

**Strengthening the Supply of Routinely Recommended  
Vaccines in the United States**

**A Report of the  
National Vaccine Advisory Committee**

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**U.S. Department of Health and Human Services  
National Vaccine Program Office**

## Contents

|  |    |
|--|----|
| Introduction.....  | 1  |
| Background.....  | 3  |
| Valuation of Vaccines.....   | 3  |
| Vaccine Purchase, Distribution, and Administration.....  | 3  |
| Vaccine Manufacture.....   | 4  |
| Regulatory Processes.....  | 4  |
| The Reality of Profit Margins.....   | 5  |
| Cost, Complexity, and Uncertainty of Development of New Product.....                             | 5  |
| Problems in Manufacturing Approved Products.....   | 5  |
| Change in Vaccine Recommendations Necessitated by Shortages.....                                 | 7  |
| Problems of Vaccine Supply n 2001-2002.....  | 7  |
| Strategies.....  | 9  |
| Increasing Financial Incentives for Research, Development, Production<br>and Administration..... | 9  |
| Streamlining Regulatory Process.....   | 11 |
| The Role of Government-Directed Programs.....  | 13 |
| Utilizing Vaccine Stockpiles.....  | 14 |
| Liability Issues.....  | 16 |
| Enhancing Communication and Collaboration<br>Among Key Stakeholders.....                         | 17 |
| Summary and Conclusions.....   | 18 |

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## **Strengthening the Supply of Routinely Recommended Vaccines in the United States**

### **INTRODUCTION**

An unprecedented and unanticipated shortage of routinely recommended vaccines occurred in the United States beginning in 2001, resulting in significant and extended shortages of routinely administered vaccines against 8 of the 11 vaccine-preventable childhood infectious diseases. The affected vaccines included DTaP, MMR, varicella and pneumococcal conjugate vaccines; adult tetanus and diphtheria toxoids (Td) were also in short supply. Shortages of some vaccines have been more acute in the public sector than in the private sector. These shortages led the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) to recommend deferral of certain immunizations and to set priorities for high risk patients until supplies of vaccine returned to normal. These deferrals posed an increased risk of otherwise preventable infectious diseases.

The shortages were frustrating for physicians, parents and public health officials. Although supplies of DTaP, Td, MMR and varicella vaccines returned to normal by the summer of 2002, the shortages have led to an examination of the causes and the strategies needed to resolve the issues associated with vaccine supply. Why did the problem occur at this time? Was the multiplicity of vaccine shortages an untimely confluence of manufacturing problems or a systemic problem in development, manufacturing and regulation of vaccines? Why has an apparent fragility of vaccine supply occurred and what can be done to strengthen the supply?

The Department of Health and Human Services (DHHS) in 2001 requested that the National Vaccine Advisory Committee (NVAC) evaluate the problems of vaccine supply and prepare a report on strengthening the supply of routinely recommended vaccines in the United States. Accordingly, to identify potential causes of vaccine supply shortages, develop a comprehensive list of strategies to address and prevent future shortages, and enlist key stakeholders to consider the applicability, feasibility and effectiveness of these strategies, Georges Peter, MD, Chairman of NVAC, appointed a Work Group chaired by Jerome O. Klein, MD in April 2001. To meet these objectives, the Work Group convened a national workshop of stakeholders, including industry, regulatory authorities, public health officials, providers, purchasers, consumers and legislators. The workshop, “Strengthening the Supply of Routinely Recommended Vaccines in the United States”, was held in Washington, DC on February 11-12, 2002. This report is a collaborative effort by members of the Work Group and NVAC. It summarizes the workshop discussions and subsequent deliberations of the Work Group, and resulting conclusions and recommendations of NVAC to the Department to develop possible long- and short-term pragmatic strategies and solutions to avert shortages of routinely recommended vaccines. They address the following goals:

1. Maintenance of a predictable supply of licensed vaccines that are safe and effective;
2. Assurance of availability of routinely recommended vaccines for every eligible child and adult in the United States; and



3. Stimulation of development of new vaccines to decrease further the burden of disease.

This report by NVAC to DHHS will be complemented by a subsequent, detailed review of the current status of vaccine supply authored by NVAC. This subsequent review will provide documentation of the information on which this report and its recommendations are based.

