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**Publication Date**

2009

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A Case Study of the Development and Promotion of the Gardasil Vaccine

by

Nicole Elizabeth Wolfe

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Sociology

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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## Acknowledgements

I am grateful to many people who have helped me accomplish this goal of getting my PhD. I first want to thank the Department of Social and Behavioral Sciences at UCSF for accepting me into this program and believing in my abilities. Second, I want to thank my advisor and dissertation chair, Charlene Harrington who provided a great deal of direction and advice over the years. She was always supportive of my work and the direction that I wanted to go. As busy as she was, she always made time for me and always provided me with constructive and useful feedback on my work. I feel very lucky to have worked with her.

I also want to thank my other committee chairs, Ruth Malone and Lisa Bero, whom I also feel very lucky to have had the chance to work with. Ruth served as my third area chair, which really helped to shape my dissertation project. She provided direction and was always very present throughout the process. Lisa Bero brought another dimension to my work, which was very much appreciated. She provided me with useful suggestions when crafting my project and helped me to shape many of the questions that I asked my study participants. I feel very honored to have worked with three such accomplished and highly regarded women.

I am particularly grateful to my husband, Joe Barefoot whose complete support of me throughout this process enabled me to complete this program in the timeframe that I had set for myself. He always believed in my ability to accomplish this goal and encouraged me throughout the process. He was always understanding of the time that I had to spend doing schoolwork even when that took time away from being together. He has been my biggest source of support and my biggest fan, and I am eternally grateful and lucky to have him in my life.

I also want to thank my friends and family for also believing in me and for their excitement throughout this process. I am the first person in my family to get a PhD, so they have been particularly proud and encouraging.

To everyone at SBS, I want to thank you all for your support through the years. Linda Tracy has been a great source of support and has been incredibly helpful navigating through the bureaucracy of UCSF and providing advice whenever I needed it. To the students in the program, I want to thank you for the support, encouragement, and camaraderie over the years. It really helped to get through various stages of this program. To all of the administrative staff, thank you for all the help you have given me over the years. And to all of the faculty, I have learned so much in these five years and have grown so much academically and personally. Thank you!

**A Case Study of the Development and Promotion of the Gardasil Vaccine**  
**Nicole Wolfe**  
**Abstract**

In 2006, Gardasil, the first human papillomavirus (HPV) vaccine was approved by the Food and Drug Administration to protect women age 9-26 against four strains of HPV, 16, 18, 6, and 11 that cause 70 percent of cervical cancer cases and 90 percent of genital warts cases respectively. The objective of this dissertation was to understand the process of the development, approval, and marketing of the Gardasil vaccine. This project used a qualitative, exploratory, single case study research method using data collected from articles, press releases, government, and industry documents, as well as interviews from key informants in 2008 and 2009. After the technology was acquired by Merck in 1995, the clinical trials were conducted from 1997 to 2005, and Gardasil was approved with five years of data to support claims of safety and efficacy. Promotional campaigns began in 2005 prior to Gardasil's release through awareness efforts that linked HPV and cervical cancer. The primary marketing campaign for Gardasil began after its approval and release to encourage females to visit their physicians to discuss vaccination and to encourage physicians to give the vaccine. The campaign has been a success, resulting in about 25 percent of eligible females receiving the vaccine and making Gardasil a profitable venture. Gardasil is sold at high prices largely in the United States where cervical cancer has been largely mitigated by pap smears and preventive health care. Merck facilitated the social construction of the human papillomavirus as a problem needing treatment and successfully positioned Gardasil to be the solution to that problem.

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## **Chapter One - Introduction**

The Gardasil vaccine was approved by the Food and Drug Administration in June 2006, and is the first vaccine to prevent four strains of the Human Papillomavirus. Gardasil was developed and marketed by Merck, one of the largest pharmaceutical companies worldwide and the number four drug maker in America in terms of sales, with a market value of approximately \$60 billion with \$6.8 billion in cash and short-term investments (Smith, 2007b). Gardasil is revolutionary as it is the first vaccine released to protect against a virus that causes cancer, making it an important and timely topic to study.

The Human Papillomavirus (HPV) is a ubiquitous sexually transmitted virus with over 100 identified strains. Most people contract one or more strains of this virus during their lifetime, yet show no signs as the body naturally clears it. As such, many of these strains are relatively innocuous, but there are some that can cause longer lasting problems including genital warts and dysplasia; cervical dysplasia, if left untreated can develop into cervical cancer. Two of the oncogenic strains of HPV that Gardasil targets, HPV-18 and HPV-16, are responsible for approximately 70% of cervical cancer cases (Charo, 2007; Garland et al., 2007; Sawaya & Smith-McCune, 2007)

Prior to the licensing and release of Gardasil, Merck began its marketing campaign through awareness efforts that stressed the link between cervical cancer and HPV (J. Schwartz, 2006). This campaign worked synergistically with the marketing campaign that was rolled out upon the release of Gardasil because by that time, women knew that cervical cancer was caused by the human papillomavirus. The marketing

campaign for Gardasil then clearly stated that it protected against the two strains of HPV responsible for the majority of cervical cancer cases. Through these complimentary campaigns, Merck was able to secure a market for its product prior to it being approved and released.

This project is unique and provocative for several reasons. First, Gardasil is a vaccine, not a drug. Vaccines differ from drugs in that they are preventative and are given in 1-3 shots over the course of 1-6 months, whereas drugs are used to treat existing conditions, and are generally taken daily, often for an indefinite period of time. Second, pharmaceutical companies tend to focus attention more on treatment than on prevention, making vaccine development less competitive than drug development; there are fewer companies developing vaccines than are developing drugs. Third, Gardasil was and continues to be heavily promoted through direct-to-consumer ads. Fourth, attempts to mandate Gardasil coupled with the fact that HPV is sexually transmitted has made Gardasil more controversial than other recently released vaccines. Fifth, Gardasil exemplifies many of the issues and concerns that have been raised regarding the pharmaceutical industry; Merck has maintained control over the science and messaging behind Gardasil, Merck is a highly successful company backed by a powerful lobby, and Gardasil was approved through an expedited review with approximately five years of clinical trial data to support claims of effectiveness. Finally, this issue is timely as Gardasil was released in 2006, which provides a unique opportunity to study an issue that is still prominently in the public consciousness.

Following the trajectory of the development and marketing of Gardasil helps to understand the following: how the construction of HPV as a social problem fostered the

acceptance of Gardasil and of its widespread use, and how power is used in the construction of specific social problems through the management of science and the media, how that translates into social control, and how that impacts public health. This was accomplished through the three aims of this study.

### *Aims of the Project*

This sociological case study has three aims. The first aim is to describe the process of the development and testing of the Gardasil vaccine. This focused on how Merck became involved with the technology used to create Gardasil, the development, and testing of Gardasil. Included are descriptions of the clinical trials, as well as information about the safety and efficacy of the vaccine. To put this in context, information is presented about the human papillomavirus, cervical cancer, and the rates of preventive care in the United States.

The second aim of this project is to describe the process for the approval of Gardasil. This focused on how Merck worked with government agencies throughout the testing process to gain approval of the vaccine and to have guidelines set for its use. This focused on how Merck controlled the science behind Gardasil as well as its relationship to the federal government and its agencies. The relationship to the government examined the connection between Merck and the federal agencies responsible for oversight, approval of medication, and the setting of guidelines for their use, including the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). This aim also incorporated looking at the lobbying effort by Merck and its effect.

The third aim of this project is to describe how Merck promoted and marketed Gardasil and how HPV was constructed to be a social problem needing treatment. This

included looking at issues of direct-to-consumer advertising and how Merck's power may have influenced that promotion. It involved analyzing the ads and how the messaging has changed since the promotional campaign started and how that may have contributed to sales of the vaccine. It also involved looking internally at Merck, its budget, and its philosophy. More details of these aims and the methods used are addressed in chapter three. Understanding the issue of Gardasil not only required understanding the issues stated above, but understanding the industry as a whole to help put this issue in context.

### *The Pharmaceutical Industry*

The pharmaceutical industry is one of the most profitable industries both nationally and globally, with sales of roughly \$200 billion and \$500 billion respectively (Angell, 2004; Conrad & Leiter, 2004; Moynihan & Cassels, 2005). For over two decades, the pharmaceutical industry has been the most profitable industry in the United States (Angell, 2004). In addition to an increase in profits, the pharmaceutical industry has also benefited from changes in the areas of drug pricing and marketing; drug laws and regulations; clinical trials and the publication of results; as well as changes within the health care system and regarding conceptions about health (Angell, 2004; Boggs, 2005; Busfield, 2006; Moynihan & Cassels, 2005)

National sales of prescription drugs continue to rise annually, making prescription drugs the fastest growing part of health care costs (Wilkes & Bell, 2000). In the past ten years, national spending on prescription drugs has more than tripled (Robinson et al., 2004). The result of this rise has been an increase in profits for the pharmaceutical industry (see Table 1), which have increased disproportionately to other industries (Angell, 2004; Boggs, 2005). By the year 2000, the top ten leading pharmaceutical

companies amassed a greater profit than the remaining Fortune 500 corporations put together, and had achieved an overall profit level more than three times the median for other Fortune 500 companies. By 2001, these ten corporations had accounted for almost half of all global pharmaceutical revenue (Boggs, 2005; Busfield, 2006).

Table 1 **Top Ten Pharmaceutical Companies**

<i>Company</i>	<i>Country HQ</i>	<i>Main Products</i>	<i>Employees worldwide</i>	<i>2004 Marketing Costs (billions)</i>	<i>2004 R&amp;D Costs (billions)</i>	<i>2006 Profits (Jan-June) (billions)</i>	<i>2005 Profits (Jan-June) (billions)</i>
AstraZenica	UK	Nexium, Prilosec	66,000	7.84	3.80	3.02	2.27
Bristol-MyersSquibb	USA	Plavix, Pravachol	43,000	6.43	2.50	1.38	1.54
GlaxoSmithKline	UK	Paxil, Valtrex, Wellbutrin	15,000	12.93	5.20	5.13	4.53
Hoffman LaRoche	Switzerland	Tamiflu, Valium,	74,000	7.24	4.01	3.60	2.80
Johnson & Johnson	USA	Procrit, Remicade	122,200	15.86	5.20	6.12	5.43
Merck	USA	Fosamax, Vioxx, Gardasil	60,000	7.35	4.01	3.02	2.10
Novartis	Switzerland	Ritalin, Gleevec/ Glivec, Zelnorm	90, 900	8.87	4.21	3.67	3.12
Pfizer	USA	Celebrex, Lipitor, Viagra, Zolof	115,000	16.90	7.68	6.52	3.76
Sanofi-Aventis	France	Plavix, Ambien, Allegra	100,000	5.59	9.26	5.14	3.82
Wyeth	USA	Effexor, Prempro	50,000	5.80	2.46	2.18	2.05

(Ismail, 2006; Waxman, 2006)

The rising use of prescription drugs has seemingly increased the power of the pharmaceutical industry due to the dependence that is created as more people need, or are led to believe that they need the drugs that the pharmaceutical industry is developing and marketing. Much of this power comes from being the “gatekeepers” to these drugs in the sense that the pharmaceutical industry determines the amount of drugs manufactured as well as their cost. The industry determines which drugs are brought to market, and there has arguably been an emphasis on drugs that have the highest potential for profit (Busfield, 2006; Gilbert, Walley, & New, 2000). This can be problematic for the obvious financial roadblocks that some people may face if they cannot afford the drugs they need. This can also be problematic if more profitable drugs are being marketed, while other less expensive, and possibly equally effective drugs are being marginalized or excluded. Since the United States is the only industrialized country that does not regulate drug prices, the pharmaceutical industry maintains sole discretion over drug prices (Boggs, 2005).

Most drugs require a prescription for their use, but physicians are not the gatekeepers in the sense that they used to be (Conrad, 2005). Historically, people tended to have one physician that they saw throughout their adult lives, and knowing that person’s history, the physician could make informed decisions about which medications were necessary at which times for which conditions. Seeing patients throughout the course of their lives allowed the physician the benefit of knowing their patients' long term health history, thus making it easier to make informed determinations about medications. Within the current managed care health system, most people switch physicians at various points throughout their lives, and now have less time to spend with their physician at each

visit. The physician therefore is operating under less time and with less historical health knowledge of that patient, potentially impacting the prescribing of medication.

Regulatory changes allowing direct-to-consumer ads greatly affected the prescribing of medication. The effect of this is that many people now visit their physician not only knowing which medications they want, but expecting to leave their physician's office with that prescription (Kessler & Levy, 2007; Robinson et al., 2004; Stange, 2007).

Receiving a prescription has become a barometer for people to measure the level of care they received and many people feel that if they were not given the prescription they requested, then they received inadequate care (Robinson et al., 2004). As a result, the amount of prescriptions being written is increasing. By 2003 “physicians were prescribing 146 medications for every 100 physician visits, mostly for such conditions as depression, anxiety, sleeplessness, pain, sexual dysfunction, high blood pressure, cholesterol, and arthritis” (Boggs, 2005, p. 409).

Americans are the largest consumers of prescription drugs, accounting for almost 50% of the global market (Moynihan & Cassels, 2005). Over half of the American population is using drugs for dozens of physiological and psychological conditions; this does not including over-the-counter (OTC) or illegal substance (CDC, 2004a). Without any price caps or restrictions, prices for many of the most heavily prescribed drugs are increased regularly, leaving many people unable to afford all of the medications they need.

The public is often told that the high price of drugs is necessary in order for the pharmaceutical companies to continue with their research and development (R&D), though that is not necessarily the case. Research and Development is a relatively small

part of a pharmaceutical company's budget (see Table 1). In many cases R&D costs are less than half of what is spent on marketing and public relations (Moynihan & Cassels, 2005). In fact, “according to Securities and Exchange Commission (SEC) and shareholder reports for 2001, the biggest drug companies spent on average about 35 percent of their revenues on ‘marketing and administration’”, making it the largest single item in drug companies’ budgets (Angell, 2004, p. 119). The large portion of money that is going into marketing can help to explain the increased use of prescription drugs. Additionally, this industry is comprised of publicly traded companies that have an obligation to their shareholders to maximize profits. This obligation to “maximize shareholder value” requires that top managers “pay more attention to increasing the returns on assets of the firm in order to increase the value of those assets to shareholders, and less attention to other constituencies, such as employees and communities” (Fligstein & Shin, 2007, p. 2). When companies are legally required to maximize shareholder value then they are naturally putting their shareholders first, to the possible detriment of those using their products. This is of particular concern when the product is a pharmaceutical, in this case a vaccine, and has the potential for adverse events, thus affecting public health.

### *Gardasil*

In June 2006, the Food and Drug Administration approved Gardasil. Gardasil is the first vaccine to be released that has the potential to protect against a certain type of cancer, by protecting against the virus that causes the cancer. Gardasil protects against four strains of the Human Papillomavirus (HPV), HPV-6, HPV-11, HPV-16, and HPV-



18. HPV-16 and HPV-18 are the two strains responsible for 70% of cervical cancer cases, while HPV-6 and HPV-11 are responsible for 90% of genital warts in both men and women (Charo, 2007; Garland et al., 2007; Sawaya & Smith-McCune, 2007). After its approval by the Food and Drug Administration (FDA), the Advisory Committee on Immunization Practices (ACIP) through the Centers for Disease Control and Prevention (CDC) was charged with setting the guidelines for its use. After reviewing the data, the committee voted to recommend Gardasil to females ages 9-26. The target population was 11-12 year old girls with catch up vaccinations for all females 13 years and older, though the vaccine could be given to girls as young as 9.

Merck rolled out an extensive national media campaign for Gardasil, which began prior to its release and continues to this day. The media can be an effective tool in swaying public opinion as well as in assisting in the construction of social problems. Direct-to-Consumer advertising has been a key feature of that marketing campaign. The initial campaign was focused on awareness and stressed the link between cervical cancer and HPV, which assisted in laying the groundwork for the acceptance and use of Gardasil (J. Schwartz, 2006). Once Gardasil was available to the public, the initial marketing campaign had already made the public aware of the “problem” of HPV such that Gardasil could enter the marketplace as the solution, and the continued marketing campaign reinforced that message. These two campaigns were complimentary, where first women were informed about the issue, were asked to tell other women they knew, and then finally encouraged to visit their physician to discuss their risk of HPV and whether Gardasil was right for them. These campaigns linked learning about the issue, sharing it with friends and family, and seeing a physician with empowerment. The underlying

message was about taking control of your health, about being a knowledgeable woman, and taking action to prevent disease. These direct-to-consumer ads utilized an often used tactic in these type of ads – the emotional plea. Emotional pleas have been shown to affect how patients speak to their physicians, and may also affect the way people speak to each other about the issue (Frosch, Krueger, Hornik, Cronholm, & Barg, 2007; Weissman et al., 2003).

Upon its release, Merck began waging a behind-the-scenes lobbying campaign in approximately twenty states in an attempt to persuade state legislatures to mandate the incorporation of Gardasil into the standard vaccine schedule for young girls. Funding for many of these campaigns was funneled through an advocacy group called Women in Government. Women in Government is “headquartered in Washington, DC, is a national 501(c)(3), non-profit, bi-partisan organization of women state legislators providing leadership opportunities, networking, expert forums, and educational resources to address and resolve complex public policy issues”

[\(http://www.womeningovernment.org/\)](http://www.womeningovernment.org/). Women in Government, which itself has accepted large amounts of funding from Merck, was responsible for introducing similar bills around the country that sought to mandate vaccination of young girls with Gardasil, and make it a requirement for entry into school, similar to most other vaccines. Merck has since suspended its lobbying efforts after a large public outcry, which questioned its motives about why it would push so hard to mandate a vaccine so soon after its release. Vaccines that do become mandated are done so after several years on the market with substantial epidemiological data to support both their safety and efficacy. Much of the concern about Merck’s attempts to make Gardasil mandatory was that it was financially

motivated as opposed to being in the public interest. Merck posted \$1.4 billion in sales for Gardasil in 2007 alone, making Gardasil its top selling vaccine and Merck's 4<sup>th</sup> highest selling product (Securities and Exchange Commission, 2008).

