

**DIPHTHERIA, TETANUS AND ACELLULAR PERTUSSIS
VACCINE (DTaP): A CASE STUDY**

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Introduction

This case study provides an overview of the U.S. experience with DTaP B the combination vaccine that includes diphtheria, tetanus and acellular pertussis components. While DTaP is a relatively new vaccine, first approved for use in the U.S. in 1991, its history spans well over half a century and its story in many ways reflects key developments in immunization markets, infrastructure and policy.

In tracing the history of DTaP, this review is divided into four sections: (1) The Legacy of DTP; (2) Initial Development and Licensure of DTaP; (3) Market History: Production, Supply, Purchase, and Pricing Issues; and (4) Future Directions for DTaP.

The Legacy of DTP

To understand the history of DTaP, it is necessary to understand the legacy of its whole-cell predecessor, DTP (diphtheria, tetanus, and whole-cell pertussis) vaccine. Simply put, over the course of two decades (from the 1970s to the 1990s) safety issues related to the whole-cell pertussis component of DTP drove a series of events that dramatically impacted the vaccine industry, led to a reshaping of vaccine policies and programs, and resulted in an intensive international search for a new, acellular pertussis vaccine.

Early History of DTP

One of the first combination vaccines to be licensed by the Food and Drug Administration (FDA), DTP was integrated into routine pediatric care in the late 1940s and remained a staple of preventive services in the U.S. through the mid-1990s (CDC, 1992d). With its introduction and widespread use, the incidence of three life-threatening illnesses plummeted. For those who had observed first-hand the ravages of diphtheria, tetanus or pertussis, the three vaccines were nothing short of a miracle. And combining all three antigens into one Ashot@ meant that children could be protected in an efficient manner with the least possible trauma.

Unfortunately, there was also a downside to DTP. While clearly effective in preventing disease, the whole-cell pertussis component was associated with a range of adverse events, including rare but serious neurological consequences. Concerns about the safety of whole-cell pertussis vaccine date back to the 30s and 40s (Mowery and Mitchell, 1995). By the 1950s, concern about potential adverse events led some researchers to begin searching for a more refined, acellular version of pertussis vaccine that would confer immunity with less reactogenicity (Felton, 1957).

International Concerns about DTP Safety Mount in the 1970s

In the early to mid-1970s, the safety of whole-cell pertussis came under increasing scrutiny both in the U.S. and abroad. Newly heightened concerns were in part related to reports published in Great Britain and Germany linking whole-cell pertussis vaccine to long term neurologic effects. Consumer concerns translated into rapidly declining immunization rates in several countries, including Great Britain and Japan, among others (Gangarosa et al.,1998).

Public concern about the safety of DTP reached a tipping point in Japan and Great Britain in the mid-1970s. In 1975, in response to the deaths of two infants within 24 hours after DTP vaccination, Japanese health authorities temporarily suspended the routine use of pertussis vaccine in infants, and soon after recommended that immunization against pertussis start instead at age two years. What followed was a decline in immunization coverage and a dramatic increase in pertussis cases and deaths among Japanese children, peaking in 1979 (CDC, 1992d). In Britain, while health authorities continued to recommend routine DTP immunization for infants, the public became increasingly wary of potential adverse effects, and many parents chose not to immunize their children. In the absence of mandates or other enforcement mechanisms, Great Britain, like Japan, experienced a rapid increase in pertussis cases and deaths (Gangarosa et al.,1998).

During this same period, Japanese researchers accelerated efforts to find a safer vaccine, utilizing a pertussis component that was acellular rather than whole-cell. By 1981, their efforts had paid off: several diphtheria, tetanus and acellular pertussis (DTaP) vaccines had been licensed by Japanese health authorities (CDC, 1992d; Noble et al., 1987).

The U.S. Experience: Safety Concerns Reshape the Market in the 1980s

In the U.S., while public concerns about the safety of DTP gained momentum starting in the 1970s, it was not until the early 1980s that the issue exploded domestically. Three related sets of events converged to reshape the U.S. market for DTP and for childhood vaccines more generally: (1) dramatic increases in media coverage of potential adverse effects of DTP; (2) exponential growth in product liability lawsuits brought by consumers against pertussis manufacturers, and (3) exiting of manufacturers from the market.

More specifically, television documentaries such as *Vaccine Roulette*, which aired in 1982, helped to sensitize the public and policy makers to safety concerns. Between 1981 and 1982, the number of news stories covering pertussis more than tripled, from fewer than 30 to over 100. Product liability suits saw an even greater increase: From 1978 through 1981, a total of nine product liability lawsuits were filed against DTP manufacturers in the U.S.. For the single year 1982, however, 17 DTP lawsuits were filed; and by 1986, the number of pertussis product-liability suits filed during the year reached an all-time high of 225 (Sing and Willian, 1996). During a six-month period in 1984, in response to the growing liability crisis, two of the three manufacturers distributing DTP in the U.S. market B Wyeth and Connaught B dropped out, leaving Lederle as the sole supplier in the U.S. (CDC, 1984).

U.S. Public Health Response: Immunization of Infants Maintained

As the nation faced declining public trust in vaccines and manufacturers pulled out of the market, public health officials grappled with a crisis in vaccine supply and the very real prospect of major outbreaks of vaccine preventable disease. U.S. health authorities took a somewhat different route from their international counterparts, hoping to avoid the kind of upsurge in childhood pertussis that Japan, Britain and other nations had experienced. In the U.S., health officials continued to recommend routinely immunizing infants and young children with five doses of DTP, with doses to be administered at ages 2, 4, 6 and 15-18 months of age, and a fifth booster dose administered at 4-6 years. This recommendation held until December 1984, when a severe shortage of DTP necessitated a temporary revision in the schedule. Forced by the shortage to cut back on coverage in some way, the U.S. Public Health Service chose to continue the first three doses of DTP and to postpone the fourth and fifth doses, thus assuring coverage for infants in the most vulnerable population (CDC, 1984).

At the same time, U.S. immunization officials also stepped up research in two areas: first, they sought new information on the relationship between whole-cell pertussis vaccine and serious neurologic consequences, and second, they accelerated research efforts to develop and assess the safety and efficacy of acellular pertussis vaccines (CDC, 1992d). (See below for the role of the National Institutes of Health in financing and accelerating clinical trials of acellular pertussis.)

Congressional Response: The National Childhood Vaccine Injury Act

Against this backdrop, Congress responded by passing the National Childhood Vaccine Injury Act of 1986, a comprehensive legislative package that established: (1) the National Vaccine Injury Compensation Program (NVICP), a no-fault compensation program that limits manufacturer liability and provides substantial payments to the families of children who sustain documented injuries following routine immunization with recommended childhood vaccines; (2) the National Vaccine Program, which was charged with developing and coordinating a comprehensive National Vaccine Plan; (3) the Advisory Commission on Childhood Vaccines, which advises the Secretary of Health and Human Services on the injury compensation program; and (4) the National Vaccine Advisory Committee, which advises the Secretary on national vaccine policy. Both of the advisory committees include a range of immunization stakeholders: parents and other community representatives; public health officials; clinical practitioners; and manufacturers, among others. The Act also mandated that the Secretary of Health and Human Services promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market...and promote the refinement of such vaccines@ (National Vaccine Injury Act of 1986. Pub. L. No.99B660). Finally, a 1987 amendment to the Compensation Act established a federal excise tax on childhood vaccines, the proceeds from which are used to finance NVICP payments to families of affected children (Johnson et al., 2000).

The compensation program was almost immediately effective in controlling DTP lawsuits. Following its enactment in October 1988, the number of DTP liability suits against manufacturers

declined markedly from 114 in 1988 to only 18 in 1991 (Sing and Willian, 1996.) In addition, the mandate to promote safer childhood vaccines helped to assure that acellular pertussis vaccine would become a high priority on the NIH research agenda. In short, this sweeping legislation dramatically restructured the market and significantly enhanced the government=s role in maintaining an adequate and safe vaccine supply. In addition, the Act has gone well beyond the immediate concerns relating to DTP: Since both the compensation program and the related federal excise tax cover all routinely recommended childhood vaccines, the National Childhood Vaccine Compensation Act and subsequent amendments have affected availability, price, and safety considerations for all essential childhood vaccines.

Lessons Learned

The DTP legacy yields important lessons for the future, including the following:

- ***Safety issues B and especially public perception of safety B have a profound effect on immunization coverage, production decisions, vaccine development and government policies and programs.*** Safety concerns about DTP from the mid-1970s through the mid-1990s impacted the number of manufacturers in the market; shaped the government=s role in financing clinical trials and accelerating research; and led to new federal policies and programs providing liability relief for manufacturers and compensation for families. In addition, safety concerns brought new attention to a long-standing need for better coordination to assure the safety and availability of the nation=s vaccine supply.
- ***The government=s role in providing liability relief through the Vaccine Injury Compensation Program was crucial to retaining manufacturers in the U.S. market.*** Faced with mounting liability claims related to DTP, even the largest manufacturers announced they would withdraw from production of the vaccine. The Vaccine Injury Compensation Program is credited with retaining manufacturers for pertussis as well as other vaccines in the U.S. market.