## **BACKGROUND**

### **Valuation of Vaccines**

Prevention of infectious diseases by immunization has been one of the great public health achievements of the 20<sup>th</sup> century. Success has resulted from the development, availability, and acceptance of vaccines as safe and effective products for prevention of disease. Nevertheless, vaccines often are undervalued and many parents and physicians have no recall of the scourge of a vaccine-preventable disease. In addition, media reports and websites that impugn the safety of various vaccines cause alarm, raise concerns about liability, and disrupt the predictability of market demand of available vaccines.

### **Vaccine Purchase, Distribution and Administration**

Childhood vaccination in the United States, including vaccine purchase, distribution, and administration, occurs via a collaboration of public and private efforts. Approximately 56 percent of all childhood vaccine is purchased with public dollars, including federal, state and local funds; the remaining vaccine is purchased privately. The majority of publicly-purchased vaccine is distributed to and administered by health care professionals in the private sector. Privately purchased vaccine is administered almost exclusively within the private sector.

### **Vaccine Manufacture**

Vaccines typically are developed and produced by companies that manufacture a number of other pharmaceutical products. Vaccines must compete with other products within a manufacturer's portfolio. Factors such as the relatively long research and development period, the need for maintaining production facilities to meet current Good Manufacturing Practices (cGMP), and the relatively fixed market size (since vaccines are typically given only once or a few times to an individual) may hinder the competitive position of some vaccines relative to other pharmaceutical products. Nevertheless, manufacturers have a guaranteed but variable market based on recommendations for universal use of childhood vaccines.

### **Regulatory Processes**

The development of new vaccines may take many years, starting with the pre-clinical work and progressing through clinical studies that are needed to establish the safety and efficacy of the product. Manufacturing consistency and quality also have to be demonstrated as part of the development program. Licensing applications for new vaccines are reviewed by the Food and Drug Administration (FDA) in accordance with the Prescription Drug User Fee Act (PDUFA). This Act, first passed in 1992, was intended to provide resources to expedite review of biologicals and drugs and to set timelines and performance goals for these reviews. The FDA Modernization Act (FDAMA) of 1997 renewed PDUFA for 5 years and PDUFA was again renewed this year through 2007. Since enactment of FDAMA, under PDUFA, review times are 6 months for priority applications, and 10 months for standard applications. One section of FDAMA mandates that under a sponsor's request, FDA facilitate the development and expedite the review of certain products including vaccines, that have been designated by the agency as fast track, i.e., intended for treatment or prevention of serious or life threatening conditions and have demonstrated the

potential to address unmet medical needs for such conditions.

### **The Reality of Profit Margins**

Manufacturers must identify the optimal return on investment. New capital is available only for products that will provide an adequate return. Low profit margin products with increased production costs may lead to withdrawal from the market. Increasing cost of vaccine development and production, mergers of manufacturers and the relatively low revenues from sales contrasted with other pharmaceutical products may have contributed to a reduction in the number of vaccine manufacturers during the past 25 years.

### **Cost, Complexity, and Uncertainty of Development of New Product**

Barriers to production of new vaccines are the uncertainty of the market, the complexity of the products, the cost of large scale clinical trials that are necessary to document safety and efficacy, and the unpredictability of the demand for the new product. The recent withdrawal of rotavirus vaccine (as the result of association of intussusception with administration of the vaccine) and Lyme disease vaccine (resulting from limited use) illustrates the uncertainty for manufacturers even after successful clinical trials and FDA approval.

### **Problems in Manufacturing Approved Products**

Vaccine manufacturing is complex and involves uncertainties that do not exist in pharmaceutical drug manufacturing. For example, influenza virus vaccines pose unique problems, since the composition changes almost every year, the yield of candidate strains sometimes is not as high as desired which results in fewer doses, or strains may take additional time to obtain optimal yields, resulting in delays in the availability of vaccine. Changes in manufacturing may be necessitated by new requirements resulting from scientific developments,

such as new tests for adventitious agents. Production lead times for vaccines in general are long, often in the order of a year. Supply and demand may be misaligned when public health policy changes, such as when new or revised ACIP recommendations are issued, and results in increased demand before a sufficient supply is available.