The approval and release of Gardasil was predicated on the results of the clinical trials. While the results from the studies are positive in that almost all of the participants did not develop cervical abnormalities, all of the trials were designed, funded, and analyzed by Merck (Garland et al., 2007; The Future II Study Group, 2007). Merck maintained control over the information from those trials, and the manuscripts of the results were drafted by Merck employees, with collaboration from academic authors who had full access to the analyses and approved the final manuscript (Garland et al., 2007). Additionally the results that the FDA and CDC reviewed were from the completed phase II trials and preliminary phase III results; results from the phase III trial are still being analyzed, with publications of those results expected in the fourth quarter of 2009 (N. B. Miller, 2006; VRBPAC, May 18, 2006).

Several concerns have been raised about Gardasil, one of the most pressing being the cost. Gardasil is relatively expensive, priced at approximately \$360 for the three-shot series, though the cost can be substantially higher if one is uninsured or underinsured and has to pay for the vaccine and/or the physician's visits out of pocket. There are many insurance companies that cover the total or partial cost of the vaccine. Currently in California, Medi-Cal (California's Medicaid) does cover the cost of the vaccine for low income women covered under its plan as it considers the vaccine a "medically necessary preventive service for girls and women 9 to 26 years of age" (Baird, 2007).

Another concern stems from the attempts to mandate the vaccine to all young girls, despite the low rates of cervical cancer in the United States. Roughly 80% of the cases of cervical cancer occur in developing countries, yet this vaccine is being primarily marketed to women in the developed world – women who have lower rates of cervical cancer, yet who are more likely to be able to afford the vaccine due to living in a more affluent society (Laurance, 2006). In the U.S., a comparatively small portion of the population develop cervical cancer and that is often mitigated by access to preventative care in the form of pap smears, which have been responsible for the decrease in the number of deaths from cervical cancer (American Cancer Society, 2006; eHealth MD, 2004).

Current estimations in the U.S. suggest that approximately 20 million women have some form of HPV, yet fewer than 12,000 are diagnosed with cervical cancer in a year and of those, less than 4,000 die of the disease. Cervical Intraepithelial Neoplasia, which is abnormal cell growth on the cervix and which can lead to cervical cancer if left untreated, is classified as a rare disease by the National Institutes of Health (National Institutes of Health, 2009). The disparity between the numbers of women who have HPV and cervical cancer suggest that only a small number of women have the strains of HPV that may eventually lead to cervical cancer; the strains that are protected by Gardasil.

A final concern is the nature of HPV and how it is transmitted. HPV is a sexually transmitted virus, meaning that it can only be transmitted through sexual contact. It is not casually communicable like polio, the measles, or the flu. Proponents of the vaccine argue that the fact that approximately 20 million people are currently infected with HPV is reason enough to require wholesale vaccination of young females, though as previously

mentioned, that number does not break down by strain, making it difficult to know how many people have the two strains that are responsible for the 70% of cervical cancer cases (Stewart, 2007). Additionally, the body naturally clears most instances of HPV infection. Women are not tested for HPV infection prior to being vaccinated, so it remains unknown how many of these females have any type of HPV at the time of vaccination. The nature of the transmission of HPV makes it unclear as to why there is a push to vaccinate *all* young girls with Gardasil. Vaccines are generally on the market for several years prior to being mandated and the campaign to mandate Gardasil has been unprecedented, particularly since HPV is not a childhood disease and is not casually communicable. In light of this, Gardasil vaccination may be more appropriate for some females who may be at a higher risk, or unable to access regular, preventative health care, than it may be for others, though even those who have been vaccinated are still advised to continue receiving regular pap smears.

The release of Gardasil has provided women with an unprecedented means of prevention against both a sexually transmitted virus and a certain type of cancer. The release of Gardasil has also been fraught with controversy because of the sexual nature of HPV and the attempts to make the vaccine mandatory. The issues of Merck's relationship to the government, its sole handling of the clinical trials, and its extensive marketing campaign make this an interesting case to study, and it exemplifies many of the issues that have been raised regarding the pharmaceutical industry. To help understand and explain the issue, a sociological theoretical framework was used.

### *Theoretical Framework*

This study draws from two theoretical frameworks; C. Wright Mills' *The Power Elite*, and Jill Quadagno's stakeholder mobilization. In Mills' analysis, power is structural and is situated within what he determined to be the three major institutions within American society; military, corporate, and political institutions (Mills, 1956). Those at the top of these institutions are who Mills defined as the "power elite." As a result of their position, the power elite are able to make decisions having national and increasingly international consequences. It is the institutions that hold the power and those in the top positions within these institutions are only powerful by proxy of their position; if they leave their position within that institution they lose power, with their successor gaining that power (Mills, 1956). The pharmaceutical industry is situated within the corporate arm of Mills' tripartite, with top executives exerting their power in ways that have benefitted the industry. Being part of the corporate institution allows for access to the government, which can allow for regulatory changes because of the nature of that relationship. This framework helped to situate the pharmaceutical industry generally, and Merck specifically, within the current power structure.

Jill Quadagno's analysis centers around the stakeholders involved. This analysis dovetails with Mills analysis because some of the stakeholders analyzed in this study are part of the power elite. Whereas Mills situates power in the position of the institution, Quadagno places more emphasis on strategy. Stakeholder mobilization parallels social movement theory except that in this case, it is the powerful, not just the powerless who are also able to organize to effect change. Despite the access that the powerful have, they must also have the resources necessary to exert political power. Quadagno states that those in the powerful institutions must use the resources they have wisely in order to

mobilize and garner the support needed to shape public perception of the issue at hand (Quadagno, 2004). It is not just the person or the position that holds the power to make change, but rather the ability to make change lies in the strategy and the effective use of resources. In order to be politically effective, stakeholders need “leadership, an administrative structure, incentives, some mechanisms for garnering resources and marshalling support, and a setting where grassroots activity can be organized” (Quadagno, 2004, p. 28).

In this study, I looked at different stakeholder groups with differing levels of power, including physicians, researchers/scientists, Merck employees, and government officials. Some of these stakeholder groups have acknowledged conflicts of interest. The use of these two frameworks enriched this study because of their complementary nature. The position of the pharmaceutical industry has been integral to its ability to make regulatory changes that benefit the industry. The pharmaceutical industry has also used various tactics to sway public opinion and shift support in its favor. It has been the combination of the position within the power elite as well as the strategy for mobilization that has resulted in its success. The other stakeholders, while not necessarily part of the power elite, have used their resources to present and make public their position regarding Gardasil.

Within these two frameworks are four theoretical areas that are discussed: power, political economy, social control, and social construction. The discussion of power from *The Power Elite* helped to expand the concept of power itself and how it manifests within the power elite structure. The concentration of power results in a relatively small group of people at the top whose decisions affect the much larger majority at the bottom.

Consequently, this majority, whom Mills refers to as the mass society, is not able to weigh in, in any meaningful way, on decisions that impact their lives. Often, “the issues that now shape man's fate are neither raised nor decided by the public at large” (Mills, 1956, p. 300). This is demonstrated in the relative lack of control the public has over aspects of the pharmaceutical industry, such as control over drug pricing; access to drug trial information, not just the published results; or drug advertising.

Political Economy assisted in explaining the ideology behind the concentration of wealth within the corporate world, as well as its relationship to the State and government agencies. There is a large concentration of economic, political, social, and cultural power in the world today and political economy can help to understand how and why that power structure exists (Navarro, 2004). This concentration has enabled institutions to position themselves such that their level of power has increased thereby making those at the top of those institutions part of the Power Elite. It has also allowed for the maintenance of the status quo in the health care sector leaving the U.S. as the only industrialized country to have a completely privatized health care system that does not regulate drug prices. This persists despite the fact that the health care system in the U.S. does not benefit the majority of the population; it benefits a relatively small percentage of the population, about the top 20% (Navarro, 1999).

The theory of social construction is taken from Peter Berger and Thomas Luckmann (Berger & Luckmann, 1966). This process begins with the dissemination of information, which begets internalization, and results in institutionalization also termed habitualization. Internalization is when members of society take on the attitudes and ideas set forth for them and make them their own. These attitudes and beliefs guide their



actions and lead to institutionalization, whereby those actions are cast into a pattern, which can then be reproduced (Berger & Luckmann, 1966). The exchange of information among members of society creates the society; therefore the society in which people live is a reality that is socially constructed. Reality can change, and that change largely depends on who has power and who is in control of the information being disseminated. People take in the information that they receive and process it in accordance with the social factors that make up themselves and their environment – they internalize that information (Berger & Luckmann, 1966).

A theme connected to social construction, is a concept called disease mongering, which originated with Lynn Payer, and has been advanced by Ray Moynihan (Moynihan, Heath, & Henry, 2002). Disease mongering takes the concept of medicalization one step further suggesting a situation where, “the social construction of illness is being replaced by the corporate construction of disease” (Moynihan et al., 2002, p. 886). Disease mongering occurs when the boundaries of treatable illnesses are broadened to expand the market for new drugs, and can include “turning ordinary ailments into medical problems, seeing mild symptoms as serious, treating personal problems as medical, seeing risks as diseases, and framing prevalence estimates to maximize potential markets” (Moynihan et al., 2002, p. 888).

Social control occurs when people act in accordance with the internalized ideas perpetuated by those with power and helped to further analyze this issue. Language is a means of facilitation, and the nature of the messages that people receive about their health and health care in general vis-a-vis pharmaceuticals, is a feature of the control that the pharmaceutical industry currently has. As the pharmaceutical industry exerts more

control over the population, the population becomes more acutely aware of their health, instilling a sense of vigilance in people in regards to their health. Symptoms that may have once been perceived by the individual as benign might now be viewed more seriously and in need of pharmaceutical intervention. It is not just a matter of treating a current condition, but of preventing future problems as well, which includes not only preventative medicine, but vaccination. Women who may not have heard of HPV or who visited their physician regularly and received pap smears may now feel as though they are at risk. Internalizing the messages about the connection between HPV and cervical cancer may motivate women to get vaccinated or may motivate parents to vaccinate their young daughters.

### *Conclusion*

The release of Gardasil has provided women with an unprecedented means of prevention against both a sexually transmitted virus and a certain type of cancer. The release of Gardasil has also been fraught with controversy because of the sexual nature of HPV and the attempts to make the vaccine mandatory. The issues of Merck's relationship to the government, its sole handling of the clinical trials, and its extensive marketing campaign make this an interesting case to study, and it exemplifies many of the issues that have been raised regarding the pharmaceutical industry.

The pharmaceutical industry has a large measure of control over people's health as it is the industry that is producing the medications that people need for various health situations. Even for those who argue that there are many unnecessary medications in the market place, the people using those medications still rely on them. Without adequate

levels of regulation and oversight on the industry, the power that the industry has can be used as a form of control due to the level of autonomy they have in the areas of drug production, marketing, and pricing. Therefore, the pharmaceutical industry must be examined, not just in terms of how its medications may affect people individually, but how society as a whole is affected. This means looking at: how its power is used politically, and how that affects the development and marketing of drugs; how a relationship with the government can positively affect the development, approval, and marketing of drugs; and how the tactics of the industry, and the messaging behind the drug promotion affects people's perceptions of that drug, all of which is addressed in this dissertation.

This study aimed to address some of the concerns about the pharmaceutical industry by using Merck's Gardasil as a case study. This project addressed the social construction of HPV as a problem needing treatment, the media and promotional campaigns for Gardasil, and the relationship between Merck and the federal government. This is not just a public health issue where concern lies solely in the potential adverse effects of a medication, but an issue of control. If Merck is able to construct HPV as a problem needing the treatment that it is providing, control the science behind the development of the drug, control the promotion and messaging of that drug, and rely on connections within the government to smooth the path for approval, then it is essential that this issue is analyzed through a sociological lens to provide a level of analysis that has not yet been put forth. Using Gardasil as an example is one approach to bringing a new analysis to many of the issues regarding the pharmaceutical industry. The following chapters discuss in detail; the theoretical areas; the existing literature surrounding the

issue; the study methods as well as the limitations; the findings of this study organized by each of the three aims; a thorough analysis of those findings; and where I see the future of this research and my work.

## **Chapter Two - Literature and Theory Review**

The following chapter discusses both the theoretical areas that helped to analyze and understand the issue as well as the literature review which puts Merck and the Gardasil case in the context of the larger industry in which it occurred. Theories are an essential component to this project. They help to frame the issue and facilitate a deeper understanding of the issue by adding additional layers of understanding. This can sometimes result in a more complete picture of the area under study or can help to view the issue from a different perspective. The theoretical areas discussed in this chapter are power, political economy, social control, and social construction.

The literature review in this chapter looks at the pharmaceutical industry and traces its trajectory to help contextualize the Gardasil issue. It includes an overview of Gardasil and its development as well the promotional and marketing campaigns that were launched both before and after its release. This section also includes information about HPV and its prevalence in this country and how researchers felt about its effectiveness. This chapter begins with a review of the theories used for analysis.

### ***Theory***

#### ***Power***

The concept of power used in this analysis was taken largely from C. Wright Mills' analysis of power in *The Power Elite*. In Mills' analysis, power is structural and is situated within what he determined to be the three major institutions within American society; military, corporate, and political (Mills, 1956). For this analysis, the military

component of Mills' tripartite was not engaged; the focus was primarily on the corporate and political institutions. Those at the top of these institutions are who Mills defined as the "power elite." They refer to "those political, economic, and military circles which as an intricate set of overlapping cliques share decisions having at least national consequences. In so far as national events are decided, the power elite are those who decide them" (Mills, 1956, p. 18).

The result of power being concentrated in the way Mills described is that there is a relatively small group of people at the top whose decisions affect the much larger majority at the bottom. Consequently, this majority, whom Mills refers to as the mass society, is not able to weigh in, in any meaningful way, on the decisions that will be affecting their lives. Indeed, "the issues that now shape man's fate are neither raised nor decided by the public at large" (Mills, 1956, p. 300). This is demonstrated in the relative lack of control the public has over certain aspects of the pharmaceutical industry such as: control over drug pricing; access to drug trial information, not just the published results; or drug advertising – where and when they will be exposed to direct-to-consumer ads.

The physician-patient relationship has also been affected, whereby an increasing number of people are now visiting their physicians with expectations of receiving certain prescriptions for medications (J. Abramson, 2004; Conrad & Leiter, 2004; Friedman & Gould, 2007; Kessler & Levy, 2007; Pitts, 2004; Robinson et al., 2004; Stange, 2007; Wilkes, Bell, & Kravitz, 2000). Drug advertising encourages viewers to discuss the drug with their physician, though in the office, "'discuss' usually morphs into 'request' or 'demand'" (J. Abramson, 2004, pp. 151-152). This works to the advantage of the drug companies and seems to be a result of regulatory changes that have increased the

industry's access to the population through direct-to-consumer ads (J. Abramson, 2004; Angell, 2004; Robinson et al., 2004; Wilkes et al., 2000). The ads are a way for the pharmaceutical companies to bring awareness of their medications to a large segment of the population, who are then asked to speak to their physician about that medication. The ads have the potential to be beneficial, as they can raise people's awareness of various treatments that are available. Additionally, there may be people who have certain symptoms, yet did not realize that those symptoms may be indicative of a certain condition for which there are currently treatments. While direct-to-consumer ads may be beneficial for some, they are often not as informative as they could be and tend to be based on an emotional plea, "not facts, and few provide necessary details about the causes of a medical condition, risk factors, or lifestyle changes that may be appropriate alternatives to pharmaceutical interventions" (Kessler & Levy, 2007, p. 4). The use of direct-to-consumer ads also highlights the changes that are occurring for people as they are now viewed less as patients, and more as consumers (Conrad, 2005). Additionally, it seems that people in this case are being used as unwitting pharmaceutical sales representatives. When a certain drug is advertised extensively, prompting many people to request that drug from their physicians and fill the prescription, then those people have effectively increased the sales of that drug.

What happens at the top levels consequently affects the society at large where "the community of publics has been transformed into a society of masses" (Mills, 1956, p. 300). Having a larger mass at the bottom increases their separation from those at the top, which actually serves the interests of those at the top. As more resources become concentrated among fewer people at the top, other people lose access to those resources,

so people who may have been in the middle of these two groups, are now likely to move down into the masses, instead of up into the powerful. The mechanisms of communication change in these instances, and the media become necessary and invaluable tools for communication as well as serving as “unique instruments of psychic management and manipulation” (Mills, 1956, p. 310). The media are effective at accessing a large portion of the population, which can be advantageous because “the decisions that are made must *take into account* those who are important – the elite – but they must be *sold* to the mass memberships” (Mills, 1956, p. 308).

The pharmaceutical industry is situated within the corporate arm of Mills' tripartite, with top executives exerting their power in ways that maximize shareholder value (Fligstein & Shin, 2007). The media have proven to be effective tools as well for this industry, with direct-to-consumer ads being the most recognizable example. While the media can be an effective means of imparting necessary and useful information, they can also be equally effective as a source of entertainment. When this occurs, it can leave the masses distracted from the main issue at hand because the masses have not necessarily been informed, but merely entertained (Wrong, 1956).

The relationship with the media allows the power elite to make decisions among themselves without necessarily having to answer for them directly because the media serve as the buffer between the masses and the powerful. The masses therefore have no real recourse against the powerful and it would be a near impossibility for an individual to contact a top official at one of the pharmaceutical companies to discuss any aspect of their product or business practice. People can consult their physician, though there is no guarantee that the physician had accurate information as that physician may not have



been given factual information him/herself. The pharmaceutical industry has largely influenced the design and analysis of clinical trials, which affect the results that are disseminated (J. Abramson, 2004; Angell, 2004; Bero, Oostvogel, Bacchetti, & Lee, 2007; Bodenheimer, 2006; Busfield, 2006). They have also sponsored many conferences and continuing education talks that are given, which again has the potential for bias (J. Abramson, 2004; Bodenheimer, 2006; Moynihan & Cassels, 2005). Physicians attend these conferences and talks to remain up-to-date on the current medical treatments. If they are receiving skewed or inaccurate information, it could potentially affect their patient's treatment as well as the physician's practice and credibility.

