

Vaccine Shortages Put Spotlight on Production

Bioterrorism and common infections create challenges for manufacturers

Vaccine development and manufacture have become hot topics in Washington, DC. The terrorist attack last September and the subsequent anthrax scare focused public attention on vaccines to protect the nation against anthrax, smallpox, and other possible bioweapons. At the same time, shortages and delays in obtaining even routine vaccines have become serious public health issues. Some experts want the government to move into vaccine research and production. Members of Congress are proposing legislative action. Vaccine pricing and supply are under review along with regulatory policies affecting production of modern and effective products.

Responding to Bioterrorism

The events of last fall set off major tremors about the possible use of biological weapons. Sudden demand for increased production of anthrax vaccine put the spotlight on Michigan vaccine maker BioPort Corporation (www.bioport.com). The company had halted production of anthrax vaccine adsorbed (AVA) for more than a year because of continuing problems

complying with FDA good manufacturing practices (GMPs).

A report from Congress' General Accounting Office (GAO) summarizes the story: The original anthrax vaccine was developed in the 1950s, tested in mill workers, and licensed to a Michigan state agency that sold the operation to BioPort in 1998 (1). FDA reported numerous GMP violations during inspections at BioPort in the mid-1990s. That noncompliance became a serious concern in 1998 when the Department of Defense (DOD) announced plans to vaccinate all members of the armed forces for anthrax.

According to the GAO report, BioPort had failed to inform FDA of numerous changes to its manufacturing process such as installing new fermentors and filters. It took more than two years for the company to correct problems with validation, aseptic processing, filling operations, stability testing, and environmental monitoring, among others. BioPort finally closed its filling operation and contracted the job, which led to FDA approval of a manufacturing supplement in January 2002 (2). The approval letter requires BioPort to provide real-time stability data on three lots for 18 months and to complete a suitable extraction study on its stoppers.

Improving Smallpox Vaccines

The 11 September attack also prompted efforts by the Department of Health and Human Services (HHS) to expand the nation's stockpile of smallpox vaccine. U.S. health authorities stopped routinely vaccinating children for smallpox in the

1970s. At that time, evidence showed that the disease had been eradicated and that dangerous side effects from widespread vaccination were more dangerous than the prospect of anyone contracting the disease. As of last September, the CDC had 15 million doses of an old Wyeth (www.wyeth.com) smallpox vaccine in its stockpile. That amount increased dramatically in March when Aventis Pasteur (www.aventispasteur.com) announced that it would donate about 80 million doses to the stockpile. The Aventis supply, which had been kept frozen, was found to be as potent as that in the stockpile. In addition, testing by the National Institutes of Health (NIH) indicated that these older vaccines could be diluted fivefold or more and remain effective.

Government officials plan to use the old vaccine only in an emergency. They plan to replace it in a few years with a new vaccine produced in cell banks (instead of by scraping vaccinia from calf bellies). DOD contracted several years ago with DynPort Vaccine Company (www.dyncorp.com/dynport/) to develop such a therapy. HHS then signed up OraVax (a British biotechnology company that subsequently changed its name to Acambis, www.acambis.com) to produce 40 million doses using a cell-based technology. Such technology offers higher yields and greater purity than older methods, and avoids using animal materials in the culture. After 11 September, HHS asked Acambis to expand production and provide 54 million doses in 2002. In an effort to do that, the



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CURRENT vaccine

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company has begun manufacturing vaccine at its Massachusetts facility while clinical trials are under way. Those initial supplies will be available only for experimental use until trials, tests, and plant inspections are completed.

HHS secretary Tommy Thompson subsequently moved to further expand

supplies of the new smallpox vaccine. In November 2001, HHS awarded a \$428 million contract for 155 million doses to Acambis and Baxter International (www.baxter.com). Baxter will produce the vaccine at a European facility and ship it to Acambis in the United States for testing, filling, and distribution. Baxter plans to produce similar vaccines for the European market, and Aventis is testing another in Europe, which it expects to distribute in France and Canada by year-end.

Short Supplies

Notably, HHS did not award the large smallpox vaccine contract to a major vaccine maker such as Merck (www.merck.com), Aventis (www.aventis.com), or GlaxoSmithKline (www.gsk.com). The agency was trying to avoid overtaxing already stretched production capacity and further aggravating shortages for several common vaccines. Last December, the Center for Disease Control and Prevention's (CDC, www.cdc.gov) National Immunization Program (NIP) acknowledged

shortages of vaccines against diphtheria, tetanus, pertussis (DTaP), and pneumococcal disease. At that time, NIP advised physicians to reduce administration of the diphtheria, tetanus, pertussis vaccine. A few months ago CDC also announced shortages of Merck vaccines for measles, mumps, and rubella (MMR) and for varicella (chickenpox) (3).