If manufacturing problems arise and the product has only a single manufacturer, the shortage is immediate and acute. Pneumococcal conjugate vaccine (Wyeth), MMR vaccine (Merck), varicella vaccine (Merck) and IPV (Aventis Pasteur) are available only from a single US license holder. The problem also is acute in the case of only two or three manufacturers and one ceases manufacture, since a loss of 30 percent to 50 percent poses a substantial diminution of supply.

The requirements of cGMP balanced against predicted market share (and earnings) may be such that manufacturers will choose to cease production rather than invest in plant changes to meet regulatory requirements. In addition, introduction of new products such as combination vaccines may give some manufacturers a competitive disadvantage. The national distribution of adult tetanus and diphtheria toxoids decreased from 16.1 million doses in 1998 to 9.7 million doses in 2001 due to cessation of manufacture of the product by a major producer. The availability of DTaP likewise was affected by the decision to discontinue manufacture of this vaccine by the same major producer. Reasons for the shortages and delays in distribution of the pneumococcal conjugate vaccine include demand exceeding manufacturing projections as well as production problems.

### **Change in Vaccine Recommendations Necessitated by Shortages**

Changes in vaccine recommendations by authoritative groups such as the AAP and ACIP

may have significant ramifications. State regulations for vaccines for school entry may need to be modified and a recall system will need to be established to enhance catch-up so that children receive the requisite number of immunizations when vaccine becomes available.

Removal or reduction of the mercury-containing preservative, thimerosal, from vaccines for infants and young children has been recommended by the AAP, AAFP, ACIP and the Public Health Service. To a large extent, this recommendation resulted from FDA's review of mercury-containing products as mandated by the FDAMA. This review indicated that in some cases administration of mercury-containing childhood vaccines could lead to childhood exposures in excess of those recommended in some federal guidelines, although no evidence has been identified of a causal link between thimerosal and neurodevelopmental adverse events. The resulting transition to thimerosal-free and thimerosal-reduced vaccines is a contributing factor to the decreased supply of DTaP vaccine. Without a preservative, single-dose packaging is required for most vaccines. Single-dose filling of vials is less efficient than multi-dose filling, requiring more time and overfill of each vial to ensure that the provider can remove a full dose.

### **Problems of Vaccine Supply in 2001-2002**

The categories of factors leading to the vaccine supply shortages are two-fold: 1) immediate and identifiable factors that may resolve over a short period of time; and 2) generic and contributing factors that require long-term planning and assessment of the effects of an action and subsequent reaction to change in vaccine policies. Immediate factors are responsible for the current shortage while contributing factors are long-standing issues and problems that create a vulnerability to short- and long- term disruptions in the vaccine supply.

The most important **immediate and specific factors** that led to the current vaccine supply

situations are as follows:

1. Wyeth's decision to cease production of DTaP and Td.
2. Renovations that Merck instituted in their vaccine-filling suite, resulting in a temporary interruption of the supply of MMR, varicella and other vaccines produced by the company.
3. Large initial demand and several sporadic manufacturing problems that Wyeth encountered in the production of their pneumococcal conjugate vaccine, Prevnar.
4. Problems complying with cGMP by some manufacturers. This process is meant to be a dynamic, evolving process resulting in current and improved standards for drugs and vaccines. The composition of the inspection teams changed in the 1990s to include more expertise in design and control but the regulatory requirements did not change. The focus of the inspection teams shifted to include a greater focus on quality systems, in-process testing, and facility and process validation. As a result, facilities and processes that had previously been acceptable might now require significant changes in physical plants, quality systems and processes. The FDA

has a new initiative of cGMPs for the 21<sup>st</sup> century that will focus on a risk-based assessment of product quality issues.

5. Changes in recommendations regarding vaccines such as the decision to eliminate or decrease use of the ethyl mercury-containing preservative, thimerosal. Another example is influenza virus vaccine for which the recommended age for immunization was lowered from 65 to 50 years.

**Contributing factors** to the vaccine shortage include the following:

1. Relatively low valuation of preventive measures such as vaccines contrasted with that of therapeutic medicinals (e.g., lipid-lowering agents) reflected in the price the public and legislators are willing to pay for vaccines
2. High cost and complexity of development, approval, manufacturing and distribution of vaccines
3. Decreased number of vaccine manufacturers
4. Lack of investment in some vaccine manufacturing facilities
5. Legal barriers to communication between stakeholder groups that inhibit the recognition of evolving problems and development of effective responses

## **STRATEGIES**

### **Increasing Financial Incentives for Research, Development, Production and Administration**

Manufacturers should be able to obtain an appropriate profit for the research, development, approval and distribution of vaccines for the public well-being. Appropriate incentives must exist that encourage companies to enter and remain in the manufacturing

business. Companies leave the marketplace when a product no longer provides a reasonable return on investment. Pricing of a successful product must include the costs of failed products.

