

PN 11BE-833

Working Paper #23
December 1985

65641

WHERE NEXT WITH THE U.S. EXPORT
OF NONCONFORMING CONTRACEPTIVES

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An analysis by
THE DEVELOPMENT LAW AND POLICY PROGRAM

Prepared for the
American Public Health Association
112th Annual Meeting
November 11-15, 1984
Anaheim, California

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Introduction

In the past decade there has been extensive debate about the export of drugs, including contraceptives, not approved for use in the United States (U.S.). This debate has been part of a larger debate surrounding the export of all kinds of potentially hazardous products, such as pesticides (Alston 1978; Interagency Working Group, 1980).

This paper is limited in scope to a discussion of those regulatory actions that determine the approvability of contraceptives. Contraceptives that are not approved for use in the U.S. are described here as nonconforming. The paper outlines the law regulating the U.S. export of new drugs and medical devices as it relates to nonconforming contraceptives, and discusses how this regulatory approach balances U.S. responsibilities both to respect the right of foreign nations to make their own decisions regarding their imports and to facilitate the export of safe and effective contraceptives. The paper then examines legislative proposals that would allow the export of nonconforming new drugs. In conclusion, it proposes guidelines to be observed in drafting any law allowing for the export of nonconforming contraceptives.

U.S. Law Regulating the Export of Drugs and Devices

There is no clear uniform policy regarding the export of drugs and devices that are not approved for domestic use. The federal Food, Drug and Cosmetic Act (FDC Act) prohibits the

export of new drugs that have not been approved for domestic use. The same act, however, permits the export of unapproved medical devices, provided certain conditions are met. To further complicate matters, the export of unapproved drugs and devices may or may not be hazardous. The determination of a hazard depends in part on the cause precipitating U.S. regulatory action and on how a hazard is commonly defined.

Drugs

Gertrude Stein was noted for saying "rose is a rose is a rose." Had lawyers been as clear-headed when they drafted this over-complicated act, the explanation of drugs would be far easier. The word "drugs" refers to products developed before 1938 and regulated by the 1906 Pure Food and Drug Act. "Drugs" do not fall within the definition of "new drugs" in the present law. Since contraceptive drugs were developed after 1938, they are "new drugs" and not "drugs," under the FDC Act.

A drug may be considered new for many reasons, such as that:

- o it contains a newly developed chemical,
- o it contains a chemical or substance not previously used in medicine,
- o it has previously been used in medicine, but is now recommended in different dosages or for different conditions, or
- o it has become recognized by qualified experts as safe and effective for its intended uses as a result of investigational studies, but has not otherwise been used to a material extent or for a material time.

A "new drug" may not be commercially marketed in the U.S.

unless it has been approved as safe and effective by the Food and Drug Administration (FDA). Such approval may follow submission of a New Drug Application (NDA) by the sponsor of the drug. The NDA must contain acceptable scientific data, including tests showing the drug's safety and substantial evidence of its effectiveness for the conditions for which it is to be offered and labeled. In preparation for an NDA, a drug may be approved by the FDA for investigational use.

The FDC Act prohibits the export of new drugs that have not been approved for domestic use. New drugs that have been approved for investigational use in this country may be exported, but only with a certification that they will be used for such investigational purposes abroad.

Devices

Medical devices are regulated by the 1976 Medical Device Amendments to the FDC Act. The 1976 amendments define "device" as any health care product that does not achieve any of its intended purposes by chemical action in or on the body or by being metabolized. Products that work by such chemical or metabolic action, such as the contraceptive copper intrauterine device are regulated as drugs.

Devices are governed by one or more of the following three classes of controls

- o Class I: General Controls. Class I products are subject only to the general controls that apply to all

devices. General controls include regulations on registration of manufacturers, labeling and good manufacturing practice. Arm-slings are examples of class I devices.