Another important aspect to Mills' analysis is his discussion of the connection between power, status, and prestige, three distinct, yet connected concepts. Mills simplified this somewhat by invoking the chicken-and-egg analogy where "the chicken is power and comes first, and the egg is status" (Mills, 1956, p. 264). While his analogy does not include prestige, prestige follows status. Prestige cannot exist without power and status already being present. Mills also discussed prestige as the "shadow of money and power" (Mills, 1956, p. 88). Mills stated that "an elite cannot *acquire* prestige without power" (Mills, 1956, p. 88). Like power and status, prestige is not static and it "buttresses power, turning it into authority and protecting it from social challenge" (Mills, 1956, p. 89). Where power and status are somewhat more concrete terms and can be quantified in some way by the sheer fact that it is possible to experience someone's power through their actions and observe their status due to their position within a company or by observing their access to institutions and their treatment by others, prestige is somewhat more amorphous. Prestige is an aura and adds a mystique to those in

power. It is what sets them apart from the masses and what maintains the distance between the powerful and the masses.

Aspects of this can be seen with the pharmaceutical industry as their power has increased. This industry has been successful in making cultural changes among the population as the use of prescription medication is increasing (Angell, 2004; Busfield, 2006). This was largely possible due to the level of power that the pharmaceutical company has. The status of the pharmaceutical industry also appears to have remained strong, as exemplified by its close ties to the political institutions, maintained largely through lobbying (Ismail, 2005, 2006). Access to political institutions may exemplify the pharmaceutical industry's status, but it does not do the same for the industry's prestige. It appears that the prestige of the industry has been dropping, which can be characterized by the public's perception of this industry – a perception that seems to be deteriorating. One of the main reasons for this is the high cost of drugs (Angell, 2004).

Mills discussed these three concepts in a linear fashion, Power→Status→Prestige. He stated that there can be no prestige without status and power. Prestige is rather fragile in this sense because “from the moment prestige is called into question it ceases to be prestige” (Mills, 1956, p. 89). Prestige provides a mystique to those in power which helps maintain the separation between them and the masses. If that prestige fades or disappears, then that mystique is gone and a more realistic view of the powerful may be revealed. This revelation may make the masses more inclined to challenge the powerful directly, which in turn may decrease their power and status. The current criticisms of the industry are beginning to affect its prestige, but have not yet affected its power or status.

It remains to be seen how the pharmaceutical industry fares in the long term in the face of continued criticism.

Mills' theory about the power elite also challenged the notion of democracy itself in America (Mills, 1957). Suggesting that power was concentrated and centralized among a relatively small group of people at the highest echelons of society meant that they had the potential to wield disproportionate power over the masses due to their shared interests and control over institutional resources. This limits equal opportunity and participation in the political process, which can potentially threaten a democratic society. Additionally, the members of the corporate power elite are unelected and therefore, largely unaccountable to the public.

Democracy becomes limited by the overwhelming power of money, or what Navarro terms the "milk of U.S. politics" (Navarro, 1995, p. 457). This becomes even more important when discussing the health of the population. People rely on researchers and physicians to be educated in their field and have the most up-to-date information regarding health care and health care options. If people are given false or misleading information about the medications they are being prescribed, there is the potential for dire public health consequences. This has been seen in the case of Vioxx where there was clear knowledge of the hazards of the medication prior to bringing it to market (Goldstein, 2007; Merck & Co., 2004). Since the general public is not involved in the process of drug development and trials, they rely on and trust the Food and Drug Administration to ensure the safety of the drugs that are approved to be sold, as well as the veracity of the clinical trials. When a case like Vioxx occurs, that trust is shaken. In the case of clinical trials, there is evidence of bias when a trial is sponsored by the

company that developed and plans to market the drug (Bero et al., 2007). This is not suggesting that this happens in every case, but since this bias has been documented to occur with certain classes of drug, such as statins it can be presumed that this is occurring with other classes of drugs as well (Bero et al., 2007). This suggests that there might be a large number of clinical trials whose results are potentially biased based on the fact that a pharmaceutical company is sponsoring a trial of its own drug.

Mills was concerned that a large majority would be subjected to the rules and dictates of a small minority, the power elite, who do not have the same needs as the masses on the bottom. The example of clinical trials bolsters this claim, as the pharmaceutical companies have an interest in bringing drugs to market in a timely fashion, to maximize shareholder value (Fligstein & Shin, 2007; Wilkes et al., 2000). Maintaining financial success and therefore power and status is key to remaining part of the power elite. There is potential hazard to the public if the trials of the drugs are biased and the pharmaceutical companies have control over what results are/are not published. The fact that there does not seem to be as much scrutiny over these trials as there should be by the FDA is indicative of the relationship between the political and corporate institutions. The public should be able to feel comfortable taking the medication they need and confident that medication will not harm or kill them.

What makes Mills' discussion of the power elite in America unique is that "the power elite is not an aristocracy, which is to say that it is not a political ruling group based upon a nobility of hereditary origin" (Mills, 1956, p. 278), though they do derive "in substantial proportion from the upper classes" (Mills, 1956, p. 279). The power elite are not solitary rulers, nor are they inherently powerful because no one can be "truly

powerful unless he has access to the command of the major institutions, for it is over these institutional means of power that the truly powerful are, in the first instance, powerful” (Mills, 1956, p. 9). This is an important distinction that Mills makes. It is not the individual per se who is powerful. That individual can only be powerful because of the institution within which he/she is situated. The institution holds the power and the person at the top of that institution (the CEO) is only powerful by proxy (Powell & Smith-Doerr, 1995). When that person leaves the institution, the power does not necessarily go with him/her.

Mills discussed the backgrounds of the chief executives of industry and noted that the vast majority of them come from fairly wealthy families. At this level, one is not seeing someone who has “pulled themselves up by their bootstraps,” but rather, just the opposite. Understanding that power lies in the institution, allows those within the institution to carefully select who is allowed to ascend the corporate ladder, thereby ensuring that the “right” people obtain those positions. This is also connected to education because those who came from wealthy families have a better chance of going onto higher education, meaning undergraduate and graduate level degrees. They are also more likely to have gone to a private preparatory school in their youth, which can serve two purposes (Mills, 1956). The first is that an education at a private school is generally superior to that of a public school. This can give those students an advantage when entering an undergraduate program, as well as positioning them to attend higher ranked universities. Second, attending a private school can be insulating because of the homogeneity at many of these schools. This ensures that children of the wealthy remain

among others of the same socioeconomic status virtually throughout their lives, which works effectively as a socializing mechanism.

The objective in business is to keep the corporation running and “to make the corporation self-perpetuating, the chief executives feel that they must perpetuate themselves, or men like themselves – future men not only trained, but indoctrinated” (Mills, 1956, p. 139). It makes sense that only people who are ensured of maintaining the integrity of the corporation would be allowed to rise through the ranks and be rewarded with the top jobs.

Mills discussed Americans as “the most individualistic people in the world,” yet “the impersonal corporation has proceeded the farthest and now reaches into every area and detail of daily life” (Mills, 1956, p. 120). The pharmaceutical industry is reaching into nearly every aspect of people’s lives by trying to market and sell medications that address nearly every aspect of life. Additionally, this industry has also been responsible for developing conditions to fit existing drugs (Pre-Menstrual Dysphoric Disorder, PMDD, for example) or for expanding or changing certain health indicators (cholesterol levels), in order to sell more of a certain type of medication, such as the statins, which are prescribed for lowering cholesterol (J. Abramson, 2004; Greenslit, 2002; Moynihan & Cassels, 2005). For example, the cholesterol levels deemed necessary for treatment were lowered by an expert panel in 2001, thus expanding the number of people who could be targeted for drug treatment therapy from 13 million to 36 million (National Cholesterol Education Program, 2001). Pre-Menstrual Dysphoric Disorder (PMDD) as mentioned above, is an example of creating a condition to fit a drug, whereby the makers of Prozac merely repackaged that drug in new colors (pink and purple) and sold it under a different

brand name, Sarafem. Prior to this, PMDD was not a known disorder. It was created around the same time that the patent on Prozac ran out as a means to continue profiting from of this drug (Angell, 2004; Greenslit, 2002; Moynihan & Cassels, 2005).

Corporations are “not just a set of splendidly isolated giants. They have been knit together by explicit associations within their respective industries” (Mills, 1956, p. 122). These associations bring each corporation within the industry together to ensure their collective survival. Lobbying groups represent the whole industry, not just the individual pharmaceutical companies. There is a recognition that it is in their best interest to work together to expand their industry-wide powers (Mills, 1956). A larger group can have more influence than a smaller group and working collectively can ensure that decisions are made that they can all benefit from. This not only increases their power among the population, but at the political level as well, which is how they have been able to influence the regulatory and legislative changes that have occurred. Their connection to the State also allows them to make largely unquestioned decisions, such as the pricing, packaging, and to a lesser extent, advertising of their drugs (Mills, 1956). The restrictions on advertising to the public have been relaxed since the 1997 Food and Drug Administration Modernization Act, though there are still some guidelines that must be followed. In the end, the “the chief executives who sit in the political directorate, by fact or by proxy, hold the power and the means of defending the privileges of their corporate world. If they do not reign, they do govern at many of the vital points of everyday life in America, and no powers effectively and consistently countervail against them, nor have they as corporate-made men developed any effectively restraining conscience” (Mills, 1956, p. 125).

There are no real countervailing powers against this industry. There is no mass movement, such as a labor movement to balance any of this industry's excesses (Navarro, 1988). Groups have formed to protest against certain actions of this industry, and the industry has countered those groups by creating front groups (Angell, 2004; Busfield, 2006; Moynihan & Cassels, 2005). So, even if the groups could generate enough membership to act as a real countervailing force to this industry, the industry so far has enough of its own power to stymie their efforts.

In terms of analysis, Mills asserts that "undue attention to the middle levels of power obscures the structure of power as a whole, especially the top and bottom" (Mills, 1956, p. 245). In terms of politics, attention is often placed on individual senators or congressmen, who may not be part of the power elite as they may not rank high enough. There is a hierarchy within each of the institutions that Mills discussed, yet it is the top positions within each of those institutions that hold the most power, and it is those people in those top positions who are the power elite. Simply working within one of the institutions does not make one a part of the power elite. While there are some members of Congress who can be considered part of the power elite, there are many others who cannot. This is not to say that these other members of Congress do not hold some level of power, but a junior Congressperson is not as powerful as the Speaker of the House. This marks a distinction between having power and being part of the power elite. While those in power certainly have the ability to make important decisions, the decisions made by the power elite are more consequential at the national and international levels (Mills, 1956).



When Mills was writing in the early 1950's, he noted that the Senators and Congressmen were not part of the rank and file, but were “of the privileged white, native-born of native parents, Protestant Americans” (Mills, 1956, p. 248). While there are now women, people of color, and of different religions in the Congress, they are still a relatively small minority. Most of the people in Congress are either from a privileged background or were successful prior to being elected into the Congress due to the fact that getting elected is a very costly enterprise, starting at approximately one million dollars for a congressional seat and increasing from there. These are costs that continue to increase (Birnbaum, 2004). This is important because members of Congress are supposed to represent their constituents, but if they come from a markedly different background than their constituents how can they fully understand their constituents’ needs? When so much of politics is money-based, how can elected officials be expected to work in the best interests of their constituents when they have received and continue to receive contributions and donations from corporations? Individual constituents cannot easily rival that kind of power.

Mills spoke about the increasing costs of elections and was writing at a time when this was a relatively new phenomenon. Most people today could hardly conceive of an electoral system any other way, particularly now that corporations play such a large role in elections through campaign contributions and funding of legislative initiatives. There is no doubt about the influence of money in politics (Navarro, 1995). When the political world relies so heavily on money, and when there is a corporate world with a large amount of money, then the symbiotic connection between these two institutions is much clearer. The administration of George W. Bush was demonstrative of this

connection as many of the people within that administration were part of the corporate world before entering into office and many went back to the corporate world after leaving office. It is not just elected officials that deserve scrutiny, but other government officials who were not elected at all, but were appointed, often with the approval of Congress. This is the case for regulatory agencies such as the Food and Drug Administration.

Where other social scientists may focus on the marginalized within society and create an analysis around their situation, Mills shined the light directly into the eyes of the powerful and onto the institutions in which they derive their power. He was in fact challenging the system and by proxy every member who derives their power from that system. The pharmaceutical industry has become a formidable part of the corporate arm of Mills' tripartite, and as such deserves analysis, particularly when public health is of concern.

When Mills was writing, he was seeing a corporate evolution occurring where society "consists of an economy in which small entrepreneurs have been replaced in key areas by a handful of centralized corporations, of a polity in which the division of authority has become imbalanced in such a way that the executive branch is supreme...the new society is clearly a political economy in which political and economic affairs are intricately and deeply joined together" (Mills, 1956, p. 260). This imbalance has only grown in the last 60 years and the current political economy is arguably more deeply joined together than ever before.

### *Political Economy*

The previous discussion of Mills' theory of the Power Elite situated the pharmaceutical industry within the larger power structure. The following section discusses how and why that power structure exists. There is a large concentration of economic, political, social, and cultural power in the world today, and it is this concentration that has enabled institutions to position themselves such that their level of power has increased (Navarro, 2004). This concentration also prevents the redistribution of wealth to the poorer elements within society because doing so would decrease the power of the wealthy. Power exists when one group has what another does not.

Since the Reagan administration, privatization and commodification have been the dominant ideologies regarding health care in this country, with other countries being pressured to adopt it as well (Navarro, 2004). Countries that do not adopt this ideology and either institute or remain with their national health care service are often demonized through propaganda, which can result in possible political repercussions. The for-profit model of healthcare in the US has been beneficial for industry and for the State, yet it has not been as beneficial for the average citizen. Individuals are often beset by problems with their insurance companies often due to being under or uninsured (Navarro, 2004). These problems transfer to areas of prescription medication as well.

Insurance companies have the discretion not to approve certain treatments for their customers as well as having discretion over what medications they are covered. Insurance companies each have their own formulary, which is a list of the drugs for which they cover the total or partial costs. The formularies can change without warning resulting in some people unable to obtain their medication due to cost increases. This can result in people taking less than the recommended dose or discontinuing that medication

(Angell, 2004). Despite the fact that federal health expenditures have been cut, the U.S. still spends more per capita on health care than any other industrialized country, yet health indicators are not better for Americans (G. Anderson, Reinhardt, Hussey, & Petrosyan, 2003; Navarro, 1999, 2004).

Various interests shape the domestic and international policies of the current administration, the pharmaceutical industry being one of them (Navarro, 2004). Internationally, the U.S. government has defended the financial interests of the pharmaceutical industry by allowing them to continue to develop higher priced medications to treat conditions prevalent in the West (such as depression, high cholesterol, high blood pressure) rather than encouraging them to develop medications to treat diseases prevalent in the third world (malaria), from which they would not reap an equivalent profit (Laurance, 2006; Navarro, 2004).

The U.S. is also influential within the World Trade Organization, and has the ability to pressure countries with an existing national health service to dismantle their system and institute a commercial health care system (Navarro, 1999, 2004). The pharmaceutical industry has the potential to benefit from this change. Currently the U.S. is the only industrialized country to have a completely privatized health care system as well as not regulating drug prices. If other countries privatized their national health services to model the American system, then there is the possibility that their regulations regarding drug pricing would change as well. This could be a potential windfall for the pharmaceutical industry if it was able to price its drugs in other countries as the drugs have been priced in the U.S.

The merit of an “economic policy is measured primarily or even exclusively by its impact on the health and welfare of the population” (Navarro, 2004, p. 7). By this metric, it seems as if the current economic policy is not particularly meritorious. The economic interests of the State often do not concur with the interests of the public. The public is, among other things, interested in maintaining its’ health and safety. If the first priority is to make money, then the health and safety of the people using these medications naturally comes second. The trend therefore is that the interests of the industry are met before those of the public, bolstering Navarro’s claim that class interests tend to trump national interests (Fligstein & Shin, 2007; Navarro, 1995, 1999).

The health care system in the U.S. does not benefit the majority of the population; it benefits a relatively small percentage of the population, approximately the top 20% as well as large companies and industry (Navarro, 1999). Financial capital is a driving force in the U.S. and the pharmaceutical industry has amassed a large enough arsenal of capital to become a driving force in health care. Ironically, it is in the U.S. and other countries where capital is the driving force, where not only are the health indicators the worst, but economic growth is lower and unemployment higher (Navarro, 1999). This stands in conflict to the myth that America has the best health care system in the world (LeBow, 2002). This system is also problematic when one considers that in the U.S., health insurance is tied to employment (Navarro, 1995), even though many people who work full time remain uninsured (Center on Budget and Policy Priorities, 2006; Kaiser Commission on Medicaid and the Uninsured, 2003). Therefore, if unemployment is high, the rate of the uninsured increases as well. This does not take into account the people who are underinsured – those people who may have some form of health insurance, but it

is not comprehensive enough to cover all of their health care needs. For those people who lose their job, but still need their medication, this can be potentially life threatening if they become unable to afford their medication.