Incentives for research, development and production to provide a fair return on capital expenditure may be made available by means other than increased price. Such incentives could include tax relief for new facilities or reconstruction of old facilities, or other forms of subsidy as well as guaranteed market and price.

Developing contracts between government and manufacturers that reward performance, such as delivering an adequate supply of vaccine in a predictable manner, should be explored. This type of contract could encourage manufacturers to maintain an adequate inventory as a buffer against unexpected problems in production.

Preventive services need to be appropriately compensated. Proposed reductions in reimbursement and compensation for administering vaccines are disincentives for physicians and providers. The rates should include a realistic administration fee that reflects physician work as well as professional liability and practice expenses in order to encourage compliance with vaccine recommendations.

The Institute of Medicine (IOM) initiated an 18 month project in the fall of 2001 to develop a framework for identifying pricing strategies that can contribute to achieving current and future national immunization goals for children and adults. The Department of Health and Human Services should consider a request to the IOM to expand the current project or initiate a new one that would determine the nature of appropriate incentives based on accurate cost data so



that manufacturers can sustain the supply of existing vaccines and be stimulated to develop new vaccines.

### **Streamlining Regulatory Processes**

The FDA is the regulatory authority that is responsible for ensuring that licensed vaccines meet standards of safety and efficacy to protect the public's health. The goal of the regulatory process is to ensure that high quality, safe and effective vaccines are available. The vaccine-approval process is complex, labor intensive, expensive and time consuming. Although this industry is one of the most stringently regulated in the United States, consensus exists among the principal stakeholders that vaccine safety issues and maintaining credibility with the public demand and support the current regulatory processes. The following specific steps should be considered to enhance and streamline the regulatory processes:

1. Harmonizing the content and format for regulatory submissions of license applications in the context of the International Committee on Harmonization (e.g., the Common Technical Document) and working with other national regulatory authorities to achieve mutual recognition of lot release tests for various vaccines.
2. Reviewing the implementation of cGMP standards so that they do not have a material negative impact on vaccine supply except where needed to ensure vaccine safety. The review should ensure that science-based regulatory processes and decisions are being made. cGMPs need to be dynamic with changes that incorporate technological advances and maintain or improve facilities to current

standards but allow sufficient flexibility to ensure continued vaccine production within the context of maintaining safety and effectiveness.

3. Increased funding for the Center for Biologics Evaluation and Research (CBER). One of six centers within the FDA, CBER is a national resource for vaccine development, evaluation, regulation and research. CBER has a critical role in the translation of basic research to licensed products through applied research. The increased funding should permit CBER to recruit and sustain the work of highly qualified scientists. In the past, CBER scientists have made important contributions to the efforts of the FDA to provide knowledgeable regulation of vaccines and biologics. CBER scientists have standardized assays for potency of vaccines, including those for acellular pertussis vaccines and polysaccharide-protein conjugate vaccines. CBER has developed improved neurovirulence tests for viral vaccines (e.g., polio and mumps) and novel methods for the detection of adventitious agents.
4. Application for the designation as a fast track product should be considered by sponsors of vaccines that meet the statutory (FDAMA) criteria for such designation. This process was implemented in the review of the recently licensed pneumococcal conjugate vaccine.
5. Enhanced streamlining of the process to licensure of vaccines by early and frequent communication between FDA and sponsors, regulatory research that facilitates product development, fast track, and priority review accelerated approval programs. Legislation has been enacted to enhance and expedite the

review process including PDUFA of 1992 and FDAMA of 1997 which renewed the PDUFA for an additional 5 year period; recently PDUFA was extended through 2007. Further study is needed to determine if these provisions have fulfilled the intent of the legislation or whether additional legislation is needed.

6. Review of cGMP and regulations of vaccines and biologics. Questions to be answered by the review include whether vaccines and biologics should be regulated differently from drugs, and whether current policies and practices for vaccines create possible impediments to an adequate supply of safe and effective vaccines.

