



# The Bioterrorism Act

## Its Effect on the Import and Registration of Pharmaceutical Excipients

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Two interim final rules issued by FDA in response to the Bioterrorism and Response Act of 2002 are reviewed with respect to their impact on the excipients industry. The rules, **Registration of Food Facilities and Prior Notice of Imported Food Shipments**, include information about many materials used as excipients and therefore threaten to impact the supply chain.

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September 11, 2001 changed our lives forever. We all became acutely aware of our vulnerability and of the devious and previously unthought of acts of terrorism that could be launched against us. In response, the United States has taken steps to protect its citizens and its borders, including the development of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act). This initiative directs the Secretary of Health and Human Services (HHS) to take steps to protect the public from a threatened or actual terrorist attack on the US food supply. To carry out the provisions of the Bioterrorism Act, FDA published two interim final rules on 10 October 2003. The first, *Registration of Food Facilities*, requires domestic and foreign facilities that manufacture, process, pack, or hold food for human or animal consumption in the United States to register with FDA. The second, *Prior Notice of Imported Food Shipments*, requires that prior notice of food shipments be received and confirmed by FDA no more than five days before arrival.

### Clarifying the definitions

To understand the link between these requirements and excipients one need only look at the definition of *food* provided by the rules. For purposes of the interim final rules, *food* is defined by reference to section 201 (f) of the Federal Food, Drug, and Cosmetic (FD&C) Act. Section 201 (f) defines *food* as articles used for food or drink for humans or animals, chewing gum, and articles used for components of any such articles.

Examples of food include the following:

- dietary supplements and dietary ingredients
- infant formula
- beverages, including alcoholic beverages and bottled water
- fruits and vegetables

- fish and seafood
- food additives
- dairy products and shell eggs
- raw agricultural commodities for use as food or components of food
- canned and frozen foods
- bakery goods, snack food, and candy, including chewing gum
- live food animals
- animal feeds and pet food.

The following foods are excluded from the prior-notice requirement:

- food carried by or otherwise accompanying an individual arriving in the United States for that individual's personal use (i.e., for consumption by him or herself, family, or friends and not for sale or other distribution)
- food that is exported without leaving the port of arrival until export
- meat food products, poultry products, and egg products that are subject to the exclusive jurisdiction of the US Department of Agriculture under the Federal Meat Inspection Act, the Poultry Products Inspection Act, or the Egg Products Inspection Act
- food that was made by an individual in his or her personal residence and was sent by that individual as a personal gift (i.e., for nonbusiness purposes) to an individual living in the United States.

Several excipients can be categorized as food additives, dietary ingredients, or raw agricultural commodities for use as food or components of food. Examples of two such excipients are gelatin and glycerin. Gelatin has widespread use in the manufacture of capsules, and the use of glycerin in pediatric formulations has been a topic of concern.

In general, if a particular grade of an excipient were to be marketed strictly for pharmaceutical applications but also had food-additive applications, then it still would be considered a food additive under the definitions stated in the law. It would be difficult, for example, for a customs inspector examining a shipment at the border to determine the difference between sugar for use in food from sugar (sucrose) for use in drugs. Therefore, most excipients will be implicated by the new regulations, and it is important that both the suppliers and the users of these materials have ap-

appropriate action plans for complying with these requirements. Otherwise, the timely delivery of excipient products throughout the supply chain may be affected.

### Requirements of the interim final rules

To better understand the potential effect on the excipients industry, let's look at the key requirements established by the two rules. First, the stated intent of the rules is that they will allow quick identification and notification of food processors and other establishments involved in any deliberate or accidental contamination of food. As observed by HHS Secretary Tommy G. Thompson, "By requiring advance notice for imported food shipments and registering domestic and foreign food facilities, we are providing critical new tools for FDA to identify potentially dangerous foods and better keep our food supply safe and secure. These new requirements represent the latest steps in our ongoing efforts to respond to new threats and improve the safety of all the foods that we eat in this country."

The *Registration of Food Facilities* requires domestic and foreign food facilities that manufacture, process, pack or hold food for human or animal consumption in the United States to register with the agency by 12 December 2003. As a result, for the first time FDA will have a complete roster of foreign and domestic food facilities. The requirements will enable FDA to quickly identify and locate affected food processors and other establishments in the event of deliberate or accidental contamination of food.