- o Class II: Performance Standards. Class II devices are those for which general controls are not sufficient to assure safety and effectiveness. They are required to meet performance standards established by the FDA. These standards may specify materials, construction, components, ingredients, labeling and other properties of the device. Examples of devices in class II are condoms and diaphragms.
- o Class III: Premarket Approval. All permanently implanted devices fall in class III. The FDA must approve the safety and effectiveness of such devices before they can be marketed, unless the FDA specifically determines that premarket approval is not necessary. For a usual class III device, the manufacturer will have to provide the FDA with a premarket approval application containing evidence that the device is safe and effective before the device may be commercially distributed.

The FDC Act permits the export of a medical device that has not been approved for domestic use under classes I, II or III, provided that:

- o the device is in accord with the specifications of the foreign purchaser,
- o use of the device does not conflict with the laws of the country to which it is intended to be exported,
- o the shipping package is labeled as intended for export,
- o the device is not sold or offered for sale in domestic commerce,
- o the Secretary of Health and Human Services has determined that export of the device is not contrary to public health and safety, and
- o the device is approved by the country to which it is intended to be exported.

The FDA has authority to require that notification be given to the FDA by manufacturers who are exporting medical devices not marketable in domestic commerce. The FDA is required to notify the importing country of potentially hazardous medical devices. The deputy commissioner of the FDA has testified that experience with the administration of these provisions has been favorable (Novitch, 1984). The FDA processes 250-300 export requests per year, and has found the two most important public health safeguards in the export device provision to be the public health assurance and the approval of the importing country.

What Constitutes a Hazard

The export of new drugs and medical devices unapproved for domestic use may or may not be hazardous. There is no legal

definition of hazard. However, any drug the FDA has not, or not yet, approved is assumed to be possibly hazardous. Similarly, FDA regulatory action taken with respect to an approved drug or device also constitutes evidence that the drug or device may be hazardous.

A suspected hazard may precipitate regulatory action at any point along the continuum of drug regulation from product testing to approval, manufacturing, packaging, labeling, storage and, finally, usage. The regulatory action may result in removal of the product from the market because of a demonstrated lack of safety or efficacy. For example, the Dalkon Shield was removed from the market because of lack of safety. Another kind of regulatory action may consist in weighing the risks and benefits of a new drug that has successfully undergone initial testing within the health and social context peculiar to the U.S. For example, the FDA found Depo-Provera unacceptable for use as an injectable contraceptive because, among other reasons, the FDA thought its risks outweighed its benefits in the United States. The former regulatory action can more clearly signal a hazard than can the latter regulatory decision.

Whether or not the hazard is great enough to justify preventing export also depends on how hazard is perceived. The perception of hazardousness could be narrow, so as to cover only those products that have actually been recalled from domestic use. Alternatively, the perception could be broadened to include,

for instance, products that are being tested. An equitable export policy must include minimum threshold of safety and effectiveness to determine which drugs should and should not be exported.

International Norms Applicable to Drug Exports

There are three established or evolving international norms that may apply to the U.S. export of contraceptives: the principles of comity of nations, state responsibility and international minimum standards. These norms, which can be politically or legally binding, are usually binding only upon states or international institutions, but not necessarily upon individuals or private enterprises. The legal enforceability of such norms varies according to their acceptability and the degree to which they are enforceable by countries' internal courts.

Comity of Nations

The principle of comity of nations obligates the U.S. to respect the sovereign rights of other nations. It is founded upon the recognition in international practice of the respect and accord good neighbors use in their dealings with each other. The rights that need to be respected under this principle include the right of a nation to make determinations on the import of medicines necessary for the health and safety of its own citizens. In order for nations to make informed choices, international comity requires that the exporting country's government transmit all relevant information it possesses on the

drug at issue to the importing country.

