

June 1, 2004

Vice Admiral Richard H. Carmona, M.D., M.P.H., F.A.C.S.
Surgeon General
U. S. Department of Health and Human Services
c/o Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**RE: Prescription Drug Importation; Docket No., 2004N-0115;
(69 FR 12810, March 18, 2004)**

Dear Dr. Carmona:

On behalf of the Healthcare Distribution Management Association (HDMA), thank you for the opportunity to provide written comments on the issues related to the importation of prescription drugs. These comments are in addition to the oral testimonies we presented to the Task Force on April 5th and April 14th. HDMA is a national trade association representing full-service distribution companies responsible for ensuring that billions of units of medication are safely distributed to tens of thousands of retail pharmacies, hospitals, nursing homes, clinics, and other provider sites across the United States.

HDMA recognizes the extreme importance of this study of drug importation and commends you and the Health and Human Services' (HHS) Task Force on Drug Importation for the monumental efforts you have undertaken to date. We hope these comments provide constructive input into your assessment of this serious public health issue.

Healthcare Distribution Management Association
Formerly National Wholesale Druggists' Association (NWDA)

A. PATIENT SAFETY

As stated in our earlier presentations, when considering the feasibility of importation, the paramount concern is to ensure patient safety. With that in mind, HDMA believes there are six key safety areas that any approach to importation must address:

1. **Product Authentication.** When our citizens order their medications, they must be assured they receive the drugs in the exact specifications their physicians require. This sounds simple yet products are produced differently for different markets, based on differing standards. In addition to legal differences in same-brand-name pharmaceuticals, we know that counterfeiting is a much more pervasive criminal activity outside the United States so a greater level of security is necessary to guard the U.S. pharmaceutical supply channel and patients against the effects of this insidious practice.
2. **Product Integrity.** When a patient is in need of a medication, there should never be a question about the strength or safety it possesses. We cannot allow a system to be developed that does not properly address the multitude of factors that cause degradation of pharmaceuticals. Climate control, safe handling practices and strict adherence to manufacturer specifications are just a few of the important ways wholesalers protect the integrity of the U.S. drug supply.
3. **Availability of Supply.** The strong demand for a small supply of drugs available for importation may result in inadvertently encouraging the production of substandard, or even counterfeit, products.
4. **Recalls.** Under the U.S. domestic drug supply system, there are FDA-regulated procedures for determining and carrying out product recalls if a safety concern is found after the product has reached the market. A recall process would have to be developed for imported products.
5. **Repackaging and Relabeling.** Imported products will likely be packaged and labeled according to the requirements of the country of origin or intended use. Therefore, products will need to be repackaged and relabeled, including translation into English, to meet U.S. specifications. This additional step must be conducted in such a manner as to assure the product is not damaged or otherwise rendered unsuitable for U.S. consumption.
6. **Bioterrorism.** The potential for use of the drug importation and distribution system as a mechanism for causing harm within our borders also deserves very careful consideration prior to allowing importation.

1. PRODUCT AUTHENTICATION

It must be assured that any imported drug is the U.S.-formulation of the product and made in a U.S.-approved manufacturing facility. To avoid any chance that an imported product is counterfeit, substandard, or otherwise unsuitable for U.S. patients, it is imperative to determine these two critical factors.

Product testing has been identified as a means to verify authenticity, but this method will fall short if tests do not consider both the active and inactive ingredients, which make up the total formulation of the drug. To ensure the imported drug is the U.S.-approved formulation made in a U.S.-approved plant requires either certification from the manufacturer or analytical testing for all the inactive ingredients. Ensuring the imported drug was made in a U.S.-approved facility would require manufacturer certification. Similarly, authentication of the active ingredient would need to be certified, which would require comprehensive profiling of the imported product or certification from the manufacturer.