There is an understanding that “U.S. public policies are the result of the influence of major economic and financial interests for whom the specific policies are being developed” (Navarro, 2003, p. 65). This is certainly the case with the pharmaceutical industry as has been demonstrated with their effect on policy and regulations. Power in the U.S. is distributed by class, and the way that class power is reproduced is by strengthening the exclusion of alternative ideas, ideas that could serve as mobilization against the dominant ideology (Navarro, 1995). This is what is at play with the pharmaceutical industry. Its level of control within health care is at an unprecedented level and there seems no impetus to change. Legislation has been drafted and drugs marketed that were often unnecessary for the public, yet have served to benefit the industry’s bottom line. Medicare part D, the prescription drug benefit, is an example of legislation that greatly benefited and was largely written by the industry yet has been a source of confusion and frustration among many seniors enrolled in the program (Graham, 2005). The current emphasis on pharmaceuticals may lead some people to believe that there are no viable alternative treatments to their condition, and that pharmaceuticals are their only option.

When so much of the political process in the U.S. is funded by industry and other economic interests, it is not just the U.S. public who are negatively affected, but democracy itself. Democracy is meant to be a government run by the people, by the citizens of that country. What is happening in the U.S. is that a small portion of the

citizens, through the industries in which they are situated, have an enormous influence over the political process instead of the majority having a say. The result of this is that the democratic process in the U.S. is limited, and the lower the degree of the development of a country's democratic process, the smaller the welfare state, including the health care sector (Navarro, 2003). This is evidenced by the more than 40 million people who are uninsured in the U.S., despite spending the most on health care (G. Anderson et al., 2003).

The reach of the pharmaceutical industry can also be felt within academia due to its development partnerships. The dependency of the U.S. academic establishment "on the financial and corporate interests that shape and determine the research tenure policies of the leading universities in the United States...preempts any possibility of building a scholarship critical of the U.S. establishment" (Navarro, 2004, p. 8). Academia is often the place where researchers expose social problems, and if there is a connection between industry and that institution, then an honest evaluation of that industry is unlikely to come from the institution paired with it.

Professional dominance - a position espoused by Eliot Freidson (Freidson, 1970) - is where the medical profession dominates the health care system (Navarro, 1988; Timmermans & Kolker, 2004). This is done through the production of medical knowledge, is seen in the division of labor in health care, in the provision of health care services, and in the organization of the health care system (Navarro, 1988). Supplanting this professional dominance was the rise of corporate dominance (Moynihan & Cassels, 2005; Moynihan et al., 2002). Physicians have lost some of their control over health care since insurance companies can make decisions about courses of treatment and what is/is

not approved. This means that physicians may not be able to treat a patient the way they see fit because of decisions made by the insurance companies.

Now, the pharmaceutical industry is able to wield a similar kind of power, through changes in the physician-patient relationship (Moynihan & Cassels, 2005). Primarily through their access to the public, they have been able to convince many people of two things: first, that they have a certain condition and second, that they need this medication to treat it. Patients coming to their physician requesting medication, coupled with the fact that physicians have a limited amount of time to spend with each patient, may result in inadequate time to discuss all of the issues raised by the patient or to provide a comprehensive examination (Kessler & Levy, 2007; Stange, 2007). Even if the condition is present, the physician may not feel that particular medication is the best course of treatment or may not have the time to discuss the medication in detail with that patient. If the patient continues to request that medication and the physician's time is limited, then a dilemma may occur – give the patient the prescription with reservations, or do not write the prescription and risk losing that person as a patient or having their professionalism questioned.

McKinlay and Stoeckle discussed the transformation of management and the roles of physicians within the medical community. In many cases, physicians are being replaced at the top levels of management by people who are trained in management, not medicine (McKinlay & Stoeckle, 1997). This puts many medical decisions in the hands of management, which can result in a potential loss of autonomy for the physicians. Furthermore it can affect patient care as “managerial imperatives often compete or conflict with physicians' usual mode of practice” (McKinlay & Stoeckle, 1997, p. 176).



This may not seem problematic if the U.S. did have the best, or one of the best, health care systems in the world, but that is not the case.

Another way that physicians have seen their roles change is through their “gatekeeping function” (McKinlay & Stoeckle, 1997, p. 177), specifically, their ability to prescribe medication. Nurses and physicians’ assistants are able to prescribe a variety of medications, in almost half of the states in the U.S., which improves patient care since otherwise a patient might have to wait to see a medical physician. Additionally, there are many public health situations where medical physicians do not or will not practice. Were it not for nurse practitioners and physicians’ assistants, people in those situations might not be able to access care. While the expansion of prescribing authority is beneficial for the public, it is also beneficial for the pharmaceutical industry. The more people who are able to prescribe medication, theoretically, the more medications that are prescribed. If people had to wait to see a medical physician instead of being able to see a nurse practitioner or a physicians’ assistant, there could be longer waits for drugs. This can also be advantageous for the pharmaceutical industry due to their role in physician education, and the benefits from being able to access and “educate” nurse practitioners and physicians’ assistants in the ways that it has with physicians (Moynihan & Cassels, 2005).

The corporatization of medicine is profoundly changing the daily work of physicians. In one generation, “U.S. health care has been historically transformed – from a predominantly fee-for-service system controlled by dominant professionals to a corporatized system dominated by increasingly concentrated and globalized financial and industrial interests” (McKinlay & Marceau, 2004, p. 190).

McKinlay and Marceau discuss the failure of the Clinton plan for health care reform as being a catalyst for some of this corporatization by coalescing the opposing economic interests, including the pharmaceutical industry. Others included private insurance and the hospital sector. These interests united against any progressive change within health care – change which would undoubtedly have affected their bottom line. The State played a role in this by allowing these interests, including the pharmaceutical industry, to gain the power that they did. The New Right perspective is another way to look at this phenomenon because “its proponents argue that the state should retreat from responsibility for medical care and let market forces prevail” (McKinlay & Marceau, 2004, p. 194).

The pharmaceutical industry has been established as powerful. Their position within the larger structure has also been discussed. It is not enough to know that they are powerful, but to understand how that power becomes control through the process of social construction.

### *Social Construction*

Peter Berger and Thomas Luckmann discuss the process of social construction in society, which is largely the role of knowledge within society (Berger & Luckmann, 1966, p. 53). This process begins with the dissemination of information, which begets internalization, and results in institutionalization also termed habitualization.

Internalization is when members of society take on the attitudes and ideas set forth for them and make them their own. These attitudes and beliefs guide their actions and lead

to institutionalization, whereby those actions are cast into a pattern, which can then be reproduced with an economy of effort” (Berger & Luckmann, 1966, p. 53)

Society can be “understood in terms of an ongoing dialectical process” where people are not born members of society, but rather become members of society through this process (Berger & Luckmann, 1966). The exchange of information among members of society creates the society, hence the society in which people live is a reality that is socially constructed. Reality, therefore, is not static and is something that can and does change. That change largely depends on who has power and is therefore in control of the information being disseminated. People take in the information that they receive and process it in accordance with the social factors that make up themselves and their environment; they internalize that information (Berger & Luckmann, 1966).

Language is a means of shaping the reality of everyday life and is vital as it “marks the coordinates of life in society and fills that life with meaningful objects” (Berger & Luckmann, 1966, p. 22). Language also molds and shapes communication and is something that is taught within each society as a means of socialization. Barthes claimed that language is always socialized, even at the individual level (Barthes, 1967). Language is at once a social institution and a system of values that can be engaged following a period of learning (Barthes, 1967). It is the contextual nature in which language is used which requires attention since it used as a means of institutionalization. Seeing an ad for a drug, which has been produced by the manufacturer of that drug and is shown on a popular TV channel or is placed in a popular publication, is different than listening to a layperson discuss that same drug. Hearing about drugs in these contexts

can be effective in changing people's perceptions about those drugs, though discussions with family/friends can also be influential (Weissman et al., 2003).

The pharmaceutical industry uses language very precisely in order to influence people within society. This is done largely through the direct-to-consumer television and print ads. The ads are not just about imagery, but about language as well. The language that is used, in conjunction with the imagery, is crafted to produce the desired effects of selling medication (Frosch et al., 2007; Gahart, Duhamel, Dievler, & Price, 2003). When language is a means of socialization, it can be used in various contexts. Graduate students, for example, are introduced to a new language when beginning a graduate program and are not only expected to learn this new language, but to use it throughout their career – having done this demonstrates that they have been properly socialized into that field.

As a system of values, language is being used by the pharmaceutical industry to socialize people into an acceptance of medication. The language around the use of medication has the potential to change people's perceptions. As perceptions change, actions may follow, and as information is internalized, it becomes habitualized. Therefore, a medical condition that may have had a stigma years ago (erectile dysfunction, for example), may no longer carry that same stigma due to the increased discussion of that condition vis-a-vis drug advertisements. This does not mean that drug advertisements have the ability to remove all stigma. It does mean that the increasing discussion about certain conditions and medications have been brought into the public domain, making them a potentially more common topic of discussion, thus decreasing some of their taboo (Pitts, 2004). As the topic remains in the public domain for a longer

period of time, with more people talking about and accepting it, there is a likelihood that the level of stigma or discomfort around an issue may decrease.

The socialization process can allow for the construction of a new paradigm or bolster the existing one. In either case, the process is essentially about constructing a value system – what is/is not acceptable within that society. For the pharmaceutical industry, this process can both change people’s perceptions of drugs, the use of those drugs, as well as how they speak to others about those drugs. It is also necessary to ensure that the values of the society are effectively passed onto the next generation of citizens. This can be important for this industry because ensuring the value of taking drugs to the current generation can have an effect on the next generation. It is possible that people who are born during this time will grow up with the current pharmaceutical paradigm, and will not have the knowledge of a time when this level of acceptance of taking medication was not the case.

Knowledge and reality can be taken for granted and is often not questioned. People's reality is determined by the information that is made available to them. In the absence of any countervailing information, it is difficult to be cognizant that other realities exist, much less understand them. Peoples’ consciousness is determined by their social being, is maintained by social interactions, and is always intentional; it always intends or is directed towards its objects (Berger & Luckmann, 1966). Each new object or piece of information opens people up to new ideas and new realities. New information that is disseminated to a large enough portion of the population has the potential to affect the reality of that group and subsequently the rest of that society, particularly if that new information is regularly repeated. This phenomenon can be observed through the use of

direct-to-consumer ads, which are able to target a large portion of the population. Additionally, direct-to-consumer ads are shown regularly, so that people may see the same ads multiple times. The repetition of the message increases the chances of the information being internalized due to the fact that it becomes normalized. Hearing or seeing the same information reduces any novelty that information once had. That novelty is replaced by normality, where it then becomes part of the reality of everyday life.

One cannot exist in everyday life without interacting with others, a fact not lost on the pharmaceutical industry. The use of emotional pleas in direct-to-consumer ads, has been shown to affect how patients speak to their physicians, and it may also affect the way people to speak to each other (Frosch et al., 2007; Weissman et al., 2003). This has the potential to benefit the industry by normalizing a certain drug to the extent that others begin taking that drug. It could also serve as a detriment to the industry if a certain drug is demonized due to lack of effectiveness, or adverse events.

Habitualization occurs when actions become almost second nature. All human action is subject to habitualization because so much of everyday life is cast into a pattern (Berger & Luckmann, 1966). One example of a pattern in this society is work, whereby most people get up in the morning to go to work and come home in the evening. This is evidenced, in part, by the traffic patterns seen on the streets and highways in the mornings and evenings. These traffic patterns have even been named due to their regularity of occurrence – rush hour. On the weekends or during holidays, traffic patterns change in those same areas, highlighting the weekday pattern. Work, therefore has become habitualized for many people – they get up at the same time, leave at the same time, take the same route to/from work, and often have the same routine at work. Even

when day-to-day tasks at the workplace change, there is generally the same routine at work, where people get into work, have coffee, lunch, and leave at comparable times each day. Habitualization can be positive because people can accomplish certain tasks with an economy of effort, leaving more mental or physical energy available for other tasks. Habitualization may also be limiting because there is one prominent choice, which is generally engaged. This can be potentially dangerous in the context of pharmaceuticals. The habitualization of drugs suggests a situation where their use becomes so commonplace that it is not questioned. Berger and Luckmann have discussed habitualization in the context of freedom, or lack thereof, due to the limited choices available. In this sense, people are freed from having to make so many decisions because the process of habitualization has essentially made those decisions for them (Berger & Luckmann, 1966).

Habitualization results when people of a certain group are expected to act a certain way and therefore do act that way. This is not a suggestion that all members of a society succumb to internalization and habitualization and therefore all members of society act alike. That is not the case, and there are generally those within society who do act differently, though there are consequences for those actions. Internalization therefore is twofold. On the one hand, it acts as a form of social control because it sets up the predefined patterns of conduct, which channel behavior in one direction “against the many other directions that would theoretically be possible” (Berger & Luckmann, 1966, p. 55). On the other hand, by doing so, it sets up what is unacceptable behavior as well. Controlling how people act, can also control how they react to others who do not act accordingly. Control is not just about people’s own actions, but about how they respond

to the actions of others, both when they are and when they are not compliant with the societal values.

The pharmaceutical industry has succeeded in changing aspects of society in order to habitualize the use of their products. Language has been used to target and engage members of society in order to habitualize the use of medication for various conditions, some of which may not have previously been treated pharmaceutically. Internalization is a form of social control because once an idea is internalized it becomes the prominent idea, leading to subsequent habitualized action.

### *Social Control*

Social control occurs when people act in accordance with the internalized ideas perpetuated by those with power. Language was discussed as a means of facilitation. The nature of the messages that people receive about their health and health care in general vis-a-vis pharmaceuticals, is a feature of the control that the pharmaceutical industry currently has. This has been discussed in terms of the medical professionals as well as the general population. For the medical professionals, control is one feature among professions that elevates and distinguishes them from other occupations (Timmermans & Kolker, 2004). Professionals have control over their own work in a way that others may not because of the knowledge that they possess and the way in which that knowledge can be used in a technical way to create autonomy (Timmermans & Kolker, 2004). The assumption is that professionals are educated to such a high degree that they are the only ones capable of making decisions regarding their profession. Historically, the medical profession enjoyed a high level of autonomy and it has only been in the recent past that



this has changed. One way that this has changed has been through the development of clinical practice guidelines, which are described as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific circumstances” (Timmermans & Kolker, 2004, p. 178). These guidelines have the potential to be beneficial as they can delineate what types of treatment options works best for certain situations, which can aid physicians or other health professionals who may not be as familiar with certain conditions. It can also limit the latitude that physicians have in treating their patients because these guidelines don't allow for unconventional treatments, which may be called for in certain situations.

These changes have also affected the prescribing of medications. Psychiatry is one field where this has been observed. In three decades, Psychiatry has moved from “psychotherapy and family interaction to psychopharmacology, neuroscience, and genomics. This is reinforced when third party payers will pay for drug treatments, but severely limit individual and group therapies” (Conrad, 2005, p. 4). This suggests that there are circumstances where people are not getting the care they need because their insurance company does not approve the treatment. As a result, people may be treated ineffectively, which can potentially result in further problems for the patient, at a higher long term cost to the third party payer.

The effects of the pharmaceutical industry on health care were discussed previously in this chapter, and what happens at the national level affects those at the individual level. A major effect is that the burden of responsibility is shifted to the individual, and health then becomes an issue of personal responsibility with the onus put on the individual to attain and maintain a state of being that conforms to the certain

societal standards (Armstrong, 1995; Williams, 1998; Zola, 1971). A system is then formed that works to control people and their bodies (Scheper-Hughes & Lock, 1987). One feature of this system is the “problematization of the normal” (Armstrong, 1995). This can set up a situation where people are never viewed as entirely healthy because there is always one issue/condition/problem that can be treated medically. This changes the very notion of health because the line between health and illness becomes blurred, resulting in an “omnipresence of disorder,” where virtually any aspect of a person’s body or bodily function can be subject to medical and pharmaceutical treatment (Zola, 1971). An example of this can include the previously discussed Pre-Menstrual Dysphoric Disorder (PMDD), where women’s physical and emotional experiences during their menstrual cycle are now a medical condition with a pharmaceutical treatment.

As the pharmaceutical industry exerts more control over the population, the population becomes more acutely aware of their health, instilling a sense of vigilance in people in regards to their health. Symptoms that may have once been perceived by the individual as benign (upset stomach, pre-menstrual discomfort), might now be viewed as a serious disorder (Irritable Bowel Syndrome (IBS), Pre-Menstrual Dysphoric Disorder (PMDD)) and in need of pharmaceutical intervention. It is not just a matter of treating a current condition, but of preventing future problems as well. Many of the direct-to-consumer ads are packaged in a way that suggests using the advertised medication is a means of prevention, either preventing symptoms or a worsening of the condition. Prevention therefore reinforces the degree of responsibility placed on the individual to avoid illness (Howson, 1998; Zola, 1971). Falling ill can then be viewed as something

not accidental, but a direct result of not living right, or taking proper preventative measures, in short, not conforming to the societal ideal (Scheper-Hughes & Lock, 1987).

The pharmaceutical industry has also become adept at expanding existing medical conditions to include a much broader range of people. Erectile Dysfunction (ED) is an example of this whereby the introduction of Viagra onto the market changed people's perceptions about erectile dysfunction (Conrad, 2005). Viagra was initially intended for older men with erectile problems associated with conditions such as prostate cancer or diabetes, yet Viagra was soon aggressively advertised in order to expand the market for the drug (Conrad, 2005; Conrad & Leiter, 2004). What began as a treatment for a condition generally found in older or infirm men, was now being advertised as something that virtually any man could use as an "enhancement to sexual pleasure and relationships" (Conrad, 2005, p. 6). Viagra was approved by the FDA in March 1998 and in its first year, over 3 million men were treated with Viagra with sales of \$1.5 billion. By 2003, over 6 million men were being treated with Viagra (Conrad, 2005).

Health from a personal perspective can be viewed with a lens of freedom - freedom to choose a medical provider, freedom to choose among many different diets or fitness regimens, freedom to see a physician when it is convenient, and even freedom to speak to others about health and illness. Control is being exacted through the internalization of what are acceptable health standards, standards that people are actively working to attain. Within the confines of those standards people have some degree of freedom as to how they achieve those standards. When health is considered a social value, then achieving the socially desirable state of health is a moral responsibility (Howson, 1998). Individuals are in a sense bound by this societal duty to conform and fit

the model. Health becomes a “moral pursuit” whereby it is no longer an issue of diseases being scrutinized, but rather what the individual is doing to prevent those diseases and how that individual maintains a desirable state of health (Williams, 1998; Zola, 1971).

