Drug shortages have been in the limelight in recent months, turning attention toward pharmaceutical manufacturing regulations and standards. FDA’s Web site, www.fda.gov, lists several therapies that are in short supply as a result of production problems and manufacturing difficulties. Limited access to routine vaccines for infants and children has public health authorities concerned. Pharmacists have stepped up tracking efforts because they cannot obtain important therapies in hospitals and clinics.

The drug shortage situation has prompted FDA and other health authorities to examine the underlying factors of this troubling development. One potential cause being discussed is whether stricter FDA enforcement of good manufacturing practices (GMPs) standards and new production rules is forcing companies to close or upgrade plants or discontinue production of low-profit medicines. Manufacturers have launched limited-distribution programs to reserve available critical therapies, but such actions offer only temporary relief.

Multiple causes
FDA has identified numerous factors that contribute to drug shortages, many that fall under the manufacturing difficulties heading. Suppliers of bulk-active ingredients have encountered production problems. In some cases, packaging difficulties have prompted recalls and production delays. Problems with ensuring sterilization and proper vial-fill processes have plagued makers of parenterals and vaccines. Natural disasters such as a Caribbean hurricane have hindered active-ingredient shipments.

Manufacturers, however, point to overly strict FDA inspectors who cite them for numerous GMP violations that force them to revise production processes. Even though companies believe that many deficiency charges are unjustified, they typically accommodate the requests instead of fighting the regulators. For many companies, demands to revise production processes may lead to plant closures or decisions to discontinue the manufacture of certain therapies.

Industry consolidation has aggravated these difficulties. Only a dozen firms now produce vaccines for the US market, compared with twice that number in 1967. Problems arose with DTaP supplies in early 2001 when Wyeth Lederle announced a halt to production. That development followed a similar move by Baxter, 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 plus high demand have created shortages for this product.

Shortages of flu vaccines two years ago were compounded by FDA concerns about adherence to GMPs at Wyeth Lederle and another firm that eventually dropped out of the market. Similarly, Merck curtailed vaccine production last year to make changes at its West Point, Pennsylvania, plant in response to issues raised by FDA during a routine GMP inspection.

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An added problem is that vaccine manufacturers have had to revise formulations during the past two years to remove the preservative thimerosal (mercury) from routine children’s vaccines. This substance has been used as an additive to vaccines since the 1930s to kill bacteria and prevent contamination in multidose vials. FDA and the Institute of Medicine studied the issue in response to pressure from lawmakers and patient advocates who claimed that mercury in vaccines might be the cause of increased incidences of autism and other neurological disorders. Because they could not rule out the possibility of excess infant exposure to mercury, CDC recommended an end to mercury-containing vaccines for children by March 2002. Manufacturers have been reformulating products and revamping manufacturing systems for the past two years to produce thimerosal-free products — a task that has been much more difficult than anticipated.

Continued concern about the possible contamination of biotech products with prion proteins linked to bovine spongiform encephalopathy (BSE) also has caused some biotech product and vaccine manufacturers to update production processes. FDA has called on companies to use working seed banks and cell banks that use bovine-derived materials only from BSE-free countries. Even though agency officials emphasize that there is little risk that a product produced using an old system could spread the disease to humans, FDA has adopted a conservative approach. The agency continues to weigh further limits on drug and biologics manufacturers that use bovine-derived materials from BSE-positive or high-risk countries.

**Regulatory responses**

FDA has stepped up efforts to track how these and other issues may lead to product shortages, especially those involving critical sole-source therapies. When a shortage appears of a medically necessary drug — that is, one that is life supporting, life sustaining, or designed to prevent severe disability or disease — FDA officials develop an action plan to cope with the problem. The Center for Drug Evaluation and Research (CDER) offers the following options as possible solutions:

- develop a protocol for limited distribution of the product until production can resume or expand
- expedite review of chemistry, manufacturing, and controls data in a manu-
Efforts to streamline FDA regulation of manufacturing processes may run into a new hurdle if environmental concerns develop about possible links between increased drug consumption and harmful levels of chemical substances in the nation’s water supply. The US Geological Survey released the results of a study in March revealing that low concentrations of human and veterinary drugs and hormones were present in waterways across the nation.

Researchers at the Environmental Protection Agency (EPA) have been exploring this issue for several years, partly in response to investigations conducted in Germany, Switzerland, and England. More-sophisticated analytical and screening technology now permits engineers and chemists to identify extremely minute amounts of chemical substances in water systems.

Until a few years ago, pharmaceutical manufacturers had to file environmental assessments (EAs) in new drug applications as required by the National Environmental Policy Act of 1969. This policy was designed to document whether a new product would harm the environment. After years of receiving EAs that concluded “no significant impact,” White House regulatory reform efforts encouraged FDA to drop the EA-filing requirement in 1997 for most new drugs and biologics. However, if the public becomes alarmed about possible harm from drug substances in water systems — even without evidence of real danger — FDA could face pressure to reinstate its broader EA filing policy. Preparing such reports takes time and resources and runs counter to regulatory streamlining efforts.

Top drugs under review
Investigation of water contamination initially found excessive discharge of antibiotics, pesticides, and industrial chemicals. Today, research focuses on whether trace amounts of “useful” pharmaceuticals and personal-care products may affect aquatic or terrestrial environments. Reports suggest that high levels of hormones are disrupting fish reproduction in the United Kingdom and overuse of antibiotics may lead to resistant pathogens in the wild. Last year, the American Chemical Society published a book edited by EPA scientists about pharmaceuticals and personal-care products in the environment that raises these issues.

