

Bioterrorism Threat Shines Spotlight on Drug Manufacturing

Jill Wechsler

Anthrax contamination has put pharmaceutical quality and supply issues on the front page, along with patent and pricing policies.

The anthrax scare that hit the nation in October aroused public interest in numerous issues related to pharmaceutical operations. Newspapers discussed drug-supply chains, bulk ingredient manufacture, product labeling, generic equivalence, and, of course, pharmaceutical pricing. Although manufacturers emerged as heroes for providing the public with life-saving medicines, they also faced criticism for appearing to place more emphasis on protecting patents and prices than on

ensuring an ample supply of needed drugs. The ability of Bayer and other manufacturers to increase production quickly was critical to industry's success in quieting public fears of shortages and in protecting intellectual property rights.

The Cipro (ciprofloxacin) saga has been in the middle of these developments. Federal agencies already were in-

creasing stockpiles of Bayer's antibiotic before the September 11 terrorist attack. However, public demand skyrocketed in October when NBC news anchor Tom Brokaw pointed to Cipro as the first line of defense after a Florida man and two Washington, DC postal workers died from inhalation-type anthrax. The resulting run on pharmacies and supply problems prompted some policy-makers to call for the government to allow generics makers to produce the drug, even if that meant overriding Bayer's patent. As the debate escalated, the public wanted to know everything about Cipro and Bayer's manufacturing capabilities and operations.

Adopted by the army

Cipro emerged in the 1980s as an effective treatment for patients with serious bacterial infections such as urinary tract infections and sexually transmitted diseases. It was approved by FDA in 1987 and has developed into an important product for Bayer, generating worldwide sales of \$1.6 billion last year. The surge in demand for Cipro in recent months may have rescued Bayer's pharmaceuti-

cal business, which was on the ropes following the removal of its cholesterol-lowering drug Baycol (cerivastatin) from the market last August because of reported deaths caused by drug-drug interactions. The company's situation changed dramatically in October when Bayer's new challenge was to expand Cipro production as quickly as possible.

The drug's use as an anthrax treatment dates from the Persian Gulf War in 1990 when the Department of Defense (DoD) adopted it as its main preventive for anthrax. That decision evidently was made because the therapy was fairly new, and DoD thought that terrorists were less likely to have developed Cipro-resistant anthrax strains. Because there was little scientific data demonstrating the effectiveness of any drugs against inhalation anthrax, the US Army tested Cipro and other antibiotics on monkeys exposed to anthrax. The results were favorable. Through the 1990s, research reports citing these studies enhanced Cipro's status as the preferred preventive for inhaled anthrax after an attack. This evidence prompted FDA to approve revised labeling for Cipro in August 2000, specifying effectiveness against inhalation anthrax. The federal government expanded the National Pharmaceutical Stockpile (NPS) as part of its growing bioterrorism defense program and contracted with Bayer earlier this year to supply 15 million Cipro tablets.

Eye on manufacturing

Before the terrorist attack in September, the Department of Health and Human Services (HHS) already had a lot of information about what pharmaceuticals were available to counter biological warfare and who made them. As part of the agency's bioterrorism response program, FDA had queried manufacturers more than a year ago about which products could be used to respond to the release of dangerous biological agents (see sidebar).

Key to expanding manufacturing is lining up supplies of active pharmaceutical ingredients (APIs), explains Harvey Greenberg of FDA's Office of Generic Drugs. Greenberg is involved with FDA bioterrorism activities and its efforts to manage drug shortages. To ramp up production

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very quickly, the main challenge is to have bulk ingredients and other supplies available at the same time. US manufacturers import most of their bulk ingredients, and that can cause delays. Access to larger quantities of capsule shells also may take time. The size of production equipment can limit batch size, and the need to shift plant bottling lines may be another difficulty. Before September 11, manufacturers were concerned about limits on their production capacity. Since then, Greenberg comments, they have been telling him that "there's nothing we can't do — tell us what you want and we'll stop everything else to make it."

Bayer initially faced difficulties ramping up production following the September 11 attack because it manufactures ciprofloxacin in Germany and could not ship its bulk ingredient to the United States during the hold on air transport. To meet rising demands, Bayer increased API shipments to the United States and began running its Connecticut manufacturing facility around-the-clock. The company

FDA surveys manufacturer capabilities for combating terrorism

FDA sent a letter to manufacturers in May 2000 seeking information about production capabilities for a list of focus drugs, including streptomycin, tetracycline, chloramphenicol, ciprofloxacin, doxycycline, gentamicin, erythromycin, diazepam, atropine, pralidoxime, penicillin, and minocycline.

For each product, FDA wanted manufacturers to provide the following information:

- usual estimated inventory
- production capacity
- supplier of bulk drug substance
- estimated production lead time.