Initial Development and Licensure of DTaP

Introduction

The history of DTaP=s initial development and approval in the U.S. reflects the interplay of three major stakeholders B the public, the government, and industry. Given growing concerns about the safety of DTP and related supply and coverage issues, the development and licensure of an acellular pertussis vaccine were eagerly anticipated by the public and vigorously pursued by federal public health officials. Both the National Institutes of Health (NIH) and the Food and

Drug Administration (FDA) contributed significantly to the development of an acellular pertussis vaccine through basic research efforts. In addition, NIH took an unusually proactive and direct role in financing and overseeing clinical trials starting in the mid-1980s and continuing into the 1990s. Over the same period, the FDA oversaw licensing of DTaP vaccines, gradually phasing in over a decade, approval for use in children and then in infants. On the industry side, from the mid-1970s through the mid-1980s manufacturers became increasingly wary of the U.S. market for whole-cell pertussis vaccine. However, by the late 1990s four companies had been licensed to manufacture and distribute acellular pertussis products for the U.S. market.

Vaccine Development and Approval in the U.S.: An Overview

In the U.S., private sector sponsors B either pharmaceutical companies or biotech firms B are generally primarily responsible for development of specific vaccines. Two government agencies B NIH and FDA B also play particularly important roles, conducting basic research that leads to or improves the development of vaccines, and also providing advice to industry on the conduct and design of clinical trials. In addition, FDA is responsible for vaccine licensure: the regulatory aspects of vaccine development and approval (CDC, 2002a,b).

To develop a vaccine for the U.S. market, the sponsor B again, usually a private sector company B must first conduct preclinical trials, testing the proposed product in cell or tissue cultures, and then in animals (CDC, 2002a). If preclinical studies indicate that the vaccine is potentially safe and effective, the sponsor files an Independent New Drug (IND) application with the FDA, requesting permission to test the vaccines in humans. The IND describes the vaccine, the manufacturing process, quality control testing, safety and immunogenicity data from animal trials, and the proposed protocol for clinical (human subject) trials (CDC, 2002b). A 30-day review period follows the filing of the IND. At the end of 30 days, unless otherwise notified by the FDA, the sponsor can begin the first of three sequential phases of clinical trials (Sing and Willian, 1996). The focus of each phase is as follows (CDC, 2002b; Sing and Willian, 1996):

- Phase I studies usually involve a small number of subjects (20-80), who are carefully monitored in tests of safety and immunogenicity.
- Phase II studies are generally conducted on several hundred subjects and are used to obtain additional data on immune response and adverse effects, including data on optimal dose ranges.
- Phase III studies typically involve several thousand subjects, providing more definitive data on safety and efficacy of the vaccine.

Once Phase III clinical trials are at or near successful completion (i.e., the vaccine is deemed to be safe and efficacious), the sponsor submits two additional license applications seeking approval to manufacture and distribute the vaccine: a biologics license application (BLA), which licenses the vaccine; and an establishment license application (ELA), which licenses the

facility where the vaccine is produced. During this phase of licensure, the sponsor provides a detailed accounting of the processes by which the vaccine is to be mass produced, as well as a description of how safety and efficacy will be documented on an ongoing basis. This phase also includes the FDA's detailed, on-site review of production facilities (CDC, 2002b; Sing and Willian, 1996).

Finally, some vaccines also undergo a post-licensure fourth phase of clinical trials, used to further evaluate safety and effectiveness in the general population and to provide information on rare adverse events. Post-licensure trials generally include 100,000 or more subjects (Sing and Willian, 1996).

NIH Role in the Development of DTaP

NIH's role in the development of U.S.-approved DTaP vaccines was both significant and in some ways ground-breaking, reflecting the intensity of public and Congressional concerns stemming from safety issues. Basic research conducted by NIH scientists starting in the 1970s played a key role in the development of the initial acellular pertussis vaccine licensed in Japan in 1981. In addition, starting in the mid-1980s, in response to the National Vaccine Injury Act mandate to promote the development and refinement of safer vaccines, NIH helped to accelerate the development and licensing of acellular pertussis vaccines by sponsoring a comprehensive series of clinical trials, which provided a unique opportunity for comparisons across multiple vaccine candidates (NIH, 2002b).

By the mid-1980s, amid growing concern about vaccine safety issues, public health officials were faced with a dilemma: While Japan had already licensed an acellular pertussis vaccine, and while several acellular pertussis vaccines were under development in the U.S. and elsewhere, no company had filed an IND with the FDA. Recognizing the mounting crisis in public confidence, NIH's National Institute of Allergies and Infectious Diseases (NIAID) moved to accelerate licensure of acellular pertussis by financing and conducting a series of large-scale clinical trials, including: (1) a Swedish study conducted in the mid-1980s that compared the efficacy of two Japanese acellular pertussis vaccines; (2) a very large multi-center, multi-vaccine study starting in 1990 that compared 13 acellular and two whole-cell vaccines, and involved international collaboration of government agencies, academic researchers and manufacturers; and (3) studies in Sweden and Italy, starting in 1991-92 that specifically tested safety and efficacy of acellular pertussis vaccines in infants (NIH, 2002b).

This series of NIH-sponsored trials is of particular note for several reasons: First, starting in 1984, NIH actively and successfully recruited nine manufacturers into Phase II clinical trials, which resulted in a unique collaboration across industry and between industry and government agencies in the U.S. and abroad (Mowery and Mitchell, 1995). NIH was able to achieve an extraordinary level of cooperation and coordination among key stakeholders in part because all parties recognized that a switch to acellular pertussis was inevitable, and that the NIH study data would be critical to licensure decisions. This perception was bolstered by NIH's highly cooperative partnership with the FDA, which further reinforced the credibility and importance of the trials. Second, the study design allowed for the first time simultaneous comparisons of

efficacy and safety across 13 different candidate vaccine formulations, providing a much richer set of data than had been available on previous trials. Third, to assure a sense of fair-play and to provide a level of transparency to the process, NIH established an independent, blue-ribbon panel that evaluated data and selected candidate vaccines for the Phase III trials. Finally, NIH sponsorship of the pertussis trials represented a significant commitment of agency resources at the time: The Swedish and Italian trials alone cost NIH about \$28.5 million in direct expenses (NIH, 2003).

The NIH trials have generally been credited with accelerating the development and licensing of acellular pertussis vaccines for the U.S. market and with increasing the pool of manufacturers entering into the U.S. market, including smaller companies such as North American Vaccine. The agency's efforts were not without detractors, however: At least one U.S. company B Lederle-Praxis Biologicals B took exception to the fact that NIH selected only foreign-made vaccines for the multi-center Phase III trials, claiming that these trials Athreatened their product=s early licensure and supported foreign firms at the expense of U.S. manufacturers@ (Mowery and Mitchell, 1995). It is an interesting side-bar of history that Lederle=s DTaP vaccine B Acel-Imune B eventually became the first acellular pertussis vaccine approved for use in the U.S. (CDC, 1991).

FDA Licensure of DTaP¹

Charged with reviewing and licensing new vaccines, starting in the early 1980s FDA officials B like their counterparts in other public health agencies B were under mounting pressure to bring a safer pertussis vaccine to the U.S. market. As was the case with NIH, basic research conducted by FDA scientists contributed to the development of the first acellular pertussis vaccines approved in Japan in 1981. However, it would take the FDA a full decade more B until December 1991 B to approve an acellular pertussis vaccine for use among American children. Even then, DTaP vaccine was approved only for use as the fourth and fifth doses, for children rather than infants. It was not until 1996 that the FDA extended its approval of DTaP for use as the first three doses in the series, to be given to infants at 2, 4 and 6 months of age.

From December 1991 to the present, the FDA has approved five DTaP vaccines. Table A below lists the five approved vaccines.²

¹ This section of the report draws heavily on: FDA Product Approval Information. [Online documents]: <http://www.fda.gov/cber/efoi/approve.htm>; updated as of 7/8/02.

² Note: Appendix A provides a more detailed description of the five acellular pertussis vaccines licensed in the U.S. to date, including when and for which doses each was approved.

Table A: DTaP Vaccines Licensed in the U.S.

Vaccine Name	1 st Approval Date
Acel-Imune	12/91
Tripedia	8/92
Infanrix	1/97
Certiva	7/98
Daptacel	5/02

Source: FDA Product Approval Information.

FDA approvals of DTaP vaccines can be grouped into three major categories:

- **Initial Approval of DTaP for Booster Doses** (1991-1992) B The first two licensed acellular pertussis vaccines, Acel-Imune and Tripedia, were initially approved only for the fourth and fifth doses, following immunization with three doses of DTP. This limited approval balanced safety and efficacy issues, reflecting FDA concerns in 1991 and 1992 that there were not yet sufficient efficacy data available to warrant use of DTaP for the full, five-dose series, nor had there been adequate testing of safety for very young infants (CDC, 1992a,b).
- **Initial Approval of DTaP for Primary Doses** (1996-1998) B After a four-year hiatus, the FDA began approving new and already licensed DTaP vaccines for use in the primary series. Because the acellular pertussis component is not identical across vaccines, approval of different vaccine products for specific doses was gradually phased in based on clinical studies submitted by the manufacturers (CDC, 2000a).
- **Approval of Reduced-Thimerosal or Thimerosal-Free DTaP** (2001-2002) B In July 1999, in response to concerns about the amount of mercury in routinely given childhood vaccines, the American Academy Pediatrics and the Public Health Service (including the FDA, NIH, CDC and HRSA) issued a statement calling for the removal

of thimerisol (a mercury-containing preservative) from vaccines given to infants and children (AAP, 1999). While GSK's Infanrix was already formulated without thimerisol, other DTaP vaccines required reformulation. To date, the FDA has approved reformulation of Aventis Pasteur's Tripedia, with only trace amounts of thimerisol. It has also approved Daptacel, a second Aventis Pasteur product that is new to the U.S. market (FDA, 2002b).³

Of particular interest regarding initial FDA licensure of DTaP vaccines is the question of why the process was so lengthy, given that acellular pertussis vaccines were approved and in use in Japan starting in 1981. Several factors were involved (CDC, 1992a,d).