Information can come from many sources, yet it is access to those sources that is critical, and the information that one has access to directly determines the knowledge that one develops. Information generally comes in the form of language, which is socially constructed, therefore people must be cognizant of where they are obtaining their information (Berger & Luckmann, 1966). People who have access to a wide array of information can be at an advantage because a large amount of information can enable people to compare what they are reading. The caveat is that a wide array should be from disparate sources to ensure diversity of opinion. Reading information from various sources can help to provide differing positions on an issue. It can also help to expose some of the industry bias when read in juxtaposition to more neutral sources. Understanding that not everyone has access to the same information or to a wide variety of sources, necessarily means that stratification occurs whereby a group emerges that is more knowledgeable than others. Those with more knowledge are at an advantage, which can increase their power. This stratification is more pronounced when looking not just at those with access to this information, but more importantly, the gatekeepers of this information. These gatekeepers are not simply in control of who has access to information, they are in control of the information itself and how it is framed (Chomsky, 2002; McChesney, 2004; Seale, 2002). Controlling information increases the power that this group has over the general populace. This highlights the reciprocal nature of power and control. Power must be established in order for control to take hold, but the

continuation of that control, increases the power. Control over information is not just a matter of distribution, but of production as well.

Framing of information is a critical component in determining how that information affects those who access it (Altheide, 2002; Chomsky, 2002; Seale, 2002). Frames “focus on what will be discussed, how it will be discussed, and above all, how it will not be discussed” (Altheide, 2002, p. 231). Just like with a picture or piece of art, the right frame accentuates certain aspects while playing down others. With media so interwoven into society and into the lives of individual people the framing of information pervades every aspect of life, including health (McChesney, 2004). The goal of framing is not only to control how people take in and think about information (internalization), but ultimately how they act (habitualization).

One effective tactic in controlling people is the use of fear (Altheide, 2002; Chomsky, 2002; Schattenberg, 1981; Seale, 2002; Thomas, 1978). This tactic targets people emotionally making them more susceptible to manipulation because they may not be thinking rationally. Emotions in and of themselves are neither rational nor irrational – it is the way people act on those emotions that can often be irrational. Fear can be a powerful emotion and its effects can be maximized when used repetitively. It is the cumulative effect resulting from a “continual drip-feeding of violent or frightening images and stories” (Seale, 2002, p. 68) that bolsters its effectiveness.

Direct-to-consumer ads have the ability to invoke a sense of fear in people. This is not necessarily a fear based on physical or imminent danger, but rather a more subtle fear linked to not living right, not taking proper preventative measures, not being as healthy as other members of society, or ultimately not living up to the societal ideal. In

direct-to-consumer ads, fear can work to invoke the same result - increasing the use of pharmaceuticals - using both positive and negative images (Frosch et al., 2007). Direct-to-consumer ads can show people in various states, either regaining control of some aspect of their life due to the medication, losing control of some aspect of their life due to a lack of medication, receiving social approval due to the medication, or they are just shown in a happy and content state because of the medication (Frosch et al., 2007). Repeated images can perpetuate an ideal that is internalized by members of the society who then try to assume that identity. They can also have “profound social effects on the social construction of reality in everyday life, including identity formation and role enactments” (Altheide, 2002, p. 230).

The concept of disease mongering, which originated with Lynn Payer, and has been advanced by Ray Moynihan and his colleagues, has been discussed as a severe problem because of its use of fear (Moynihan et al., 2002). Disease mongering takes the concept of medicalization one step further suggesting a situation where, “the social construction of illness is being replaced by the corporate construction of disease” (Moynihan et al., 2002, p. 886). Disease mongering occurs when the boundaries of treatable illnesses are broadened to expand the market for new drugs, and can include “turning ordinary ailments into medical problems, seeing mild symptoms as serious, treating personal problems as medical, seeing risks as diseases, and framing prevalence estimates to maximize potential markets” (Moynihan et al., 2002).

One area where this has been observed is with the statin drugs, whereby cholesterol guidelines were updated in 2001 as part of the National Cholesterol Education Program, increasing the number of people who could be targeted for drug treatment

therapy from 13 million to 36 million (National Cholesterol Education Program, 2001). These guidelines lowered the levels of LDL cholesterol deemed necessary to qualify for medication. They also identified risk factors (age, total cholesterol, HDL cholesterol, cigarette smoking) which were given a numerical value and then calculated along with the LDL levels to determine a person's risk of developing coronary heart disease. If the end value determined the person to be at risk, then the guidelines called for treatment with a statin drug (Moynihan & Cassels, 2005; National Cholesterol Education Program, 2001). Statin drugs can generate revenues of \$25 billion a year, making it clear why the pharmaceutical industry would support these new guidelines (Moynihan & Cassels, 2005). Despite the fact that National Cholesterol Education Program is part of the National Institutes of Health, many of the members of the expert panel had ties to the pharmaceutical industry. The media uncovered those ties, forcing the National Institutes of Health to issue a press release defending the expert panel and explaining that "individuals who are most expert in a subject area are the ones most suitable to serve on a guideline panel for assessing the science and developing clinical recommendations. They are also often the very people whose advice is sought by industry. Most if not all guideline panels therefore include experts who interact with industry" (Alving, 2004).

Disease mongering can also occur with psychiatric diagnoses, particularly depression, where the diagnoses are often based on symptoms and not signs. This adds a large measure of subjectivity to the prescribing of anti-depressants due to the absence of "unambiguous biological markers" (Pilgrim & Bentall, 1999, p. 263). This has been borne out by the data. According to a report by the Centers for Disease Control and Prevention entitled, "Health, United States, 2004" the percent of adults using

antidepressants nearly tripled between 1988-1994 and 1999-2000 (CDC, 2004b). The use of antidepressants was higher among women, and the report stated that between 1999-2000, 10% of women and 4 % of men reported taking an antidepressant in the last month (CDC, 2004b).

It has also been demonstrated that people are more likely to be prescribed an antidepressant when they request one from their physician (Kravitz et al., 2005; Robinson et al., 2004). Antidepressants rank among the top direct-to-consumer advertising categories, and the more people who are exposed to these ads translates into more potential users of antidepressants. Of those currently taking anti-depressants, it is unclear how many of those people are “those who are *really* depressed or those who just appeared to share some experiences in common with depressed people” (Pilgrim & Bentall, 1999, p. 263). This is advantageous to the pharmaceutical companies because they can theoretically sell more of these drugs precisely because of the subjective nature of depression. Additionally, this can also create a situation where people (those who do not have diagnosed psychiatric disorders such as schizophrenia) become increasingly more reliant on pharmaceuticals for their mental health needs.

Disease mongering is particularly pernicious because it uses fear as a means of manipulation in order to direct people to the available pharmaceutical treatments, which are generally newly released and costly (Angell, 2004; Moynihan et al., 2002). Additionally, disease mongering relies on “the highly secretive world of drug promotion, with its new emphasis on ‘shaping’ medical and public opinion about the latest diseases” (Moynihan et al., 2002, p. 887). The main objective in disease mongering is changing the way people think about a certain condition such that pharmaceutical interventions



become the primary solution. The media are necessary tools in this endeavor because of the need to reach massive portions of the population.

These theoretical areas are connected and when woven together provide a richer basis for analysis. The use of power helps to situate the pharmaceutical industry within the larger power structure. Political economy helps to explain how and why that power structure exists in the first place, and how industries are able to grow to such a size that power is able to increase so substantially. Social construction helps to explain how messaging works, how people are socialized, and how societal manipulation can occur. Social control and disease mongering then continue in that vein to help understand the tactics used not only in the manipulation of society but in the maintenance of power.

### *Literature Review*

#### *Human Papillomavirus (HPV) and Gardasil*

The previous section discussed how the pharmaceutical industry is situated within the larger political structure and how that positionality has increased their power and subsequently their control. One example of the power of the pharmaceutical industry and the ways in which it attempts to exert control is the newly released Human Papillomavirus (HPV) vaccine, Gardasil. Gardasil was approved by the Food and Drug Administration in June 2006. Gardasil is the first vaccine to be released that protects against four strains of the Human Papillomavirus (HPV). Gardasil was developed and marketed by Merck, which is the number four drug maker in America in terms of sales (Smith, 2007b). Even prior to its release, Gardasil was viewed as a potential blockbuster, which the pharmaceutical industry felt was vitally needed to “bolster pipelines as some of

its top earners lose patent protection” (Smith, 2007a). Concerns have been expressed about Gardasil since its release.

The first concern about Gardasil was cost. Gardasil is relatively expensive, priced at approximately \$360 for the three shot series. Roughly 80% of the cases of cervical cancer occur in developing countries, yet the cost of this vaccine is unaffordable for those populations (Laurance, 2006). In the U.S., a comparatively small portion of the population develop cervical cancer and that is often mitigated by access to preventative care in the form of pap smears, which have been responsible for the decrease in the number of deaths from cervical cancer (American Cancer Society, 2006; eHealth MD, 2004). Despite the disparity in cases between the developed and developing world, this vaccine is being heavily marketed to women in the developed world, women who have lower rates of cervical cancer, yet who live in a more affluent society, and are therefore more able to afford the vaccine.

The second concern was the attempt to mandate the vaccines, despite the low rates of cervical cancer in the US. Gardasil has been heavily marketed despite pap smears being a proven preventive measure to mitigate cervical cancer development. Pap smears are non-invasive tests that have proven effectiveness in reducing cervical cancer rates. There are decades of research supporting the safety and effectiveness of pap smears. It has been shown that: Early-stage cervical cancer and precancerous cervical conditions are almost 100% curable; the five-year relative survival rate for earliest-stage cervical cancer is 91%; cervical cancer death rates fell by 74% between 1955 and 1992 and continue to drop by about 2% a year; the increased use of pap tests is mostly responsible for the decrease in the number of cervical cancer deaths; and between 60%

and 80% of women newly diagnosed with cervical cancer have not had a pap test within five years (eHealth MD, 2004).

The socio-economic factor must also be considered, whereby many low-income women are not accessing preventive care at the rates of their more affluent counterparts. For some of these women a vaccine may be a more effective prevention method, though it may also be prudent to divert some of those funds to ensure that all women have access to preventive health care. Additionally, if it is difficult for some women to access preventative care for reasons other than money, then the fact that Gardasil is a three series shot may also be problematic. If the three-shot series is not completed, there is no guarantee of effectiveness.

A third concern was regarding the safety of the vaccine itself. There have been numerous instances of adverse events or death from prescribed drugs, as they are “implicated in at least 100,000 deaths annually along with 2.2 million reactions harmful enough to require hospitalization” (Boggs, 2005, p. 411). There are also general concerns about vaccinations some of which have been linked to mercury based preservatives that were found in some vaccines as well as concern about adding another vaccine to the already full childhood vaccine schedule (Geier & Geier, 2007). Gardasil does not contain a mercury preservative, but the vaccine is produced in yeast, so anyone with an allergy to yeast is cautioned not to get vaccinated (Merck & Co., 2006).

One final concern was the nature of the Human Papillomavirus, which is sexually transmitted, not casually communicable like polio or the measles. Some do not find this to be a meaningful distinction as there are 20 million people currently infected with HPV, though that number does not break down by strain, making it difficult to know how many

people have the two strains that are responsible for the 70% of cervical cancer cases (Stewart, 2007). A sexually transmitted infection is something that cannot be contracted until a person is sexually active. This is why the guidelines were set for girls as young as 9, so that physicians and public health officials could be reasonably sure that those young girls getting vaccinated had not yet been sexually active and had therefore not yet been exposed to or contracted HPV. This has sparked controversy among some groups who felt that vaccinating young girls against a sexually transmitted virus would encourage those girls to engage in sexual activity

### *Marketing*

Direct-to-Consumer ads have been a key feature in the marketing of Gardasil by Merck. Their marketing strategy began prior to Gardasil being licensed in 2006 by laying the groundwork for the release of the drug (J. Schwartz, 2006). Merck began their ad campaign through awareness efforts that stressed the link between cervical cancer and HPV.

There were two campaigns launched called “Make the Connection” (Merck & Co., 2005b) and “Tell Someone” (Merck & Co., 2005a). The “Make the Connection” campaign was the first of the campaigns and was launched in the fall of 2005, and was focused on spreading the word about the link between cervical cancer and HPV. It asked women to make the commitment to visit their physician to discuss HPV and cervical cancer and to assess their risk. Part of that campaign was beaded bracelet kits that could be ordered online; the idea was that as girls were stringing together the beads they were stringing together the facts about HPV and cervical cancer, which were included in the

accompanying educational packet. The campaign was run by the industry-backed not-for-profit *Cancer Research and Prevention Foundation* and celebrity charity *Step Up Women's Network* (Medical News Today, 2006). The campaign included publicity events, a television public service announcement and cameos by celebrities wearing beaded bracelets to highlight the link between cervical cancer and HPV (Medical News Today, 2006). Celebrities were also seen at public events wearing the bracelets and Merck pledged \$1 (up to \$100,000) to the Cancer Research and Prevention Foundation for every bracelet kit ordered. (Herskovits, 2007a; Merck & Co., 2005b).

The “Tell Someone” campaign was launched in April 2006, and tapped into “women’s natural inclinations as talkers and sharers” according to a Merck executive in charge of the marketing campaign (Herskovits, 2007a). This campaign focused on having women reach out to other women they knew to tell them about what they just learned regarding the connection between HPV and cervical cancer. Each woman that they told was one more woman who could be educated and potentially saved from developing cervical cancer. Women were told not to ignore this information, and not to be shy about sharing it (Herskovits, 2007a). The website had images of women with the caption, “Did you know cervical cancer is caused by certain types of a common virus? Neither did we” (Merck & Co., 2005a). From this site, girls could send out personalized “tell someone” e-cards. Television ads showed actresses talking directly to the camera as if they were talking to each girl or woman personally. The disease awareness efforts drew on themes of safeguarding your children (for mothers) and empowerment (for girls). The campaign was effective and showed an increase in the percentage of females

who could make the link between HPV and cervical cancer (Herskovits, 2007a; Rosenthal, 2008).

These two campaigns worked synergistically, where first women were informed about the issue, were asked to tell other women they knew, and then finally to visit their physician to discuss their risk of contracting HPV and possibly developing cervical cancer. These campaigns linked learning about the issue, sharing it with friends and family, and seeing a physician with empowerment. The underlying message was about taking control of your health, about being a knowledgeable woman and doing what is necessary to prevent disease (Merck & Co., 2005b). Once the connection was made between HPV and cervical cancer, and Gardasil was approved, the next stage of the campaign could begin.

Once Gardasil was released in June 2006, their “One Less” campaign was launched November 13, 2006. This campaign involved images of vibrant young women and the catch phrase of “one less” as in you and the other women in your life could be one less woman to get cervical cancer. This campaign followed up on the themes of the previous campaigns and “the idea was really to deliver on the strong and powerful message of empowerment” (Herskovits, 2007a). The accompanying website had information, FAQs, quizzes to test ones' knowledge on the subject, and e-cards to send to friends/family in order to impart this information <http://www.gardasil.com/>. Each page on the website had a video that took up the top 1/3 of the page. The video had the same four women; 3 young women of diverse ethnicities (white, Asian, African-American) and one white older woman representing a motherly figure. Each video featured each of the women talking directly into the camera discussing the importance of getting vaccinated

and encouraging viewers to get vaccinated as well. The remaining women are sitting on a couch in what looks like a living room interacting with each other. Below the video were four tabs to navigate the site; get the facts about HPV, learn about Gardasil, make an impact, and more for parents. The bottom section of the site had important facts about Gardasil, which gave a brief description about the vaccine, what it does, and what the reported side effects are. The site stressed the importance of continuing to receive pap tests, reminding women that a pap test can detect abnormal cells not limited to issues of cervical cancer (Merck & Co., 2005a).

The website not only contained information about HPV and Gardasil, but had resources for girls, young women, and their parents. The “make an impact” area of the site had three areas to choose from; tools to share, watch real life stories, and have some fun. The “tools to share” section had an HPV information sheet as well as a PowerPoint presentation that could be downloaded. There was also an event planner for girls to plan a social gathering to “get the word out about HPV and cervical cancer.” The “watch real life stories” had videos of young women discussing HPV and cervical cancer and the importance of getting vaccinated. The “have some fun section” had wallpaper and screensavers, t-shirt designs, icons that could be used for instant messaging, as well as a banner that could be added to a blog; all of these are available to download for free. Girls can also sign up to get both mail and e-mail reminders for their remaining shots. The catch phrase used for this is “3 is key” <http://www.gardasil.com/what-is-gardasil/3-is-Key/three-is-key/index.html>. Additionally, items such as bags, pens, buttons, and posters were also available and had the Gardasil name and the slogan “one less” printed on them.

The Gardasil television ads stressed that the target population for the vaccine was young girls who had not yet become sexually active, yet the ads tended to show teenagers, who statistically are more likely to have engaged in sexual activity. The “one less” ads showed vital young women usually in their mid-late teens engaging in physical activity such as playing sports, skateboarding, riding horses, and dancing. The girl in each scene would speak straight into the camera saying that she could be one less women infected with HPV and at risk for cervical cancer. The girls would incorporate the slogan “one less” into their activity, where the skateboarder had “one less” written on her skateboard, the soccer player wrote “one less” on her shoe, and a girl sewed the word onto her sweatshirt. Other girls in the commercial held up signs saying “one less”

<http://www.youtube.com/watch?v=hJ8x3KR75fA&feature=related>.