FDA officials passed this information to HHS and continued to update its database. Since September 11, the agency has been contacting main

manufacturers to gain additional data, particularly for doxycycline and penicillin. The agency has sought current reports about

- production capability at specific facilities
- manufacturer's available bulk inventory
- rate-limiting factors that could hinder production ramp-up.

In some cases, FDA is inquiring about how long it would take a manufacturer to obtain additional bulk ingredients from usual sources and what process changes are involved for a firm to expand a batch from, say, 1 million to 10 million capsules. A related issue is how much such a shift in production output would affect supplies of other products.

shifted bottling lines to Cipro from other products and halted distribution of Cipro samples to physicians to increase its own stocks. In addition, the company reopened a plant in Germany to manufacture more Cipro APIs. By mid-October, Bayer announced that it would be able to triple worldwide production from 60 million to

200 million Cipro tablets over the next three months.

Probing patents

In addition to fears about Bayer's ability to manufacture enough Cipro, health policymakers pointed to Cipro's relatively high price as a major impediment to ob-

taining enough of the medicine to treat the growing population exposed to anthrax. Senator Charles Schumer (D-NY) called on HHS Secretary Tommy Thompson to invoke a federal law that allows the government to override a company's patent during a national emergency. A number of generics makers offered to produce millions of tablets very cheaply if the government took this action.

The Canadian government moved ahead, announcing that it would disregard Bayer's patent and purchase a generic version of Cipro from Toronto-based Apotex to ensure adequate supplies of an affordable treatment. Bayer responded with an offer of free pills for Health Canada and a promise to provide ample quantities in the future. Canadian officials backed down and decided to obtain the drug from Bayer, much to the relief of the research-based pharmaceutical industry.

The situation focused public attention on the highly complex exclusivity arrangements involving innovator and generics firms. Bayer's patent on Cipro currently

is scheduled to expire at the end of 2003. However, several generics companies already have conditional FDA approval to produce the drug when the patent expires, as permitted by current law. The generics manufacturers on the tentative-approval list include Barr Laboratories (Pomona, NY), Par Pharmaceuticals (Spring Valley, NY), Ranbaxy (New Delhi, India), Teva (Petach-Tikva, Tel Aviv, Israel), Mylan (Greensboro, NC), and Genpharm (San Jose, CA). When demand soared for Cipro in October, Barr and Ranbaxy said they could produce millions of ciprofloxacin pills within weeks, if desired by HHS.

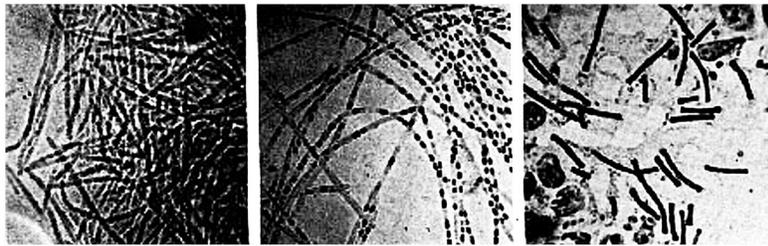
One item that came to light during this discussion is Bayer's 1997 agreement with Barr. The generics firm had been poised to challenge Bayer's Cipro patent when the two companies made a deal for Bayer to pay Barr an estimated \$30 million per year to hold off production of the drug. The Federal Trade Commission is investigating the agreement as a possible violation of antitrust laws, and members of Congress have objected that such agreements

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raise prices to consumers. The Senate recently approved a bill requiring manufacturers to disclose such agreements as a way to deter potentially collusive behavior.

Pressure on prices

Although Thompson was reluctant to circumvent Bayer's patent outright, he used



US National Library of Medicine

Original micrographs of *Bacillus anthracis*. During the 1870s Robert Koch (1843–1910) demonstrated for the first time that a microorganism was the direct cause of an infectious disease when he discovered that anthrax developed in mice only when the disease-bearing material injected into a mouse's bloodstream contained visible rods or spores of *Bacillus anthracis*

the threat of such a move to pressure Bayer to provide Cipro for the pharmaceutical stockpile at nearly half its already low government price. Bayer and HHS officials announced an agreement on 24 October allowing the government to purchase 100 tablets of Cipro at \$0.95 per pill, over a five-year time period for the drug stockpile. That purchase price is much less than Bayer's current Federal Supply Schedule

price of \$1.83 per tablet and also below the \$1.60 the company usually charges the Public Health Service 340B Drug Pricing Program. The program supplies medicines at highly discounted prices to public hospitals and clinics for distribution to low-income patients. Because Bayer recently dropped its 340B price to \$0.43 per tablet honoring a one-time agreement with another customer, there was some criticism

of Thompson's deal with Bayer. HHS, however, maintains that the stockpile has the lowest price for Cipro.