- First, the initial Japanese data on acellular pertussis safety and efficacy were deemed insufficient for approval by the FDA. This was an issue both of the type and rigor of data and of the age group tested: The Japanese approved acellular pertussis vaccines to be administered to children starting at age two years, while the U.S. recommendations were and are for a five-dose series starting at age two months.
- Second, comparability to existing vaccines was a factor: acellular vaccines needed to be at least comparable in safety and efficacy to whole cell vaccines already on the market. But clinical trials in the 1940s when whole cell pertussis was first licensed were not comparable in rigor to studies required in the 1980s and 1990s. Therefore, NIH and other trials had to include efficacy data for DTP vaccines then in use as well as for DTaP vaccine candidates.
- In addition, the NIH multi-center study design comparing 13 different vaccine formulations presented both an unusual opportunity and a level of greater complexity for the licensure process. Different formulations yielded varying results on efficacy and safety, which needed to be closely monitored and evaluated by FDA scientists.
- Finally, in general, safety data on acellular pertussis vaccines compared quite favorably to data on whole-cell pertussis: acellular pertussis vaccine was associated with reduced rates of common adverse events. But reliable data on the most rare events B those that were most controversial B were not available from the pre-licensure trials, primarily because a much larger pool of subjects was required.

In the end, FDA needed to weigh a growing body of data, balancing high profile public concerns about safety with compelling public health concerns about whether the efficacy of acellular vaccine would afford the level of protection needed to maintain a low incidence of pertussis in the U.S.. The FDA's approach was to gradually phase in specific acellular pertussis

³ See section on ASupply Issues@ for a discussion of issues related to thimerosal.

vaccine formulations, by dose, as additional data became available. Thus, the U.S. transition from whole-cell to acellular pertussis vaccine (from an all DTP to an all-DTaP vaccine schedule for infants and children) took place incrementally, over a 10-year period.

Advisory Committee Recommendations for Use

Finally, three national advisory bodies on immunization also played key roles in the story of DTaP's initial licensure and use: (1) the Vaccines and Related Biological Products Advisory Committee (VRBPAC), which advises the FDA; (2) the Advisory Committee on Immunization Practices (ACIP), which advises the CDC; and (3) the Advisory Committee on Infectious Disease (COID, commonly known as the Red Book Committee), which advises the membership of the American Academy of Pediatrics (AAP)(NPI, 2003).

VRBPAC provides recommendations on vaccine license approval to the FDA based on a review of available safety, purity and potency data submitted by the vaccine sponsor as well as by outside advisors (NPI, 2003). In the case of acellular pertussis vaccines, VRBPAC's advice was critical to helping assure that the FDA heard and considered opinions from the broad range of knowledgeable parties represented on the advisory committee, which includes representatives from the research, practice and consumer communities.

ACIP is a scientific advisory committee of outside, non-governmental experts and provides advice to the Director of the CDC and to the Secretary of Health and Human Services on the use of vaccines, including recommended immunization schedules as well as vaccine safety information (Satcher D, 1999). ACIP recommendations serve as the primary immunization guidelines for public health practice. The Red Book Committee monitors and reports to AAP members on infectious disease prevention, diagnosis and treatment in children. Among the Committee's responsibilities is making recommendations to AAP members regarding vaccine use (NPI, 2003).

Although they advise two separate constituencies, ACIP and the Red Book Committee try to coordinate their recommendations so that whenever possible there is one message going to both public and private sector clinicians administering childhood vaccines. For example, in the Fall of 1991, both ACIP and the Red Book Committee debated whether DTaP vaccine should be given as primary doses to children age two and older. After considerable discussion, the two committees jointly agreed that DTaP should be given only for the fourth and fifth doses, regardless of the age of the child, and each issued recommendations to that effect (CDC, 1992c).

ACIP and the Red Book Committee must also coordinate closely with the FDA, so that their recommendations are issued soon after a new vaccine is licensed. In general, ACIP and Red Book Committee recommendations closely follow FDA licensure language. Occasionally, the advisory groups' recommendations vary slightly from each other or from FDA language. An example in the case of DTaP is ACIP's supplemental recommendation in November 2000, which clarified that under certain circumstances DTaP formulations could be used interchangeably to complete the vaccination series (CDC, 2000a). These kinds of changes generally reflect the ACIP and Red Book Committee focus on clarifying potential points of confusion for clinicians who administer the vaccines.

Lessons Learned ⁴

The history of DTaP development and licensing yields several important lessons for the future:

- ***NIH-supported clinical trials were crucial to the accelerated development and licensure of DTaP, providing a model for the development of selected future vaccines.*** In addition to providing data critical to FDA approval, the NIH-supported trials encouraged entry into the U.S. market in at least two ways: First, with costs of clinical trials partially borne by NIH, smaller firms could more easily compete for entry into the U.S. market (Mowery and Mitchell, 1995). Second, NIH's substantial investment in the clinical trials reinforced the signal sent by Congress that vaccine safety was a priority and, therefore, it was only a matter of time before the U.S. would shift to acellular pertussis vaccine, thus opening a new market (which by the late 1980's, with implementation of the National Vaccine Injury Compensation Program, had once again become viable) (NIH, 2002a).
- ***The NIH-supported acellular pertussis vaccine trials were very resource intensive B in terms of both time and money.*** Given the costs of the acellular pertussis trials, future efforts of this kind likely would have to be targeted to vaccines of special import (Mowery and Mitchell, 1995). The costs also imply the need for a certain amount of flexibility in federal agency budgeting and staffing to accommodate a shift of resources to accelerated development of high-profile vaccines.
- ***Even with accelerated development of vaccines, licensure can take many years.*** U.S. vaccine licensure always requires a careful weighing of safety and efficacy issues. If, in addition, there are multiple vaccine candidates or the new vaccines are likely to replace vaccines already on the market, the licensure process can become even more complex and potentially more time-consuming.

Market History: Production, Supply, Purchase and Pricing Issues

Production

Overview of Industry Trends B Production of vaccines for the U.S. market over the past three decades has been characterized by three major trends:

⁴ Conclusions drawn in part from: Mowery and Mitchell, 1995.

- The total number of firms producing vaccines for the U.S. market has decreased dramatically.* Between 1967 and 1980, the number of manufacturers licensed to distribute vaccines in the U.S. dropped from 26 to 17 (Cohen J, 2002). In recent years the nation has experienced a similar decline in the number of producers of childhood vaccines: In 1996, a combination of eight firms and labs produced recommended childhood vaccines for the U.S. market (Sing and Willian, 1996). In 2002, only four firms remained (GAO, 2002). A 1993 IOM report concludes there were at least three major factors driving manufacturers out of the U.S. market from the mid-1960s through the early 1980s: (1) new FDA regulations starting in 1972 that required evaluation of all previously licensed biological products (rather than submit data for evaluation, many firms simply withdrew from the market and requested that FDA revoke their licenses without prejudice); (2) growing concerns about liability; and (3) poor returns on investments relative to pharmaceutical and other products in the corporate portfolio (IOM, 1993). Observers of the more recent decline in the number of producers of U.S. childhood vaccines have cited similar factors for market departures, including: new, safety-related requirements (removal of the mercury-containing preservative Thimerosal); regulatory compliance issues; and investment decisions based on the larger portfolio of parent companies (GAO, 2002; Orenstein, 2002).
- The proportion of domestic firms in the U.S. market has declined markedly.* The decline in manufacturers of vaccines for the U.S. market between 1967 and 1980 was driven almost entirely by the departure of U.S.- based firms: Of the nine producers leaving the U.S. market during this period, eight were domestic firms (Sing and Willian, 1996).
- International consolidation and globalization within the vaccine industry have resulted in multi-national firms dominating current markets in the U.S. and other wealthy countries.* Prior to the 1980s, vaccine markets tended to be regionally B but not globally B dominated. Thus, Pasteur-Merieux and SmithKline led the European market, Merck and Lederle-Praxis were major suppliers for the U.S. market, and three Japanese firms B Takeda, Eisai, and the Research Foundation of Osaka University B were prominent in their own domestic market. By the early to mid-1990's, however, as with other industries, global acquisitions, mergers and joint ventures had taken off in earnest and had begun to reshape the industry as a whole (Mowery and Mitchell, 1995). A 2002 analysis by Mercer Management Consulting points to five major categories of vaccine producers in the current world market: U.S. multinationals, European multinationals, OECD suppliers, emerging suppliers, and developing country suppliers. Of these, only two include as their customer focus high income countries willing to pay for newer, more expensive vaccines: U.S. multinationals (e.g., Wyeth, Merck) and European multinationals (e.g., Aventis, Chiron, GlaxoSmithKline). Thus, the U.S. vaccine market B like that of other highly developed nations B is dominated

by multinational corporations (Mercer, 2002). Of the four companies that currently produce recommended childhood vaccines in the U.S., for example, two are U.S. multinationals (Merck and Wyeth) and two are European multinationals (Aventis Pasteur and GlaxoSmithKline).

DTaP Production in the U.S. B Production of DTaP for the U.S. market over the past decade reflects trends for the industry as a whole.