State Responsibility

The claim to exercise of sovereign rights is subject to certain limitations. One limiting principle, found in the state responsibility doctrine, is that a state is not allowed to interfere with the sovereign rights of other nations, just as one cannot interfere with one's neighbors' enjoyment of their own property (Genrubi, 1983). If a state permits activities within its control to interfere in a detrimental way with the sovereign interests of another state, it can be liable under international law. The export of contraceptives is within a state's control, because it is regulated by national law.

Liability that might well arise under international law could be for allowing the export of nonconforming contraceptives without proper notification of the foreseeable harm to citizens of importing countries. Such responsibility would follow logically from the developing norm that requires notification of predictable harm to foreign countries' natural resources. A notification requirement is especially appropriate in cases where the information is publicly available and in the hands of the U.S. government.

Some national legal systems make manufacturers and other suppliers strictly liable for injuries resulting from use of products likely to be hazardous; that is, they are liable for damages without an injured party's having to prove actual fault.

seems unlikely at this point that international law would go so far as to impose a strict liability standard for the export of potentially hazardous drugs. As a result, it is unlikely that trade of producer nations would be restricted by imposition of liability for injury resulting from the export of hazardous drugs as such. For countries that do not adequately observe notification requirements, however, trade might be restricted by imposition of liability for inadequate notification.

International Minimum Standards

The exercise of sovereign rights is increasingly limited by the gradual development of international minimum standards of conduct that apply to all nations (Schulberg, 1979). It is argued that neither unilateral efforts nor bilateral efforts by treaty between two nations are sufficient to ensure a healthy and equitable world. There is a growing trend toward the development of international codes or agreements on minimum standards for conduct in many fields, including health (e.g., the International Code of Marketing of Breast Milk Substitutes, 1981), the environment (e.g., the Stockholm Declaration, 1972) and economic matters (e.g., the New International Economic Order, 1974). These international codes or declarations are not necessarily legally binding, but are morally and politically persuasive.

Their legitimacy is founded upon provisions of the United Nations (UN) Charter calling for international cooperation to

improve standards of living (Art. 1(2) and 55(B)). The UN Charter, which became effective in 1945, was followed in 1946 by the adoption of the Constitution of the World Health Organization (WHO). The WHO constitution authorizes the World Health Assembly to adopt international regulations in specific health areas, including that of pharmaceuticals (Art. 21 (d), (e)). The World Health Assembly can also make recommendations, which are not legally binding but are an important method of building an international consensus, while leaving actual implementation to states (Art. 23). An example of this kind of recommendation is the 1981 International Code of Marketing of Breast Milk Substitutes.

Proposals have been made for a code for the international marketing of pharmaceuticals that would be similar to the International Code of Marketing of Breast Milk Substitutes. These proposals include a 1978 World Health Assembly resolution requesting the WHO director-general to investigate the development of a code of marketing practice for the pharmaceutical industry and a 1981 UN General Assembly resolution (entitled "Exchange of Information on Banned Hazardous Chemicals and Unsafe Pharmaceutical Products") requesting the UN secretary-general and the relevant UN organs to, among other actions, "establish an adequate system for monitoring the import of unsafe pharmaceutical products of doubtful therapeutic value...." A resolution was passed by the 1984 World Health Assembly calling

for the rational use of drugs and for a meeting of experts from governments, industry and consumer groups to examine pharmaceutical marketing practices.

It is hard to determine whether these resolutions will result in an international marketing code for pharmaceuticals. However, it is clear that the intent is to establish an international minimum standard for the production, sale, export, labeling and usage of therapeutic drugs, which in turn will affect national export laws.

WHO Certification Scheme

In 1975, the WHO established a Certification Scheme on the Quality of Pharmaceutical Products moving in international commerce, and set standards for good practices in the manufacture and quality control of drugs through the Good Manufacturing Practices Act (Cone, 1983). The certification scheme requires that the relevant authority of the exporting member state certify its exported pharmaceuticals by issuing a Certificate of Pharmaceutical Products. This certificate, issued at the request of the importing state, includes two assurances:

- o that the exporting country has approved the product for domestic sale, or if it has not, why not, and

- o that the plant manufacturing the drug is subject to regular inspection and conforms with standards set by the WHO in its Good Manufacturing Practices Act.

