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Regulating the Export of Unapproved Drugs

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Prior to 1986, it was not possible under the Federal Food Drug and Cosmetics Act to export drugs which did not have FDA approval. The law was changed by the Drug Export Amendments Act of 1986 after nearly a decade of debate.¹ Those who favored liberalizing the drug export law argued that American companies were at a competitive disadvantage in foreign markets because of the prohibitions, and the pharmaceutical industry suffered as a result. They argued that the national sovereignty of those countries that decided that unapproved drugs were appropriate for use by their citizens should be respected, and that it would be excessively paternalistic to deny these countries the products they desired. Those who opposed lifting the ban on exporting unapproved drugs argued that economic concerns were not sufficient to overcome the ethical difficulty in creating a double standard which allowed drugs that had not been determined safe and effective for use by U.S. citizens to be used by the citizens of foreign nations.

The Drug Export Amendments Act of 1986 is a compromise that allows export of FDA unapproved drugs to twenty-one countries that have been judged by Congress to have a drug regulatory system sufficiently robust for the protection of their citizens. The act contains safeguards for preventing the re-export of unapproved drugs to countries that are not well equipped to protect

¹. The Ethics and Economics of Unapproved New Drug Export, 21 Geo. Wash. J. Int'l L. & Econ. 315, 333 (1987).

their citizens, and safeguards for the prevention of other unethical and abusive export practices. It is now possible to re-examine the policy choices made in the legislation with the benefit of some years of experience operating under the new rules. There is evidence to support the conclusion that American firms have benefitted significantly from the export reforms, although the gains have been modest in some respects. Further streamlining of the process can provide additional gain with little, if any, added health risks.

Concerns that the citizens of foreign countries face health risks from the importation of unapproved drugs still exist. The prohibitions against exporting unapproved drugs to those countries that have an unsophisticated regulatory system provide little actual protection to the citizens of those countries, and a more effective policy would allow American companies to export certain unapproved drugs to those countries under FDA supervision.

The Drug Export Amendments Act of 1986

The 1986 Amendments became section 802 of the Federal Food Drug and Cosmetic Act. It divided unapproved drug and biological products into three categories, each with a different set of requirements for export.

The primary category included unapproved new drugs and biological products. Products in this category can be exported to any of twenty-one foreign countries listed in the Amendments. These twenty-one countries are developed nations that have regulatory systems sophisticated enough to responsibly manage the distribution and use of unapproved drugs. The Amendments require that; (1) the product is approved for marketing in the receiving country;

(2) an application for FDA approval for the product in the U.S. has not been denied; (3) the product is the subject of an investigational new drug exemption (IND), and approval for the product in the U.S. is being actively pursued; (4) the product is manufactured in conformity with good manufacturing practices (GMP), and is not adulterated; (5) the shipping label lists the countries for which the product is authorized for export; (6) the export of the product is not contrary to the public health and safety of the U.S.; and (7) the four export requirements for all drug exports have been met. Importing countries are required to agree in writing not to export the drug to an unlisted country.

Export of unapproved drugs to unlisted countries is prohibited unless the Secretary of Health and Human Services determines that the drug is safe and effective for the treatment of a particular disease in that country. That determination must be based on credible scientific evidence including clinical investigation. Thus the safety precaution for a new drug to enter an unlisted country is higher, since in a listed country the unapproved drug has to be the subject of an investigational new drug exemption which may be obtained before clinical testing has begun.

The second category covers tropical disease drugs. These drugs are not required to be approved in the receiving country. Nor is it required that the drug is under active investigation in the U.S.. The export of tropical disease drugs is not restricted to the twenty-one statutorily listed countries. These products may be shipped to any country that the FDA determines there is credible scientific evidence, including clinical investigations that the drug is

safe and effective for its intended use. This category exists to promote the development of drugs for the treatment of diseases which are not common in the U.S., and therefore would normally not be the subject of investigation in the U.S..

The third category covers partially processed biological products. The 1986 Amendments amends The Public Health Service Act to allow the FDA to approve export of a partially processed biological product which is not in a form applicable to the prevention, treatment, or cure of disease, and which requires further manufacture into a final dosage form in the receiving country. These products can only be exported to one of the twenty-one listed company, however there is no restriction against trans-shipment. The final product to be developed from the partially processed biological product must be approved in the receiving country, or the FDA must be satisfied that such approval is being sought. This category was included to give biotechnology firms the flexibility to export biological intermediates, which are regulated as final products by the FDA, under less restrictive regulation. The privilege is comparable to the flexible that pharmaceutical companies have to export chemical intermediates under less restriction conditions than those applied to finished drug products.