In addition, flu vaccines have been in short supply. Two years ago, the major delay in access to flu vaccine was blamed largely on manufacturers' problems identifying and growing the appropriate influenza strain in a limited time frame. A GAO report notes that, fortunately, the 2000–2001 flu season arrived late and was less severe than normal (4). Flu vaccine shortages were less noticeable during the 2001–2002 season, but some supply disruptions did occur.

Market Liabilities

The CDC points to “multifactorial, complex” issues underlying vaccine supply problems. Only a dozen companies now produce vaccines for the U.S. market, compared with twice that number in 1967. Four major pharma companies — Merck, Glaxo, Wyeth, and Aventis — dominate the market, and some of those have reduced production of older vaccines that are no longer profitable. Even though smaller companies are looking to fill specific niches, production problems at a major company can create serious supply disruptions.

Government stockpile programs are intended to prevent shortages and deal with emergencies, but they are limited. CDC now stockpiles only a few single-source vaccines. Those will do little to bolster supplies if a major manufacturer runs into production problems. But expanding the stockpile is expensive because many vaccine stocks have to be turned over every few months, and demand is unpredictable. New flu vaccines are made each year, ruling out any stockpile program for them.

One reason the vaccine market is unattractive for large manufacturers is continued concern about liability. Following a wave of lawsuits in the mid-1980s, the federal government stepped in to maintain viable U.S. vaccine production capability. It established a no-fault compensation program for individuals injured by vaccines, which reduced immediate concerns. However, trial

Research Expands

The drive to develop safer and more potent vaccines is expanding as government agencies and researchers investigate modern genetic engineering approaches. The U.S. Army is working on a recombinant protective antigen (rPA) anthrax vaccine that is expected to yield a more consistent, safe, and effective product. Researchers and manufacturers also are developing next generation smallpox vaccines based on recombinant DNA processes.

Although most past and current vaccines were designed to prevent disease, a host of new therapies in the research pipeline aim to treat conditions. New vaccines are being tested against herpes, colon and stomach cancer, and malignant melanoma. New discoveries in immunology are spurring R&D, as is international pressure on industry to invest more in combating global infections. The Bill and Melinda Gates

Foundation (www.gatesfoundation.org), for example, is providing millions of dollars for research on new vaccines and therapies to treat infectious diseases and AIDS.

At the same time, disappointments are all too common in vaccine research. In February, researchers halted early trials at Elan (www.elan.com). The company's experimental vaccine to reverse the course of Alzheimer's disease resulted in several cases of severe brain inflammation. In March, the NIH decided not to fund phase 3 clinical trials of a prime AIDS vaccine candidate because of signs of a weak immune response against HIV. Other AIDS vaccine studies have shown promise, but years of research have so far produced no preventive treatments. Vaccine development is a very lengthy process, and new gene-based vaccines are years away.

lawyers now are filing suits claiming harm from the preservative thimerosal (mercury) in vaccines, prompting manufacturers to seek stronger protections.

Moreover, profits can be limited in the vaccine market. Federal and state governments purchase more than half of all childhood vaccines used in the United States, primarily through the 10-year-old Vaccines for Children program. Although the program does not impose price controls directly on vaccines, the favorable prices it

negotiates set a standard for the private sector.

Production Difficulties

Vaccine manufacturing is a complex, lengthy, and expensive process that has been complicated by several new factors in the past few years.

More stringent regulatory requirements.

Shortages in flu vaccine two years ago were compounded by FDA concerns about adherence to GMPs at Wyeth Lederle and another company that eventually dropped

out of the market. Similarly, Merck curtailed vaccine production last year to make changes at its West Point, PA, plant in response to issues raised by FDA during a routine GMP inspection. FDA's increased emphasis on GMP compliance has created problems at many biotech companies.

Manufacturer departures. Problems arose with DTaP supplies in early 2001 when Wyeth Lederle announced that it had stopped production of the vaccine. Baxter, having purchased North American Vaccine, had recently made a similar move, leaving only Aventis and Glaxo in the market. One reason Wyeth stopped manufacturing DTaP vaccine was to boost production of its new pneumococcal conjugate vaccine (PCV-7), but manufacturing problems and high demand also resulted in shortages for that product.

Eliminating mercury. Major production delays have resulted from recent demands that manufacturers remove the preservative thimerosal from infant vaccines. The derivative of ethylmercury has been used as an additive to vaccines since the 1930s to kill bacteria and prevent contamination, particularly in multidose vials (3). In 1999, FDA reported little evidence of harm from thimerosal in vaccines (5), and a study by the Institute of Medicine (www.iom.com) in 2001 reached a similar conclusion (6). However, because neither report could rule out the possibility of excess infant exposure to mercury, the CDC recommended ending use of mercury-containing vaccines by March 2002. Government agencies were under pressure from lawmakers and patient advocates who claimed that mercury in vaccines might be the cause of rising

incidences of autism and other neurological disorders.

