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Good morning. On behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA), I am pleased to appear at this hearing today on childhood vaccines. I am Wayne Pisano, Executive Vice President of Aventis Pasteur North America. PhRMA represents the country's major research-based pharmaceutical and biotechnology companies, including the four PhRMA companies that make 100% of children's vaccines, and 90% of all vaccines. Many people are surprised that the industry is so small, but that fact is largely the result of the liability crisis of the 1980's that drove most companies out of the market. I will talk more on this later in my testimony.

We are all keenly aware of the vaccine shortages facing our nation today. Although most of these shortages will be resolved in 2002, this hearing provides an excellent forum for understanding the underlying causes as well as addressing what can be done to minimize the chances of recurrences and how best to act if there are recurrences. The fact that the private sector has the capacity to respond reasonably quickly to supply issues demonstrates the strength and vitality of our industry. While we are addressing supply issues successfully, I will offer six specific suggestions as to how our nation's vaccine supply can be strengthened while maintaining a vital and productive industry.

Our nation benefits from the efforts of several world-class vaccine companies. At Aventis Pasteur, for example, vaccine production began at our Swiftwater, Pennsylvania site in 1897, with an immediate goal of providing an improved smallpox vaccine. More than a hundred years later, this campus continues to develop and manufacture improved and new vaccines to protect against a variety of diseases. Over the years, we've had some enormous successes, including the first application of conjugate vaccine technology and the first infant acellular pertussis vaccine. We have also invested enormous resources into vaccines that, for a variety of reasons, did not reach the marketplace. Although these new product failures do not affect supply directly, the economics do impact the attractiveness of the industry. The full cost of development – contrasted with historical vaccine pricing – is at odds.

We have in the country a unique and amazing vaccine enterprise that has resulted in freedom from disease for millions of children. Many of today's parents have never heard of diseases such as polio, Hib or measles, outside of the context of the vaccines that prevent them. Many physicians would be treating some of the tens of thousands of cases of rubella, diphtheria, pertussis and other potential killers if not for our successful efforts. Smallpox has been eradicated. Wild poliovirus has been eliminated in the U.S. and many other countries with global eradications underway or being discussed. Diphtheria, rubella, tetanus, mumps measles – even Hib disease – are now rarely seen. Since the introduction of a vaccine for Hib a few short years ago, the incidence of this disease has plummeted 98 percent! Vaccines, in the hands of a robust, cooperative public and private health delivery system, have made these diseases historical artifacts.

This success story is not restricted to the millions of children who receive a vaccine each year. Adults also have benefited enormously from immunization. Nearly 80 million people received an influenza vaccine this season, nearly triple the number that did so a decade ago. While the flu vaccine's most important benefit is the number of lives it saves, it also has contributed to reduced incidence and severity of disease, and, as more healthy younger people opt for an annual shot, a payoff to employers in reduced absenteeism and healthcare costs as well.

With that as background, it is time to take a step back and consider <u>how</u> the immunization enterprise in the country works, what we are doing right and what might be improved.

There are several characteristics of the vaccine enterprise that make the close cooperation of all participants, within the bonds of the antitrust laws, critical for proper alignment of supply with demand.

First, unlike almost any other aspect of our healthcare system, vaccines protect our entire society in addition to improving personal health. So, there needs to be much closer collaboration during vaccine production, distribution and administration than for other healthcare interventions. Everyone participating in the immunization enterprise must be involved, be they manufacturers or physicians, nurses or public health workers, policy makers or managed care.

Second, whether or not a vaccine will ever be used widely – or at all -- will depend on recommendations formulated through extensive public discussion. That collaborative approach, accompanied by adequate timeframes, has moved mountains over the years.

Third, the regulatory approval process for new vaccines, and for changes to existing vaccines, is highly complex and lengthy with timetables that are difficult to predict. Taking into consideration the fact that production schedules can run 12 months and longer, any abrupt changes in policies that can influence demand for a vaccine, or the unanticipated departure of a manufacturer, can result in supply interruptions that last for months.