- *The total number of firms producing DTaP for the U.S. market has declined.* While five DTaP vaccines have been licensed in the U.S. since 1991, only three are currently being produced; and of these, two are produced by subsidiaries of the same multinational corporation, Aventis-Pasteur.⁵
- *The portion of the market represented by U.S.- based firms has not only diminished, it has been reduced to zero.* Of the five firms originally licensed by the FDA to produce DTaP, two (Lederle and North American Vaccine) had corporate headquarters in the U.S.. Today, all three DTaP vaccines currently on the U.S. market are produced by two European-based corporations: GlaxoSmithKline and Aventis-Pasteur (which produces both Tripedia and Daptacel).
- *Finally, the corporate history of the five DTaP vaccines licensed in the U.S. reflects both the astounding number of acquisitions and mergers that have taken place within the industry and the extent to which these activities have concentrated production of relatively high-end vaccines in the hands of very large American or European multinational corporations.* Of the five vaccines licensed in the U.S. to date, only Daptacel, approved in May 2002, is still produced by the same company B Aventis Pasteur, Ltd., a Canadian subsidiary of French-based Aventis Pasteur. Of the remaining companies originally licensed to produce DTaP in the U.S., all have undergone one or more mergers or acquisitions since licensure and all have become part of major multinational corporations.

Table B below summarizes the history of DTaP manufacturers in the U.S. market.

⁵ For a discussion of why Wyeth and Baxter pulled out of the U.S. DTaP market, see section on Supply Issues.

Table B
DTaP Manufacturers in the U.S. Market: 1991 - 2002

Vaccine Trade Name	Name of Original Manufacturer (date of initial licensure)	Name of Most Recent Manufacturer (date of acquisition or merger)	Additional History/ Comments
Acel-Imune (No longer on U.S. market)	Lederle (12/91)	Wyeth-Lederle (1995)	<ul style="list-style-type: none"> • Wyeth, a U.S. firm, was acquired by American Home Products in 1931. • AHP acquired Lederle in 1995, as well as many other companies over a 70 year period, including: Ayerst, McKenna & Harrison Ltd., A.H. Robins., and Immunex . • Wyeth announced in 12/00 its decision to withdraw from the U.S. market for DTaP as of 1/01. • In 2002, AHP changed its corporate name back to Wyeth.
Tripedia	Connaught (8/92)	Aventis Pasteur, Inc. (1999)	<ul style="list-style-type: none"> • In 1989, Pasteur-Merieux Serums & Vaccins, S.A. (French-based) acquired Connaught (a Canadian firm with a U.S. affiliate). • Pasteur-Merieux Connaught became a wholly-owned subsidiary of the Rhone-Poulec Group in 1994. • Rhone-Poulec and Hoechst united to form Aventis and Pasteur Merieux. Connaught became Aventis Pasteur in 1999. • Aventis Pasteur, Inc is the US.-based subsidiary.
Infanrix	Smith Kline Beecham (1/97)	GlaxoSmithKline (2000)	<ul style="list-style-type: none"> • In 1989, SmithKline Beckman (US-based) merged with Beecham (UK) to form SmithKline Beecham (UK). • In 1995, Glaxo and Wellcome merged (UK). • In 2000, Glaxo Wellcome and SmithKline Beecham merged to form GlaxoSmithKline (GSK), with corporate headquarters in the UK.
Certiva (No longer on U.S. market)	North American Vaccines (7/98)	Baxter International, Inc. (2000)	<ul style="list-style-type: none"> • Baxter International, Inc.(a U.S. firm) acquired North American Vaccines in 2000. • Baxter still holds a license, but as of late 2000, stopped producing DTaP for the U.S. market.
Daptacel	Aventis Pasteur, Ltd. (5/02)	(None)	<ul style="list-style-type: none"> • Aventis Pasteur, Ltd. is a Canadian-based subsidiary of French-based Aventis Pasteur. See Tripedia history above.

Source: Table draws heavily on histories provided in Wyeth, Aventis-Pasteur, GlaxoSmithKline and Baxter Websites. Licensure dates taken from FDA approval letters, found on FDA Website.

Supply

Industry Overview B Over the past 20 years, the nation has experienced two major periods of vaccine supply shortages. As described earlier in this report, the first was related to the product liability crisis of the mid-1980s, when production of DTP vaccine was greatly curtailed as a result of manufacturers leaving the U.S. market. The second period of supply shortages had its origins in Fall 2000 and peaked in 2001-2002. During this period, the U.S. experienced nationwide shortages in five childhood vaccines that protect against eight of the eleven childhood diseases prevented through routine immunization (GAO, 2002). Nationwide shortages involve all manufacturers of a vaccine; manufacturer-specific shortages involve some, but not all, manufacturers. The recent shortages affected most of the manufacturers of childhood vaccines, with three of the four experiencing supply problems during this period (Orenstein, 2002). Table C, below, lists childhood vaccines for which there were nation-wide shortages in 2001-2002.

**Table C: Childhood Vaccines in Short Supply, 2001-2002
(Nationwide Shortages)**

Vaccine	Vaccine - Preventable Disease/s
DTaP	Diphtheria, tetanus and pertussis
MMR	Measles, mumps and rubella
PCV	Pneumococcal Infection
Td	Tetanus and diphtheria
Varicella	Varicella (chicken pox)

Source: (GAO, 2002)

By Summer 2002, most of these shortages had ended or lessened considerably; however, pneumococcal vaccine remained in short supply (GAO, 2002). While for the most part this recent supply crisis appears to be under control, there remains an underlying fragility of the U.S. market.

For example, in January 2003 the nation was experiencing delays in getting two childhood vaccines B Hib (Haemophilus influenzae type b) and PPV (pneumococcal polysaccharide) (CDC, 2003).

Experts monitoring the situation agree that the most recent shortages were a result of the convergence of multiple, underlying causes, most of which could surface again at any time. Among the factors most frequently cited as contributing to recent vaccine shortages are: (1) problems with manufacturers= production capacity; (2) unanticipated demand for a new vaccine; (3) regulatory compliance issues (including problems with process documentation, as well as problems requiring substantial investments in plant upgrades); (4) a decline in production related to new safety recommendations (i.e., the removal of thimerosal, a mercury-containing preservative); (5) limited government stockpiles of recommended vaccines; and (6) corporate business decisions to discontinue production of specific vaccines (based on a range of assessments, including current and anticipated profits, the corporate vaccine portfolio, the total

corporate portfolio, and anticipated future vaccine combinations)(CDC, 2001; Crawford, 2002; GAO, 2002; Orenstein, 2002). When these underlying factors are coupled with a market dominated by only a few producers B currently only four manufacturers produce all recommended childhood vaccines for the U.S. B long-term stability of the U.S. childhood vaccine supply is questionable, at best.

DTaP History B DTaP=s history is closely intertwined with both the U.S. vaccine supply crisis of the mid-1980s and the more recent shortages of 2001-2002. As described earlier in this report, safety concerns about the whole-cell pertussis component of DTP vaccine led to the product liability crisis and related vaccine shortages of the mid-1980's. It was this crisis that eventually gave rise to the development and initial approval of DTaP for domestic use in late 1991. Between 1991 and 1999, no significant DTaP supply problems occurred in the U.S. market. Instead, as the FDA gradually approved the vaccine B first for booster doses and then for primary doses B supply kept pace with demand. In fact, by the late 1990s, DTaP supply in the U.S. appeared to be one of the most robust among recommended childhood vaccines. Several factors point to this conclusion:

- Starting in July 1998, a total of four manufacturers were producing DTaP for the U.S. market. (See Table B.)
- By 1999, 95% of U.S. children 19-35 months old had received 3 doses and 83% had received 4 doses of DTP or DTaP (CDC, 2000c). With DTaP/DTP coverage rates high and gradually rising in the mid-to late-1990s, it was unlikely that there would be an immediate surge in demand.
- Last, since DTaP was developed as a safer alternative to whole-cell pertussis and its introduction was welcomed by consumers as well as providers, by the late 1990s it seemed that significant safety concerns had been addressed.

In summary, DTaP supply issues likely would not have jumped out as a matter of serious concern to most observers in the late 1990s, particularly if compared to other childhood vaccines such as those with only one or two manufacturers; new, higher-priced vaccines with little or no market history; or vaccines under public scrutiny due to emerging safety concerns.

By January 2001, however, the DTaP supply picture had deteriorated significantly: There was a nationwide shortage of the vaccine, leading the CDC to temporarily revise its recommended childhood immunization schedule for DTaP (CDC, 2001; GAO, 2002). As with other vaccine shortages in 2001-2002, the DTaP shortages have been attributed to multiple factors B both immediate and underlying. The most proximal causes included the abrupt withdrawal from the U.S. market by two manufacturers (Wyeth and North American Vaccine), and a serious slow down in production by a third producer (Aventis Pasteur), as the company worked to remove the preservative thimerosal from its product. This left GlaxoSmithKline as the remaining manufacturer available to produce at or above its previous capacity. In fact, GSK was able to temporarily increase the amount of vaccine it supplied to the U.S., but even with this increase a

nationwide shortage occurred (GAO, 2002).

