pharmaceuticals, please consider the enclosed documents which discuss how these proposals would deter the research patients depend upon.

Sincerely,

Stevan Gibson  
Vice President

The ALS Association is the only national not-for-profit voluntary health organization whose sole mission is to find a cure for and improve living with ALS

*Member National Health Council*

2004N-0115

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## **Memorandum on the impact on the research and development of drugs – and the associated impact on consumers and patients – if importation were permitted**

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Importation of foreign prescription drugs is a means to import foreign government price controls into the U.S. Price controls in foreign countries, however, have led to reduced R&D investment in those countries. They have also had a negative impact on patient access to and use of new medicines. Evidence from other countries demonstrates that regulation of prescription drug prices in the United States could have a precipitous effect on innovation in the long run and a harmful effect on patient access to and use of new medicines.

### ***Importation Of Prescription Drugs Is Importation Of Foreign Government Price Controls.***

The debate over whether to regulate prescription drug prices in the U.S. has intensified recently. Advocates for lowering prescription drug prices in the U.S. have argued that Congress should legalize the importation of prescription drugs from other countries, where prices are controlled by the government. Some who support importation have argued that legalizing importation of prescription drugs from other countries is a way to use the free market to bring lower cost medicines to American consumers.

Economists and trade experts have, however, argued that importation would not further free market principles, but instead would amount to “importing” foreign government price control regimes. For example, John E. Calfee of the American Enterprise Institute (AEI) writes that “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.”<sup>1</sup>

Similarly, Doug Bandow, Senior Fellow at the CATO Institute, has stated, “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.”<sup>2</sup>

In a *Wall Street Journal* editorial, James K. Glassman and John R. Lott, Jr. explained, “In effect, re-importation of drugs would import something else to the U.S.: price controls, where the lack of such practices is the oxygen that allows

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<sup>1</sup> John E. Calfee, “The High Price of Cheap Drugs,” *The Weekly Standard*, July 21, 2003.

<sup>2</sup> Doug Bandow, “Reimportation: Trojan Horse, Not Free Trade,” Institute for Policy Innovation Publication, June 2003.

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.”<sup>3</sup>

David Kendall of the Progressive Policy Institute wrote, “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.”<sup>4</sup>

### ***Prescription Drug Price Controls Have Had A Negative Impact On Research And Development In Europe***

In light of the fact that importation is a mechanism to import foreign government price controls in the U.S., it is important to understand the impact that price controls have had on research and development (R&D) in countries that have employed them.

Price controls have had a negative impact on R&D conducted in the European Union (EU). Over the past several years, European pharmaceutical companies have begun to depart Europe and head to the U.S. There are several reasons for this transfer of research and facilities from Europe to the U.S. These include the science and technology base in U.S. as well as the opportunity for public-private research partnership in the U.S. One of the primary reasons for the transfer of research and facilities, however, is the price control policies and other cost-containment measures that have led to a lack of competitiveness in Europe. According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), “The European pharmaceuticals industry has lost its competitiveness because there is a problem of price – and innovation is not compensated.” EFPIA adds, “Europe lacks a climate which favours and rewards innovation....Compared to the U.S., Europe is seen as a less attractive R&D investment location in terms of market size and incentives for the creation of new biotech companies.”<sup>5</sup>

In a November 2002 report, the Directorate General Enterprise of the European Commission described the global competitiveness in pharmaceuticals from a European perspective, where price control programs have been in effect

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<sup>3</sup> James K. Glassman and John R. Lott, Jr., “The Drug World’s Easy Riders,” Commentary, *The Wall Street Journal*, July 23, 2003.

<sup>4</sup> David B. Kendall, “Don’t Import Foreign Price Controls on Prescription Drugs,” Progressive Policy Institute, July 21, 2003.

<sup>5</sup> European Federation of Pharmaceutical Industries and Associations, *The Pharmaceutical Industry in Figures* (Brussels, Belgium: EFPIA, 2003).

for years. The authors found that national regulation of prices in many EU markets has restricted competition. They conclude that "the relative position of the U.S. as a locus of innovation in pharmaceuticals has increased over the past decade compared to Europe."<sup>6</sup> The report credits the U.S. as the industry of "new drug research tool producers." In addition, according to analysts at SG Cowen, "Major 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 USA."<sup>7</sup>

By way of contrast with the EU, according to a *Wall Street Journal* editorial the United States offers pharmaceutical companies an environment that "reward[s] innovation" through a "comparatively free medical market." Over the past 10 years, R&D investments have increased significantly in the U.S., about twice the rate of R&D growth in Europe. In fact, during the 1990s, the U.S. surpassed Europe as the leading site for pharmaceutical R&D. The latest data on new chemical and biological entities (for the period between 1998 and 2002) show the predominance of the U.S. as the leading inventor of new molecules in the world.<sup>8</sup>