### **The Role of Government-Directed Programs**

Through the National Vaccine Program Office (NVPO) and NVAC, the mechanism is in place for a unified program and voice that identifies federal prioritization of vaccine development and distribution. The NVPO is constituted to perform the critically important task of coordination of the many federal agencies involved in vaccines and should be supported to accomplish this task. The mission of NVAC, as given in the 1986 legislation that established NVPO and the Committee, includes the following objectives: develop goals and initiatives for an annual National Vaccine Plan that shall establish priorities in research and development; identify annually the most important areas of government and non-government cooperation that should be considered in implementing the National Vaccine Program; and advise on the direction of the National Vaccine Program with regard to vaccine activities carried out by or through other government agencies, including the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Department of Defense and the Agency

for International Development. Thus, the goal of a government agency that can provide a unified approach to questions of federal prioritization of vaccine development and distribution to assure that public health needs are met is now in place.

Government owned or operated facilities (GOCOs) are less likely to be advantageous for production of routinely administered vaccines and are not likely to accomplish longer-term vaccine production goals. Such GOCOs may be useful or critical to national defense needs and those of the military but would appear to be limited in ability to respond to the needs of routinely administered vaccines. If the federal government becomes a vaccine manufacturer, industry may not be able to compete with a government-subsidized program. The result may be the further withdrawal of private manufacturers from the United States market and the loss of innovation and introduction of new products.

### **Utilizing Vaccine Stockpiles**

Vaccine stockpiles can be used to ameliorate short-lived production problems, which are likely to occur from time to time. Stockpiles are the most effective short-term solution to overcome some vaccine shortages but may be of limited value for long-term disruptions. At the initiation of the vaccine stockpile program in 1983, stockpiles of six-month total national supply were the goal. The current stockpile includes partial stockpiles for MMR, IPV, and, most recently, varicella vaccines; a small stockpile of diphtheria and tetanus toxoids for children (DT) also is maintained. The inventory is dynamic with storage and rotation of vaccines. As new vaccine is produced, it enters the stockpile and older vaccine is rotated into distribution and use. According to CDC, the stockpile has been utilized advantageously on at least eight occasions since 1983 to alleviate vaccine supply problems. Limitations and challenges in developing an

effective stockpile program to address short-term shortages include varying storage conditions, changing vaccine formularies, varying market share, and generating adequate supplies of newly licensed vaccines.

A comprehensive plan to overcome these challenges should be formulated. In doing so, consideration must be given to the size of the stockpiles, the formulation of vaccine (ready-to-ship vs. unpackaged or unlabeled product), procedures for monitoring and accountability, procedures for stockpile activation, and the costs for vaccine purchase as well as storage and rotation.

The development of strategic inventories has risks. Even though vaccines in the inventory can be stored temporarily and then rotated to be distributed to providers, in cases where the inventory may exceed baseline demand as the result of change in perceived need or national recommendations, some of the vaccine may become outdated. The government needs to assume the financial risk of unused vaccine or vaccine for which no demand exists. Although most vaccines can be stockpiled, influenzavirus vaccine is an exception because a different vaccine is created each year.

The concept of a national stockpile to be used in times of shortage appears to be the most advantageous short-term solution to prevent future shortage crises. The CDC should be provided with additional resources for stockpiling a larger number and sufficient quantity of routinely administered vaccines.

## **Liability Issues**

The Vaccine Injury Compensation Program (VICP) enacted in the late 1980s has been of immense value in stabilizing the vaccine market. Prior to its enactment, litigation led to national shortages, withdrawal of manufacturers from the marketplace, and instability of supply of essential childhood vaccines. The VICP was designed to compensate individuals who suffered a serious adverse event as a result of administration of a covered vaccine in a manner that was rapid, simple, generous and appropriate. The VICP has assisted in stimulating the availability of new vaccines since its inception in 1988. Despite the success of the program, criticism of the VICP could lead to significant legislative changes, including a more relaxed burden of proof standard for determining eligibility for compensation. Today, litigation again threatens stability of the vaccine program in the form of class action law suits, exemplified by those that have been filed involving vaccines that contain thimerosal. The VICP is currently understaffed to meet the new increased numbers of claims. While current vaccine shortages do not appear to be liability related, the VICP should be maintained and strengthened as supported by scientific evidence, including continuing expansion of VICP to include additional vaccines as they are recommended for routine administration to children. The VICP coverage of vaccines should recognize that “vaccine” includes the active ingredient as well as preservatives, additives and other excipients. Strengthening the VICP would benefit manufacturers, providers and consumers and further safeguard the nation’s vaccine supply.

