WRITTEN SUBMISSION ON BEHALF OF
THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA (PHRMA)

IN RESPONSE TO THE REQUEST FOR COMMENTS
REGARDING THE U.S. – E.U. TRANSATLANTIC RELATIONSHIP
BY THE OFFICE OF THE U.S. TRADE REPRESENTATIVES
(69 FEDERAL REGISTER 51139)

The Pharmaceutical Research and Manufacturers of America (PhRMA) submit these comments in response to an invitation by the Office of the United States Trade Representative (USTR) published in the *Federal Register* (69 FR 51139, August 17, 2004). A subsequent *Federal Register* notice extended that comment period to December 30, 2004 (69 FR 65018, November 9, 2004). PhRMA welcomes the opportunity to participate in the public dialogue on enhancing the transatlantic economic relationship between the United States and the European Union, and PhRMA members remain committed to providing patients the safest and most innovative pharmaceuticals possible.

Overview

These comments outline in detail PhRMA's greatest concern: European price and access controls on pharmaceuticals that inhibit innovation innovation, delay and deny effective market access, undermine the value of intellectual property rights, and ultimately shift the burden of paying for the discoveries of new medicines to American patients.

In addition, these comments outline other issues of concern to PhRMA members, areas for increased transatlantic cooperation and specific responses to questions posed by USTR in its August *Federal Register* notice.

PhRMA's comments should be viewed in conjunction with our submissions relating to the Commerce Department's Drug Pricing Study and USTR's Annual National Trade Estimate on Foreign Trade Barriers and our upcoming submission on USTR's Special 301 Report.

EU Price and Access Controls on Pharmaceuticals

Correcting the market distortions caused by European government price and access controls on pharmaceuticals should be a core theme in the U.S. Government's discussions with the EU on strengthening the transatlantic economic relationship because these market access barriers shift the burden of funding innovation to American patients. One of the greatest challenges facing the transatlantic economic relationship today is European price and access controls on pharmaceuticals that inhibit innovation, delay and deny effective market access, and undermine the value of intellectual property rights. Those controls serve as a barrier to trade and discriminate against the innovative and safe pharmaceutical products of American companies.

Undermining Innovation

The results of past innovation and investment in R&D have improved both the length and quality of patients' lives. But the market-distorting policies of governments that engage in pharmaceutical price and access controls have begun to threaten the progress made over the past decade. A study by the Boston Consulting Group concludes that, based on economic literature, an additional 110 to 140 branded drugs

would have been launched over the past decade had it not been for the price controls used in OECD countries, many of which are members of the European Union. Moreover, the same study concluded that, without these controls, there would be about 35 to 40 entirely new classes of drugs today.

One clear example of access controls that undermine innovation is found in Italy. In 2003, Italy passed a new rebate scheme pursuant to which pharmaceutical manufacturers are responsible for repaying to the government any amount by which public spending on pharmaceuticals exceeds government budget targets for such spending. For clear political and protectionist reasons, local pharmacists and distributors (whose fees are included within the budgetary spending targets) have nevertheless been exempted from the payback obligation. These types of policies threaten the innovation that has resulted in dramatic improvements in human health, but they serve also as a discriminatory trade barrier against American companies.

Delay and Denial of Effective Market Access

European price control mechanisms deny market access to products of PhRMA companies. They do so in two ways: (1) by delaying the availability of new products; and (2) by denying the availability of new products. Given that national health insurance schemes typically dominate the European 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 EU country is a highly opaque one and the process of obtaining a government-approved

price can be lengthy. These processes operate to delay market access (and diminish the effective patent term) for many U.S. medicines. Governments often delay adding new products to national reimbursement lists merely to avoid the cost of providing those treatment options to patients.

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

PhRMA believes that EU price and access controls constitute non-science-based, non-tariff barriers and significantly undermine the export potential of the U.S. pharmaceutical industry. Even the EU's G10 report acknowledged that market forces should be permitted to determine prices for at least some drugs. While PhRMA strongly believes that price controls are damaging and market-distorting in all cases, we view as a positive first step the recommendation of the G10 report that "[f]ull competition should be allowed for medicines not reimbursed by State systems or medicines sold into private markets."