FDA expects nearly 420,000 facilities to register under this requirement. Facilities that must register include domestic or foreign facilities that manufacture, process, pack, or hold food for human or animal consumption in the United States. In addition, a foreign facility must designate a US agent (e.g., a facility's importer or broker) who must live or maintain a place of business in the United States and be physically present in the United States for purposes of the registration. Facilities that are not required to register include

- private residences of individuals
- non-bottled-water drinking-water collection and distribution establishments and structures

- transport vehicles that hold food only in the usual course of their business as carriers
- farms
- restaurants
- retail food establishments
- nonprofit food establishments
- fishing vessels
- facilities regulated exclusively and throughout the entire facility by the US Department of Agriculture.

Registrants must use Form 3537 to register or update a registration. Facilities can register on-line at [www.fda.gov/furls](http://www.fda.gov/furls). In addition, a registration help desk can be accessed by doing the following:

- In the United States, call 1.800.216.7331 or 301.575.0156.
- Outside of the United States, call 301.575.0156
- Fax questions to 301.210.0247.
- E-mail questions to [furls@fda.gov](mailto:furls@fda.gov).

These phone numbers are staffed on business days from 7:00 am to 11:00 pm, US Eastern Time.

If a facility does not have reasonable access to the Internet, a paper copy of the form may be obtained from FDA by calling 800.216.7331 or 301.575.0156 or by mailing a request to

US FDA, HFS-681, 5600 Fishers Lane, Rockville, MD 20857, USA

When the form has been completed, it must be mailed to this address or faxed to 301.210.0247. Registrations for multiple facilities may be submitted to FDA on a CD-ROM.

Failure of a domestic or foreign facility to register, update required elements, or cancel its registration in accordance with this regulation is a prohibited act under the FD&C Act. The federal government can bring a civil action to ask a federal court to enjoin persons who commit a prohibited act, or it can bring a criminal action in federal court to prosecute persons who are responsible for the commission of a prohibited act. If a foreign facility is required to register but fails to do so, then food from that foreign facility that is offered for import into the United States is subject to being held at the port of entry unless otherwise directed by FDA or the Bureau of Customs and Border Protection (CBP).

FDA plans to issue enforcement guidance on its policies regarding the refusals of imported food under section 801(m)(1)

or holds of imported food under section 801(l) of the FD&C Act. This guidance document will be available to the public, and FDA will publish a notice of its availability in the *Federal Register*.

It's possible that some facilities may not be clear about the need to register. Many chemical substances have multiple uses, and the manufacturer may or may not be aware of the use of the substance as a food, excipient, or both. This leads to the potential for confusion and the possibility of the material being held at the border, which results in delays in the supply chain for pharmaceutical applications.

If in doubt, register!

Once a facility determines that it must register and does so, it must comply with further requirements concerning which changes trigger the need to update the registration information (e.g., changes in ownership). In addition, these updates have timing requirements. The rule should be reviewed in detail to ensure compliance with these requirements.

The *Prior Notice of Imported Food Shipments* rule requires that notice be received and confirmed electronically by FDA no more than five days before arrival and, as specified by the mode of transportation below, no fewer than

- two hours before arrival by land by road
- four hours before arrival by air or by land by rail
- eight hours before arrival by water
- The time consistent with the timeframe established for the mode of transportation for an article of food carried by or otherwise accompanying an individual if it is subject to prior notice. The food also must be accompanied by FDA confirmation.

In addition, prior notice must be received and confirmed electronically by FDA before food is mailed by international mail. In such cases, the parcel must be accompanied by confirmation of FDA receipt of prior notice.

Prior notice must be submitted electronically. FDA estimates that more than 80% of prior notice of imported-food shipment submissions can be transmitted through automated broker interface of the automated commercial system (ABI/ACS). Prior notice for international-mail food shipments, other transaction types that cannot be made through ABI/ACS, or articles

of food that have been refused admission under section 801(m)(1) of the FD&C Act must be submitted to the FDA prior notice system interface at [www.access.fda.gov](http://www.access.fda.gov). Technical assistance for submitting prior notice may be obtained as follows:

- In the United States, call 800.216.7331 or 301.575.0156
- From outside the United States, call 301.575.0156

- Fax to 301.210.0247.