Fourth, as I stated earlier, the liability crisis of the 1980's drove most vaccine manufacturers out of the market. Over a dozen vaccine companies existed in the early 1980's but liability problems shrunk that number to the four that exist today. In 1986, Congress created the Vaccine Injury Compensation Program, which helped alleviate some of the liability concerns. But the industry is once again facing the possibility of massive lawsuits and mounting legal bills, which we are convinced warrants shoring up the VICP.

For the most part, the immunization enterprise is quite efficient. Every child in the United States has access to immunization. No one needs to go without because of cost; both public and private sectors have honed programs over the years that get children to vaccines and vaccines to children. Nearly 20 million routine pediatric visits take place each year, often because immunization is the incentive.

Fifty years ago there were only four antigens available to children: smallpox, diphtheria, tetanus and pertussis. By the 1960's we had added polio, measles, mumps and rubella to the regimen; in the following decades Hib, hepatitis B, varicella and pneumococcus were included. Today, twelve diseases are largely prevented through the pediatric immunization series. We believe that we are still in the early stages of a remarkable era in disease prevention and that additional vaccines will be available during the next few years as current vaccine candidates progress through the pipeline. These new vaccines will either be new combinations allowing a greater number of antigens to be given in a single injection or entirely new vaccines to protect against diseases for which we have no vaccine today.

Yet, with what has become nearly universal access, tremendous coverage and added protection, there are still deficiencies in the system that require a tune-up.

During the past few years, we have had several vaccine shortages, mostly because of short-term acute reasons. Some, as in the case of flu vaccine, reflect the inherent difficulty in biologics manufacturing such as when the vaccine needs to be reformulated every year. There is always some degree of uncertainty and the solution lies with the vaccine enterprise that manages distribution and immunization policy. We need to look at what causes shortages, what exacerbates them and what might mitigate them. We have seen a confluence of factors over the past two years that has led to the recent shortages.

Nature of Vaccine Manufacturing

Let's look for a minute at the nature of vaccine manufacturing, which is complex and involves a number of variables that don't exist in pharmaceutical manufacturing. Vaccines require the use of biological organisms, viruses and bacteria, which will not always grow or respond on demand. It is not a matter of opening a tap and pouring out vaccine, no matter who controls the tap. Production lead times are long and the quality control process is the strictest possible. Every lot must pass purity and potency testing not just by the manufacturer but by the FDA as well. As a result, supply and demand will be misaligned when policy changes increase demand before supply is available. We have experienced several such acute shortages during the past several years.

Discontinuation of Vaccine Production

The decision by manufacturers to discontinue production of certain vaccines has been the most significant factor in a series of serious but temporary shortages. In the last two years – after a period of relative stability – we have lost production of several vaccines. Companies may decide to leave marketplaces when a product no longer provides, in a particular company's assessment, a sufficient potential return on investment. Some of the factors that influence return on investment are cost of new product development, cost of manufacturing, product demand and the existence of free market pricing versus various forms of government price controls. When a manufacturer discontinues production, ramp up by other manufacturers to fill the gap may take more than a year for some products.

Tetanus Shortage 2001-2002

Tetanus vaccine is an example of an acute shortage that we anticipate resolving this year. Last year, there was an unanticipated withdrawal by a tetanus vaccine manufacturer leaving Aventis Pasteur as the only manufacturer of Td, DT and TT. Aventis Pasteur had taken a hard look at there own tetanus operations several years prior to this and decided to make the infrastructure upgrades necessary for this essential product. However, at the time we did so we expected that we would be supplying only part of the marketplace. Since it takes approximately 11 months to produce a batch of tetanus vaccine, it soon became evident that there would probably be a national shortage following the other company's exit. We immediately began working with the CDC to manage the available Td doses to ensure that all critical immunization needs were being met and that tracking of deferred booster doses was implemented. This shortage has resulted in some inconvenience, to be sure, but, because of strong collaboration between the manufacturer, the CDC and medical societies, we have succeeded in protecting the health of our citizens. We are implementing plans to return to a normal supply situation – in an orderly manner – by the end of the year.