In short, current European policies have negatively impacted the competitiveness of the EU pharmaceutical sector, as compared to the pharmaceutical industry in the U.S. For example:

- For most of the past century, Europe has been leading the world in pharmaceutical innovation. But in 1997, the U.S. overtook Europe for the first time both in terms of innovative efforts [R&D investment] and in terms of the output of its innovative activity [new molecular entities].
- Over the past 10 years, R&D investments have doubled in Europe to reach 17 billion in 2000, but they have been multiplied by nearly five times in the U.S. to reach 24 billion in 2000.
- Over the past decade, the U.S. pharmaceutical market grew nearly twice as fast as the European market [15% compared to less than 10%].
- The European share of the world pharmaceutical market has decreased from 32% to 22% over the past decade, whereas it has increased from 31% to 43% in the U.S.
- American companies now file over 60% of pharmaceutical patent applications in Europe.

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<sup>6</sup> Pammolli F., et al., "Global Competitiveness in Pharmaceuticals: A European Perspective," Prepared for the Directorate General Enterprise of the European Commission," November 2000, p.7.

<sup>7</sup> *Ibid.*

<sup>8</sup> *Ibid.*

- On the top 10 worldwide products by sale, 6 now originate from the U.S. compared to only 3 from Europe.
- In 1990, major European research-based companies spent 73% of their worldwide R&D expenditures on the EU territory, whereas in 1999, they spent only 59% on the EU territory. The U.S. was the main beneficiary of this transfer of R&D investment.<sup>9</sup>

***If Price Controls Were Adopted In The U.S. (Or Imported To The U.S.), Innovation And Competition In The Pharmaceutical And Biotechnology Sectors Would Suffer.***

While it is clear that price controls and other forms of cost-containment have had a negative impact on R&D in Europe, it is also important to understand the impact on R&D and innovation if price controls were adopted in the U.S.

During consideration of the Health Care Reform Act of 1993, various types of pharmaceutical price controls were proposed. While this legislation did not pass, the mere threat of price controls had a negative impact on the market value of many pharmaceutical firms.<sup>10</sup> 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 biotech venture capital funding from 1993 to 2000 indicates declines of 6 and 16 percent in 1994 and 1995 respectively. Investment levels grew by 44 percent in 1996, when it was clear that Clinton's plan would not be pursued.

Source: Ernst & Young 15<sup>th</sup> Annual Biotechnology Report, Arthur D. Little Analysis

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. biotech firms feared that they would have to delay or curtail research because of the negative impact of health care reform on capital markets.<sup>11</sup> 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.<sup>12</sup> Had

<sup>9</sup> "Pfizer Leader Calls for a New Relationship Between Pharmaceutical Innovation and Europe Governments," *PR Newswire European*, February 11, 2002.

<sup>10</sup> 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).

<sup>11</sup> "BIO Airlifts Scientists, CEOs into D.C. for Lobbying Push," *Biotechnology Newswatch*, August 1, 1994.

<sup>12</sup> *Ibid.*

the legislation actually passed, Professors Grabowski and Vernon hypothesized that a substantial decline in R&D and innovative activity would have occurred.<sup>13</sup>

Professor Frank Lichtenberg of Columbia University has argued that perception regarding future profits greatly influences current R&D spending and concludes, "policies that threaten to diminish future profits will reduce R&D investment today, even if they do not affect current profits."<sup>14</sup>

According to a recent study conducted by Professor John A. Vernon, the regulation of price controls in the U.S. could have a "precipitous effect on pharmaceutical innovation in the long run."<sup>15</sup> 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 and 37% 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 and 24%.<sup>16</sup> Vernon pointed out that the simulation experiments provide interesting 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 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

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<sup>13</sup> 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.

<sup>14</sup> F.R. Lichtenberg, "Probing the Link Between Gross Profitability and R&D Spending," *Health Affairs*, September/October 2001: 221-222.

<sup>15</sup> John A. Vernon, "Simulating the Impact of Price Regulation on Pharmaceutical Innovation," *Pharm Dev Regul* 2003;1 (1):1. 2003.

<sup>16</sup> *Ibid.*

330 to 365 fewer new drugs being brought to market during that same period of time.<sup>17</sup>

### ***Price Controls Have A Detrimental Impact on Patient Access To And Use Of New Medicines.***

Not only do price controls have a negative effect on R&D, they also have a harmful impact on patient access to and use of new medicines. As nearly all would agree, new medications are a critical element of quality health care. Yet many patients in countries that employ cost-containment measures, such as price controls, often wait years before gaining access to breakthrough drugs.