Another commercial used the slogan “I chose” and had the same type of young women talking straight into the camera and telling the reason why they chose to be vaccinated. In these commercials, the girls were in their bedrooms, in their living rooms, and at the kitchen table. It ends with a young woman saying she chose to get vaccinated because “my dreams don’t include cervical cancer”

<http://www.youtube.com/watch?v=gd4ypCXusrl&NR=1>. In both of these ads, the young women are ethnically diverse, and portray different personality types; the athlete, the artist, the rebel, the intellectual, and even the girl next door. The ads do mention the reported side effects, the population it is intended for, and that young women still need to see their physicians for regular pap smears. Girls are encouraged to speak to their physicians and find out if Gardasil is right for them.



The desired outcome of these ads was to make people aware of the product in order to increase sales. For pharmaceutical companies, the use of direct-to-consumer advertising appears to be working. Consumers are aware of the ads and it does appear that the ads influence consumer behavior (Findlay, 2002a; Pitts, 2004). Between 1997-1999, the drugs that were the most heavily prescribed by physicians, were also the most heavily advertised (Findlay, 2002a). Two telephone surveys, one conducted by the FDA in 1999 and one by Prevention magazine in 2000, both with over 1000 respondents similarly concluded that about 6% of the total sample received a prescription drug they asked for by name because they saw an ad for it (Findlay, 2002a, 2002b). This could suggest that the longer the ads run, the more people are affected by them, and therefore more prescriptions are written and filled.

One of the largest effects of direct-to-consumer advertising is that it is getting people to visit their physicians (Pitts, 2004). The ads serve to bring people into their physician's office and data show that most people who come to their physician requesting a brand name drug for a certain condition, do in fact have that condition (Pitts, 2004). For those that did not have the condition, there is the possibility that they have another condition, which might not have been identified had they not visited their physician. Proponents of direct-to-consumer ads believe that the ads create an opportunity for patient education by encouraging communication between patients and their physicians. This would be a positive outcome, yet the current ads tend to be based on emotional pleas, minimizing their educational value in terms of improving health awareness (Findlay, 2002a; Frosch et al., 2007; Robinson et al., 2004). This is the aspect of direct-to-consumer ads that opponents are concerned about. The educational quality of direct-

to-consumer ads has also been questioned as many impart little information beyond providing the name of the condition that the drug treats, some of the symptoms of that condition, and the potential side effects of that drug (Wilkes et al., 2000). Other information found only in a minority of direct-to-consumer ads, yet would be valuable to include more broadly have to do with cause or risk factors, prevalence information, myths or misconceptions about the condition, and alternative treatments (Wilkes et al., 2000). Consumers do have the option of visiting the drug's website and obtaining further information, though it is unclear how many consumers actually do this. The one thing that both sides agree on is that direct-to-consumer ads are likely to increase prescription drug use and cost, as drugs that are promoted directly to consumers are often among the best selling drugs (Gahart et al., 2003; Robinson et al., 2004).

Between 1997-2001 spending on direct-to-consumer ads increased 145% from \$1.1 billion in 1997 to \$2.5 billion in 2000 (Findlay, 2002a; Gahart et al., 2003). During that same time, prescription drug spending rose 18%. In 2000 and 2001, pharmaceutical companies spent \$2.5 billion and \$2.7 billion respectively on direct-to-consumer advertising, most of which is concentrated on a small number of drugs that treat chronic conditions such as allergies, high cholesterol, and arthritis (Gahart et al., 2003; Robinson et al., 2004). The amount spent on direct-to-consumer ads seems small compared to the \$15.7 billion spent during 2000 on other promotional activities, most of which is spent on physicians (Parker & Pettijohn, 2005). 80% of the spending went to physicians in the forms of drug samples, as well as the costs of sending sales representatives to meet with those physicians (Findlay, 2002a; Gahart et al., 2003). While the amount spent on drug promotion may seem high, the pharmaceutical industry must continue to sell as many of

their drugs as they can. The power of this industry makes the study of it an important enterprise, and one that needs to be continually engaged by researchers.

### *Industry Research/Study*

Most of the research on the pharmaceutical industry has been conducted by journalists and academics, yet there remains a consensus that this industry has not received enough scrutiny (Angell, 2004; Busfield, 2006; Conrad, 2005; Moynihan & Cassels, 2005; Moynihan et al., 2002). PriceWaterhouseCoopers, an audit, tax, and advisory service for the pharmaceutical, medical device, and life sciences industry, conducted a survey in 2006 of pharmaceutical industry executives, consumers and stakeholders (physicians in physician groups, researchers in academia, former health policy makers, hospital executives, managed care organization executives, and corporate executives) to identify the problems that have contributed to one overarching issue: the industry's reputation (PriceWaterhouseCoopers, 2006). The reputation of the pharmaceutical industry began to falter in 2000 due to problems with prescription medication, both the adverse effects and rising costs (Angell, 2004). Side effects of various drugs began to come to light, which highlighted the potential dangers of taking certain drugs. Additionally, the cost of many drugs was high and increasing. There was push back against rising drug costs from private health insurers and consumers.

Managed care plans create formularies which are lists of drugs that they cover. Due to rising drugs costs, many managed care plans instituted a tiered formulary system where they would cover the cost of generic drugs, partially pay for useful brand name drugs, and not cover expensive brand name drugs that showed no benefit over their

cheaper counterparts (Angell, 2004). Many people either cannot or will not pay out of pocket for an expensive brand name drug if their managed care plan does not cover the cost of a generic equivalent. The public also became aware that they were paying a higher price for their drugs than people in both Europe and Canada. Subsequently, groups began organizing trips to Canada to purchase their medication at a discounted price in addition to purchasing medication from Canadian drugstores online (Foundation for Taxpayer and Consumer Rights, 2007).

The pharmaceutical lobby (PhRMA) is actively trying to correct these problems, which they feel have affected their reputation. They suggest that their financial success has “blurred the industry's greater purpose of improving human health” (PriceWaterhouseCoopers, 2006). The criticisms faced by the industry have arguably affected their prestige because their actions and motivations have been called into question, which Mills states is precisely when prestige ceases to exist (Mills, 1956). The industry remains powerful due to their continued financial success. Their status has remained intact, demonstrated by their strong and effective lobbying efforts as well as their continued ties to the State. Despite this, the industry is aware that its reputation has degraded, and participated in this survey to try to correct the problem.

PriceWaterhouseCoopers maintains an industry bias and the purpose of its survey was primarily to improve the image of the industry, as opposed to improving the consumer experience. Although the industry seems to understand that the cost of its drugs can be prohibitive both to individuals and private health care plans, they remain beholden to their shareholders (Fligstein & Shin, 2007).

Continuing to maximize shareholder value is another problem the industry faces. As many blockbuster drugs go off patent, there is a related decrease in profits as the generic equivalents come to market. Between 2001-2005, some of the industry's top selling brand name drugs such as Eli Lilly's Prozac, Bristol-Myers Squibb's Glucophage and Pravachol, Schering-Plough's Claritin, GlaxoSmithKline's Augmentin, Abbott's Prevacid, and AstraZeneca's Prilosec, went off patent. In 2000, the revenue from these drugs was \$35 billion. Generally within 12 months of a patent expiration, 80% of the sales move from the brand name to the generic drug (Aitken, Berndt, & Cutler, 2009).

Many of the pharmaceutical companies are not developing new, innovative drugs, but are licensing so called "me-too" drugs (Angell, 2004; Moynihan & Cassels, 2005; Wilkes et al., 2000). These are drugs that are variations of older drugs that are often not deemed any more effective than the existing, older, yet are more expensive (J. Abramson, 2004). The FDA requires only that pharmaceutical companies prove that their drug is effective, not that it is more effective than an existing drug. This is why they are only required to test against a placebo in clinical trials as opposed to testing against the existing medication, a feature of the 1997 Food and Drug Administration Modernization Act. In the five years 1998-2002, 415 new drugs were approved by the FDA, of which 77% were "me-too" drugs (Angell, 2004). If this trend continues, then the pharmaceutical industry may be left without any potential blockbuster products to market. Despite the fact that this industry continues to generate record profits, a lack of innovation can affect future profits. Having the public perceive of the industry negatively may impact their prestige, but a negative view by their shareholders due to a decrease in profits has the potential to affect their status and power.

## *Conclusion*

The previous chapter discussed both the theoretical areas that were used to analyze the data as well as the literature review that discussed Merck and Gardasil within the larger context of the pharmaceutical industry. The theoretical areas that were discussed in this chapter and were used for analysis were power, political economy, social construction, and social control; all four of which complement each other. Power, as discussed by C. Wright Mills in *The Power Elite*, helped to position the industry within the larger structure within which it exists. Political economy helped to explain why the structure exists in the first place and how it is perpetuated. Social construction examined language and messaging and discussed how those in power are able to use that power as a means of constructing the types of messages that best serve their interests. Finally, social control helped to explain how those messages actually become a means of control and how various tactics can be used to manipulate people into action. A theoretical analysis is essential to this project because it helped to explain why the Gardasil case unfolded as it did, as well as what mechanisms were in place to help facilitate that.

The literature review in this chapter looked at the pharmaceutical industry and traced its trajectory to help contextualize the Gardasil issue. It included an overview of Gardasil and its development as well the promotional and marketing campaigns that were launched both before and after its release. Concerns about Gardasil were also addressed. These included concerns about safety and efficacy, cost issues, and the fact that HPV is a sexually transmitted virus. Despite the high rates of HPV in the population, cervical

cancer remains relatively rare in this country, which is an issue that has been discussed in terms of attempts to mandate the use of Gardasil for all young girls. The primary clinical trials, the two FUTURE studies were also discussed; summarizations of all of the twelve trials are in chapter four. The marketing of Gardasil has been the primary means of raising public awareness about the vaccine and one that is linked to the larger issue of direct-to-consumer marketing. Finally, this section discussed the issue of the pharmaceutical industry in general, some of the research that has been conducted in that area and the fact that there is still more that can be done.

The following chapter discussed the methods that were used in this project including the study aims, data gathering, and data analysis.

## Chapter Three - Methods

The objective of this proposed project was to understand the origin and the process of the development, the approval, and the marketing of the Gardasil vaccine and how that process facilitated the social construction of HPV as a problem needing treatment and how Merck positioned Gardasil to be the solution to that problem. This project had three specific aims.

Aim 1: To describe the process of the development and testing of the Gardasil vaccine.

Aim 2: To describe the process for the approval of the Gardasil vaccine

Aim 3: To describe how Merck constructed HPV to be a social problem needing treatment and how Gardasil was promoted and marketed

Aim 1 involved first examining how Merck obtained the technology to create the Gardasil vaccine, its development of the vaccine, and the clinical trial program. Second, this aim examined the efficacy, safety, and side effects of the vaccine including past and current monitoring efforts. Finally this aim documented the information regarding incidence and prevalence of HPV and cervical cancer as well as the rates of preventive care that can also mitigate infection with HPV and the possible subsequent diseases that can follow.

Aim 2 first examined the available documentation related to Gardasil's development and approval. Second, this aim reviewed the meetings that occurred between Merck and the FDA and Merck and the CDC. Included in the examination of the approval process was the issue of fast-tracking and how and why Gardasil was given that status. Third, the issues of cost and cost effectiveness were examined. Finally, this aim addressed the post marketing plans for Gardasil including continued safety



monitoring and Merck's attempts to both extend the patent on Gardasil and expand its use to older women and males.

Aim 3 analyzed how Gardasil was promoted. First, this involved discussing the label claim of the vaccine, which determines how the product is marketed to the public. Second, this aim examined the attempts by Merck to mandate vaccination with Gardasil. Third, the two main direct-to-consumer advertising campaigns were analyzed. Fourth, this aim involved examining the use and acceptability of Gardasil. Finally, this aim also assessed Merck as a company based on interviewee responses. Details of how each aim was analyzed are discussed later in this chapter.

### *Significance*

This study has several implications for the field of sociology. It was the first sociological analysis of Gardasil. Second, it was a case study of one of the top four drug companies. Third, it broadened our understanding of how power is used in the construction of a specific social problem by controlling the science and media to aid in that construction, and how that translated into social control. Fourth, it helped to underscore the importance of powerful stakeholder groups, like the pharmaceutical industry, to influence the construction of social problems. Finally, this study aimed to contribute to the body of research work examining the pharmaceutical industry.

### *Research Design and Methods*

## *Design*

In order to gain a comprehensive understanding of the issues surrounding the development and promotion of Gardasil and its related issues, and to effectively answer the questions set forth by this project, a qualitative, case study research method was utilized in the collection and analysis of the data. The proposed study was a qualitative, explanatory, single-case study.

Case studies are one of the oldest techniques for presenting data and one of the major research strategies (Jocher, 1928; Thacher, 2006). Case studies allows for the case to be analyzed in relation to other factors in the society within which it occurs (Jocher, 1928). Case studies are the preferred strategy “when ‘how’ or ‘why’ questions are being posed, when the investigator has little control over events, and when the focus is on a contemporary phenomenon within some real-life context” (Yin, 2003, p. 1). The tacit assumption with case studies is that “every case is unique, that there never has been not ever could be another case exactly like it, yet it may be presumed that there are points of similarity as well as of difference” (Jocher, 1928, p. 206). Gardasil is a unique case because it is the first vaccine released that targets a virus that leads to cancer, attempts to mandate its use were unprecedented in the area of vaccines, and most studies of pharmaceuticals tend to look at drugs, not vaccines. This makes the case study an appropriate method for studying Gardasil because the aims for this study are to understand the development of Gardasil, how Merck constructed HPV to be a social problem needing treatment, and how the promotional campaign for Gardasil affected public perception of it. These aims also connect to what Yin discussed as the essence of a case study which “tries to illuminate a decision or set of decisions: why they were taken, how they were implemented, and with what result” (Yin, 2003, p. 12).

The case study method is a comprehensive research strategy that can be either qualitative or quantitative, and is a good method to understand complex social phenomena (Yin, 1981, 2003). As a research strategy, “the distinguishing characteristic of the case study is that it attempts to examine a contemporary phenomenon in its real-life context” (Yin, 1981, p. 59). Case studies can help to identify causal relationships (Thacher, 2006) and require a level of thoroughness whereby facts must be ascertained and interpreted (Jocher, 1928). The issue of Gardasil specifically connects to the larger social phenomena of the increased use of pharmaceuticals, a complex issue currently affecting this country. The case study is also a good research method because it concentrates on experiential knowledge of the case and close attention to the influence of its social, political, and other contexts, which is an objective of this project (Stake, 1995).

#### *Data Collection*

The study period covered the years 1995-2008. The data were all collected between the years 2007-2009. The technology for Gardasil was obtained by Merck in 1995, applications were submitted to the FDA in 1997, which is also when the first trials began. The main analyses of the trial results were released in and after 2003, which is when Gardasil began to be discussed more among researchers and within federal regulatory agencies. The documentation prior to 2003 was comprised of government documents related to the application process for Gardasil as well as public meeting minutes between Merck and the Food and Drug Administration. The remaining documentation was between the years 2003-2008. Data sources were comprised of two main components; documents and semi-structured, in-depth interviews.

### *Documents*

Documents collected for analysis included press articles, peer-reviewed journal articles, one unpublished manuscript, government documents including reports and applications to the FDA, meeting proceedings, SEC documents, books, Gardasil ads, and websites. With the exception of the unpublished manuscript, all of the documents mentioned above were publicly available and were accessed online. I obtained the SEC documents through the SEC website by searching for the annual 10-K documents for Merck & Co. I used Lexis Nexis and ProQuest databases to search for full text articles appearing in any US publication between 2003-2007, using the search terms Gardasil, HPV, Merck, and cervical cancer. I also searched online news sites CNN, Alternet, Truthout, Commondreams, CorpWatch, and the American Prospect, as well as Google using the same search terms. To search for peer-reviewed journal articles and books, I used PubMed, SocAbstracts, PsychINFO, and Google Scholar using the same search terms mentioned above as well as doing more advanced searches including terms such as power, social control, social construction, and pharmaceutical industry. This resulted in large amounts of articles, but a look at the titles weeded out many of them. I reviewed the abstracts of the remaining articles to determine relevancy to this project. Additional articles were collected through a snowball method where they were referenced in other articles I had read for this project.

The unpublished manuscript was given to me by a former faculty member at UCSF. The government documents were obtained in different ways. The minutes to the public meetings that Merck held with the FDA and the CDC were available online

through a search of the websites of those government agencies. The meetings were discussed in some of Merck's documents that were obtained through its website, which then led me to the FDA or the CDC's websites. Documents such as the reports of side effects through the Vaccine Adverse Event Reporting System and some of the applications that Merck submitted to the FDA were obtained through the website for the organization Judicial Watch. Judicial Watch filed a Freedom of Information Act for those documents and posted them on their website (Judicial Watch, 2007). Industry documents, such as press releases and reports were searched on the websites for Merck, FDA, and CDC as well through a Google search. For the Google search, I used terms such as "Merck's application Gardasil," "Merck FDA Gardasil," "Merck CDC Gardasil," "Gardasil approval."

The Gardasil ads, some of which are still being aired on television, are also publicly available online on YouTube. When searching YouTube, I used just the name of the vaccine as well as in combination with the name of the campaign, such as "Gardasil," "Gardasil one less." The Gardasil website does not show the direct-to-consumer ads, but it is interactive and has information about HPV and cervical cancer, about Gardasil and it has a section for girls and young women as well as a section for parents.

All attempts were made to collect a comprehensive set of these documents in order to enrich this project and effectively respond to the specific aims of this study. I do acknowledge that there were industry and government documents that were proprietary and which I was therefore unable to obtain. Secondary documents and interviews were used when possible to try to fill in the gaps left by those documents that I could not obtain.

### *Sampling – Semi-Structured Interviews*

Semi-structured interviews were the other key component of data collection for this study. I conducted eleven interviews and received e-mail responses for two others. Of the eleven people that I interviewed, three were in person and the remainder of the interviews were conducted over the phone as those people were either out of state or out of the country; two of the people I interviewed were in Australia. The three in-person interviews were recorded and transcribed. Three of the phone interviews were recorded. The remainder of the phone interviews were not recorded either due to technical issues or to the person's request to not have the interview recorded. In those instances, I took detailed notes.