Undercutting Intellectual Property Rights

Intervention strategies by EU governments in the pharmaceutical marketplace drastically undermine the value of intellectual property protection in those markets. A patent right that gives the patent holder the right to exclude others from selling his

invention in a market, but that is limited by a requirement that the product be sold at marginal cost, is of little commercial value to the right holder. A country cannot be said to protect intellectual property adequately and effectively within the meaning of the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) if that country puts in place regulations that effectively nullify the value of the patent rights granted.

The United States routinely treats weak enforcement of intellectual property laws as a major trade issue. Allowing copycat manufacturers to pirate U.S. intellectual property, whether it is embodied in software, audiovisual recordings or medicines, undermines the export possibilities of those industries. Foreign laws that allow free-riding through other means – *i.e.*, price and volume controls – equally diminish the value of U.S. intellectual property rights and hurt U.S. exporters that rely on intellectual property protection. The delays caused by the bureaucratic pricing process described above also undermine the value of pharmaceutical patent holders' intellectual property. By delaying market access, these regimes waste potentially valuable patent term that cannot be recovered by the patent holder.

U.S. Dept of Commerce Report

The recent report by the U.S. Dept of Commerce on "Pharmaceutical Price Controls in OCED Countries – Implications for U.S. Consumers, Pricing, Research & Development and Innovation," (Dec. 2004) was written in response to congressional concern and interest in these matters, and reaffirms many of the industry's own findings.

The report is critical of price controls and other interventionist measures adopted by European governments that prevent market based pricing, and concludes that the reduced revenue available to develop new drugs due to pharmaceutical price controls and related measures has reduced worldwide private R&D investment by 11 to 16 percent (i.e., $5-8 billion) annually. The Department goes further to conclude that this translates into three to four fewer new drugs being launched each year. PhRMA looks forward to working with the Department and the Office of the U.S. Trade Representative in the months ahead to eliminate the market access barriers created by these artificial price controls in a strategic and progressive manner.

Where should the US-EU economic relationship be in 10 years?

Achieving the goals of removing trade barriers and regulatory harmonization over the next ten years would result in major gains in trade and economic cooperation between the United States and the European Union. Moreover, such changes would eliminate the current inequitable situation in which European countries pay less than their fair share for biomedical innovation. As two of the world's most advanced economies, the United States and the European Union have a historic opportunity over the next decade to make substantial progress in the removal of barriers on trade in pharmaceuticals. Regulatory harmonization in the approval and monitoring of medicines would spur unprecedented innovation in pharmaceutical development, the result of which would be improved patient care and patient longevity. With 380 million inhabitants, the European Union serves as a major market for safe and innovative

pharmaceuticals, particularly given the steady increase in standard of living that provides inhabitants the means to afford better, more innovative medicines.

Where are there opportunities for further and deeper cooperation, and how can the US and EU do more to advance competitiveness and innovation?

The pharmaceutical industry is one of the most heavily regulated sectors and regulatory harmonization between the United States and the European Union would be particularly valuable in terms of reducing duplicate testing and encouraging innovation. An important benefit of harmonization activities is leveraging and improving relationships with other regulatory authorities. The United States Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) enjoy a unique history of close cooperation and collaboration. PhRMA continues to support this relationship and its evolution and encourages the FDA and the EMEA to capture the positive components of each agency's approach to regulation and scientific assessment. The EMEA plays an important role in developing the EU pharmaceutical regulatory environment.

It is important, however, for USTR to understand the primary role that the European Commission plays in the proposal of Directives and Regulations and in the preparation of pharmacological guidelines. Accordingly, USTR's discussions with the European Union should focus on cooperative opportunities between the FDA and the EMEA and the Commission to streamline and open the rulemaking process to stakeholders. PhRMA believes that the FDA has valuable experience in the use of an

open and transparent regulatory process to share with its European counterparts. Successfully addressing the issue of open and transparent rulemaking will achieve the long-term goal of joint scientific advice and common conclusions, which would enhance global drug development and patient treatment.

In terms of innovation, the European Union made an important commitment in the Lisbon Strategy to focus on ways to spur innovation. The Strategy states that "Europe must do more to harness research, finance and business talent…" Specifically, the Strategy sets the target of increasing research and development ("R&D") spending to 3% of gross domestic product by 2010, with two-thirds of this new investment coming from the private sector. Using the Lisbon Method of open coordination, the G10 Medicines Group – which was established after a December 2000 symposium on Pharmaceutical Industry Competitiveness – drafted a report that reviewed the extent to which current pharmaceutical, health and enterprise policies in the European Union can achieve the twin goals of both encouraging innovation and competitiveness.