A closer look at why Wyeth and North American left the market, points to several potential underlying causes:

- *Wyeth* B Wyeth=s withdrawal has been attributed to at least three underlying causes: (1) By late 2000, Wyeth had received repeated notices from the FDA indicating that the company=s DTaP production facilities were out of compliance with Current Good Manufacturing Practices (CGMP). Substantial facility investments were needed in order to comply with regulations. (2) In addition, the Wyeth DTaP product contained the preservative thimerosal. Again, in order to comply with AAP/PHS recommendations for removal of thimerosal, the company would have incurred substantial expenses. (3) Finally, in recent years the vaccine industry has been working toward using DTaP as a platform on which to build larger, multivalent vaccines combining six, seven or more antigens into a single Ashot@. Manufacturers have been positioning themselves to develop the larger combination vaccines by acquiring the capacity to produce the antigens most likely to be combined with DTaP. These new, larger combination vaccines are seen as advantageous to consumers and providers because they decrease the total number of injections children must receive. They are advantageous to manufacturers because they will allow companies to charge increased prices for the new combinations and, most importantly, because companies producing them will presumably have a competitive edge in the market. Conversely, companies that do not have the capacity to build the new combinations are likely to lose market share. By 2001, it was clear that Wyeth had not acquired the additional vaccines needed to effectively compete with the European multinationals in the race to develop a large combination vaccine for the U.S. market based on a DTaP platform (GAO, 2002).
- *North American (Baxter-North American)* B The causes of Baxter-North American=s withdrawal from the U.S. DTaP market have not been as clearly documented; however, several potential causes emerge: (1) Like Wyeth, North American had a history of compliance issues (FDA, 1999), and would have had to invest in changes to meet regulatory standards. (2) Since North American supplied only a small portion of the U.S. DTaP market (GAO, 2002), the return on facility investments would have been relatively small. (3) In 2000, North American was acquired by Baxter International. As part of the transition, DTaP production, like that of all other newly acquired products, would have undergone a review regarding potential for future growth, contribution to the parent company=s portfolio, and other factors related to the functioning of the parent company, any one of which might have led to the corporate decision to withdraw its newly acquired DTaP vaccine from the U.S. market. (4) With regard to the development of a larger combination vaccine based on DTaP, the situation for North American is ambiguous. While the company discontinued DTaP production for the U.S. market in late 2000, it maintained its production license for its DTaP formulation (Certiva), and a fact sheet posted on the

company's Website in August 2002 states: "Using Certiva as the anchor, North American Vaccine is developing combination vaccines to provide immunization against additional diseases, including polio and meningitis, in a single injectable product" (Baxter-North American Vaccine, 2002). Thus, it is possible that North American has departed only temporarily from the U.S. market, and the company might re-enter the market with a larger combination vaccine built on its DTaP (Certiva) platform.

While there may have been additional factors leading to the withdrawal of Wyeth and North American from the DTaP market, they are likely to remain proprietary information. The factors listed above, however, are quite consistent with underlying factors cited for other vaccines involved in the shortages of 2001-2002, and point to the kinds of issues that need to be addressed to better assure the nation's vaccine supply in the future.

Purchase and Pricing

Overview Vaccine purchase in the U.S. is roughly equally divided between the public and private sectors. Correspondingly, there is a two-tiered system of pricing for vaccines: one for the private sector (catalog price) and one for the public sector (federal contract price), which is considerably lower.

The federal government first started purchasing and distributing vaccines in the mid-1950s, following the licensing of polio vaccine. Starting in the late 1960s, and continuing through the present, CDC has been responsible for negotiating public sector contract rates with manufacturers, primarily for childhood vaccines. The CDC-negotiated rates apply to vaccines purchased through three primary routes: (1) the Vaccines for Children (VFC) program (a federal entitlement for needy children nationwide); (2) Section 317 of the Public Health Service Act (which provides funds to the states for vaccine purchase as well as for immunization infrastructure); and (3) state public health programs (Orenstein, 2002).

In negotiating contracts, the CDC seeks to balance two sets of concerns, reflecting two of its multiple roles related to immunization: On the one hand, as a government purchaser it seeks to be fiscally prudent by negotiating lower costs. On the other hand, as a steward of immunization for the nation, it seeks a contracting approach that will encourage manufacturers to stay in the market, thereby maintaining an adequate vaccine supply. Over the past decade in particular, CDC contract negotiation policies have been revised and fine-tuned to better balance cost and supply concerns.

Federal contracting for vaccines is triggered by ACIP (Advisory Committee on Immunization Practices) recommendations. Once the ACIP recommends a vaccine for routine use, the CDC begins contract negotiations. The price the government pays for vaccines is affected in part by two Congressional mandates:

- *A Federal Excise Tax on Recommended Childhood Vaccines* Starting in January 1988, under the National Childhood Vaccine Injury Act, a federal excise tax was

imposed on all recommended childhood vaccines, including vaccines purchased by the CDC. The CDC negotiates a federal contract rate, and then the price of the excise tax is added to the purchase cost. In 1988, when the tax was first implemented, the tax per dose varied by vaccine and was based on the safety history of each vaccine. In 1997, the rate for all covered vaccines was changed to \$0.75 per dose, per antigen. (Thus, the tax on a three-antigen vaccine would cost \$2.25 per dose.) (Department of the Treasury, 1994; CDC, 2002c).

- *Price Caps on Selected Childhood Vaccines B* In 1993, the VFC legislation (OBRA >93) mandated price caps on all vaccines for which federal contracts were already in place. These caps do not cover new or newly formulated vaccines introduced on the market subsequent to passage of the VFC legislation. The caps applicable to current CDC contracts range from \$5.75 to \$13.28 per dose (exclusive of the federal excise tax). It should be noted that under federal statute both Td and DT vaccines are also subject to price caps. However, at \$0.15 and \$0.20, respectively, the caps are so low that since 1998, the sole remaining producer in the U.S. market, Aventis, has refused to negotiate a contract with the CDC, noting that the cost of production exceeds the mandated price limits (Johnson, et al., 2000; CDC, 2002d). Table D below lists the vaccines purchased under federal contract that were subject to price caps in 2001-2002.

The public sector share of vaccine purchases has continued to grow over the decades, so that today approximately 52% of all childhood vaccines recommended for routine use in the U.S. are purchased under the federal contract. In 1998, 65% of expenditures under CDC-negotiated contract prices were VFC purchases, 22% were Section 317; and 12% were state public health purchases (Orenstein, 2002; IOM, 2000).

**Table D
Federal Contract Vaccines Subject to Price Caps**

Vaccine	Price Cap
MMR	\$13.28
Measles	\$6.15
Mumps	\$8.49
Rubella	\$5.75
Hib Conjugate -4 dose	\$6.55
Hib Conjugate - 3 dose	\$8.72
IPV	\$8.90

Source: CDC, 2002d

Price Trends for Childhood Vaccines B Cost concerns are a major issue for public and private purchasers of vaccines alike. The past two decades have been characterized by a dramatic increase in the U.S. price tag for childhood vaccines. There are at least four components to the rapid growth in the cost of childhood vaccines for the nation:

- *Starting in the 1980s there was a striking increase in the price of established childhood vaccines (i.e., those already on the market).* Prior to the early 1980s, the prices of recommended childhood vaccines remained remarkably low and stable. From 1977- 1982, the government price for DTP vaccine remained constant at \$0.15 per dose, and the catalog price remained quite low, increasing from \$0.19 to \$0.37 per dose. (Note: the price of DTP was so low at the time, that there was no federal contract. This price represents the average cost to state programs.) By the mid-1980s, however, prices for many vaccines had climbed dramatically. Between 1983 and 1986, for example, the cost of a single dose of DTP vaccine increased from \$0.45 to \$11.40 in the private sector, and from \$0.42 to \$3.01 in the public sector (Sing and Willian, 1996). Over a 15-year period, from 1977-1992, the nation experienced remarkable cumulative increases in the prices of established, recommended childhood vaccines B for both public and private sector purchasers. Table E below summarizes these increases as reported by the Institute of Medicine in 1993:

Table E
Cumulative Increases in U.S. Vaccine Prices: 1977 - 1992*
 (Prices in 1993 dollars, excluding federal excise tax)

Vaccine	Contract Price: \$ Increase	Contract Price : % Increase	Catalog Price: \$ Increase	Catalog Price: % Increase
DTP**	\$1.55	1,033 %	\$5.22	2,847%
OPV	\$8.62	500%	\$1.50	862%
MMR	\$8.47	350%	\$14.84	247 %

Source: (IOM, 1993)

* During this period the CPI rose 122% and the PPPI rose 232%

** Data for DTP for 1977-1991

- *In addition to rising prices for established vaccines, the prices of new vaccines introduced since the late-1980s have been significantly higher than for older products.* For example, Hib (haemophilus influenza type B) vaccine was introduced in 1988 priced at \$13.75 per dose for the private sector and \$11.00 per dose under federal contract. More recently, varicella (chicken pox) vaccine was introduced in 1995-96, at \$40.66 per dose for the private sector and at \$31.95 per dose for the public sector. And Prevnar, a pneumococcal vaccine introduced in 2001, reflects the highest entry prices to date: \$58.00 per dose for private purchase and \$43.50 per dose for public sector buyers. It should be noted as well that the federal contract prices for varicella and pneumococcal vaccines B both introduced after 1993 B are uncapped. (CDC, 2002e).
- *As new vaccines have been added to the recommended schedule of childhood vaccines, the total costs of fully immunizing a child have grown substantially.* Both public and private sector purchasers are not only paying more per dose of vaccine, they are also purchasing many more vaccines. Fifty years ago, children were immunized with only four antigens. Today, they are immunized with twelve, and more are currently under development (Pisano, 2002).
- *Finally, for the public sector, as the government=s purchases have increased, its share of the total cost of vaccines has also increased, not only because of volume, but also because government discounts have declined: while 1987 federal contract prices averaged about 25% of private sector prices, by 1997 federal contract prices averaged about 50% of catalog prices (IOM, 2000).*

The question of why U.S. vaccine prices have climbed so dramatically is a matter of some debate, with price increases attributed to multiple factors. Among the most frequently cited are

the following: (1) The sharp rise in vaccine liability suits in the mid-1980s led affected companies to increase prices. (2) During the same period, many companies exited the market altogether, giving the remaining companies greater market power. (3) The federal excise tax imposed on vaccines under the injury compensation act added to the price of childhood vaccines (although prices also rose significantly, independent of the tax). (4) Expanded investment in R & D for new vaccines has resulted in higher prices as these vaccines come onto the market. (5) Within the industry, a shift in manufacturer and investor expectations has led companies to seek a greater return on investment from vaccines. (6) Due to changes in FDA regulatory enforcement practices in recent years, companies must invest more heavily in facility improvements and in process documentation. (7) Finally, with over half of purchases now under federal contract prices, some analysts feel that federal contracts have forced industry to drive up private sector prices in order to obtain an acceptable return on investments (IOM, 1993; Pisano, 2002; Sing and Willian, 1996). This combined set of factors reflects issues that are both systemic and long-term in nature. In the absence of major restructuring or shifts in market forces, the U.S. continues to face the prospect of increasing vaccine prices in the coming years.