Consequently, manufacturers have been reformulating products and revamping manufacturing systems for the past two years to produce thimerosal-free products. The task has been much more difficult than anticipated in many cases. Wayne Pisano, executive vice president of Aventis Pasteur North America, told a February meeting of the National Vaccine Advisory Committee that removing thimerosal from its childhood vaccines was a two-year effort that involved product reformulation, testing, and shifting to single-dose packaging. Those changes have reduced manufacturing yields approximately 25% because the fill process is slower and each single vial must be overfilled to ensure an adequate dose. Now all routine pediatric vaccines are thimerosal-free, and manufacturers are looking at similar changes for other products, but the overhaul has come at considerable cost and questionable benefit.

Blocking BSE. The possibility of contamination with prion proteins linked to

bovine spongiform encephalopathy (BSE) also is requiring vaccine makers to update some production processes. FDA has asked manufacturers to rederive working bacterial and viral seed banks and working cell banks using bovine-derived materials only from BSE-free countries. FDA's website lists several vaccines still made with materials from BSE-affected countries (7). Agency officials emphasize that such a vaccine is unlikely to spread disease to humans. Nevertheless, FDA is considering whether to impose a total prohibition on bovine-derived materials from BSE-positive or high-risk countries in manufacturing drugs and biologics. Meanwhile, the agency continues to work with manufacturers to develop overhaul plans.

Government Takeover?

Current vaccine shortages and R&D challenges have generated increased talk about a federal government vaccine manufacturing operation. Last year a DOD review panel recommended that the military establish a government-owned, contractor-

operated (GOCO) vaccine production facility. The estimated cost to build such a facility and produce three or four of the 20 some vaccines on DOD's wish list is \$400 million. The rationale is that the military's large but variable demand is hard for the private sector to accommodate, especially in light of the current shortage situation.

In November, the Council of the Institute of Medicine (www.iom.edu) asked the federal government to support a National Vaccine Authority (NVA). The NVA would research and produce vaccines to protect against bioterrorism, and also supply vaccines in "scarce supply" to meet public health needs. The IOM statement points to manufacturing difficulties and slow progress involving the anthrax and cell-culture smallpox vaccines as evidence that "major changes are needed at the national level" (8). NVA would help companies produce pilot lots of new vaccines. It also would manufacture vaccines when "market forces are not sufficient to facilitate large-scale production." Other tasks would be to promote communication among vaccine researchers, examine the need for expanded liability protection for manufacturers, and work with FDA to "reduce regulatory complexities." HHS secretary Thompson objected to the proposal, as did other Bush administration officials, but the idea is gaining support on Capitol Hill.

Congress is weighing its own proposals to promote vaccine development. In March, Senator Bill Frist (Rep-TN) introduced a bill to reduce vaccine shortages by bolstering stockpiles, expanding liability protections for manufacturers, and boosting grants to states for expanding flu immunization programs. Senator Mike DeWine (Rep-OH) takes another tack with legislation requiring that manufacturers notify FDA of plans to discontinue production of biologics and vaccines, as they are required to do for drugs. Congress is slated to review such proposals later this year when GAO issues a new report on vaccine shortages. That study will examine why vaccine manufacturers have left the business and what the federal government's role should be in ensuring adequate vaccine supplies.

Meanwhile, the Institute of Medicine has launched a project to evaluate vaccine purchase financing in the United States. A

committee chaired by Duke University economist Frank Sloan will hold its second meeting this month (May 20–21). It is gathering information on vaccine patents, licensing, price caps, pricing patterns, and other issues affecting shortages. A report is expected in the summer of 2003.

FDA also is examining regulatory changes that might stimulate vaccine R&D. Additional antibioterrorism funds are supporting efforts to develop standardized assays for different vaccines and improved methods for detecting adventitious agents. Options are being explored for modifying lot release requirements, possibly by relying more on validated manufacturing processes and increased quality control. Agency officials are promoting international harmonization of vaccine testing and oversight requirements as a way to streamline the development and registration process.

Manufacturers also are expressing their views and concerns. Pisano of Aventis pointed out at the February meeting that establishing NVA would be costly and could

lead private manufacturers to withdraw from the U.S. market. He echoed recommendations for expanded vaccine stockpiles, stronger liability protections for manufacturers, and added support for FDA vaccine testing and research. Pisano envisioned a system that would permit CDC to inform manufacturers of competitors' anticipated production problems. He also backed a voluntary system — rather than new, difficult to implement legal requirements — for advance notice of plans to cease vaccine production. Such approaches may make sense, but policymakers will want to take stronger action if shortages continue.

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