The U.S., along with at least 100 other countries, participates in the certification scheme, and thereby facilitates the use of appropriate testing standards and adequate facilities.

and ensures that the manufacturers comply with the WHO's Good Manufacturing Practices Act.

Consistent with the principle of international comity, the relevant health authority of the importing country is provided with the information it needs to make its own independent judgment as to whether to authorize domestic sale. If the importing country considers the certification procedure inadequate, it can apply to the exporting country for further information. This certification scheme enables countries to import drugs without establishing their own expensive control and evaluation facilities. Although the problems of relying on exporting countries are still present, importers can expect a degree of certainty in the quality of the imported drug.

The use of international standards begins to alleviate the problems of variance in standards between countries. Nonetheless, the importer still needs to set its own threshold for quality and to compare it with the claimed standards of the exporter. The success of this international agreement for coordination to ensure quality pharmaceuticals depends upon the voluntary compliance of its member states. In addition to U.S. participation in the WHO certification scheme, the U.S. regularly submits information on drugs and U.S. regulatory actions to the WHO for subsequent dissemination in the WHO Drug Information Circular and the WHO Drug Information Bulletin.

Opposing Views on Export Policy

In the debate in the past decade over the export of nonconforming products, including nonconforming contraceptives, the positions taken by interested parties have fallen along a continuum that runs from an extremely paternalistic stance to a position of extreme sovereignty (Duby, 1982).

The advocates of paternalism rely on the state responsibility doctrine and international minimum standards to argue that the U.S. should not export products that are not approved for sale domestically. They argue that to do otherwise would create a double standard of treatment between U.S. citizens and citizens of other countries. They further buttress their position by the alleged need to "protect" the health of U.S. citizens who travel abroad. Another argument used by advocates of paternalism is that importing countries, particularly those of the Third World, have inadequate drug regulatory control mechanisms. In particular, it is argued that many countries have neither the legislation required nor the enforcement mechanisms necessary to ensure the promotion of drugs only for the indications for which they are approved.

The proponents of respect for national sovereignty stress that the principle of comity requires respect for the rights of nations to decide for themselves whether their citizens may use a particular drug, regardless of the regulatory status of that drug in the exporting country (Phelps, 1982). They argue that it is a

matter not of double standards, but of a standard that best enables countries to decide what medicines they will import on the basis of their own assessment of their own health needs, the diseases and health-related characteristics of their populations, the nature of their health care delivery systems, the availability of treatment alternatives and their own evaluation of risk-benefit potential. Proponents of this position argue that if an importing country wants to have the same approval standards as the exporting country, it can adopt a country-of-origin rule, as many countries have. This rule allows the import of drugs only if approved in the country of origin, that is the manufacturing country. Advocates of this approach maintain that for health reasons generally and for compliance with international minimum health standards, it is better to have regulatory control over the export of unapproved drugs than to have no control at all. Currently, American drug manufacturers establish subsidiaries in countries from which unapproved new drugs are legally exportable to avoid the existing U.S. prohibition against export of unapproved new drugs.

Legislative Models

There have been several legislative proposals since 1979 that serve as useful models for legislation on the export of drugs and devices. Most proposals have attempted to apply the same conditions that are presently required for the export of nonconforming devices to the export of nonconforming drugs, and

they have typically added other conditions for the export of new drugs. For example, the Drug Regulation Reform Act, introduced into the 95th Congress (1979) but never passed, provided that export of all drugs except those approved for domestic commerce would require a permit. This bill established procedures for applying for and granting or denying an export permit, and provided for cooperation with foreign governments through exchange of information and training.