Trends for DTaP⁶ B First licensed in December 1991, DTaP=s market history reflects several key price and purchase trends that have characterized the U.S. market as a whole. This section describes three aspects of DTaP=s history: (1) initial prices, (2) subsequent price trends, and (3) evolving federal contract policies.

- ***Initial Prices*** B As a new vaccine entering the market in the early 1990s, DTaP=s initial price tag was significantly higher than that of its predecessor, reflecting a general trend within the industry. When the first federal contract for DTaP was negotiated with Lederle, the public sector price for DTaP was set at \$9.35 per dose, five and a half times Lederle=s public sector price for DTP at the time, which was \$1.69 per dose. The initial Lederle contract covered only a brief period: March-May, 1992. By June 1992, CDC had negotiated a new contract with Connaught, covering a one-year period. At \$6.45 per dose, the new contract price was considerably lower than the initial Lederle contract price but still over four and a half times the price of Connaught=s DTP product, for which the government was paying \$1.43 per dose at the time. (Prices do not include the federal excise tax. Private sector prices unavailable.)
- ***Price Trends*** B Table F below summarizes the price history of DTaP in the U.S. from 1992 - 2002. Both nominal and real prices are listed, with real prices reflecting 2002 dollars. A review of real price trends reveals several patterns of particular note: First, while both private and public sector prices rose over the past decade, neither sector

⁶ Discussion in this section is based on data in Tables F, G, and H.

experienced continuous year-to-year increases. Second, while both private and federal contract prices rose between 1993 and 2002, initial private sector prices were higher and they rose at a greater rate than public sector prices. Between 1993 and 2002, private sector rates rose by 80% while federal contract rates rose by only 48%. Finally, public sector prices for DTaP averaged 57.7% of private sector prices between 1993 and 2002. Public sector DTaP prices do not reflect a growing percentage of private sector prices over the ten-year period. On the contrary, for most of this period (7 out of 10 years), the percentage remained relatively constant, with public sector prices ranging from 47% to 57% of private sector prices. However, the federal contract price was a considerably higher percentage of private sector prices in each of 3 years: 1993 (77%), 1996 (84%) and 2002 (63%).

Table F:
U.S. Prices for DTaP: 1992-2002
(Federal and Private Prices, Excise Taxes Excluded)*

Year	Nominal Price		Real Price (Constant 2002 Dollars)	
	Federal	Private	Federal	Private
1992	\$6.45	NA	\$8.22	NA
1993	\$5.37	\$6.97	\$6.65	\$8.63
1994	\$5.42	\$11.53	\$6.54	\$13.92
1995	\$5.71	\$11.27	\$6.70	\$13.23
1996	\$9.50	\$11.27	\$10.83	\$12.85
1997	\$8.28	\$14.63	\$9.23	\$16.31
1998	\$7.05	\$14.69	\$7.74	\$16.12
1999	\$7.00	\$14.69	\$7.52	\$15.77
2000	\$7.00	\$14.72	\$7.27	\$15.29
2001	\$8.34	\$15.33	\$8.43	\$15.49
2002	\$9.87	\$15.56	\$9.87	\$15.56

Source: Data from CDC; Data analysis by Robert Giffin, IOM, 2002.

* Note: 1992 nominal Federal price reflects second contract, which started in June 1992. All other prices weighted, reflecting multiple contracts/prices.

- *Federal Contracting* B Table G summarizes DTaP=s federal contract history. Table H summarizes federal contract prices for DTaP, by manufacturer. One clear theme that

emerges from the contract history of DTaP is that over the course of the past decade, CDC contracting policies have continuously evolved, reflecting CDC's responsibilities to both assure an adequate vaccine supply for the nation and to negotiate federal contracts in a fiscally prudent manner. The changing policies also reflect the federal government's move toward more efficient and streamlined management practices starting in the mid-1990s.

Several contract policies are of particular note: In 1997, CDC used DTaP contract negotiations to pilot test a set of policies that included: (1) awards to all licensed suppliers; (2) a provision allowing purchasers to buy from any of the federal contractors (previously, CDC chose for the states); (3) a very small guaranteed minimum purchase, to allow flexibility for state choice of products; and (4) a provision allowing contractors to revise prices at three month intervals (not to exceed their initial bid). After two years of piloting, these provisions were integrated into a new consolidated VFC contracting process in which contracts covering all VFC vaccines/manufacturers are negotiated at the same time, and all contracts cover the same one-year period. The consolidated contracting varies slightly from the DTaP pilot in that contractors may revise prices only twice during the contract period (at four month intervals).

A major impact of the DTaP pilot and subsequent Consolidated VFC Contract was a fairly rapid alignment of manufacturer contract prices starting in 1997 and continuing through early 2001. By the end of the contract period starting in April 1997, two of the three manufacturers were very close in price; by the end of the contract period starting in April 1998, all four manufacturers were selling at \$7.00/dose; and for the contract periods starting in April 1999 and April 2000, all four manufacturers provided the same initial bid B \$7.00/dose B and maintained this price for the entirety of the two contract periods. Thus, for nearly a three year period, the government contract price for all DTaP vaccines on the market remained stable at \$7.00/dose.

This stable pricing situation continued until the contract period starting in April 2001, by which point two factors had significantly reshaped the DTaP market in the U.S.: (1) the withdrawal of two companies B Baxter-North American and Wyeth B from the market; and (2) the temporary reduction in DTaP production by Aventis as it worked to remove thimerosal from its product. By January 2001, the nation was experiencing DTaP shortages, and the bidding stability of the previous years abruptly ended. Both Aventis and GSK came in with and maintained higher, but remarkably close, federal contract bids (Aventis at \$8.40/dose and GSK at \$8.33/dose).

By early 2002, the country had experienced a DTaP supply crisis for over a year. Shortages for the public sector were particularly acute: While GSK (with a thimerosal-free product) was able to meet and even exceed the maximum doses in its federal contract, Aventis (which had to reformulate to remove thimerosal) fell far short of the 8 million dose maximum it had negotiated with CDC. Faced with the choice of where to distribute its limited DTaP supply during the transition to a thimerosal-free product, Aventis chose to concentrate on private sector customers. During this period, CDC B in a departure from its consolidated contracting approach B awarded a one-month

interim contract to GSK for one million additional doses of DTaP, to cover shortfalls in the month of February 2002. The new contract price of \$9.40 per dose was \$1.17 higher than GSK's price under its then-existing contract.

By March 2002, CDC had returned to consolidated VFC contracting for DTaP. Both GSK and Aventis were awarded contracts. In its initial bid, GSK came in with a price of \$9.50 per dose for its product as originally packaged (the same price it had negotiated for its interim contract) and a slightly higher price of \$9.95 per dose for a product with syringe packaging. GSK's initial price jumped to \$11.00/dose for thimerosal-free Tripedia, and to \$12.00/dose for Daptacel, a new acellular vaccine licensed mid-year.

While this chapter of the story is not yet complete, both companies have again started to align their prices: in August 2002, in second round of bidding, Aventis matched GSK's price of \$9.50 for its original vaccine (Tripedia) and lowered the price on its newer vaccine (Daptacel) to \$10.50. GSK maintained its price of \$9.50 for Infanrix as originally packaged and lowered the syringe packaging version to \$9.75.

One additional change took place in August 2002 round of federal contracting: CDC raised the guaranteed minimum purchase of GSK products to 5 million doses. This new arrangement clearly reflects CDC's rethinking of minimum dose provisions, and may indicate a future shift in contracting policies related to both minimum and maximum dose guarantees: a change the vaccine industry may well welcome. In any case, the events of 2001-2002 clearly point to the need for better clarification of mutual expectations and responsibilities related to federal vaccine contracts.

Table G
Federal Contracting History of DTaP: 1992-2002
(Date = contract period start date. Price excludes excise tax.)