In addition, since we know that counterfeiting is a random event, total protection against counterfeit drugs from entering the U.S. market would require that every lot from every shipment would be tested, not just random samples. Considering the sophistication of the testing and the frequency with which it would have to be done, this would be costly; we estimate as much as \$15,000 per sample. (See Attachment 1)

2. PRODUCT INTEGRITY

While the challenge of authenticating imported supply is significant, assurance of product integrity is perhaps even more complex and multifaceted.

In the U.S., there are stringent storage and recordkeeping requirements to assure that adulterated product (that is, product that may have degraded due to improper handling along the way) does not enter the marketplace. This includes strict temperature and humidity controls. These requirements are unique to the U.S. and parity with these types of requirements may not exist in foreign countries. As a result, there are no guarantees as to how product coming in from foreign countries has been stored and handled and no way to guarantee, even through testing, that such product will continue to meet U.S. and FDA efficacy standards through its expiration date.

Therefore, if importation were to occur, there must be rigorous regulatory standards, registration requirements and inspection programs. These standards should be designed to ensure that all those engaged in exporting and importing pharmaceuticals, including Internet pharmacies, can be readily identified, are qualified, and possess the skills, infrastructure and interest to protect the integrity of the supply chain commensurate with U.S. standards.

Furthermore, importation should only be done at the wholesale level and then, through a linear channel, (i.e. product should flow from manufacturer to exporter to importer to pharmacy to patient) in order to provide additional security and product integrity controls on imported medicines. Patients importing pharmaceuticals for their own personal use do not have the expertise to determine if a drug is counterfeit, adulterated or misbranded or if the drug was manufactured in an FDA-approved facility with an FDA-approved formulation. They would also have no way of knowing the country of production of their

drugs when importing on their own. Moreover, personal importation also raises questions about self-medication and potential unknown drug interactions if the patient's health team is not involved or aware that these drugs are being taken.

3. AVAILABILITY OF SUPPLY

Another issue that must be addressed is product supply and demand. There will likely not be enough products to meet domestic demand under importation. For example, U.S. pharmacists fill about 10 times the number of prescriptions as are filled by their counterparts in Canada. An environment of strong demand, with low supply from Canada or other approved exporting countries, would open the door for transshipment of prescription drugs from other areas of the world and likely attract diverted, counterfeit, sub-potent and adulterated products.

4. RECALLS

While HDMA believes that the safety issues described above are the most important to address, HDMA has identified a number of other critical safety considerations. This includes the safety features incorporated into U.S. policies and regulations under the current FDA managed system for "product recalls."

Systems are in place today to facilitate domestic product recalls that are initiated by the manufacturer and processed by distributors and pharmacies. When dealing with foreign imports, it will be critical to ensure that the FDA has the authority and resources to apply the same level of oversight to international product recalls as they have to domestic product recalls. Foreign manufacturers should be held to the same standards for evaluating when a product should be recalled as is currently done in the U.S. This leads to a number of questions, such as:

- ?? Who will have responsibility for initiating, regulating and monitoring international recalls? The agency equivalent to the FDA in the country of production? The foreign manufacturer? The U.S. FDA?
- ?? Will FDA have jurisdiction and oversight over the foreign firm's recall plan, to make sure recall information is disseminated to the U.S. in a timely manner, is directed to the appropriate audiences, and includes an understandable translation?
- ?? How will post-marketing complaints and adverse event reports be gathered and assessed?
- ?? What will happen if foreign originated product is recalled but its domestic counterpart is not (or vice-versa)—will this require distributors and pharmacies to maintain separate inventories in order to distinguish one from

the other? If so, this implies a whole new set of procedures and costs that should be factored into your study.

5. REPACKAGING AND RELABELING

Imported products may have to be repackaged and relabeled to meet FDA specifications. This in turn means ensuring that the product's label that may appear in a foreign language is now accurately translated into English. In the alternative, this means conforming English language labeling to meet FDA requirements.