Common to all three categories are requirements for good manufacturing practices and that the product be labeled with the countries that it has been approved for export.

The Pharmaceutical Industry

The pharmaceutical industry lobbied hard for lifting the ban on the

export of unapproved drugs. Four characteristics of the pharmaceutical industry causes it to particularly sensitive to regulation in this area.' First, the industry has a lack of concentration. The majority of the market is shared by more than a dozen firms, and a number of smaller firms participate in the market. Second pharmaceutical companies spend a large amount of their resources in the research and development of new products. The development of a new products is a long and expensive process, and any delay can significantly effect the health of the company. Third, the pharmaceutical industry is extensively regulated. Fourth, drug companies depend on the international market for a significant portion of their revenue.

Prior to the 1986 amendments, U.S. drug companies were prevented from marketing abroad any drug that did not have FDA approval. The result was that American firms were typically late to enter foreign markets with new drug products because of the long period required for a new drug to receive FDA approval. Those in favor of lifting the ban asserted that the competitiveness of the American pharmaceutical industry was being seriously harmed.

In order to circumvent FDA restrictions, larger firms, who could afford to, transferred production of their products abroad. Transfer of production facilities abroad suppressed the growth of the domestic pharmaceutical industry, further reducing the competitiveness of the U.S. pharmaceutical industry. The lose of domestic jobs was claimed to be considerable, and production abroad denied the U.S. the benefit of export income.

Those firms that were not large enough to open facilities abroad

by necessity entered into licensing and partnership arrangements with foreign companies. This prevented small U.S. companies from profiting fully from the development of innovative products. This was presented as a major burden on the development of innovative products.

Biotechnology firms are particularly sensitive to regulatory delays in the approval of their products. They are typically small, research oriented firms supported by venture capital. New technologies such as recombinant DNA research require expensive state-of-the-art equipment and long development times. Biotechnology firms are pressed to generate income as soon as possible. These firms are usually financially incapable of establishing separate facilities abroad to circumvent FDA regulation, and frequently enter into foreign joint ventures and licensing agreements, or transfer proprietary technology abroad. Those who argued for lifting the ban on exporting unapproved products argued that the ban was causing the U.S. to literally give away its lead in biotechnology.

Those who favored keeping the export ban in place claimed that the primary reason for the movement of research and development, and production facilities abroad were due to factors such as foreign laws that required domestic research prior to domestic marketing, favorable costs of labor and facilities abroad, and the ability to enter otherwise inaccessible markets through foreign partnerships.

The Drug Export Amendments Act In Practice

An empirical study was done examining the export applications filed and processed during a five year period following the enactment of the

1986 Amendments.² The export review phase, which is the time from the date of export application to the date of export approval was calculated for all products approved for export during the study period. The market jump, which is the time from the date of export approval to the date of U.S. marketing approval, was also calculated. The market jump is the maximum amount of additional time available to a drug producer to sell his product in a foreign market upon export approval.

The average export review phase for the primary category of new drug products was 3.6 months. The time it took to approve a product for export varied from about one month to about twentyó five months. The average market jump was about one and oneóhalf years of potential foreign market access prior to a product's approval in the U.S.. The increased potential marketing time for products approved domestically during the study period ranged up to about fortyóseven months.

Over the study period there were no applications for export approval for category two products, tropical drugs. For partially processed biological products, the average export review phase was 6.4 months, about twice as long as those products in the first category.

Assuming that drug producers have been able to take advantage of the additional potential foreign market access, the study shows that the 1986 Amendments have produced measurable gain for U.S. drug producers. One area of disappointment is that the reforms so far have had a minimal effect in

². Sheila R. Schuman, Michael Manocchia, Mark Seibring, The Drug Export Amendments Act of 1986: Is It All It Was Intended To Be?, 49 Food & Drug L. J. 367 (1994).

stimulating the development of tropical drugs. Also, the breakdown of products for which export applications were filed show that a relatively small number were for biotechnological therapeutic drugs. Apparently the 1986 Amendments have not been as beneficial to biotechnology companies as hoped.