DATE	MILESTONES	CONTRACT DETAILS
3/92	First DTaP contract negotiated, as an amendment to existing Lederle contract for DTP.	<ul style="list-style-type: none"> • Contract period: 3/92 B 5/92 • Contract price: L: \$9.35 • Max doses: L: 2.1 million
10/92	First year-long contract negotiated: with Connaught, as a sole-source provider.	<ul style="list-style-type: none"> • Contract period: 10/92 B 10/93 • Contract price: C: \$6.45/dose • Max doses: C: 6.3 million
10/93	Second year-long, sole source contract awarded to Connaught. First contract stipulating minimum number of doses.	<ul style="list-style-type: none"> • Contract period: 10/93 B 10/94 • Contract price: C: \$5.37/dose • Max doses: C: 4.2 million • Min doses: C: 0.5 million
7/94	First year of dual contract awards, reflecting VFC mandate to contract with all licensed manufacturers that bid. Connaught, with lower bid, is awarded larger contract.	<ul style="list-style-type: none"> • Contract period: 7/94 B 7/95 • Contract prices: C: \$5.25 L: \$6.63 • Max doses: C: 7.5 million L: 5.0 million • Min. doses: C: 1.9 million L: 1.3 million
8/95	Second year of dual contract awards: to Connaught and Wyeth-Lederle. Connaught, with lower bid, is awarded larger contract.	<ul style="list-style-type: none"> • Contract period: 8/95 B 8/96 • Contract prices: C: \$5.14 WL: \$6.83 • Max doses: C: 5.0 million WL: 3.0 million • Min doses: C: 1.7 million WL: 1.3 million
9/96	Single contract awarded to Connaught. Price nearly doubles. There was a 2-3 week gap between expiration of old contracts and award of	<ul style="list-style-type: none"> • Contract period: 9/96 B 9/97 • Contract price: C: \$9.50

DATE	MILESTONES	CONTRACT DETAILS
	this contract.	<ul style="list-style-type: none"> • Max. doses: C: 16.0 million • Min doses: C: 4.0 million
4/97	<p>ACIP recommends DTaP use for doses 1-4. Based on these recommendations, CDC negotiates new contracts to supercede contracts from 9/96.</p> <p>First year that 3 contracts are awarded: SmithKline enters market.</p> <p>CDC pilot tests new procedures: (1) multiple awards to include all licensed suppliers; (2) purchasers can buy from any of contractors (previously, CDC chose); (3) guaranteed minimum purchase of only \$100; (4) contractors may revise price every 3 months, not to exceed initial award price.</p>	<ul style="list-style-type: none"> • Contract period: 4/97 B 3/98 • Contract prices by supplier and bid #: (1),(2),(3): C: (1) \$8.45; (2) \$7.19 SK: (1) \$9.50; (2) \$8.45 WL: (1)\$9.50; (2) \$8.75; (3) \$7.24 • Max doses: C: 16.0 million SK: 7.2 million WL: 4.0 million • Min contract for all: \$100
4/98	<p>Second year of pilot test.</p> <p>First year that 4 contracts are awarded: North American enters market.</p> <p>All suppliers end year with same price per dose.</p>	<ul style="list-style-type: none"> • Contract period: 4/98 B 3/99 • Contract prices by supplier and bid #: (1), (2), (3) C: (1) \$7.19; (2) \$7.00 NA: (1) \$7.00 SK: (1) \$7.34; (2) \$7.00 WL: (1) \$7.00 • Max doses: C: 16.0 million NA: 0.3 million SK: 16.0 million WL: 5.0 million • Min contract for all: \$100
4/99	<p>1st year of Consolidated VFC Contracts: all contracts negotiated for same 1-yr period. Provisions include: (1) multiple awards, (2) guaranteed minimums of \$100; (3) contractor option of price revision every 4 months (2x during contract period; prices may not exceed initial contract prices.)</p> <p>Four contracts awarded: all at same price.</p> <p>Aventis Pasteur acquires Connaught: change of name filed 12/99.</p>	<ul style="list-style-type: none"> • Contract period: 4/99 B 3/00 • Contract prices by supplier and bid #: C: (1)\$7.00 NA: (1)\$7.00 SK: (1) \$7.00 WL: (1) \$7.00 • Max doses: C: 12.0 million NA: 0.2 million SK: 12.0 million WL: 6.0 million • Min contract for all: \$100
4/00	2 nd year of Consolidated VFC Contracts: 4 contracts awarded, all at same price.	<ul style="list-style-type: none"> • Contract period: 4/00 B 3/01 • Contract prices by supplier and bid #:

DATE	MILESTONES	CONTRACT DETAILS
	<p>CDC switches to minimum of 100 doses, rather than \$100 minimum.</p> <p>North American Vaccine discontinues DTaP production.</p>	<p>A: (1) \$7.00 NA: (1) \$7.00 SK: (1) \$7.00 WL: (1) \$7.00</p> <ul style="list-style-type: none"> • Max doses: A: 12.0 million NA: 0.2 million SK: 12.0 million WL: 6.0 million • Min doses for all: 100
4/01	<p>3rd year of Consolidated VFC Contracts. Prices increase for first time in 3 years.</p> <p>Wyeth-Lederle exits market.</p> <p>Aventis and GlaxoSmithKline awarded contracts for thimerosal-free DTaP; Aventis also awarded contract for DTaP with thimerosal.</p>	<ul style="list-style-type: none"> • Contract period: 4/01 B 3/02 • Contract prices by supplier and bid #: A: (1) \$8.40 (<i>No thimerosal</i>) A: (1) \$8.40 (<i>With thimerosal</i>) GSK: (1) \$8.33 (<i>No thimerosal</i>) • Max doses: A: 6.0 million (<i>No thimerosal</i>) GSK: 6.0 million (<i>No thimerosal</i>) WL: 2.0 million (<i>With thimerosal</i>) • Min doses for all: 100
2/02	<p>Interim contract awarded to GSK, which had reached 6 million-dose maximum under 4/01 contract. Price increase.</p>	<ul style="list-style-type: none"> • Contract period: 2/04/02 B 2/28/02 • Contract price: GSK: \$9.50 • Max doses: GSK: 1.0 million • Min doses: GSK: 100
3/02	<p>4th year of Consolidated VFC Contracts. Price increases vary: highest for new products.</p> <p>Substantial guaranteed minimum awarded to GlaxoSmithKline.</p> <p>GlaxoSmithKline contract includes 2 types of packaging, with different prices.</p> <p>Aventis contract modified to add DAPTACEL vaccine, which is made by Canadian subsidiary</p>	<ul style="list-style-type: none"> • Contract period: 3/02 B 3/03 • Contract prices by supplier and bid #: A: (1) \$11.00 B original product (2) \$ 9.50 (1) \$12.00 B new product (2) \$ 10.50 GSK: (1) \$ 9.50 B original product (1) \$ 9.95 B syringe pkg. (2) \$9.75 • Max doses: A (orig.) 1.6 million A (new) 0.2 million GSK: 8.0 million • Min doses: A: 100 GSK: 5.0 million

Source: CDC, 2002c

Key: A = Aventis; C = Connaught; G = GlaxoSmithKline; L = Lederle; NA = North American; SK = SmithKline; WL = Wyeth Lederle.

Table H
DTaP Federal Contract Prices by Manufacturer: 1992-2002
 (Price = per dose.)

Contract Period Start Date	Lederle/ Wyeth Lederle	Connaught/ Aventis	SmithKline/ GlaxoSmith- Kline	North American/ Baxter
3/92	\$9.35			
10/92		\$6.45		
10/93		\$5.37		
7/94	\$6.63	\$5.25		
8/95	\$6.83	\$5.14		
9/96		\$9.50		
4/97 a	\$9.50 \$8.75 \$7.24	\$8.45 \$7.19	\$9.50 \$8.45	
4/98 a	\$7.00	\$7.19 \$7.00	\$7.34 \$7.00	\$7.00
4/99	\$7.00	\$7.00	\$7.00	\$7.00
4/00	\$7.00	\$7.00	\$7.00	\$7.00
4/01 b		Thimerosal - \$8.40 No Thimerosal- \$8.40	\$8.33	
2/02			\$9.50	
3/02 a, c, d		Tripedia - \$11.00 \$09.50 Daptacel - \$12.00 \$10.50	Original - \$9.50 Syringe pkg- \$9.95 \$9.75	

Source: CDC, 2002c

- a B Prices reflect multiple bids over the course of contract period, as well as sequencing of bids.
- b B Aventis prices reflect two contracts: (1) with thimerosal; (2) thimerosal- free.
- c B Aventis prices reflect awards for (1) Tripedia ; (2) Daptacel (made by Canadian subsidiary of Aventis).
- d B GSK prices reflect awards for two packaging options: (1) original; (2) syringe pkg.

Lessons Learned

DTaP=s history yields interesting insights about the U.S. vaccine market.

- ***Over the past decade (and more), global acquisitions and mergers have consolidated and reshaped the vaccine industry so that the U.S. market is currently dominated by a few large multinational corporations. These changes have several important implications for U.S. vaccine production, supply, purchase and pricing.*** First, the takeover by giant multinationals means that vaccine production decisions are now weighed as part of a much larger corporate portfolios, which may lead to very different decisions about future vaccine production. Second, in today=s extremely competitive environment, companies are looking for a higher return on vaccine investments than in previous decades, closer to the return from pharmaceuticals. This results in higher prices, especially for newer vaccines. Finally, with fewer companies in the market, reduced production by any single manufacturer is more likely to result in at least temporary supply shortages.
- ***Safety issues continue to impact U.S. vaccine production and supply.*** If anything, the country has become more sensitized to potential safety issues. In the case of DTaP and other vaccines containing thimerosal, safety-related recommendations to remove the preservative from childhood vaccines contributed in two ways to vaccine shortages in 2001-2002: for some companies, removal of thimerosal led to a temporary reduction in production capacity; and for other companies, the recommendation contributed to corporate decisions to discontinue production altogether.
- ***Regulatory compliance issues continue to influence corporate production decisions.*** This is particularly true when compliance requires substantial investments in the production facility.
- ***While CDC federal contracting practices have been highly successful in lowering public sector prices, they have been less consistently successful in maintaining the supply of DTaP and other recommended childhood vaccines.*** Under CDC contracting, public sector DTaP prices averaged 57.6% of private sector (catalog) prices over the past decade, a significant savings for public sector purchasers. However, CDC=s contracting practices could not assure an adequate supply of DTaP and other childhood vaccines in 2001-2002, particularly in the face of multiple other stressors on the market.