## **Enhancing Communication and Collaboration Among Key Stakeholders**

Manufacturers should be required to provide advance notification to the DHHS regarding termination of production of a vaccine. Currently, manufacturers can withdraw from the vaccine marketplace without advance notice. Withdrawal without sufficient planning may lead to disruptions of the vaccine supply; sufficient advance notification is essential so that authorities can plan to mitigate vaccine shortages.

Supply information is proprietary because it provides a view of capacity. The DHHS should be permitted to utilize proprietary vaccine supply forecast information so long as the information remains confidential. The CDC and/or FDA should continue to share in confidence proprietary supply information to maximize the efficiency of vaccine supply. Development of a mechanism for providing information to manufacturers to permit increased capacity to address supply limitations that threaten the public health while protecting proprietary information is needed.

The transparency of information for opinion leaders and consumers should be increased. Frustration of consumers and physicians results from the uncertainty and vagueness of information about the causes of vaccine shortages and the time to obtain adequate supplies. As a result, some professionals and non-professionals may accept rumors that the vaccine shortages are contrived by manufacturers to increase the price of the product. The role of a readily accessible website, such as that of CDC and AAP, that gives current information about vaccine supply should be enhanced so that physicians and consumers can plan catch-up immunization and maintain confidence in vaccine programs.

A national campaign to emphasize the safety and efficacy of vaccines is needed. Public

awareness of prevention as the most effective tool against disease and immunization as a cornerstone of prevention of infectious disease needs to be increased. Current efforts to encourage appropriate use of vaccines should be amplified by a coordinated program involving government, industry, academia, professional societies and consumers to emphasize the value of recommended vaccines for the individual and the community.

## **SUMMARY AND CONCLUSIONS**

Disruptions to the supply of routinely administered vaccines are likely to continue to occur. Action to implement short- and long-term solutions should be considered and initiated now. Action items discussed in this report are summarized here and a program for their implementation should be initiated at the earliest possible time.

### Solutions that may be implemented in the immediate future include the following:

1. Increase funds for vaccine stockpiles to include all routinely administered vaccines in sufficient quantity to be used for amelioration of supply problems or surge demands.
2. Increase support for the Center for Biologics, Evaluation and Research to continue to enhance its scientific and clinical base and the ability of this FDA program to review the scientific evidence that supports the safety, efficacy and quality of vaccines.
3. Identify for all stakeholders that the NVPO and NVAC provide a mechanism for a unified Federal prioritization of vaccine development and distribution as specified in the 1986 enabling legislation.



4. Maintain and strengthen the Vaccine Injury Compensation Program. Coverage of vaccines by the VICP should define “vaccine” as including the active ingredient as well as preservatives, additives and other excipients.
5. Require vaccine manufacturers to provide advance notification to the Department of Health and Human Services regarding intent to withdraw from the market.
6. Increase the availability of accurate information about vaccine supply for opinion leaders and consumers. Appropriate information about vaccine supply can be communicated by a website containing current information about the availability of vaccines.
7. Enhance the valuation of vaccines by initiating a national campaign to emphasize the safety and efficacy and great benefit of recommended vaccines for the public good.

Solutions that are more complex and will require more study include the following:

1. Convene a multi-disciplinary group to evaluate the nature of appropriate incentives for manufacturers to sustain the supply of existing vaccines and stimulate development of new vaccines.
2. Streamline and strengthen the regulatory processes and the activities of the FDA, including a) support the work of international harmonization for mutual recognition of lot releases of various vaccines; and b) review the implementation of current Good Manufacturing Practices to assure that science-based decisions regarding vaccine safety and efficacy are made.

The Committee at its June 4-5, 2002 meeting endorsed in principle the assessments and

recommendations in this report and on October 8, 2002 approved this report to be forwarded to the Assistant Secretary of Health who also is Director of the National Vaccine Program. In accordance with the further recommendations of the Committee, the Work Group will continue to consider the issues in strengthening vaccine supply and develop a prioritized list of specific implementable recommendations to be considered by the Committee and forwarded to the Assistant Secretary.