Technical assistance will be available on business days from 7:00 am to 11:00 pm, US Eastern Time. Requests for assistance also may be obtained by e-mailing [furls@fda.gov](mailto:furls@fda.gov). For assistance with ABI/ACS transmission, one should contact the nearest Bureau of Customs and Border Protection (CBP) client representative. Both the CBP and FDA systems for prior no-

tice are available 24 hours per day, 7 days per week for information submission.

If the ABI/ACS is not working, then prior notice must be submitted using the FDA PN system interface. If the FDA PN system interface does not appear to be working properly, the on-line help desk should be contacted first. If the system is not working, then the required prior notice information, which appears in the interim final rule and will be listed on FDA's Web site, must be submitted by fax or e-mail. The fax number(s) and e-mail address(es) where they can be sent will be posted on [www.fda.gov](http://www.fda.gov). Again, one can envision more possibilities of delays at the US border and confusion caused by the second rule.

### Agency collaborations

Recognizing the potential for delays in the flow of necessary food—including that of excipients—and remaining committed to the goal of protecting the safety and security of the US food supply, FDA has done an excellent job of responding to the many industry concerns that were raised during the comment period. In arriving at the interim final rule, FDA worked closely with the CBP to ensure that the new regulations promote a coordinated strategy for border protection.

FDA and CBP continue to collaborate on making the new safeguard of prior notice as efficient and effective as possible. For example, FDA and CBP have worked together so that most notices can be received through the existing CBP system. In addition, FDA and CBP have signed a memorandum of understanding to commission CBP employees to serve on FDA's behalf at ports where FDA may not currently have staff or to augment FDA staff in the enforcement of FDA's prior notice regulation. FDA plans to co-locate its Prior Notice Review Center and staff at CBP's National Targeting Center. This action will ensure that the agencies maximize their joint assets and provide consistent enforcement. It further engenders a common bond so that the two agencies most responsible for protecting the nation's imported food supply can interact in person.

FDA and CBP also are working together to develop enhanced information systems and programs to keep food imports secure without imposing unnecessary costs



or delays. FDA and other federal agencies continue to contribute to the development of CBP's state-of-the-art automated commercial environment system to screen products and to support FDA's public health mission.

Moreover, FDA will actively consider exercising its discretion for enforcing the prior notice interim final rule while at the same time ensuring public health protection, both during initial implementation of the interim final rule and thereafter. FDA recognizes that several affected parties still may need assistance understanding the interim final rule's requirements and how to comply with them even after its extensive outreach and educational activities efforts.

Accordingly, for this and other reasons, during the initial months following the effective date, FDA intends to put into place a policy that emphasizes assisting covered entities in understanding the requirements and how to comply. FDA will soon publish a notice of availability for a *Compliance Policy Guide* that will outline

how the agency generally intends to exercise its enforcement discretion. This guidance, however, will not affect FDA's ability to take actions that may be necessary, including conducting inspections for food safety and security concerns or taking any other action under the FD&C Act. This policy also will not affect the ability of the CBP to assess penalties under 19 USC 1595a(b) or to take enforcement action under any other authority.

### Summary

This will be a challenging period for all of us. Only through the efforts of all affected parties will this process operate as intended. Makers and users of excipients both will be affected and must work together to ensure both sides understand and comply with the requirements as needed.

In the end this is a worthwhile effort and provides an added measure of checks to ensure the safety of our products. The potential for disaster caused by contaminated (either by accident or intentional)

or counterfeit excipients is not theoretical. As previously mentioned, glycerin is an example of an artificial sweetener used in foods and as an excipient. The reality of a disaster that may happen became apparent in Haiti about seven years ago when 80 children died from a pediatric liquid preparation made with glycerin that turned out to be 24% diethyleneglycol (1). After an extensive investigation FDA determined that the material had originated from China and that it had passed through several brokers. An editorial in this journal, which appeared in April 1998, emphasized the need to trace the life cycle of all excipients and the need to confirm the adequacy of the origin and subsequent handling. These rules will provide one more tool for achieving that goal.

### Reference

1. K.L. O'Brien et al., "Epidemic of Pediatric Deaths from Acute Renal Failure caused by Diethylene Glycol Poisoning," *JAMA* **279**, 1175-1180 (April 1998). **PT**

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