Similar to other pharmaceutical sales to public health programs, the NPS price for Cipro does not affect the company's best price for calculating Medicaid rebates. The negotiated price is for a five-year vendor-managed inventory arrangement, which calls for the company to hold the stockpiled 100 million Cipro capsules in its inventory so that they are available to the NPS at the contract price. The manufacturer is responsible for rotating its inventory to ensure the freshness and quality of the product. When the contract expires, HHS will take possession of any of the 100 million pills not purchased during the five-year period. If HHS needs more Cipro during that time, the agreement calls for Bayer to provide another 200 million tablets at even lower prices.

HHS also contracted to purchase 1.13 billion doses of doxycycline from Ivax Pharmaceuticals (Miami, FL) for a reported \$36 million or about \$0.03 per

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dose. This will greatly increase the stockpile's supply of the antibiotic, which now is about 200 million doses. Combined with the Cipro order, the stockpile will have sufficient medication for a 60-day course of treatment for 12 million patients, based on 5 days of Cipro and 55 days of doxycycline or other antibiotic.

Expanding labeled indications

While Bayer was negotiating prices with Thompson, other brand-name manufacturers offered their latest antibiotics to HHS for free. Not only did they want to improve their public image, but they also saw this as an opportunity to build market awareness of their therapies as alternatives to Cipro. And probably more important, the companies' offers were linked to gaining formal FDA approval of their therapies for use against anthrax.

The discussion of what drugs were approved by FDA to treat anthrax infections prompted more examination of drug labeling policies. Cipro rocketed to fame because, as of September 11, it was the only drug with labeling that specified effectiveness in treating inhalation anthrax. Bayer obtained this expanded labeling almost accidentally. Even though the army's monkey tests found that several antibiotics — penicillin, doxycycline, and Cipro — demonstrated effectiveness against the inhaled form of anthrax, army researchers asked Bayer to file the necessary docu-

ments with FDA to obtain an official labeling change because Cipro was the newest drug and still on patent.

Now FDA is eager to expand the labeling for these other antibiotics to encourage prescribers and patients to use them as alternatives to Cipro. Health officials are concerned that excessive reliance on Cipro could aggravate shortages and also give rise to drug-resistant strains of bacteria. FDA announced in a 29 October *Federal Register* notice that doxycycline and penicillin G procaine are equally effective for treating all forms of anthrax infections, including the inhalational variety. The agency referred to the Army test data to support this finding and encouraged manufacturers of the cited antibiotics to submit supplemental applications to officially revise product labeling.

In addition, brand-name manufacturers of newer antibiotics began talks with FDA officials about what test data are needed to revise labeling to include anthrax treatment. Companies pursuing this action include Bristol-Myers Squibb (New

York, NY) for Tequin (gatifloxacin); Johnson & Johnson (New Brunswick, NJ) for Levaquin (levofloxacin); GlaxoSmithKline (Research Triangle Park, NC) for Augmentin (amoxicillin-clavulanate); and Abbott (Abbott Park, IL) for Biaxin (clarithromycin).

Because thousands of people are now taking Cipro, federal agencies want to learn more about its side effects, patient compliance, and the potential for drug resistance to emerge. The Centers for Disease Control and Prevention (CDC) has launched a program to track adverse events and patient compliance as well as Cipro dosing recommendations. CDC will give these data to Bayer for analysis, which the company is required to do under a Phase-4 agreement with FDA to monitor postmarketing events and compliance.

Challenges ahead

It remains to be seen how this surge in demand for medicines to treat and prevent against harmful biological agents will affect pharmaceutical R&D. Only a few

decades ago, drug companies shut down most antibiotic research on the assumption that most infectious diseases had been conquered, at least in the United States. Recently, industry began to invest more in this area as dangerous infections multiplied around the world. Now health officials are clamoring for more research on infectious diseases, and Uncle Sam is poised to authorize more than \$1 billion to purchase drugs and vaccines for the NPS. Federal agencies may spend millions more for research related to infectious diseases and programs designed to enhance government regulation of needed medicines.

Such a huge public investment in medicines promises to transform the government's relationship with pharmaceutical companies. Expansion of federal purchasing programs plus the eventual establishment of a Medicare drug benefit may require manufacturers to operate more like federal government contractors in the future. That is likely to mean increased public scrutiny of manufacturing

practices and tighter regulation of marketing, pricing, and research activities. Government agencies will want to monitor laboratories investigating dangerous microbes. The media will ask questions about traditionally low-profile operations.

The overt challenge to Bayer's patent rights and expectations that it should provide millions of pills at fire-sale prices appear to signal what lies ahead. One response from manufacturers might be to hold off investing the vast sums needed to develop critical new anti-infective medicines. Another may be to recognize that the world climate is changing and that pharmaceutical companies may have to adjust to new ways of doing business. **PT**