Table 2 – Potential Interviewees

<b>Potential Interviewees</b>	<b>Total Contacted</b>	<b>No Response</b>	<b>Refused</b>	<b>Accepted and Interviewed</b>
Journalists	3	2	1	0
Merck Employees	7	4	2	3*
Physician-researchers/experts in field of HPV, cervical cancer	6	0	1	4
Researchers from clinical trials	5	1	2	2
Vaccine researchers	2	1		1
Members of non-profit/advocacy groups	3	2	0	1**
Gov't officials	4	2	0	2
<b>Total</b>	<b>30</b>	<b>12</b>	<b>6</b>	<b>13</b>

\*I contacted 7 Merck employees individually prior to being connected to a PR person at Merck who coordinated one interview with a physician at Merck and obtained a written response from a someone in the marketing department at Merck who worked on the Gardasil campaign.

\*\* The one interview was a written response to my questions. In another instance, I was contacted by an assistant of the person I contacted, but then after other attempts, was never contacted again.

I had intended to conduct more interviews, but contacting some people proved more difficult than I had anticipated. In some cases I was unable to obtain an individual's direct contact information, I did not receive replies from some people after numerous attempts, or the potential interviewee refused to be interviewed. Therefore, the number of participants I ultimately interviewed depended on that person's willingness to participate in this study. My goal was to reach saturation, whereby I continued to interview people until no new data was obtained (Charmaz, 2005). In some areas, such as the clinical trials, efficacy, and safety, I feel that I was able to gather data that spanned the range of opinions in those areas. For each aim of the study, I feel that I gathered enough data and spoke to enough people to properly examine those areas, though certainly more interviews could have added even more nuance. This is discussed as a limitation of the study at the end of this chapter and in the discussion chapter. The following people were interviewed for this study

- Merck employees
- Physicians/Researchers and experts in the fields of HPV, cervical cancer, and vaccines
- Researchers who works on the clinical trials
- Vaccine researchers
- Members of non-profit/advocacy organizations
- Government officials within regulatory agencies

Two methods of sampling to identify the study participants were used: purposive and snowball. Purposive sampling is a nonprobability sampling technique, where potential subjects are purposely chosen because they have characteristics or knowledge that can be beneficial to the proposed study. The interviewees who were chosen through this method were named as primary authors on some of the seminal publications related to Gardasil, had been mentioned frequently in the press, or were part of the CDC's HPV working group. Snowball sampling was also utilized to identify potential interviewees. This technique relied on participants in the study to identify other individuals they felt should be included who could speak to the questions I asked based on their knowledge and relevance to the study topic. I found interviewees through both of these methods.

### *Procedures*

All recorded interviews were done so with the permission of the participants, which was obtained through verbal consent. In light of the sensitive nature of this subject matter and the professional position of some of the participants, I anticipated that some may have been uncomfortable having their interviews recorded, though initial attempts were made to record the interview. All recorded interviewees were assigned a number including the date of the interview, so that no identifying information was on the tape; this was the same for the digital recordings that were done. The digital recordings were uploaded to a website which could then be accessed by the transcriptionist. Three interviews were done with a tape recorder and those tapes were kept in a locked file cabinet. Upon completion of the study, the tapes were destroyed. For those individuals who did not want to be recorded or in the instances where I had technical difficulties,



detailed notes were taken during the interview and then I recorded myself talking about the interview, which became part of the interview transcript. All recorded interviews were transcribed and memos were written about the interviews immediately after they occurred. The transcribed interviews were coded using an open coding system where I read through the transcript and assigned codes to selected pieces of the text that were relevant to my study. The coded, transcribed interviews were imported into the qualitative data management software program, Atlas.ti.

Atlas.ti is a sophisticated qualitative analysis program that assisted in organizing the data, which helped with the final analysis. It is a program that allows for the management of large amounts of data and was instrumental in managing the data. The codes that I developed were applied to the text within the Atlas.ti program, which allowed me to then view all the data in different ways. I could select a certain code and view all of the pieces of text assigned to that particular code, which was invaluable when writing up my findings and in analyzing those findings.

The process of coding the interviews and importing them into Atlas.ti went as follows. After receiving the transcribed interview from the transcriptionist, I listened to the interview again while reading through the transcript to ensure accuracy. While this is always prudent to do, the nature of this project and the many clinical and technical terms used as well as many abbreviations made this an even more important step. I then read through the transcripts and generated codes based on my reading of the interviews. I did not have a pre-existing code list, so that I was able to remain open to the data that I collected. I was therefore able to generate codes that fit the data instead of trying to fit the data into my codes. I began the code list starting from the first reading of the first

transcript and continued the development of the code list during readings of the first several interviews. After each subsequent transcript, I re-examined the code list so that I was able to fine-tune it. Once the code list was solidified, I re-coded the first four transcripts to fit the final code list. Once the transcripts were coded, they were uploaded into Atlas.ti and those codes were applied to the transcripts in the program.

Memos were written for each of the interviews. These memos detailed my impression of the interviews, descriptive information about the interviewees, and how their information would fit into and enhance my project. In the instances where I was not able to record the interview, the memos helped to create a transcript of that interview, which was then coded and uploaded into Atlas.ti.

### *Analysis*

Case study analysis is not as well developed as other methods of analysis and does not have the same types of formulas that may be found in statistical analysis. In light of this, “much depends on an investigator’s own style of rigorous thinking, along with the sufficient presentation of evidence and careful consideration of alternative interpretations” (Yin, 2003, p. 110). This is precisely what I intended to do in my project. Without a rigid method of analysis, I had the opportunity to immerse myself in the data to determine what other interpretations might be plausible or what other factors were at play that may not have previously been considered. In this respect the case study provided me the latitude to look at the data from multiple perspectives to ensure that the conclusions that I reached were carefully considered and weighed against other potential interpretations. Case study analysis is comprised of two components: the logic linking

the data to the propositions and the criteria for interpreting the findings (Yin, 2003) meaning that there must be a clear reason for the data collected such that it directly links back to the purpose of the study and a strong strategy for analysis. The data that I collected, both through documents and interviews had direct links to my study aims, which allowed me to sufficiently address them.

One strength of the case study method is that it allows the researcher to utilize many different sources of information. Data triangulation is an important component to the case study analysis because it assists in ensuring that the descriptions of the case are accurate as well as ensuring that the interpretation of the data accurately reflects the case (Stake, 1995). Data triangulation is a means of reconciling the different sources of data - in this case, documents and interviews - to find the common meaning of that information and to assist in a more accurate interpretation. It ensures that the events or facts of the case have been supported by more than one source (Yin, 2003). Interviews with participants were used, in part, to confirm some of the information gathered from the document analysis. Document analysis was also used in some respects to verify information gathered during one or more of the interviews.

The following section discusses how I analyzed the data so that each study aim was properly addressed.

### *Analysis for Specific Aims*

Aim 1 – To describe the process of the development and testing of the Gardasil vaccine

In order to describe the process of the development and testing of the Gardasil vaccine, data were gathered through semi-structured interviews and documents.

Interviews were conducted with employees from Merck, researchers and experts in the fields of HPV, cervical cancer, and vaccines; and government officials at the CDC and members of the Advisory Committee in Immunization Practices (ACIP). In the interviews, employees from Merck as well as the researchers who could speak to this issue were asked how Merck became involved with Gardasil and how it acquired the technology to develop Gardasil. A timeline was established to mark the trajectory of Gardasil from the technology acquisition, through the promotion and rollout of the vaccine. Interviewees were also asked what their assessment was of Gardasil in terms of safety and efficacy, as well as their views on the clinical trial program, whether they had any questions or concerns about the trial results, and what Merck's role was in the analysis and write up of the data.

The documents that were collected for this aim included: the Investigational New Drug Application (IND) that Merck submitted to the FDA; transcripts from the two public meetings held by the FDA and the CDC, the Vaccines and Related Biological Products Advisory Committee and the Advisory Committee on Immunization Practices respectively; the FDA's review of the clinical trials; articles published in peer-reviewed journals; and related websites. All documents were organized according to which aspect of this aim they were related.

Aim 2 – To describe the process for the approval of the Gardasil vaccine

Data for this aim were gathered through documents and semi-structured interviews. The interviewees included employees from Merck, researchers and experts in the fields of HPV, cervical cancer, and vaccines; government officials at the CDC and

members of the Advisory Committee in Immunization Practices (ACIP); and e-mail responses were received from the organization Women in Government. Interviewees were asked to talk about the approval process for Gardasil and how Merck initiated and maintained communication with the FDA and the CDC throughout that process. They were asked to describe the approval process at the FDA, as well as questions including how expedited review status was granted to Merck for Gardasil, and to what extent Merck's lobbyists were involved in the process.

The documents that I collected included the meeting minutes between Merck and the FDA and Merck and the CDC's Advisory Committee on Immunization Practices, the investigational new drug application that Merck submitted to the FDA, CDC documents related to the trial results, Merck's briefing documents regarding Gardasil, books, press articles, peer reviewed journal articles, and related websites. All documents were organized according to which aspect of this aim they were related.

Aim 3 – To describe how Merck constructed HPV to be a social problem needing treatment and how Gardasil was promoted and marketed

In order to analyze the promotional and marketing campaign for Gardasil, data were gathered through documents and semi-structured interviews. Interviews were also conducted with employees from Merck, researchers and experts in the fields of HPV, cervical cancer, and vaccines; government officials at the CDC and members of the Advisory Committee in Immunization Practices (ACIP); and e-mail responses were received from the organization Women in Government. Interviewees were asked about their familiarity with the promotional campaigns for Gardasil, what their thoughts were

about those campaigns, how they felt about Merck's claims that Gardasil prevents cervical cancer, how they felt about attempts to mandate Gardasil's use, and finally what their assessment was of Merck as a company and in relation to other pharmaceutical companies.

Data collection focused on the promotional and marketing campaigns for Gardasil, national statistics regarding the use of Gardasil, Merck documents, press articles, peer reviewed journal articles, Gardasil's website, and the direct-to-consumer ads both before and after Gardasil was released. All documents were organized according to which aspect of this aim they were related. The data for this aim spoke to how HPV was constructed as a social problem needing treatment and how Gardasil was positioned as the solution to that problem. The promotional and marketing campaigns were primarily aimed at the public and either at the demographic that Gardasil was approved for or to those girls' parents. When looking at the ads, I developed a set of questions that assisted in analyzing them. The questions were: who is the intended audience of this ad; what is the key element of this ad/what is happening in this ad; what is the meaning behind the images in this ad; and how are the females actors in this ad being represented/how is power being constructed.

### *Limitations*

There were limitations to this study. First, many of the documents that would have been helpful were proprietary. These included documents from Merck, the FDA and the CDC. I was able to obtain several documents through the organization Judicial Watch, which filed a Freedom of Information Act. These included several reports from

the Vaccine Adverse Events Reporting System and Merck's application to the FDA to patent Gardasil. However, most of the documents between Merck and the government agencies including minutes of their meetings remained proprietary. Their internal documents about the clinical trial results were also not available. I was able to access the 400+ page FDA review of the trials, but having Merck's original documentation would have been useful.

Another limitation was with the interviews. I was not able to interview all of the people I would have liked. I was not able to contact anyone at the FDA. The few people whose contact information I was able to obtain did not return repeated requests to speak with them, therefore I was not able to interview anyone at the FDA. I was able to speak with some people at the CDC, as well as members of the Advisory Committee on Immunization Practices. Employees at Merck proved to be much more difficult to connect with. I did have contact information for all of the people I wanted to interview, but either I did not receive replies after repeated contacts or I was told that they were not interested in talking to me. Many of the researchers who worked with Gardasil have since moved into other projects at Merck. I did connect with a Merck representative who initially told me that she would coordinate an interview between me and a high ranking employee at Merck as well as with herself, but the day before our interview, she contacted me to tell me that she recently learned that Merck had a policy that prevented her and others from speaking to me. She did put me in touch with someone from Merck's public relations department who did eventually coordinate an interview between me and a physician from Merck. This physician was lower in rank than others who I was hoping to speak with and was not directly involved in the development or testing of

Gardasil. I was unable to speak with anyone about the marketing and promotion of Gardasil, though the PR person at Merck did provide e-mail responses from a director in the marketing department to questions I had in that area.

Most of the people that I did interview were out of state and two were out of the country, so having to do most of the interviews by phone also proved to be a limitation. It is much easier to develop a rapport when you are speaking to someone face to face, so having to do many of the interviews over the phone probably limited the type and amount of information I was given. Some of the interviewees were only able to allot 30 minutes to speak with me, which obviously limited what could be discussed and in how much detail. Additionally, I was not able to record some of the phone interviews due either to the interviewee's preference or to technology issues. In those cases, detailed notes had to be taken, and while I believe I captured all of the necessary information, there are likely smaller details that may not have been captured.



# Gardasil Timeline

**1996**  
Gardasil licensed to Merck

**1998**  
1/5 - Protocol 002 began  
10/12 - Protocol 004 began  
10/22 - Protocol 005 began

**2000**  
3/2 - Protocol 006 began  
5/17 - IND for Gardasil became effective - clinical testing phase began

**2002**  
Gardasil granted fast track status  
June - Protocol 015 (FUTURE II) began  
5/26 - Protocol 007 began  
5/30 - Protocol 012 began  
12/7 - Protocol 016 began

**2004**  
3/31 - Protocol 005 ended  
5/10 - Protocol 007 ended  
6/11 - Protocol 011 ended  
6/30 - Protocol 012 ended  
9/20 - Protocol 016 ended

**2006**  
April - "Tell Someone" campaign launched  
5/18 - VRBPAC meeting  
6/8 - Gardasil Approved  
6/29-30 - ACIP Meeting  
November - Merck announced launch of ad campaign for Gardasil  
Educational campaign for doctors launched  
11/1 - Gardasil added to vaccines for children program  
11/13 - "One Less" ad campaign launched

**2008**  
March  
teens  
least a  
11% re  
doses  
12% o  
18-26  
one sh  
receiv  
10/10  
17 rec  
shot o



**1995**  
Merck entered into an agreement with CSL

**1997**  
IND submitted to FDA  
9/22 - Protocol 001 began

**1999**  
Studies ongoing

**2001**  
November - VRBPAC meeting to discuss end points for clinical trials  
Merck begins planning for policy issues  
1/25 - Protocol 006 ended  
8/7 - Protocol 001 ended  
9/30 - Protocol 004 ended  
10/31 - Protocol 002 ended  
12/28 - Protocols 013 (FUTURE I), 011 began

**2003**  
May - Protocol 015 (FUTURE II) ended  
10/8 - Protocol 018 began

**2005**  
1/19 - Protocol 018 ended  
May - FDA met to discuss BLA and expedited review began  
11/4 - Protocol 013 (FUTURE I) ended  
12/7 - BLA submitted  
Fall - "Make the Connection" campaign launched

## **Chapter 4 - Findings**

The overall objective of this study was to understand the process of the development, approval, and marketing of the Gardasil vaccine, and how that process facilitated the social construction of HPV as a problem needing treatment and how Merck positioned Gardasil to be the solution to that problem. Bringing Gardasil to market was a long process and involved many different players and stakeholders. The findings in this chapter are presented by aim, with excerpts from semi-structured interviews placed in context with the documentation. This helped to lay out the stages of this process to gain a full picture of Gardasil from inception to widespread acceptance and use. The aims of this study are:

**Aim 1 – To describe the process of the development and testing of the Gardasil vaccine**

**Aim 2 – To describe the process for the approval of the Gardasil vaccine**

**Aim 3 – To describe how Merck constructed HPV to be a social problem needing treatment and how Gardasil was promoted and marketed**

A timeline is attached at the beginning of this chapter which charts the events that are discussed throughout this chapter. The timeline begins in 1995 with the acquisition of the technology that led to the development of Gardasil and runs through 2008, which provides some statistics about the rates of use of Gardasil both in California and nationwide.

This chapter follows the trajectory of Gardasil beginning with the origin of Gardasil and how Merck first became involved with the technology that preceded the development of Gardasil. The acquisition of the technology, which was developed by

Australian researchers and licensed through the Australian biotechnology company CSL led to the development of Gardasil, which led to the clinical trials that were conducted, concluding with the approval and release of the vaccine in June 2006. During this process, Merck was in regular contact with the Food and Drug Administration (FDA), and later in the process, with the Centers for Disease control and Prevention (CDC) and their working groups the Advisory Committee on Immunization Practices (ACIP). The FDA and CDC work in tandem whereby the former is responsible for the approval of new drugs and vaccines while the latter makes recommendations for their use. After the vaccine was approved, Merck rolled out a two part promotional and marketing campaign. The first part which occurred prior to the release of Gardasil was aimed at raising awareness of the link between the Human Papillomavirus (HPV) and cervical cancer. The second part of the campaign was focused on Gardasil specifically and was rolled out after its release. These campaigns were successful in raised awareness about the HPV, cervical cancer, and Gardasil among the general population. Shortly after its release, it was revealed that Merck was spearheading attempts to make the newly released vaccine mandatory and was using its financial resources through the organization Women in Government to lobby for the mandate. The controversy surrounding those efforts caused a public backlash that eventually ended those attempts. Despite that, many states have initiated legislations regarding the use of Gardasil including payment of the vaccine and screening by public and private insurance companies. Gardasil has been widely accepted and used throughout the country and has been a financial boon to Merck.

This chapter begins with data discussing the origins, development, and testing of Gardasil. There are many technical terms throughout this section due to the clinical

nature of vaccine development. Gardasil is a quadrivalent vaccine which means that it is made up of four different vaccine HPV types, 6, 11, 16 and 18. The clinical trials were broken down into two main testing groups; testing the monovalent vaccine, and then the quadrivalent vaccine, which was the final product. The monovalent vaccine tested just one of the vaccine HPV types at a time. There was one trial that tested HPV11, one that tested HPV 18 and two trials that tested HPV 16. The monovalent trials were for immunogenicity; to see if the vaccine was safe and well tolerated. Once safety was established, the second set of trials began. The quadrivalent vaccine tested all four HPV types to determine both safety and efficacy.