***Regulatory delays impede access to new medicines.*** Innovative medicines are not available to all European citizens at the same time. In some markets, patients must wait more than two years before gaining access to a new medicine.<sup>18</sup> Each Member State of the European Union has control over price and reimbursement decisions. European Union Directive 89/105 requires that applications to the competent authorities to secure a price or reimbursement for new medicines must be decided within 90 days, or 180 days where it is necessary to agree price before applying for reimbursement.<sup>19</sup> A survey by Cambridge Pharma provides evidence that all countries in the EU with formal pricing and/or reimbursement approval systems, with the exception of Ireland, Sweden and Denmark, have significantly exceeded the 90 and 180-day target for granting pricing and reimbursement status for medicines.<sup>20</sup> In Belgium, it took on average 671 days to grant new medicines reimbursement and pricing status. Austria, Finland, France, Greece and Portugal took on average between 332 and 404 days.

In the majority of Member States, a marketing authorization alone is not sufficient to enable a prescription drug to actually be sold. The medicine will appear on the market only after the competent authorities have fixed a price and/or the medicine has been registered on the positive list defining the conditions under which it is covered by health care insurance for residents of the particular Member State.

Delays can take different forms. For instance, a price delay is defined as a delay from the date from when the company submitted the pricing application to the date price approval was granted. A reimbursement delay is defined as a delay from the date when the company submitted an application for

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<sup>17</sup> 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.

<sup>18</sup> "Delays in Market Access," Cambridge Pharma Consultancy (a unit of IMS Health), December 2002.

<sup>19</sup> *Ibid.*

<sup>20</sup> *Ibid.*

reimbursement to the date the company was first informed about the reimbursement decision. Publication delays are defined as a delay from the time the company was notified of the reimbursement decision by the authorities to the actual publication of that decision in the official national reimbursement list/journals. The time to publication, according to the Cambridge Pharma survey, varies from 5 days in France to 76 days in Italy to 90 days in Belgium.<sup>21</sup> Reimbursement authorities may also impose special conditions that limit the use of a new medicine beyond any restriction in the approved label. For example, a drug might be limited to hospital use or to use after failure of first/second line treatment.<sup>22</sup>

The G10 Medicines Group, which reviewed the impact of governmental pharmaceutical, health and enterprise policies in Europe, recommended reducing the time between granting a marketing authorization and pricing and reimbursement decisions. According to the report, "The price negotiating systems and reimbursement structures in a number of Member states can lead to significant delays."<sup>23</sup>

This was corroborated by a February 2003 report in *Business Week*, which stated, "Once a drug is approved by the European Agency for the Evaluation of Medicinal Products, national governments must debate whether to make the drug available through their health systems and at what price. The process, which usually involves negotiations with manufacturers, who are under pressure to extend deep discounts, can drag on for several years...As a result of price controls, European consumers are heading toward second-class citizenship when it comes to access to medicine."<sup>24</sup>

Similarly, a study that examined regulatory delays in Canada, entitled, *Prescription Drug Costs: Has Canada Found the Answer?*, found that one way Canada tries to control costs is by dragging out the process of approving expensive new drugs, no matter how beneficial they are. The federal approval process takes 13 percent longer than in the United States. The study also found that, "Even if a drug wins federal approval [in Canada], it faces 10 more hurdles - the 10 provinces. Each province has a review committee that must approve the drug for its formulary. Of 99 new drugs approved by the federal government in 1998 and 1999, only 25 were listed on the Ontario formulary. Further, the provincial approval times vary greatly from province to province. The wait for approval in Ontario is nearly 500 days."<sup>25</sup>

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<sup>21</sup> *Ibid.*

<sup>22</sup> *Ibid.*

<sup>23</sup> European Commission, "High Level Group on Innovation and Provision of Medicines, Recommendations for Action," G10 Medicines Report, (Brussels, Belgium: European Commission, May 7, 2002).

<sup>24</sup> Kerry Capell, "Europe Pays a High Price for Cheap Drugs," *Business Week*, February 17, 2003.

<sup>25</sup> William McArthur, "Prescription Drug Costs: Has Canada Found the Answer?" National Center for Policy Analysis -Brief Analysis No. 323, May 19, 2000.