A more recent example of a legislative initiative is a bill introduced by Senators O.G. Hatch and D. Quayle into the 98th Congress (1984). This bill would amend the FDC Act to establish conditions for the export of "new drugs" specifically, in contrast to other bills which deal with drugs generally. Hatch and Quayle's bill, entitled the Pharmaceutical Export Amendment Act of 1984, is designed to allow the export of new drugs that foreign governments have approved for marketing in their jurisdiction but that have not been approved for use in the U.S. It provides for safeguards to prevent the dumping of unsafe or ineffective products in foreign countries. It does this by allowing the export of an unapproved drug when either of the following two conditions is met:

1. The drug is exported to a country listed by Health and Human Services (HHS) as one with an adequate governmental health authority to approve such drugs. The bill lists the following countries as having regulatory agencies regarded as adequate by a broad range of experts in the field: Australia, Canada, Federal Republic of Germany, France, Japan, Sweden, Switzerland, United Kingdom. This list is not meant as exhaustive, but as one that the HHS Secretary

can expand or contract depending on whether the Secretary determines that a country meets the criterion.

2. The drug is exported to an unlisted HHS foreign country that has provided documentation that the drug can be lawfully offered for sale provided four requirements are met:

a. The drug is approved by any one of the HHS-listed foreign countries, and the labeling for the drug is approved by a listed foreign country. (This provision is to ensure that labeling changes will not involve the addition of indications or other claims not permitted by the listed country; the deletion or revision of warnings, contraindications and adverse reactions; or any other changes that might relate to the drug's safe and effective use.)

b. The drug is subject to an exemption for investigational use, or an application for approval has been submitted to or approved by the FDA, or there is an outstanding notice from HHS stating that the drug nonetheless promotes the public health of the importing country.

c. The drug has completed the FDA pharmacological clinical testing requirements (phase I), and is ready for further testing under the next phase. (This ensures FDA surveillance of an unapproved new drug.)

d. Within 60 days of notice of intent to export, the drug has not been declared by HHS to be contrary to public health and safety of the importing country.

In addition to the above provisions, the bill sets forth the following eight conditions that any new drug must meet before being exported to any country, whether or not HHS-listed:

- o The drug is not subject to recall in the U.S.,
- o The drug is not the subject of a notice by HHS determining that the manufacturing in this country presents a significant risk to public health and safety in this country,
- o The drug is not subject to an action of a drug regulatory authority in an HHS-listed country determining it is unsafe or ineffective,

- o The drug accords with the specifications of the foreign purchaser,
- o The use of the drug is not in conflict with the laws of the importing country,
- o The outside of the shipping package is labeled to indicate that the drug is intended for export and is not approved for commercial marketing in the U.S.,
- o The drug has not been, and is not being, introduced or offered for introduction into domestic commerce, and
- o The drug is the subject of a notice of intent to export submitted to HHS at least 60 days prior to the date of first export to each foreign country. The notice must describe the drug, identify the establishment where it is manufactured for export and state that the use of the drug does not conflict with the importing country's laws.

Thus, there are eight conditions that must be met for the export of an unapproved drug to a listed country, and twelve conditions that must be met for the export of an unapproved drug to an unlisted country. Remaining provisions require HHS to establish procedures to inform foreign governments about U.S. drug regulatory actions and to respond to requests for additional official information on drugs.

This bill would permit the export of several different types of contraceptives. These include contraceptives that have been approved under specific conditions and with specific labeling in the U.S., but which are translated or labeled for other uses or in different ways for distribution abroad. For example, it would apply to a new contraceptive drug approved in the U.S. whose labeling is translated into a foreign language and otherwise is changed to meet the regulatory requirements and conditions of a

foreign country before it is exported. In addition, the bill would apply to a new contraceptive that is approved in final dosage form in the U.S., but is shipped abroad in an unfinished form. Currently, a drug in an unfinished form which has to be further processed or packaged for final dosage is regarded by the FDA to be an unapproved new drug. Finally, the bill would allow the export of contraceptives that are not yet approved under any conditions and are thus not used at all or are used only for investigational purposes in the U.S. For example, it would apply to a new contraceptive that is exportable to a country for approved uses there or to a listed country, but is not yet approved for any use in the U.S.