Another critical consideration over the past year has been the maintenance of safety stocks of Td vaccine. No day underlined the need for a safety stock as did September 11th. Aventis Pasteur was able to deliver 50,000 doses of tetanus to New York City and 10,000 to New Jersey within hours. Similarly, we are prepared to respond to natural disasters that may place large, sudden demands for Td deliveries.

As an added precaution, Aventis Pasteur has just obtained American licensing for our Canadian DTaP product – Daptacel – which will ameliorate shortages of this important childhood vaccine.

Likewise, supplies of mmr vaccine have stabilized and varicella vaccine supplies are improving and providers may be able to return to the recommended vaccination schedule by August of this year.

Impact of policy changes and regulatory approvals

Policy and regulatory changes also have an enormous impact. I'd like to talk about the industry's experience with two ends of the spectrum and their implications to supply.

Thimerosal

Since mid-1999, policymakers have taken the position that Thimerosal must be removed as a preservative from all childhood vaccines.

The removal of thimerosal can serve as a valuable glimpse into the cascade of events that can – and did – exacerbate a shortage of a vital childhood vaccine, dtap, following the decision to remove thimerosal from the product.

Thimerosal serves as a preservative. It also allows healthcare providers to purchase and use convenient multi-dose vials without risking bacterial contamination as they continue to draw from a vial. Without thimerosal, single-dose packaging must be used. The decision to remove thimerosal significantly impacted supply. The manufacturing process itself had to be changed in order to assure the aseptic filling of the single-dose vials. In addition, the process changes lengthened the manufacturers' timelines and yields dropped significantly since it is necessary to overfill every vial to ensure that the provider can remove a full dose. The cumulative effect of this overfill is dramatically greater for single-dose vials than for multi-dose vials.

Reformulating a vaccine, as was required in order to convert from a preservative-containing vaccine to a preservative-fee vaccine, requires first completing passage through the regulatory approval process. Any change to a vaccine is a complex endeavor. Manufacturers must take the reformulated product through a license application, with concomitant establishment of new procedures, validation, testing, labeling and getting the product into the marketplace. The net effect is that we invested approximately two years' development effort to replace an existing product.

The removal of thimerosal presented significant and complex problems as we changed from a multi-dose to single-dose presentation. This change not only took a considerable amount of time and effort, but also reduced our total output by approximately 25%. This is obviously a significant impact.

All vaccine manufacturers strive to supply safe and effective products. However, the point here is that actions have consequences and that those who make the rules need to carefully weigh credible evidence so as to avoid decisions based on unreliable data, and must factor in the implications of their decisions on supply and allow realistic time frames when considering such changes. Every independent action has dependent reactions, some of which are very detrimental.

CGMPs and Team Biologics

While the current Good Manufacturing Practices (CGMP) have not technically changed, interpretation by regulators is in a constant state of flux. CGMP regulations are very broadly stated guidelines not constrained by detailed regulatory requirements. With guidelines it is possible to functionally incorporate technological advances, procedural changes or industrial advancement of what was previously called "best practices." This explains why the very name of the regulation was changed by the FDA to Current Good Manufacturing Practices to add emphasis to the fact these are dynamic standards.

This is based on the very process of how the FDA inspects vaccine manufacturers. Several years ago, the FDA established Team Biologics and increased the emphasis on CGMP quality issues for all biologics companies, starting with blood products manufacturers and moving to vaccine manufacturers.

The requirement that vaccine manufacturers stay current with technological advances has necessitated a significant and ongoing investment in facilities, including older facilities in which older commodity priced products are produced. These requirements are sometimes put into effect even in the absence of any demonstrated concerns with the vaccines produced in those facilities. New investments have also been made necessary in process validation, and in the hiring and training of personnel with high levels of expertise needed to ensure that long-term CGMP quality standards are being met and sustained. The important point for a discussion in strengthening supply is that we must be realistic about the necessary investments in time and money involved in operating a modern vaccine production facility, even while manufacturing products that were licensed decades ago and continue to be produced safely and effectively.