**Cost containment measures, including price controls, lead to less diffusion of new medicines.** Even after a drug is approved in Europe, cost containment measures lead to less diffusion of new medicines in Europe compared to the U.S. A 2002 survey entitled, "Diffusion of Medicines in Europe," found shortfalls in the diffusion of state-of-the-art medicines between European countries for 20 key diseases. The study noted that the shortfalls in diffusion of new medicines resulted in large part from price containment measures. According to the study, "The most important factors for the diffusion of innovative medicines are policy related. Some examples are drug pricing policies, insufficient recognition of the (global and long term) economic effects of innovative medicine, inadequate governmental planning and last but not least cost containment strategies of every kind."<sup>26</sup>

Specific examples of the impact of price controls on patient access follow:

- **Cardiovascular Disease** - In Germany, 87 percent of all patients with coronary heart disease there was a lack of provision of modern lipid-lowering drugs.
- In Italy, 83 percent of eligible patients did not receive statins.
- **Diabetes** - In Germany, 30 percent of 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] eligible for treatment with beta interferons actually receive it (only 10,000 from about 25,000 to 30,000)."
- **Schizophrenia** - In France it is estimated that there are 4.4 schizophrenia sufferers for every 1,000 people aged between 31 and 50 years, but only 2.4 people for every 1,000 are treated. For the treated patients the level of the use of innovative second generation drugs continues to be at a very low level.
- **Depression** - "The European average shows that only 18 percent of patients with severe depression received treatment with antidepressants."
- In Germany, of the percent of patients treated with antidepressants, "only one in three received an up-to-date treatment with modern antidepressants (SSRIs). The other 8 percent are treated with older substances with more side effects or less effective drugs like herbal preparations."

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<sup>26</sup> O. Schöffski, "Diffusion of Medicines in Europe," Prepared for the European Federation of Pharmaceutical Industries and Associations (EFPIA), September 2002.

- In France, “recent studies have shown that 50 to 70 percent of patients with symptomatic depression are not treated at all, either with interpersonal or behavioural psychotherapies nor with antidepressant medication or a combination of both.”

***Cost-containment measures increase the use of older medicines.***

Not only have cost-containment measures, such as price controls, led to delays in the use of new medicines in Europe, but they have also increased the use of older medicines. A recent study by IMS Consulting examined data from the U.S. and Europe, the two largest biotech markets, over the last ten years, and found that American patients have benefited through the introduction of more biotech medicines, and these medicines have been on the market for longer periods of time. The report also noted that not only do Americans have access to a greater number of biotech medicines than Europeans, they also tend to use relatively newer products.<sup>27</sup>

Similarly, a December 2002 report from the U.S. International Trade Commission examined pricing of prescription drugs and found that when a drug is widely available in the market the “effect of the cost-containment programs in some countries is the increased likelihood that older, lower cost products would be prescribed rather than newer, more innovative products.”<sup>28</sup>

***The use of newer, innovative medicines can actually result in cost reductions to the healthcare system.*** Recent studies and reports have confirmed what many have assumed for years – pharmaceuticals often substitute for more costly hospital and physician care. It’s no surprise that spending on pharmaceuticals has increased over the years, given the ability of medication to substitute for more costly hospital and physician care and thus lower overall health care costs in many instances.

A study in the September/October 2001 issue of *Health Affairs* by Frank R. Lichtenberg of Columbia University examined the association between the use of newer medicines and morbidity, mortality, and health spending. Lichtenberg found that patients using newer drugs were significantly less likely to die and lose workdays than those using older drugs. He also found that the use of newer medicines increased drug costs by \$18, but reduced hospital and other non-drug costs by \$129,<sup>29</sup> meaning that for each additional \$1 spent on newer pharmaceuticals, \$6.17 is saved in total health care spending, \$4.44 of which comes from savings in hospital spending. This is powerful evidence that new drugs not only save lives – they save money by reducing the need for other,

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<sup>27</sup> IMS Health, “U.S. Outpaces Europe in Growth of Emerging Biotech Market: Industry Prospective”, January 17, 2003.

<sup>28</sup> U.S. International Trade Commission, “Pricing of Prescription Drugs,” Publication 3333, (Washington, D.C.: U.S. International Trade Commission, December 2000.)

<sup>29</sup> F. Lichtenberg, “Benefits and Costs of Newer Drugs: An Update,” National Bureau of Economic Research, June 2002.

more expensive treatments such as hospitalizations, emergency-room visits, and nursing-home care.

### ***Conclusion***

In sum, importation of prescription drugs is the equivalent of importation of foreign government price controls. Price controls in foreign countries, such as the EU and Canada, have led to reduced R&D investment by the pharmaceutical sector and reduced capital investment in new biotechnology. Price controls have also had a significant negative impact on patient access to and use of new medicines. Importation, like other efforts to regulate prescription drug prices in the U.S., would have a precipitous effect on innovation and a harmful effect on patient access to and use of new medicines.