This 1984 Pharmaceutical Export Amendment Bill provides a useful legislative model, which balances the interests in the export of safe and effective new drugs with the health needs of importing countries.

Conclusion

An ideal export policy is one that consistently balances respect for the sovereignty of other nations with an exporting nation's responsibility not to knowingly inflict potentially hazardous drugs and devices on citizens of importing nations. Moreover, such a policy should be uniform with regard to the export of unapproved drugs and devices. Thus, the question becomes how and under what conditions exports should be permitted. The overriding goal has to be informed choice (Shaikh

and Reich, 1981). The U.S. has to provide the information necessary for an importing nation to make an informed choice as to whether the imported product would enhance the health of its citizens.

In order to achieve the goal of informed choice, the following provisions might serve as useful guidelines to the export of unapproved new drugs and devices.

1. The export of unapproved new products that pose a substantial threat to the health and safety of any person should be prohibited.

Current law on the export of unapproved new drugs and medical devices prohibits the export of such products, and the law should continue to do so. A further safeguard against the export of drugs contrary to international minimum standards of safety and effectiveness is that countries exporting such drugs, while not necessarily legally liable, would be morally and politically liable, with the consequent inhibition or prevention of such exports.

2. Permission should be granted for the export of unapproved new products that meet threshold safety and effectiveness requirements, and that clearly contribute to the health and safety of persons within the importing nation.

While the FDA weighs the extent to which the benefits of not introducing a product outweigh the resulting potential therapeutic loss of treatment for its own citizens, countries seeking the

therapeutic benefit of a new drug should not be prevented from obtaining it. For example, when the copper IUD 380 had successfully completed phase 2 clinical trials, which attested to its basic safety and effectiveness, a number of countries with full knowledge of those results chose to import it before it completed the FDA regulatory process. That choice should have been respected, but was not because of the FDC Act prohibitions. The copper IUD 380 has now been approved by the FDA.

3. Information on the safety and efficacy of the unapproved new product should be provided to importing nations and relevant institutions.

This is necessary for governments to make an informed choice about whether to import a new product and for those cooperating in their deliberations, such as the WHO. Provision of information on predictable and foreseeable risks is necessary for risk-benefit assessments, which are particularly important for countries with different risks associated with pregnancy and limited alternative contraceptive options.

4. Safety and efficacy of unapproved new products whose export is permitted should be monitored, and export suspended if it becomes contrary to public health.

usually establish subsidiaries in other countries where export is permitted, thus avoiding FDA regulations. If export of new drugs that have completed phase 1 of the FDA clinical trials were permitted, as proposed by the Hatch and Quayle bill, then the FDA could monitor the export.

5. Deceptive practices by U.S. manufacturers should be strictly prohibited by applying relevant domestic quality control, labeling and promotional standards to exported products.

U.S. manufacturers currently can avoid domestic quality control standards by establishing subsidiaries in other countries. By enabling the export of unapproved new drugs, deceptive practices of U.S. manufacturers can be more readily deterred. This is particularly important because manufacturers have been known to promote drugs for a wider range of indications in developing countries than is allowed in developed countries, and to omit mentioning side effects in promotional literature.

In conclusion, it may be noted that these guidelines currently form the basis of export regulations for new medical devices. They could usefully be applied to new drugs to establish a uniform policy with respect to the export of unapproved new drugs and devices that meet a minimum threshold of safety and effectiveness. To ignore the inconsistencies in current export policy and to avoid molding a more uniform policy

will result in the denial of potential therapeutic benefits of existing and emerging contraceptives to citizens of requesting nations.

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