Return on Investment

As I mentioned earlier, a major cause of supply fragility is what has been characterized as a poor potential return on investment, particularly for older vaccines. Historically, vaccine purchasers have wanted to treat vaccines as commodities, even though they are not, and the system has driven prices down. Raising prices can be difficult, or impossible, yet ongoing investments are required to meet evolving CGMPs and to develop improved formulations. It should be no surprise that, when manufacturers find themselves holding low margin commodity products with increasing production costs, some choose to opt out. In order to ensure that we have state-of-the-art formulations and the most modern way to produce them, manufacturers should be encouraged to invest in infrastructure rather than disincented as is too often the case today.

What We Don't Need

Industry is up to the challenge of producing childhood vaccines which are safe, effective and in sufficient number of doses to immunize America's children.

Several proposals in Congress would undermine incentives for existing and potential manufacturers to produce vaccines. Whether called "national vaccine authority" or "GOCOs" (Government-Owned, Company Operated), the common theme of these proposals is to have the federal government get into the business of manufacturing vaccines.

Government competition would stifle new vaccine entrants into the market without guaranteeing any more supply of vaccines and requires the limited universe of top scientists in the field to develop them.

There are no shortcuts to making vaccines. It is a long, expensive and cumbersome process – a process which the government would have to go through before its first dose ever reached the market – probably at least a decade from now. A GOCO would not have alleviated any of the recent shortages experienced in the U.S.

A GOCO would not result in faster changeover of production lines than commercial plants in the event of a vaccine shortage, and wouldn't be able to switch from one vaccine to another. Usually you can't even use the same lines for spore, fermented, viral products and particularly bioterrorism agents. Even if it were possible it requires special air handling, multiple re-inspections before switchovers to prevent contamination. Different vaccines require different features on filling lines. These features need to be re-standardized and tested every time a change occurs. No plant could simply have switched to produce influenza or DTaP. Different complements of technicians may well have to work on different lines given exposure risk issues. If one vaccine exposure problem occurred it would cause a ripple of inspections to all lines to prevent cross contamination. Even government vaccines would need to be safe and effective.

It is often overlooked that it is science, not manufacturing, that is the limiting factor in developing new vaccines. All the manufacturing capacity in the world can't produce a vaccine until science develops the product.

What We Do Need – Strengthening Vaccine Supply

Today we offer six proposals to ensure a stronger vaccine supply. They involve cooperation, between government and industry providers and, we believe, will have a positive impact on strengthening our system by building on what is already in place.

1) We support expanded stockpiles for use if supplies are disrupted

   We support additional funding for the CDC to establish stockpiles for both single and multi-source products. In recent years, the number of vaccine stockpiles has decreased. It is time to look at how to use them as a significant source of stabilization of supply in the face of unforeseen fluctuations or the loss of a manufacturer for which advance notice cannot be provided.

   For example, had there been a national tetanus stockpile we would not have had the shortages we recently experienced while the remaining company expanded its production – a process that takes up to a year.

   It has been suggested that such a stockpile would cost some $750 million but we believe that is a worthwhile expenditure for the nation's health. The recently-passed bioterrorism bill includes authorization for stockpiles for bioterrorism vaccines but not childhood vaccines.

2) Use the expertise of vaccine manufacturers to help formulate sound immunization policy.

   Manufacturers have and continue to have ongoing information discussions with policymakers and government officials at agencies like the CDC. This is because manufacturers can provide realistic assessments and expertise about how vaccines are developed and produced, the challenges in doing so as well as a view into how providers practice and use vaccines. We deal with tens of thousands of providers each year, public and private, and cutting across the specialties, and we can share our insights to help improve delivery. It is important that those making vaccine policy, both on staff and on expert committees, have this expertise available to them. However, in more formalized settings, this

is no longer occurring. An example is CDC Working Groups where industry representatives are no longer permitted to fully participate in discussions. To exclude industry from these considerations risks that regulations and guidance will be based on incomplete information that could result in wasted resources, inefficient implementation of policy changes and ultimately a loss of faith in our immunization system. We are a resource that should be used. Making policy in a vacuum is a recipe for future supply problems.