IV. Future Directions for DTaP

While it is hazardous at best to predict future directions both for markets and for public policy, knowledgeable observers suggest at least two likely directions for DTaP in the near future:

- ***DTaP will serve as a platform for several larger combination vaccines*** B The most likely and certainly the most imminent scenario for the future is that DTaP will become the platform on which larger combination vaccines will be built, combining five, six, seven or more antigens into a single Ashot@. As noted earlier in this report, larger combination vaccines are seen as advantageous to consumers and providers because they decrease the total number of injections children must receive. They are advantageous to manufacturers because they will allow companies to charge increased prices for the new combinations and, most importantly, because companies producing them will presumably have a competitive edge in the market.

In December 2002, a license application for the first of the new, larger combination DTaP-based vaccines was approved by the FDA. Developed by GSK, the new vaccine B Pediarix B combines five antigens: diphtheria, tetanus, and acellular pertussis (DTaP); hepatitis B (HBV); and polio (IPV). Pediarix was approved as a three-dose primary series for infants beginning at 6 weeks of age (FDA, 2002a).

Larger combination vaccines of this kind have already been successfully introduced in the European market. In addition to Pediarix, GSK has also developed and licensed in other countries four other DTaP-based combination vaccines, including two that combine DTaP with Hib (Haemophilus influenzae type b) vaccine, a potential next candidate for the U.S. market (SmithKline Beecham, 2000).

- ***DTaP may become a routine booster for adolescents and adults.*** There is growing international interest in the use of DTaP as a booster for adolescents and adults. The impetus is twofold: to reduce pertussis incidence in the adolescent and adult population and to reduce transmission of pertussis from adolescents and adults to infants.

During the decades when only whole-cell pertussis vaccine was available, its use in adolescents and adults was precluded due to serious side-effects of the vaccine in this older population. However, with the development and widespread use of acellular pertussis vaccine, which is associated with fewer side effects, routine immunization of adolescents and adults is once again under consideration, and several countries have begun incorporating adolescent and adult boosters into their national immunization programs.

In January, 2000, Germany became the first country to recommend a booster dose of acellular pertussis vaccine for adolescents aged 11-18 (GSK, 2003). Closer to home, Canada=s National Advisory Committee on Immunization (NACI) issued a statement in May, 2000, announcing the approval of a DTaP formulation manufactured by Aventis Pasteur Limited (Adacel), for use as a booster dose in individuals 12 - 54 years of age. The Canadian advisory group has not yet recommended universal use in either adolescents or adults. Instead, it notes that A[t]here are no data available at the moment on which to base a recommendation for universal routine use@, and further, that A[u]ntil data about safety of repeated doses is available, more than one dose cannot be recommended.@ Nevertheless the NACI statement approves the use of Adacel as a replacement for Td in adolescents or adults, for those individuals who wish to have protection against pertussis (NACI, 2000).

In December 2001, the International Consensus Group on Pertussis Immunization

called for a re-examination of national pertussis vaccination policies with an eye toward reducing transmission from and to adolescents/adult populations. The Consensus Group, representing international experts from 11 countries, recommended targeting pertussis booster doses to adolescents and to adults likely to come into contact with very young infants, as an achievable approach to preventing pertussis-related morbidity and mortality (GSK, 2003).

While the U.S. has not yet licensed use of DTaP in adolescents or adults, it is clearly a strategy under consideration, with recommendations for routine DTaP boosters in adolescents as one likely starting point. A 1999 paper by the head of the CDC's National Immunization Program reviews the epidemiology of pertussis in older populations and concludes adolescents should be targeted for routine pertussis boosters (GSK, 2003). The ACIP (Advisory Committee on Immunization Practices) has also discussed the potential for adolescent/adult pertussis boosters, reviewing preliminary findings from clinical trials, and discussing potential criteria for making a recommendation (CDC, 2000b).

It remains to be seen how these and other potential developments for DTaP will play out in the U.S.. While there has been good acceptance of larger vaccine combinations in European countries, some consumer groups in the U.S. are opposed to combining a greater number of antigens into a single shot, noting concerns about overloading the immune systems of infants and young children. In addition, these groups fear that combined vaccines may make it more difficult to identify causal agents should adverse events occur following immunization. On the other hand, many providers, as well as many consumers, will welcome the opportunity to simplify the immunization schedule and reduce the total number of shots infants and young children now receive. Consumer concerns about the safety of pertussis vaccine may also hinder efforts to expand routine immunization to include a booster for adolescents. And growing concerns in the provider and public health communities regarding the total costs of immunization may well put the issue of adolescent DTaP boosters on the back burner, at least in the near future.

Finally, in the post-9/11 environment, concerns about anthrax, smallpox and other bioterrorist threats may well change the way our nation and its various constituencies consider risks and benefits of all vaccines, including DTaP and other pertussis-containing combinations. The current environment also brings with it new concerns about costs, public health infrastructure and state fiscal capacity, all of which may impact purchase, pricing, production, and supply of current and future vaccines in the U.S. market.

As the nation faces both old and new challenges in reducing communicable disease morbidity and mortality, it is important to understand the complex nature of vaccine development and use, which sits at the intersection of four domains: science, public opinion, government policy and private sector market forces. Perhaps the key lesson learned from this brief history of DTaP is that all four domains will continue to evolve sometimes in surprising ways and it is in the best interests of all to work collaboratively to improve immunization options, policies, programs, and safety in the future.

APPENDIX A
Licensure History of DTaP Vaccines Approved by FDA
 (Note: initial approval in **bold**)

Vaccine Name	Company (and Location)	Approval Date	Comments
1. Acel-Imune			
	Lederle Laboratories (Pearl River, NY)	12/91	Licensed only for use as the 4 th and 5 th doses, for children aged 15 months - 6 years, who were previously vaccinated with 3 doses of whole-cell DTP (CDC, 1991). Note: AThe acellular pertussis vaccine component is produced by Takeda Chemical Industries, Ltd. (Osaka, Japan), and is combined with diphtheria and tetanus toxoids manufactured by Lederle Laboratories.@ (CDC, 1992d).
	Lederle Laboratories (Pearl River, NY)	12/96	Approved for use as a 3-dose primary series in children at least 6 weeks of age and for the 4 th and 5 th dose in children who have received 3 doses of DTaP (FDA, 2002c).

Vaccine Name	Company (and Location)	Approval Date	Comments
2. Tripedia			
	Connaught (Swiftwater, PA)	8/92	Licensed only for use as the 4 th and 5 th doses, for children aged 15 months - 6 years, who were previously vaccinated with 3 doses of whole-cell DTP (CDC, 1992b). Note: AThe purified acellular pertussis component in produced by BIKEN/Tanabe Corporation (Osaka, Japan) and is combined with diphtheria and tetanus toxoids manufactured by Connaught Laboratories, Inc.@ (CDC, 1996).
	Connaught (Swiftwater, PA)	7/96	Licensed for the initial 4 doses, to be administered at ages 2 months, 4 months, 6 months, and 15-20 months. Data available at the time were insufficient to determine immunogenicity and safety of a 5 th dose of the same acellular vaccine; however, it was anticipated that data would be available before infants using the new schedule reached 4-6 years and required a 5 th dose. Note: the 5 th dose of DTaP or DTP is not necessary if a 4 th dose was administered on or after the 4 th birthday. Also see note above re: manufacture of purified pertussis component of vaccine (CDC, 1996).
	Aventis Pasteur, Inc. (Swiftwater, PA)	8/00	Licensed for a 5 th dose at 4-6 years of age after 4 prior doses of Tripedia (FDA, 2002c).
Tripedia, contd.	Aventis Pasteur, Inc. (Swiftwater, PA)	3/01	The new, preservative-free, single dose reformulation of Tripedia contains only trace amounts of thimerosal B less than 5% of the amount of thimerosal found in the original formulation approved in 1992. It is licensed for doses 1-5, as described under previous approvals.(FDA, 2001).

Vaccine Name	Company (and Location)	Approval Date	Comments
3. Infanrix			
	SmithKline Beecham Biologicals (Rixensart, Belgium)	1/97	Licensed for primary and booster doses (1-5) except as a 5 th dose in children who have previously received 4 doses of DTaP (FDA, 2002c).
4. Certiva			
	North American Vaccine, Inc. (Beltsville, MD)	7/98	Licensed for both primary and booster doses (1-5) except as a 5 th dose in children who have previously received 4 doses of DTaP (FDA, 2002c).
5. Daptacel			
	Aventis Pasteur Limited (Toronto, Ontario, CA)	5/02	Licensed for doses 1-4. Product manufactured, labeled and packaged in single dose vials in Canada; distributed in the U.S. by Aventis Pasteur, Inc... (FDA, 2002c,d).

Sources: Product Approval Information from FDA Website: www.fda.gov/cber; *Morbidity Mortality Weekly Report* from CDC Website: www.cdc.gov/

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