Furthermore, the labeling requirements become more problematic when dealing with product sourced from locations outside Canada. Generally, products sold in Europe come in blister or unit dose packaging. The expiration dating for those products is determined by a foreign jurisdiction based upon packaging components used in that country. This dating determination may not be in accord with the time parameters set forth by the FDA in the U.S. Thus, there may be a discrepancy on how long the product can be used by consumers regardless of how they are originally labeled. Additionally, the English language labeling requirements become more difficult to address if product is from sources where blister or unit dose packaging is predominately used.

The repackaging of blister packages is a more laborious process subject to more opportunities for error. Moreover, FDA's position on the repackaging of unit dose product into other unit dose packaging limits that product's expiration dating to six (6) months dating unless costly stability studies are conducted to validate that longer expiration dating is warranted.

All of these steps are critical, and they will result in additional time in getting drugs to the patient and have costs associated with them that also need to be factored in.

6. BIOTERRORISM

The potential for using drug importation as a route for a terrorist organization to threaten the United States was discussed during the Task Force's public meetings. It is a significant concern and cannot be overemphasized. Bioterrorism represents a unique safety concern since it is not merely a criminal act of greed, as they would be well planned attacks with the expressed purpose of doing harm.

As FDA Deputy Commissioner Lester Crawford pointed out when asked to comment on "whether reimportation (from Canada) now raises greater challenges than it did previously [to September 11, 2001]" and "what is your view... [of the] safety of drugs for the consuming Americans?"

The problem would be if it becomes apparent to the rest of the world, including the world of terrorists, that we are not interdicting shipments

of drugs that come from Canada...I think this is a signal to a would be terrorist that this might be a way to enter the United States.... It also would be a signal to...the transshippers and these would be people in various countries that may not have a regulatory system or may not have a regulatory system for exported drugs...¹

Thus, it is certain that opening up our borders to the purchase of substances that are intended for human consumption means that we are exposing the U.S. to a unique form of vulnerability.

HDMA is aware that the Task Force has already consulted with various U.S. governmental agencies and departments that would be involved in a drug importation program including the U.S. Customs and the Justice Departments. However, if there is a decision to allow importation, we urge full partnership with the Department of Homeland Security in defining the security and regulatory requirements that will accompany importation.

B. COST FACTORS

In addition to the costs associated with the safety concerns we have addressed above-- product authentication, product integrity, product availability, recalls, repackaging and relabeling and bioterrorism-- there are still additional cost elements that must be factored in when considering the feasibility of a drug re/importation program. The four factors we address in detail include:

1. **Liability.** With importation, distributors may experience an increased level of liability exposure, because of the increased risks and responsibilities involved, and the differences in the way the U.S. laws would apply to imported products vs. domestic ones.
2. **Documentation and Recordkeeping.** Imported products will require new and extended documentation and recordkeeping to be able to identify the imported products, e.g., to identify recalled products and to verify of the products' source.
3. **Treatment/Allocation/Reimbursement.** Determining which patients receive which products i.e., domestic versus imported, raises additional questions such as how to ensure that patients receive the formulation specified by their physician, determining who will be entitled to the "lower cost" product, and how insurance or Medicare/Medicaid reimbursement will be handled.
4. **Customs and other Cost Factors.** HDMA has provided a list of such additional factors as customs fees, tariffs, and other associated importation expenses that will impact the total costs.

¹ March 21, 2002 House Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration and Related Agencies hearing.

1. LIABILITY

Liability issues are likely to become a significant cost factor in determining whether a drug importation program should be developed. As with any activity involving the handling and sale of consumer products, patterns of liability develop over time and through insurance actuarial analysis and claims experience. The roles and functions of drug distributors are well established, and so is their product liability exposure. As drug distributors undertake new roles and functions in importing or reimporting pharmaceuticals, their liability exposure will likely increase.

