Establishing Government-Operated Vaccine Programs: An Industry Perspective

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During 2000–2002, shortages of numerous routinely administered pediatric vaccines occurred. The reasons for these shortages were varied, but they included policy, manufacturing, and regulatory issues. The use of government manufacturing programs has been proposed as a way to stabilize the fragile vaccine supply and to prevent periodic shortages. Although such programs might be useful for defense needs, it is likely that such an approach would have limited value for routinely administered vaccines. Each of the vaccine components would require a dedicated manufacturing facility, and many components are administered in combination vaccines. Timing is also an important consideration. The restarting of an idled manufacturing facility would take many months; in addition, it often takes nearly 12 months to produce and release a single lot of vaccine. Finally, government-owned programs would face the same issues of regulatory changes, technological advancements, and facility updates as non–government-owned programs do—all of which would require sustained operation and investment. A secure and stable vaccine supply is best built by establishing the importance and value of our vaccine programs, which would, in turn, provide incentives to manufacturers to build capacity and inventories.

The recent spate of shortages of childhood vaccines has been serious and diverse. The concept of government-operated vaccine programs, which would include manufacturing of the vaccines, has been proposed by the Institute of Medicine as a way to alleviate vaccine shortages [1]. To assess the potential solutions to the problems with vaccine supply, it is important to understand the reasons for the shortages and then to review potential solutions in that context.

During the 3-year period of 2000–2002, shortages of the combined diphtheria and tetanus toxoids and acellular pertussis vaccine and its component toxoids, influenza virus vaccine, 7-valent polysaccharide-protein conjugate pneumococcal vaccine, measles-mumps-rubella vaccine, and varicella vaccine occurred. There were 3 main reasons for the shortages. The first reason is related to vaccine policies and is best exemplified by the decision to eliminate thimerosal from childhood vaccines, which led to shortages related to supplies of preservative-free vaccine formulations. Some of the past delays in distribution of influenza virus vaccine can also be put into this category, because the decision and the timing of the decision to change vaccine strains each year affects vaccine supply. The second reason for vaccine shortages is problems associated with the manufacture of vaccines. Because vaccines are made in biological systems, these problems occur periodically, are vaccine specific, are difficult to predict, and are empirical in their solution. In general, these problems cannot be completely prevented, but they can be managed by planning to have excess supplies on hand. The planning for excess supply adds to the cost of vaccine manufacture. The third reason for vaccine shortages is related to the regulatory and compliance environment. Over the past several years, the framework of regulations applied to vaccines has gradually changed from a primarily scientific-based framework to a primarily systems control–based framework, much like that applied to drug products. This initiative by the US Food and Drug Administration has resulted in broad changes...
in compliance and quality control systems for all manufacturers, and the adaptation has required considerable changes in the way vaccines are made, filled into vials or syringes, and released. Once these changes are in place, they should have less effect on vaccine supply as they have during the current transition.

Government manufacturing programs have been proposed for the purposes of dealing with the shortages of different categories of vaccines, including childhood vaccines, that occur periodically and of supplying vaccines for which there is a limited market, including routinely administered vaccines, defense vaccines, and vaccines that are in scarce supply and would not otherwise be provided in the public or private sector [1]. For childhood vaccines, excess or standby manufacturing capacity would be owned by the government and would be available in case of shortages. Given the diversity of childhood vaccines, the government effort would be focused on the vaccines for which the risk of shortage is greatest. A logical approach would be to match the government effort to those vaccines for which there are the fewest private suppliers on the market, as has been done for vaccine stockpile programs in the past.

The concept of government-manufactured vaccines faces major obstacles, particularly with regard to routinely administered vaccines. First, each vaccine requires a manufacturing facility that is largely independent and is dedicated to a specific product. For example, diphtheria and tetanus toxoids and acellular pertussis vaccine requires 3 separate manufacturing areas that each can be used only for a specific purpose. Tetanus toxoid, in particular, must be produced in a free-standing facility, because it is produced from spore-forming bacteria. The manufacture of the aforementioned routinely administered vaccines would require at least 9 different manufacturing areas.

A second important consideration is timing. In general, the time required to produce a vaccine, from purchase and release of raw materials to the release of final bottled product, is ~1 year. Therefore, short-term shortages are relieved only by products that are already in the process of being manufactured. Third, manufacturing facilities cannot be started and stopped easily and, therefore, cannot respond quickly. Maintaining production of licensed vaccines requires a regular schedule of production to maintain the expertise of the production staff and the validation of processes and facilities. Restarting production at facilities or making changes in vaccines requires that facilities be revalidated before manufacturing can be reinitiated. Thus, even longer-term supply issues will not be easily alleviated. Furthermore, obviously, any government facility will have to meet the same standards and achieve the same continuous improvement required of all manufacturers, which would require considerable ongoing investment.

A recent report on biological warfare and defense vaccine research-and-development programs [2] has suggested that government-owned, contract-operated vaccine manufacturing programs be used for the supply of defense vaccines. Eight priority vaccines (i.e., anthrax vaccine adsorbed and smallpox, plague, tularemia, multivalent botulinum, next-generation anthrax, ricin, and multivalent equine encephalitis virus vaccines) were specified. It was estimated that the cost of development of these products would be $8 billion over the course of 8–12 years. This cost would include the cost of vaccine development, as well as the costs of the facilities required for production of the vaccines.

The idea of government-owned, contract-operated programs is probably most applicable to defense needs, because such programs would focus on vaccines for which there is not a general interest or demand from the private sector and would be generated only through government contracts. In addition, such programs would give the government greater control over long-term vaccine supplies. Whether the net cost would be reduced is not clear, because, in the report, assumptions about costs were based on industry standards.

The goal of developing and licensing 8 new vaccines over the course of 12 years is very ambitious, especially when one considers that most of the vaccine projects would require basic research at their inception. The recent experience in the private sector is that vaccine programs require 10–15 years for development, and, given the new regulatory requirements, this timeline is unlikely to get shorter. The vaccine programs described above would, therefore, require long-term, sustained funding, not only during the development and licensure period, but also throughout the life cycle of the product. Updates to aging facilities, changes in regulations, and technological improvements all must be sustained over time and within the context of normal government operating systems for funding, hiring, and capital expenditures. History suggests that facilities operated under these conditions are difficult to sustain in the long term because of the rapid evolution of both technology and competition. In the United States, state-run laboratories in Michigan and Massachusetts have been unable to sustain their role in the current environment. Similarly, numerous government-run facilities in Europe, which, in the past, supplied national vaccine needs, have also been unable to sustain that role.

The way to sustain ongoing vaccine supply must be linked to an appreciation of not only the value of vaccines but, also, the value of a dependable vaccine supply. In an environment where vaccine shortages occurred, there was little incentive or plan to build strategic inventories of vaccine anywhere in the supply chain. It is clear from the very short interval between the occurrence of supply problems at the manufacturer’s step and the occurrence of supply problems in the provider’s office that there was no cushion anywhere in the system. Manufacturers did not have inventories in reserve, public purchasers
did not have strategic inventories in place for most vaccines, and providers had only enough vaccine on hand for immediate needs. Building these inventories at each step in the supply chain will go a long way toward alleviating the majority of vaccine supply issues that are likely to occur on an ongoing basis, and it is the only way that plans to sustain the vaccine supply can work from a manufacturing perspective, because solutions that respond to crises after they occur will always be too late. It is for this reason that solutions such as government-owned, contract-operated programs will probably not be effective for routinely used vaccines.

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References