The consensus-based document reflected some G10 recommendations supported and previously promoted by PhRMA:

- EU Member States should examine the scope for improving time taken between the granting of marketing authorization and pricing and reimbursement decisions fully consistent with Community legislation.

- In order to increase generic penetration in individual markets, particular attention should be given to improved market mechanisms in full respect of public health considerations.

- Full competition should be allowed for medicines not reimbursed by State systems or medicines sold into private markets.

PhRMA supports the EU's effort to maximize research and development. However, PhRMA remains concerned that the outcomes of the Lisbon Strategy talks and the G10 Report do not recognize the serious impact that European price and access controls and diminished intellectual property protection have as disincentives for investment by the private sector into research and development. Moreover, those recommendations with which PhRMA agrees have not been acted upon in a timely manner to meet the Lisbon Strategy goal of increasing private sector investment in research and development.

The payoff from investment in research and development is clear, particularly in light of the enormous advances in drug therapies that treat rheumatoid arthritis, HIV/AIDS, Parkinson's disease, Alzheimer's disease, schizophrenia, diabetes, high cholesterol and many more conditions. Moreover, increased investment in R&D also creates jobs and economic opportunities for Europeans. Thus, increased research and development in the European Union should enhance the ability of European and American pharmaceutical companies to reach high levels of innovation.

An additional area for cooperation arises in sharing ways to better inform U.S. and E.U. patients. Some EU countries limit drug manufacturers' access to consumers and physicians. They contend that allowing promotion and direct-to-consumer advertising raises costs, promotes inappropriate drug use, and gives doctors ready

access to information about new innovative drugs from other sources. The innovative drug industry maintains that obstacles to promotion are designed to reduce demand for new drugs for which the government does not want to pay. It claims that governments are worried that if consumers were made aware of the "true" benefits of innovative drugs, they would demand that these drugs be reimbursed. A dialogue on the merits of more informed patients is warranted, particularly on restrictions that inhibit patients' information and access to life-saving cures.

What should be done to better mesh US and EU regulatory approaches?

Due to social and system-based differences, the FDA and the EMEA both offer areas of advantage that may complement each agency's existing practices. PhRMA encourages both agencies to leverage this type of cooperative relationship to enhance regulatory procedures based on each other's strengths and experiences.

Two such areas, where PhRMA believes the FDA has established best practices that could be considered by the EMEA and the Commission, are transparency in regulatory practices and rule-making and stakeholder input. Under the existing EU system, the industry lacks information during the regulatory process and is not sufficiently involved in the development of new regulations and guidance that would affect industry development plans. To improve this situation, PhRMA would like to see increased communication and discussion between the FDA, the EMEA and the Commission during the approval process and in the development of scientific guidelines, and at the EU level, during the revision and development of the legal

framework. A step-wise process of regular communication at such milestones and posting of official communications, as established at the FDA, would help greatly towards establishing more transparent practices.

PhRMA also encourages the FDA and EMEA to provide more public information and clarity surrounding their interactions. In September 2003, the FDA and the EMEA adopted a bilateral agreement on sharing information, scientific advice and draft guidance. In general, we believe there could be great benefits resulting from this arrangement, but clear rules and procedures for information exchange and applicant consultation will be critical to its success. PhRMA believes strongly in the need for transparency on how, when and what information is being shared, as well as how this implementation is being handled. In addition, confidentiality, consultation and consent of the applicant are important and valuable in this process. Applicants should be involved in discussions of differing scientific opinions, as their experience and perspective can contribute to a better understanding of the situation.