Increased liability exposure is a particular and expensive concern when an importing distributor is put in a position of new and expanded responsibilities. This could include, for example, authenticating the product, ensuring the integrity of the product when it has come from a source outside the U.S. with no assurances as to whether the product was appropriately stored and handled, and facing additional risks as a result of a substantial likelihood of an increasing number of drug counterfeits getting into the U.S. pharmaceutical distribution channel. Moreover, the importer could be held liable for product manufacturing or performance defects, especially if such problems are difficult to distinguish from those that may occur during handling.

There are other forms of liability that will become more significant should importation become commonplace. For example, the importer may be at increased risk if the original product producer does not want an importer to buy a product at a lower price from a foreign country and sell it at a higher price in the U.S. and can make a case that their product patent rights have been violated. An importer may also be at risk of violating trademark and/or copyrighting laws when the imported product is repackaged and relabeled, and that risk may be exacerbated when language translations are involved.

Currently, most domestic distributors are indemnified by the drug manufacturers they do business with due to the controlled nature of the U.S. supply system. However, if importation becomes a reality, this indemnification would likely disappear. Manufacturers understand that importation, even if it is limited to Canada, will diminish the oversight and protections that characterize the U.S. prescription drug supply system. U.S. manufacturers are not likely to indemnify distributors dealing with products that may or may not have been manufactured by them.

Based on the above considerations, the distributor may need to factor higher litigation costs, or higher costs for measures to avoid these forms of liability (e.g., additional records, legal consultation, etc.) into their total costs of importation.

2. DOCUMENTATION AND RECORDKEEPING

Once a decision is made to import product from a foreign source, the importer may be required to obtain documentation from foreign suppliers all the way back to the manufacturer of the imported goods. The required information is likely to include the amount of product in each lot received by the importer, documentation from the foreign exporter that they received the product from the manufacturer, and other documentation about the product shipped from the manufacturer to the exporter. It is uncertain whether these records would be readily available, as other countries often do not require that such records be kept.

The importer may also be required to confirm that the imported product has been appropriately stored and handled by foreign suppliers. Because other countries do not necessarily adhere to the strict storage and recordkeeping requirements that we have in the U.S., there is no way to guarantee this. Even if an importer required certification from the foreign entity, back up and/or documentation to the certification may not be available if in fact a problem is found long after the product had been sold in the U.S. As a result, the distributor may be forced to bear an unreasonable amount of product liability exposure.

Because of the recordkeeping requirements associated with imported product, it may be necessary to maintain dual inventories. This also involves a whole new set of administrative and operating procedures and costs. Identical products with different and/or redundant processes for ordering, receiving, invoicing, handling returns and recalls, and many other steps will only serve to put additional pressure on drug distributors' already slim net profit margins of 0.73 percent.

3. TREATMENT/ALLOCATION/REIMBURSEMENT

Another significant issue that must be addressed will be who receives the imported products, and how reimbursement will be determined.

Care must be taken that the patient receives the exact formulation prescribed by the patient's physician, which may involve additional administrative tracking costs on the part of the importer and the pharmacy. Also significant will be determining which patients will be offered the "lower cost" drug, and whether the same lower cost drug will be available to the same patient if refills are required. Even if the policy and medical treatment implications of offering different priced drugs for the same prescriptions and/or patients can be addressed satisfactorily, there are significant cost implications. The need to ensure that the same patients are given the same drugs with the same formulations during the course of their therapy will likely reinforce the need for dual inventories discussed previously. Importers, pharmacies, and payers, including Medicare and

Medicaid, may also be expected to keep multiple product payment tracking systems to accommodate reimbursement requirements.

All of these complex administrative issues are likely to add to the increased cost of offering imported products to U.S. patients.

4. CUSTOMS AND OTHER COSTS

As evidenced at the public meetings, one of the Task Force's greatest challenges will be to determine the total costs of an importation program and whether the consumer will actually receive the anticipated benefits.

From the distribution perspective, for example, distribution costs for storage space and segregation mechanisms will certainly be significant. In order to offset the increased inventory costs, the importer could be forced to increase the selling price for these products. This would be one more factor that could mitigate the cost differential being sought.