The benefit to pharmaceutical companies under the 1986 Amendments could be increased if the review period for export applications were decreased, thereby increasing the market jump. Currently, the review period typically runs well over the statutorily indicated thirty day period. The Pharmaceutical Manufacturers Association (PMA) produced a white paper which contained suggestions for reducing the review period.³ The PMA identified differences in the way in which different FDA reviewing divisions processed applications as responsible for some of the delay. The PMA suggests that a standard export application form would alleviate the problem. Also, delay would be eliminated by allowing the applicant for export to provide the

FDA with proof that the drug product has been approved for use in the receiving country, rather than requiring that the proof be provided directly by the importing government. These two suggestions are reasonable, and ought to be adopted by the FDA.

Although it seems clear that pharmaceutical companies enjoy the benefit of increased foreign market access under the 1986 Amendments, it is not as clear whether the promise of growth in the domestic pharmaceutical industries and the accompanying increase in domestic jobs has been fulfilled. The

³. Pharmaceutical Mfrs. Ass'n, Drug Export Amendments Act of 1986: Proposed Administrative Modifications.

number of domestic jobs within the pharmaceutical industry, and the number of pharmaceutical companies increased approximately threefold over the period from 1987 to 1992,⁴ however, it is uncertain what portion of this growth can be attributed to the export reform, since over that period the industry benefited from a number of financial, tax, and business assistance initiatives and incentives meant to encourage growth in the industry.

U.S. Responsibility For Unapproved Drugs Abroad

The 1986 Amendments addressed three conflicting policy concerns. The challenge was for the United States to promote the growth of its domestic pharmaceutical industry without compromising its moral responsibility to regard the health and safety of citizens of foreign countries as highly as it regards the health and safety of U.S. citizens, while at the same time respecting the sovereign right of foreign nations to make their own decisions.

By allowing American pharmaceutical companies to export their unapproved drugs to twenty-one developed nations, the 1986 Amendments improves the U.S. trade balance, creates short-term profits for the pharmaceutical industry, and potentially produces long-term growth and innovation in the industry. In addition the amendments may bring a halt to large pharmaceutical companies building plants abroad in order to circumvent the U.S. regulatory system. Do the 1986 Amendments satisfy the ethical and sovereignty policy goals as well as they satisfy the domestic economic concerns?

Those who opposed lifting the ban on the exportation of unap-

⁴. Sheila R. Schuman, Michael Manocchia, Mark Seibring, *The Drug Export Amendments Act of 1986: Is It All It Was Intended To Be?*, 49 *Food & Drug L. J.* 367, 384 (1994).

proved drugs for ethical reasons believed that a drug not considered safe and effective for U.S. consumers should not be sold to foreign consumers either. It did not matter that these same drugs were readily available from other sources. Even if the drugs were available from other sources, that did not justify the United States also providing them. They argued that the creation of a double standard which implied that drugs that aren't good enough for us are good enough for you diminished the United States moral standing in the international community.

Supporters of lifting the ban answered that this did not create a double standard, but rather affirmed each nation's right to set its own standards. Aside from purely abstract principles of national sovereignty, there were sound reasons for allowing nations to make their own health regulatory decisions. For one, the FDA's drug approval process is not always rational. It is subject to American political pressures which are inapplicable to foreign nations and should not be imposed on other nations.

Second, permitting nations to set their own health standards, recognizes that different countries may have different health needs, depending on such factors as climate, race, geography, life expectancy, and disease patterns. Other countries may evaluate the safety and effectiveness of a drug using a different, yet completely valid, set of social priorities and different risk benefit calculations than those appropriate for the U.S.. A popular example of such a drug is Depo-Provera, which is an injected contraceptive banned in the United States because of the possibility that it promotes cancer. In countries where life

expectancy is short and mortality during pregnancy and childbirth is high, the possibility of developing cancer at age sixty-five from use of drug would be of relatively less concern.

Given the sound reasons why one nation's view of a drug may differ from that of the United States's, it was strongly asserted that imposing U.S. drug standards on other countries was unnecessary and offensive paternalistic interference with the sovereign right of a nation to establish its own health standards.

Neither side of this debate won a complete victory in the 1986 Amendments. The policy adopted is one that attempts to address the valid concerns of both sides.