EPA is encouraging more research in this area through grants to scientists at major universities. A Johns Hopkins University team is examining which of the top 200 drugs in the United States are most prevalent in the nation’s streams. Currently, no evidence exists that pharmaceutical elements in the water pose any danger for human health. However, EPA scientists suggest the following preventive measures if future research indicates that such elements create unacceptable risks:

- improve screening of the environmental effect of new products such as efflux pump inhibitors
- increase efforts to minimize drug misuse and overuse in products identified as having environmental consequences
- create policies to discourage Internet dispensing of medicines to prevent overprescribing
- individualize therapy to tailor drug doses and encourage the use of lowest effective doses
- create policies to encourage proper disposal of unused or expired products
- develop alternative routes of drug delivery such as sustained-release products, patches, implants, and inhalants to reduce discharges into water systems
- research alternative excipients to improve dissolution of medicines in the body
- design more environmentally friendly chemicals.
Manufacturers claim that additional guidance could help resolve manufacturing disputes more rapidly and prevent parallel problems at multiple plants and companies.

expedite review of pharmacological and toxicologic data if the problem involves impurities
quickly assess preclinical and clinical data in an application from an alternative supplier
expedite review of an application for a new supplier.

Advance notice
Pharmacists complain that the lack of information about looming supply disruptions makes it difficult to address short-supply situations. They also note that some wholesalers offer very expensive alternatives to some unavailable products, which raises questions about the real cause of the shortages. While manufacturers point to increased use of just-in-time inventory systems at hospital pharmacies for aggravating temporary shortages, pharmacists are calling for FDA to do more to provide advance warnings of possible supply problems. The American Society of Health-System Pharmacists Web site, www.ashp.org, is a valuable source of information and contains a long list of drug shortages tracked by the University of Utah Drug Information Center.

The FDA Modernization Act of 1997 requires a sole-source manufacturer to notify FDA six months in advance about plans to discontinue production of any life-saving drug. Manufacturers can get a waiver from the six-months requirement if special circumstances such as a biomaterials shortage prevent continued production. CDER’s “to be discontinued” list currently contains two products, but pharmacists and health policymakers believe that many more items should be included. Senator Mike DeWine (R-OH) has proposed legislation that would require manufacturers to notify FDA about plans to discontinue production of biologics and vaccines in addition to drugs. Manufacturers counter that a voluntary notification system works for most products and that companies face too much uncertainty to anticipate all major manufacturing disruptions.

An added problem is ongoing confusion about which products fall under the medical-necessity definition. FDA has been drafting a guidance for months about which products would require advance notice but has had difficulty clarifying the issue.
Federal intervention
Meanwhile, government officials seek to prevent future shortages of critical drugs and vaccines by enlarging pharmaceutical stockpiles. Efforts to ensure adequate supplies during emergencies have expanded since the terror attack last September, but the strategy has limited ability to handle broader shortage problems. CDC stockpiles still include only a few vaccines and drugs and would offer little help if a manufacturer encountered production problems with most therapies. Expanding stockpiles also is expensive because stocks of most vaccines and drugs must be turned over every few months, and demand is unpredictable.

Another idea is to create a government-owned vaccine manufacturing operation. Last year, a Department of Defense review panel recommended such an initiative, despite an estimated $400-million price tag. In November 2001, the Council of the Institute of Medicine called for the federal government to support the formation of the National Vaccine Authority (NVA) to research and produce vaccines and critical therapies to protect against bioterrorism and meet public-health needs. The NVA would promote communication among researchers, examine the need for expanded liability protection for manufacturers, and work with FDA to reduce regulatory complexities. Bush administration officials objected to the proposal, but the idea is gaining support on Capitol Hill.

Congress is slated to review such initiatives later this year when the General Accounting Office issues a new report about vaccine shortages. The study examines why vaccine manufacturers have left the business and what the federal government’s role should be in ensuring an adequate supply.

Focus on GMPs
FDA also is examining how its policies may contribute to shortages of regulated products. At the annual meeting of the Food and Drug Law Institute (FDLI) in April, FDA deputy commissioner Lester Washington Report

An FDA official has pointed to the need for an agency-wide, systems-based approach to GMPs and also has recommended increasing the emphasis on quality systems for plant inspections.
FDA chief counsel Daniel Troy similarly cited a serious communications gap between the agency and manufacturers about GMPs and pointed out that some companies continue to cut corners and ignore compliance problems. Troy called for new thinking regarding GMP compliance efforts. His office now is reviewing all FDA warning letters before they are sent. Although some consumer advocates fear this process would soften FDA enforcement efforts, Troy says its goal is to ensure that warning letters have “teeth” and prompt speedy compliance by industry rather than create drawn-out disputes about compliance issues.

Manufacturers say they need more guidance from FDA about GMP issues to avoid compliance problems. One hot issue is aseptic processing; FDA has been working to update a 15-year-old guidance in this area for several years, but progress has been slow. Manufacturers claim that additional guidance could help resolve manufacturing disputes more rapidly and prevent parallel problems at multiple plants and companies. However, FDA points to a lack of resources to tackle such an effort.

Added funds for antibioterrorism programs may support agency efforts to address some manufacturing and formulation challenges associated with vaccines. Efforts could include developing standardized assays and improving methods for detecting adventitious agents. FDA also is considering a stronger reliance on validated manufacturing processes and increased quality control for modifying lot-release requirements.

Crawford indicated that he would promote such efforts. At the FDLI conference he noted a need to build on international standards to ensure quality manufacturing. He said that providing more-helpful instructions to the industry could reduce old practices of building on accidents and mistakes and may “pave the way for better, safer products.”