Similarly, early industry involvement in the development of scientific guidelines is beneficial, as it promotes open dialogue and predictability in regulatory practices. As this applies to the sharing of draft guidance between the EMEA and the FDA, PhRMA supports this exchange and seeks industry participation in such discussions. The following are specific areas where PhRMA encourages further cooperative activities that would benefit both the regulatory agencies, industry and the patients we serve, and shape the direction of the field:

Clinical Trials

PhRMA encourages USTR and relevant US agencies to engage EU officials in a comprehensive discussion about streamlining the burdensome and inconsistently applied EU Clinical Trials Directive ("Directive") and to collaborate more generally with the EU on streamlining clinical trial requirements, reducing the regulatory burden for agencies and improving the drug development environment for sponsors. As drug development has become increasingly global, there is a pressing need for national and international consensus among regulators, physicians, and sponsors for appropriate clinical trial outcome measures. PhRMA is concerned that the Directive creates a significant administrative burden on the pharmaceutical industry that is not necessary to achieve safety in clinical trials. For instance, the Directive requires sponsors established outside the European Union to be represented by a "legal representative," although the Directive provides no common definition for that term and no immunity from suit for those representatives. Moreover, those representatives may face criminal sanctions for failure to properly supervise the sponsor or take necessary remedial action in the course of a clinical trial, even though it is likely they would have little direct involvement in a clinical trial.

These factors may be a disincentive for EU persons to serve as "legal representatives" of external sponsors engaged in clinical trials of new and innovative drugs, thus delaying or preventing the introduction of innovative drugs to European patients. Additionally, the Directive creates extremely burdensome reporting regulations

on the sponsor, any violation of which could result in legal sanctions against the sponsor and the "legal representative."

Good Manufacturing Practice (GMP) Inspections

PhRMA encourages USTR and relevant US agencies to engage EU officials in discussions about what concrete steps may be taken to conduct joint EU and US inspections of pharmaceutical manufacturing plants, exchange agency inspectors to gain extended experience in one another's region and consider sharing GMP information relating to the validation of manufacturing sites. Similar to drug development, the industry is adopting a more global approach to manufacturing. Accordingly, redundant plant inspections become an unnecessary burden to a pharmaceutical company and regulator especially when resources and competencies can be pooled. Indeed, to the extent that these plant inspections fall under the definition of "conformity assessment procedures," the EU must ensure that these procedures are not more strict than necessary to give the EU adequate confidence of conformity, consistent with Article 5.1.2 of the WTO Agreement on Technical Barriers to Trade ("TBT").

PhRMA supports the conduct of joint EU and US inspections that would validate the manufacturing plant for both authorities and facilitate the understanding of respective GMP and inspection standards and regulatory harmonization. An exchange program allowing for inspectors of each agency to gain extended experience in one another's regions would be a plausible way towards this working partnership. Further,

as each agency has GMP information databases, sharing the validation status of sites should be considered in the near future.

EU Regulation of Pediatric Medicinal Use

PhRMA encourages USTR and relevant US agencies to offer US assistance in creating a reasonable and productive regulation on pediatric medicinal use that (1) minimizes the delay in authorization of non-pediatric medicines, (2) creates incentives, like a one-year patent extension, for pharmaceutical firms to conduct pediatric clinical trials, (3) eliminates mandatory application of pediatric regulations to simple line extensions of previously authorized medicines, (4) removes the requirement that MRP products be authorized in all EU member states, (5) establishes a competent and qualified pediatric board, with a pharmaceutical member, (6) establishes Pediatric Board decisions as Commission decisions, and (7) defines clearly what information will be made public and only publishes competition-sensitive information after a product has been authorized. PhRMA supports the aim of the European Union to improve children's health in Europe through increased development of medicines for use in pediatric populations. PhRMA believes that the United States can offer tremendous assistance with this EU effort given the FDA's extensive experience in this area. The achievement of this objective, through a regulation on medicinal products for pediatric use ("pediatric regulation"), requires balancing the obligation to conduct clinical studies on pediatric populations against the benefit for the pediatric populations, ethical concerns, complexity and costs and incentives provided. When such a balance is properly

achieved, the results are impressive, as the experience in the United States with the Better Pharmaceuticals for Children Act (BPfCA) has shown.

For some 18 years prior to the enactment of the BPfCA, the US Food and Drug Administration had attempted to address inadequate pediatric use information in drug labeling by imposing several types of mandatory solutions on companies conducting pharmaceutical research. While these efforts did produce some gains in pediatric labeling, they did not substantially increase the number of drugs for which there was adequate pediatric use information. However, with the enactment of the BPfCA and its voluntary incentive program, this landscape changed dramatically. In the FDA's January 2001 Status Report to Congress on the Pediatric Exclusivity Provision, the FDA stated, "The pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date."