The 1986 Amendments implicitly divides the world into two classes of countries. In the first class are those countries with a health regulatory system sophisticated enough that the United States can allow them to make their own regulatory decisions without incurring moral blame for their errors. These are the twenty-one statutorily listed countries; the nations listed roughly correspond to what would be considered the world's developed nations. The second class of unlisted countries is comprised of those countries which lack the sophisticated regulatory processes and resources necessary to make their own health and safety decisions, and which therefore must rely on the FDA'S regulatory processes to protect them from importing drugs which may prove to be injurious.

This approach, although it addresses the moral and ethical concerns of the United States, is less satisfying in its approach to the sovereignty of foreign

nations. Only a limited number of countries, exactly twenty-one, are allowed to exercise sovereignty in regards to which drugs they wish to import from the United States.

However, a more serious problem with the two class system implemented by the 1986 amendments is that it fails to protect unlisted nations from the unsupervised distribution of risky drugs if unapproved drugs are reóexported from a listed country to an unlisted country. The export amendments do provide safeguards against reóexport. Importing countries must agree in writing not to reóexport unapproved drugs to unlisted companies. Exporting firms are responsible for insuring that unapproved drugs are exported only in a quantity that could reasonably be used by the receiving country. However, as a practical matter, it is nearly impossible to prevent the trans-shipment of unapproved drugs to unlisted countries.

Since trans-shipment of unapproved drugs can not be prevented, the two class system breaks down, and the result is that unlisted countries which have been judged to be ill-equipped to manage the risk of unapproved drugs, receive them from listed countries with no FDA oversight at all. The FDA has no power to determine whether trans-shipped drugs have become adulterated or misbranded, or have been prepared according to good manufacturing standards. The current law, because of the inability to prevent transóshipment of drugs, permits the sale of unapproved drugs anywhere in the world, while exercising oversight only over those

I drugs sold to listed countries, which by definition, are least in

need of FDA regulatory oversight.

Rather than returning to a complete ban, the United states could address the difficulties listed above by lifting the ban completely. The U.S. would allow all foreign governments to exercise their responsibility over the health and safety of their citizens. The FDA would then directly oversee the quality and manufacturing of all American drugs exported to foreign countries.

However, the United States would still be faced with the dilemma that numerous countries which are potentially recipients of risky products are ill-equipped to make the necessary riskbenefit analysis and develop appropriate drug regulation. In order to best meet its moral responsibility to insure that these countries are not harmed by American products, the U.S. would have to provide importing governments with full information about the products and assistance in making the necessary riskbenefit analysis and developing and implementing appropriate controls.

However, it is not feasible for the FDA, which already has its hands full with the regulation of the U.S. market, to take on the additional responsibility of assisting other countries with their drug regulation. The United States should therefore maintain the distinction between countries that have sophisticated drug regulatory processes, and those which do not. However, once a drug with FDA approval has been approved for use by one of the listed countries, opening the way for exports of the drug abroad, all countries, including unlisted ones should be permitted to import the drug from the United States. This policy concedes that the U.S. can not adequately prevent the transshipment

of U.S. drugs, and takes the pragmatic approach that it is better for unlisted countries to acquire the drugs from the United States, where the FDA can exercise oversight of quality control, labeling, and promotion of the drug. Although this variation of the present policy does little to increase the competency of the supervision of drug products in unlisted countries, it does have the benefit of insuring that those drug products that do enter the country are as safe as possible under the circumstances.

The FDA should further require that exporting firms provide notice to receiving countries if FDA takes any action to ban or restrict the domestic use and distribution of a drug.

Conclusion

The current export law for drugs which have not received FDA approval is a fair attempt to simultaneously satisfy three contradictory policy concerns. The present law adequately promotes the growth of the U.S. pharmaceutical industry, although more benefit under the law can be obtained by modifying the application process to reduce the review period for export applications.

The current law, as it reads, favors protecting underdeveloped countries from risky drugs over concerns for respecting principles of national sovereignty. However, in practice the safeguards which appear in the law can not be adequately enforced. While on the books, it appears that the United States has adequately addressed its moral and ethical obligations, the reality is somewhat different. Therefore, the United States should permit direct ex-

portation of unapproved drugs to unlisted countries once that drug becomes available to a foreign market. Although this policy would expose the U.S. to wider criticism that its export policy unethically provides risky drugs to vulnerable nations, it would be a significant step toward expanding the protection that those nations actually receive.

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