Preventing poisoned pills

The Bioterrorism Act of 2002 works against sabotage of the drug supply; it also promotes and regulates R&D.

BY MARK S. LESNEY

In the developed world, the era of local medicine production is long past. Pharmacists do not grow and gather medicinal components to be prepared into drugs. And other than medical marijuana and the aloe plant on the kitchen windowsill, most individuals do not produce their own medications. To the contrary, most people in this age of urban humanity depend on manufactured and packaged drugs obtained from the pharmacy (prescription) or supermarket (OTC).

After the attacks of September 11, 2001, despite numerous regulations maintaining the routine safety of food, water, and pharmaceuticals in the United States, Congress determined that the infrastructure remained fragile when it came to sabotage and the potential for bioterrorism. The Bioterrorism Act, designed to ameliorate these threats, was passed in 2002 through a bipartisan effort led by Sens. Judd Gregg (R-NH) and Edward Kennedy (D-MA) and Reps. John Dingell (D-MI) and Billy Tauzin (R-LA). The drug-related aspects of its regulations are already in effect; more infrastructure-related provisions will come into play throughout 2004.

The provisions

The Public Health Security and Bioterrorism Preparedness and Response Act became law on June 12, 2002 (*1*). It consists of five main sections that spell out new authority for several of the most important regulatory divisions of the federal government. These sections are:

- Title I: National Preparedness for Bioterrorism and Other Public Health Emergencies,
- Title II: Enhancing Controls on Dangerous Biological Agents and Toxins,
- Title III: Protecting Safety and Security of Food and Drug Supply,
- Title IV: Drinking Water Security and Safety, and
- Title V: Additional Provisions.

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The act gave a more active role in the federal war against terrorism to the FDA, Environmental Protection Agency (EPA), U.S. Department of Agriculture (USDA), and Centers for Disease Control and Prevention (CDC).

Borne by the FDA

A key concern for the possibility of bioterrorism lies in the adulteration of drug products. Tamperproof seals and proper packaging are valid protections against postmanufacturing adulteration, but they do nothing to prevent dangerous manipulation of drugs by sabotaging the raw materials or interfering with processing.

Under Title III of the act, the FDA is given additional powers to protect the drug supply through annual registration of non-U.S. manufacturers, collection of shipping information on materials imported into the United States, and requiring non-U.S. manufacturers to provide (when necessary) additional information on the import of components intended for use in products targeted to the United States (*1*).

Tracking the provenance of drugs throughout the manufacturing process and inspecting suspicious shipments give some assurance of protecting the public, but more importantly, they also allow rapid backtracking to the source for the prevention of further distribution of adulterated drugs, enhancing the ability to locate, warn, or treat individuals at risk from exposure.

Because of the fears of bioterrorism, the FDA is also trying to expedite the development of treatments to protect against and counteract dangerous biological agents. Normally, the FDA requires clinical trials to present proof of efficacy in humans before a drug can be marketed. But under the Bioterrorism Act, this has changed significantly—at least for new drugs and products designed to counter biological agents relevant to terrorism. The FDA had been seeking similar authorization ability since 1999 for promoting treatments of deadly diseases, but it took the events of September 11, 2001, to jump-start legislative approval.

Now animal tests can be considered sufficient to prove efficacy for licensing and marketing approval when efficacy studies in humans are not feasible without endangering patients (*2*). For instance, rPA102, an anthrax vaccine developed by VaxGen (*www.vaxgen.com*) that recently received $80 million in federal funding for development, will be probed for efficacy on the basis of the FDA's two-animal protocol instead of human Phase III trials (*3*). Clinical trials, however, are still required to demonstrate that safety requirements in humans are met.

The Bioterrorism Act of 2002 set aside monies for research and development of a smallpox vaccine, and it encouraged research into relevant pathogens and countermeasures against them—with fast-tracking of approval specifically promulgated. The FDA, in fulfilling its counterterrorism role, is actively encouraging research in a variety of areas, including the submission of NDAs (New Drug Applications).