PhRMA believes that the US experience both of using mandates and incentives has provided important lessons from which the EU may benefit.

Better Regulation Initiative

PhRMA encourages USTR to highlight the benefits to industry and government in the streamlining of regulations, particularly when such activities are undertaken in a transparent and collaborative manner. PhRMA supports the concept of the EU's Better Regulation Initiative, a key outcome of the Lisbon Strategy, that is meant "to establish a reliable, up-to-date and user-friendly body of EU law for the benefit of citizens, workers

and businesses across Europe." PhRMA welcomes the simplification of regulations anticipated under the Initiative. It is vital, however, that this process be transparent and open to stakeholder input.

How can the US and EU cooperate more effectively in third markets, such as a promoting transparency and protection of intellectual property rights?

PhRMA encourages USTR to engage EU officials in a comprehensive discussion about the establishment and enforcement of adequate intellectual property rights, particularly in pharmaceuticals, and to invite the European Union to join the US Strategy Targeting Organized Piracy (US-STOP) effort to combat illegal piracy and counterfeiting. The authors of the November 2000 report on "Global Competitiveness in Pharmaceuticals: A European Perspective" note that "it is widely acknowledged that patents are a fundamental incentive to innovative activities in pharmaceuticals and biotechnology." The report also acknowledges that "the establishment of clearly defined property rights also played a major role in making possible the explosion of new biotechnology firms in the USA," while highlighting that broad claims on patents are "greatly reduced" in Europe. The protection of intellectual property and the prosecution of counterfeiting is perhaps the most promising area of US-EU cooperation. Companies and innovators both in the United States and the European Union have much to lose from weak IPR regulation and counterfeiting.

PhRMA strongly believes that the recent addition to Europe of the accession countries (EU-25) threatens previously uniformly high intellectual property protection

standards. All members of the European Union (EU) are obligated by November, 2005 to implement the new harmonized regulatory data protection contained in the Future of Medicines Legislation (so-called "8/2/1" protection) that was enacted on May 1, 2004. Under "8/2/1," a subsequent applicant that seeks to rely on the originator's data may not file an application during the eight years following marketing approval of the originator's product. If the applicant files after eight years, it may not market its product until ten years following marketing approval of the originator's product. Thus, an application for marketing approval of a subsequent product based on the same active ingredient may not rely on the originator's data during the first eight years of the exclusivity. The legislation also provides for one additional year of exclusivity for all indications, if the originator conducts additional clinical research to develop a new indication of significant clinical benefit over what is available and receives marketing approval for the new indication during the first eight years of marketing authorization. "8/2/1" protection will significantly improve the level of data protection in the new Europe and PhRMA member companies believe that any requests for derogations of fifteen years made by accession countries should be rejected, since it would further segment the European pharmaceutical market and continue to reward copiers of originator pharmaceutical products.

The Transatlantic Business Dialogue (TABD) has recommended the establishment of a forum to enhance the effectiveness of IPR protection, the devotion of additional resources to combat counterfeiting and piracy, and the establishment of an outreach program to raise awareness of IPR issues. Moreover, the recent introduction

of the US-STOP program provides an important opportunity for the US and EU to cooperate in confronting the international problem of counterfeiting. Through information exchange and discussion facilitated by the TABD, the US and EU should be able to more effectively address the problems of intellectual property violations in third markets.

Summary

PhRMA welcomes the initiative of the United States and the European Union in pursuing ways to strengthen the transatlantic economic relationship. With all complex relationships come areas for improvement, and the US-EU relationship is no different.

One of biggest problems facing this relationship, and PhRMA's primary concern, is the pervasive use of price and access controls on pharmaceuticals by EU countries. These controls inhibit innovation, delay and deny effective market access, and undermine the value of intellectual property rights, and shift the burden of funding new medical discoveries to American patients. Moreover, they serve as a major barrier to trade and discriminate against American pharmaceutical products that could improve the lives and longevity of European patients. PhRMA looks forward to working with the Office of the U.S. Trade Representative in the months ahead to eliminate these barriers and enhance patients' access to life-saving medicines.

Finally, PhRMA also has taken the liberty to comment on other issues of concern to the industry and potential areas for transatlantic cooperation. We look forward to discussing these measures with U.S. Government officials in the future as well.