Industry does not expect to participate in decision-making but, given the limited universe of vaccine expertise, government can benefit from the views of vaccine experts in industry.

3) Government and advisory bodies need to act with greater predictability

Continued uninterrupted manufacturing and distribution of vaccines is dependent upon reasonably predictable action by government agencies and advisory committees as well as open lines of communication between those bodies and the manufacturers. Government agencies and advisory committees need to be aware that changes in manufacturing or other regulatory policies could impact future supply, and should take such possibilities into consideration when proposing new policies. Specifically, we suggest that government agencies and advisory committees need to allow adequate advance notice whenever manufacturing changes are necessary. Simply put, if the changes are required before manufacturers can make them and the FDA can approve them, shortages will occur. To this end, the regulatory and guideline process needs to be kept predictable, without abrupt changes in requirements of guidelines and with ample opportunity to communicate about the implications.

4) The Vaccine Injury Compensation Program should be strengthened.

The Vaccine Injury Compensation Program stabilized our national immunization program since the late 1980's, reducing the frequency of the liability uncertainty that had destabilized the industry. The VICP provides a system of compensation and requires that injury claims be litigated initially within the VICP. Prior to its enactment, litigation had left a trail of national shortages and instability of supply of essential childhood vaccines. Recently, new strategies have emerged for vaccine injury claims which are intended to circumvent the Program. Once again, manufacturers are facing liability exposure that measures in the billions of dollars. This trend is evidenced in large part by the upswing in the number of lawsuits primarily involving Thimerosal. We are concerned that, without a re-doubling of the effort needed to address these issues, we will once again be in the same position that we were in nearly twenty years ago, this time encompassing both pediatric and adult vaccines. We propose strengthening the existing VICP effort.

Recently, Senator Frist introduced a thoughtful and comprehensive vaccine bill, S. 2053. It contains a section on VICP, which adopts the recommendations of the Advisory Commission on Childhood Vaccines to make the system more user friendly.

In addition, it reiterates that the intent of VICP is that vaccine claims proceed initially through the program. We strongly recommend the provisions of the Frist bill to you.

5) Strengthen our messages that prevention is the most desirable intervention.

A reorientation of healthcare priorities to emphasize prevention over cure will provide incentives to doctors to immunize patients and to manufacturers to maintain their commitment to vaccine production.

Our society has traditionally preferred to pay for treating a disease rather than preventing it. People are prepared to spend thousands of dollars a year on a treatment once they contract a disease but will balk at paying modest sums to prevent it from ever happening. If we are to realize the potential of vaccines, we need to change that thinking. Otherwise, people will continue to gamble that they won't get a disease and use insurance if they lose.

There needs to be sufficient willingness to pay for preventive services. Recent reductions in CMS reimbursement are disincentives to physicians. Reimbursement rates should reflect the full value of vaccines including a realistic administration fee.

6) Heed the warning signs of a real and present danger – increasing lack of confidence in immunization.

The good news is that parents no longer fear many infectious diseases, because of the success of our immunization programs. Yet, they have also lost an understanding of the importance of vaccines, as they lack first hand experience or knowledge of the devastating damage vaccine preventable diseases can cause. It would be a failure of immense magnitude if we allow old and conquered scourges to regain a foothold because of misinformation. We urge you to look at ways to bring the public into the process and boost its confidence in immunization. There is as much of an urgent need to address misinformation about immunization as any other aspect of this issue. In a sense, the entire immunization enterprise is under siege

The vaccine enterprise in this country is a remarkable success story. I hope you will give consideration to the proposals we have laid out to protect and strengthen it. Fortunately, we have an industry that wants to partner with government and with all elements of our nation's immunization enterprise to achieve even greater successes.

Thank you very much for your attention and your commitment to the immunization system in this country.