Customs requirements are also a factor, since a product must go through customs before it can enter the U.S. Related cost items that must be considered include:

- ?? Bonds required by customs for the payment of liquidated damages in the event of default;
- ?? Broker fees;
- ?? Expenses incurred by government officers or company employees responsible for the destruction, supervision of relabeling or other required action;
- ?? Customs' storage expenses in connection with the storage, cartage or labor for articles refused immediate admission;
- ?? Attorney's fees if product is detained for any reason.

HDMA has identified further costs that we have not discussed at length, but we recommend factoring into the Task Force's analysis, including:

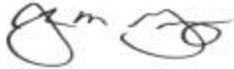
- ?? Import license fees;
- ?? Tariffs;
- ?? Costs of expenses of government officers or employees in connection with the destruction, supervision of re-labeling or other action conducted;
- ?? Cost of transportation of product;
- ?? Inventory costs associated with quarantining product if testing is required;
- ?? Destruction/appropriate handling of adulterated product, and
- ?? Potential new state requirements such as a different type of license to import, certificates of authenticity, etc.

SUMMARY/CONCLUSION

In summary, patient safety must be the paramount concern in the determination of whether or not a drug importation program should be instituted. Distributors are best positioned to help maintain the integrity and security of the national drug supply. However, importing product from foreign sources introduces significant challenges that must be addressed to ensure the broad safety of imported products while maintaining the desired cost benefits for consumers. Limiting commercial re/importation to products in a particular country or select list of countries does not preclude the likelihood of counterfeit or adulterated drugs entering the United States and assuring patient safety in any re/importation scenario is likely to be very costly. Before the green light is given to importation, the safety, liability logistics and cost issues we have discussed above should be thoroughly evaluated by this Task Force.

We extend our appreciation for the opportunity to share our views with you and the Task Force. If you have any questions, please do not hesitate to contact us.

Sincerely,

A handwritten signature in black ink, appearing to read 'John Gray', with a stylized flourish at the end.

John Gray
President and CEO

Scope of Product Authentication Testing

In order to confirm that a drug is the authentic U.S. product, it is critical to establish three essential conditions.

- (1) The drug was made with the U.S. approved active ingredient manufactured by the plant and process approved for the U.S. market.
- (2) The drug was manufactured with the inactive ingredients in proportions and amounts approved for the U.S. formulation.
- (3) The drug was manufactured by a plant and process approved for the U.S. market.

Testing should be designed to confirm primarily that conditions (1) and (2) have been met and that the drug is the genuine U.S. approved product. Proving either condition will require sophisticated testing as outlined below.

<u>Condition</u>	<u>Testing</u>
(1) Confirm that the drug was made with the U.S. approved active ingredient made by the U.S. approved plant and process	?? LCMS to fingerprint the active ingredient in the product and to confirm the impurity profile matches the active ingredient in the genuine U.S. product. ?? Capillary Electrophoresis (CE) used in combination with or as an alternative to LCMS to fingerprint the active ingredient and to confirm the impurity profile matches the active ingredient in the genuine U.S. product.
(2) Confirm the drug was made with the U.S. approved formulation of inactive ingredients and U.S. approved process.	?? HPLC, GC, FTIR, and NMR used in various combinations to confirm that the inactive ingredients in the product match the U.S. approved formulation for the product. ?? Dissolution profile to establish that the product behaves similar to the U.S. approved product. ?? Microbial quality to confirm liquid products are aseptic.

This type of testing would be both time consuming and expensive, totaling possibly as much as \$15,000 per sample. The challenge of such a scheme is that it would have to be applied to each lot of each product received in every shipment by the importing entity. The introduction of counterfeit drugs into the pharmaceutical supply chain has been a random and unpredictable event in the past. The only way the American consumer could be reasonably protected against a counterfeit drug under these circumstances is to conduct testing on every shipment as outlined.