In September 2003, the FDA specifically requested NDAs for compounds that have been used experimentally to enhance excretion of plutonium, americium, and curium into the urine. To assist potential sponsors in bringing these products to market, the agency has prepared draft labeling along with guidance documents (*4*).

Stockpiling drugs

In the Bioterrorism Act, the U.S. Secretary of Health and Human Services (HHS), in coordination with the Secretary of Veterans Affairs, was given the responsibility to "maintain a stockpile or stockpiles of drugs, vaccines, and other biological products, medical devices, and other supplies in such numbers, types, and amounts as are determined by the Secretary to be appropriate and practicable, taking into account other available sources, to provide for the emergency health security of the United States, including the emergency health security of children and other vulnerable populations, in the event of a bioterrorist attack or other public health emergency" (*1*).

Included in this issue of stockpiling counterterrorism drugs are considerations related to distribution and appropriate dosing, especially for pediatric cases. In April 2003, the FDA provided a report on how, once emergency stockpiles are distributed, a parent or caregiver can prepare emergency doses at home of the antibiotic doxycycline for treating infants exposed to inhalation anthrax (*5*). Chillingly, the introduction says that "this document explains how to mix a crushed doxycycline tablet with food or a drink, which foods and drinks work best, and how much to give to a child." The fact that doxycycline permanently darkens teeth and affects bone development in children is addressed by pointing out that the alternative of not using the drug is far worse.

Monitoring the research

Under Title II of the Bioterrorism Act, it falls to the HHS (for humans) and to the USDA (for plants and animals) to share regulation and monitoring of the possession and transfer by legitimate research entities of biological agents and toxins on a designated list of materials liable to be of use to potential terrorists. As the instrument for regulation, the HHS has decided to work through the CDC, and the USDA has designated the Animal and Plant Health Inspection Service (APHIS).

Previously, the CDC operated under the Select Agent Rule (*6*), which required facilities to register with the program if they intended to transfer from one facility to another in the United States any of 38 biological agents and toxins "that have the potential to pose a severe threat to public health and safety." In updating this rule, the Bioterrorism Act made mere possession of such agents subject to registration.

One provision of the Bioterrorism Act reauthorized the 1992 Prescription Drug User Fee Act.

For both the CDC and APHIS, authority also now extends beyond a simple accounting of possessors to an evaluation and regulation of the method by which designated materials are stored and protected from potential terrorist access. The requirement for permits to possess or transport these materials provides the necessary stage for input and inspection. The initial lists of biological agents and toxins covered are located in 7 *CFR* 331.2 and 9 *CFR* 121.2 and are subject to continual updating (*7*).

Pharmaceutical pork?

One provision of the Bioterrorism Act reauthorized what many critics consider to be an inappropriate relationship between regulator and the regulated. This provision reauthorized the 1992 Prescription Drug User Fee Act, which set up a system of user fees that permits the FDA to collect money from drug and biologic companies. These fees allow the FDA to dedicate the resources needed to review new drug and biologic products within a set time frame. The reauthorization is a general one and not specifically related to drugs associated to bioterrorism.

Proponents argue that such user fees allow the FDA to hire more people and expedite the approval process without compromising safety. Critics, such as Sen. Edward Kennedy, argue that there might be unintended consequences and blame the agency for moving too quickly in some cases, especially as 9 drugs that were authorized in the past 10 years (since user fees) have had to be withdrawn because of lethal side effects. These issues were extensively discussed in a General Accounting Office analysis in September 2002 (*www.gao.gov*).

Unintended effects

The policies and procedures of the Bioterrorism Act of 2002 that are used to protect the public from acts of terrorism are also capable of enabling the rapid discovery of, and quick response to, natural or accidental incursions of deadly bacteria, viruses, pesticides, and other toxins into the drug, food, and water supply.

And, over time, the drug development provisions of the act have the potential to expand the repertoire of vaccines and prophylactics for a wide variety of human scourges. So even though the events that launched the act must be decried, the long-term benefits of some of its provisions may still protect and enhance the drug supply, even after the current troubles have subsided.

References

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(3) Cleaves, K. *Modern Drug Discov.*, Jan 2004, p 15.
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