Clinical trials are also divided into phases. Phase I and II are the preliminary clinical trials that a company conducts on their product. These generally test to ensure safety and tolerability of the vaccine. The phase III trials are often referred to as the “gold standard” of the clinical trials because they are done on a larger population than the phase I or II trials, and they are testing for efficacy of the vaccine as well as to support the earlier tests that established safety and whether or not the vaccine produced an immune response.

Gardasil differs from some other vaccines in that it does not carry a live virus; it is a shell of a virus called a Virus Like Particle or VLP. The VLP does not have any infectious properties and just looks like the virus to the body, which enables the body to mount antibodies. Many of the titles of the individual trials have that abbreviation VLP in the title because that is what is being tested. All vaccines have what is called an adjuvant, which helps boost the immune response to the vaccine. Gardasil has an adjuvant that is proprietary to Merck and is called amorphous-aluminum-hydroxy-

phosphate-sulfate and is abbreviated as AAHS, which will also be referred to in the first section of this chapter.

This chapter begins with the first aim of the study and the development and description of Gardasil. This section also includes summarizations of the clinical trials, and a discussion about side effects, safety, and effectiveness. The section concludes with information about the prevalence of HPV and cervical cancer and rates of pap smears and preventive care in this country.

The second section of this chapter focuses on the process for the approval of Gardasil. There were two main meetings that occurred prior to Gardasil's approval and release; one was with the FDA and one was with the CDC's Advisory Committee on Immunization Practices (ACIP). Both of these meetings were public and information discussed in this chapter regarding the meetings was taken from the actual meeting minutes. The FDA sponsored meeting was a meeting of the Vaccines and Related Biological Products Advisory Committee, which is abbreviated as VRBPAC and is referred to throughout that section primarily by that abbreviation. This section also discusses the expedited review that Gardasil received and issues of cost effectiveness including insurance payments as well as post marketing surveillance studies and requests to expand Gardasil's use.

The third section focuses on the third aim of how Gardasil was promoted and marketed, which includes how HPV was constructed as a social problem needing treatment. Included in this section are discussions on the label claim, which is the claim made about Gardasil's utility, as well as attempts to mandate the vaccine, the advertising and promotional campaign for Gardasil, and the rates of uptake of Gardasil. This section

concludes with my study participant's views about Merck as a company and in relation to other pharmaceutical companies to place it in context with the industry as a whole

*Aim I: The Development and Testing of the Gardasil Vaccine*

This chapter follows the developmental trajectory of Gardasil beginning with a description of Gardasil, followed by how it originated, and was ultimately developed by Merck. The clinical trials are discussed with a summary of each of the 12 trials. Side effects of Gardasil have generated a lot of attention and are addressed in this section followed by Gardasil's safety and effectiveness. To put the utility of Gardasil in context, this section concludes with information on the background and incidence/prevalence of HPV, cervical cancer and the rates of pap smears and preventive care in this country.

*Description of Gardasil*

Gardasil is a quadrivalent vaccine that contains four HPV types, 6, 11, 16, and 18. Six and 11 are responsible for 90% of genital warts cases while 16 and 18 are responsible for 70% of cervical cancer cases. Gardasil is a prophylactic vaccine and is most effective when administered prior to any potential infection with HPV. Gardasil is not a therapeutic vaccine and does not impact the course of infections that are already present at day one, nor does it cause regression of high grade cervical dysplasia (VRBPAC, May 18, 2006, p. 57). Gardasil is given intramuscularly in a three shot series given at zero, 2, and 6 months. The decision to break the vaccine up into three shots was discussed in two interviews. One physician researcher said that breaking up the vaccine into three doses "has to do with setting up vaccine - a memory response" and that "most vaccinations do

require more than one” shot (Interview #7). A member of the CDC’s HPV working group also discussed why the vaccine would be broken up into three shots because

the vaccinologists felt there has to be a priming dose, which is the first and the second dose, and then the third dose which is - I don't want to call it a booster dose but it's a third dose after the first two priming doses. A lot of that was based - even the spacing of the three doses was based on prior experience that the companies had developing other vaccines (Interview #10)

Gardasil is a vaccine that can be generally defined as being indicated for the “prevention of cancer, pre-cancerous or dysplastic lesions, genital warts, and infection caused by HPV types targeted by the vaccine” (FDA, 2006). Specifically, Gardasil is indicated for the prevention of the following diseases, due to HPV types 6, 11, 16, and 18: cervical cancer, genital warts (*condyloma acuminata*), cervical adenocarcinoma *in situ* (AIS), cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3, vulvar and vaginal cancer, vulvar intraepithelial neoplasia (VIN) grades 2 and 3, Vaginal intraepithelial neoplasia (VaIN) grades 2 and 3, and HPV infection (FDA, 2006, p. 15; N. B. Miller, 2006)

The vaccine manufacturing method is well established, and uses virus-like particles (VLP) that are manufactured in yeast, which are then absorbed into Merck’s proprietary amorphous aluminum-hydroxy-phosphate-sulfate (AAHS) adjuvant. Dr. Nancy Miller of the FDA stated, “The L1 proteins are produced by fermentation in recombinant *saccharomyces cerevisiae*, and self-assembled into virus-like particles that...are purified and absorbed onto aluminum” (VRBPAC, May 18, 2006, p. 89). This method of using a yeast host system was utilized by Merck for its Hepatitis B vaccine, and the adjuvant is a necessary component in a vaccine to bolster the immune response to the antigen (Bryan, 2007). The adjuvant, according to Merck and the FDA, has a well

established safety record (Bryan, 2007; FDA, 2006). The adjuvant “carries approximately zero charge at neutral pH. Under physiological formulation conditions it was found that AAHS had the greatest capacity to bind HPV VLPs and that mice immunized with HPV 16 VLPs adsorbed to AAHS generated substantially higher antibody titers than mice immunized with VLPs adsorbed” into an aluminum hydroxide adjuvant (Bryan, 2007, p. 3002). One scientist from Merck said,

the aluminum adjuvant in Gardasil is a proprietary aluminum adjuvant called amorphous aluminum hydroxide and it is one that has been in millions and millions of doses, it’s been in our hepatitis vaccine and so the safety of that adjuvant is very well established and also... in clinical trials it had a higher antibody level than aluminum alone. So aluminum hydroxide is a really good adjuvant but this one was better in clinical trials than aluminum hydroxide alone, so that’s how this one was the one that was chosen for the vaccine as well as its safety profile (Interview #3).

#### *Development and Origin of Gardasil*

The technology used to create the vaccine, was based “on the observation that when the L1 capsid protein, the outer coat protein of the virus, is expressed in recombinant systems, it self-assembles into a virus-like particle (VLP) that looks...very similar to the wild-type virus, without of course, the infectious properties” (VRBPAC, May 18, 2006, p. 23). In animal models of papillomavirus infections using these L1 VLP's, Merck was able to show that vaccination resulted in protection from infection related disease and neutralizing antibodies were induced. To create the vaccine, Merck developed a technique to manufacture highly purified L1 virus-like particles using recombinant yeast technology, a technology that has been used in a variety of vaccines that have been given in hundreds of millions of doses (CDC, 2006).



The development of Gardasil was also discussed in an article published by a Merck researcher in the journal, *Vaccine* (Bryan, 2007). That article stated that while the Gardasil vaccine itself was manufactured by Merck Research Laboratories, the discovery that the L1 capsid protein could be expressed as a recombinant protein and the L1 molecules would self-associate and form virus-like particles (VLP) was made by a number of academic and institution investigators not associated with Merck (Bryan, 2007). The challenge to Merck was to “produce VLPs of HPV types 16, 18, 6, and 11 as complex, safe antigens which would induce a robust immune response and to demonstrate that the immune response was efficacious” (Bryan, 2007, p. 3002).

Each dose of Gardasil contains 20 micrograms of HPV 6, 20 micrograms of HPV 18, and 40 micrograms of each of HPV 11, and 16 (N. B. Miller, 2006). The rest of the product formulation is as follows; 225 mcg aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, and water for injection. It is not a live virus and can therefore not cause infection or disease. It is intended to be given intramuscularly as a three dose regimen at zero, two, and six months.

One of the researchers I interviewed at Merck discussed the origin of Gardasil and how Merck initially became involved with this vaccine. “Merck bought the technology from an Australian vaccine company CSL. They isolated the first genetic sequence. Merck had already created the Hepatitis B vaccine in yeast, so they were able to use the technology from CSL along with their use of yeast to create the vaccine” (Interview #3). CSL is an Australian biotechnology company, and it licensed the vaccine to Merck in the late 1990s. Dr. Ian Frazier, an Australian researcher developed the vaccine along with

his colleague Dr. Jian Zhou at the University of Queensland more than 15 years ago that led to the development of the vaccine for cervical cancer (Unknown, 2006). Since the developed world has effective pap smear programs that lower the incidence of cervical cancer, Dr. Frazer felt that this vaccine would be most beneficial in the developing world where most of the 250,000 deaths from cervical cancer each year occur (Unknown, 2006).

A researcher directly involved in the development of the technology which led to Gardasil stated that he and his colleagues

spent time mapping out immune responses to naturally occurring human papillomavirus infection and I realized that there was something missing in the whole equation and that was being able to make the virus because we needed to be able to use viruses to infect cells to make targets to test out cellular immune responses...he and his wife and I sort of had this project of building papillomaviruses and using recombinant vaccinia virus as a vector to actually produce the capsid proteins of the virus. One of the things that we thought was important was to try and get the capsid proteins to assemble to make the shell of the virus. He worked on that with me for about a year unsuccessfully and we went through a whole range of reasons why it wasn't working... We sat and scratched our heads a bit and came to the conclusion this wasn't working probably because we were doing it in the wrong cell type and then secondly because we were not using the right bit of the viral gene to express and after a bit of playing around with that we actually came up with a way of getting these capsid proteins to self-assemble and produce a virus-like particle which we could see down the electron microscope and that was about in April 1991. When we saw that, one of the things that we immediately realized was that since they had self-assembled that that could potentially be the basis of a vaccine to help prevent papillomavirus infection (Interview #13).

The researchers subsequently published their work and presented it at several professional meetings. This made many other researchers in industry and in academia aware of their work and their discovery. This interviewee discussed this as well as his connection to CSL, and how that company eventually licensed the technology to Merck.

Obviously having talked about it at meetings and filed provisional patents people were aware of the work and we also formally made CSL, an Australian Biotech Company aware of the work because we had an existing research agreement with them concerning therapeutic vaccines. The idea was that we were trying to develop vaccines which could be used to treat existing papillomavirus infection but the agreement between us and them gained them first right of refusal on any work in the papillomavirus field that we did that related to vaccine development. So we told them about that and they sort of got interested a little bit over the course of the next couple of years and became more interested as it became more clear from the work done by many other people that papillomaviruses were not just *a* cause of cervical cancer but *the* cause of cervical cancer and that basically all cervical cancer was a papilloma virus related disease. By 1994 we were being approached on a weekly basis by companies, many different companies – small biotech, big biotech, big pharma, small pharma – who were interested in getting rights to the patents that we had and/or developing vaccines along with us. But we stuck with CSL as a partner at that time and they negotiated with Merck a deal whereby a number of vaccines that they wanted to develop were licensed across to Merck. We don't know all the details of that particular transaction but one part of it was that they licensed on our technology to Merck (Interview #13).

After being licensed to Merck, this researcher and his colleagues were not involved in any of the development work that occurred at Merck. Due to conflict of interest, he did not have any involvement in the clinical trial design or their business strategy, though he did sit on the scientific advisory board in 2004 after the conclusion of the clinical trials.

### *Clinical Trial Development*

In 2001, Merck met with an advisory committee at the FDA to discuss the

clinical endpoints that would serve as the basis for licensure...Merck proposed that studying cancer itself isn't feasible because it takes too long and disadvantages too many women. We also had to consider that most HPV infections in pre-cancers regress. So, there was the need to consider an endpoint that had a direct link to cancer. And pointing to the success of cervical cancer screening programs, their success is due to the detection and definitive therapy for CIN 2/3, and that's what we recommended as the basis of licensure and ultimately, that's what the Advisory Committee recommended (FDA, 2006, p. 13).

The CDC concurred that it is unethical to use cervical cancer as an endpoint since cervical cancer can be prevented by detection and treatment of pre-cancer lesions. Since most cancers progress through well-defined stages that include the pre-cancer lesions that Merck used as endpoints, prevention of the pre-cancer lesion theoretically prevents the cancer (CDC, 2007; VRBPAC, May 18, 2006).

Once the vaccine was developed, Merck designed a clinical trial program that would address the “prophylactic efficacy” of the vaccine (VRBPAC, May 18, 2006, p. 25). The primary objective of the trials was to demonstrate that the vaccine prevented the development of HPV 16 and 18 related CIN grades 2 or 3 and AIS caused by new infections. When developing the clinical trial program, Merck considered earlier end points, initially considering HPV infection itself since it is a necessary pre-requisite to cervical cancer. This proved to be inadequate because most HPV infections clear on their own. Merck next looked at CIN 1, though these lesions also tend to clear on their own and would not provide an accurate picture of the vaccine’s efficacy. That is when attention focused on CIN 2 and 3 and AIS, which became the primary end points for the trials (Bryan, 2007; Pratt, Goldenthal, & Gerber, 2001; Rambout, Hopkins, Hutton, & Fergusson, 2007; VRBPAC, May 18, 2006).

During this process, Merck was in discussion with the FDA and the World Health Organization, which helped to make the determination that “although monitoring prevention of the first step, HPV infection, is useful, monitoring a disease stage that is a necessary direct precursor (CIN 2/3) to cervical cancer would provide the best, most direct correlate of vaccine efficacy to prevent cervical cancer (Bryan, 2007, p. 3003). Therefore, if the vaccine could prevent these lesions from occurring from the outset, then

Merck could demonstrate efficacy of the vaccine. Not discussed as much as cervical cancer is the vaccine's prevention of vulvar and vaginal cancer. Merck followed the same approach as it did for cervical cancer and used the end points focusing on vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) grades 2 and 3.

Women were enrolled in the clinical trials regardless of baseline HPV status, though they were tested at baseline to determine their status and upon analysis were broken out into two groups, the per protocol population and the modified intention to treat population (MITT). This allowed Merck to get a more accurate picture of how the vaccine affected those who were naïve to the HPV types and those who were not. All women were randomized into the trials because there was an understanding that the vaccine would be administered to women without prescreening, so there would be no definitive way to know whether some of the females being vaccinated had been exposed to HPV. This allowed Merck to get information on how this vaccine would work in the general population. Enrolling females in this fashion was also a recommendation that came out of a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held in 2001, where they felt strongly that women who were infected at baseline be included to evaluate the safety of the vaccine in this population (VRBPAC, May 18, 2006).

The next step in the clinical trial program was the immunogenicity studies, which bridged the efficacy findings in the 16-26 year olds to the 9-15 year olds by demonstrating that the immune response in the children was non-inferior to those in adults. It was not feasible to do efficacy studies in this younger population because of limitations on

discussions of sexuality and because genital HPV sampling on this population would be inappropriate. The FDA approved Merck's plan to bridge the efficacy findings in the 16-26 year olds to the younger age range using the immunobridging approaches (VRBPAC, May 18, 2006). Dr. Eliav Barr from Merck described the immunobridging study in the following quote,

We measured that in at month seven, which is one month post-dose three and we looked at the Geometric Mean Titers in the children and compared them to the adults. We did a ratio of the GMT's in kids versus adults, and of course, if they're not inferior, then the ratio would be at least one. And what we saw was...the anti-HPV levels at month seven are substantially higher in all of the children compared to the adults, and particularly high in boys. And so, these results -- so, we met the criterion for immuno-bridging in this study at -- using the month seven data (VRBPAC, May 18, 2006, p. 55)

This approach modeled the impact of young women who are completely naïve to HPV - meaning they do not have the strains of HPV - not only to the four vaccine types, but to 14 other genital HPV types that combined, account for 95% of cervical cancer cases. If the women were naïve to all of these types, then they were a good model for the youngest girls that were to be included in the vaccination population; girls who had not yet had a sexual experience (often referred to as sexual debut), and therefore had not been exposed to HPV.

The overall age range for use of the vaccine was chosen by breaking out the group into the two cohorts of 16-26 and 9-15. Starting at the time of sexual debut, there is a large increase in risk of HPV related diseases, and the peak ages for this risk is 16-26, which was where the main efficacy studies were focused. The 9-15 years olds were looked at because that is the period just prior to sexual debut and thus to acquisition of (potential) HPV infection. Therefore, Merck was looking to have Gardasil approved for use in females 9-26.

Looking at boys specifically, Dr. Barr mentioned that the vaccine was highly immunogenic and well tolerated in this population (VRBPAC, May 18, 2006). Efficacy was shown for external genital lesions, “lesions that are comparable between the genders, caused by the same HPV types, same response to therapy” (VRBPAC, May 18, 2006, p. 72). Based on this, Merck felt that the efficacy of the vaccine was highly likely to be present in males.

Most of the subjects in the trial were given a placebo with the aluminum-hydroxy-phosphate-sulfate adjuvant. There was a small subset of females in trial #6, protocol 018, who were given a saline placebo – 320 as opposed to 3470 who got the aluminum-containing placebo – and there was a marked difference in the experience of the women who received the saline placebo. Pain at the injection site was experienced by 83.9% of those who received Gardasil, 75.4% of those who received the aluminum-containing placebo, and 48.6% of those who received the saline placebo. Swelling at the injection site was 25.4% for those who received Gardasil, 15.8% for the aluminum-containing group, and 7.3% for the saline group (CDC, 2006).

The clinical trial program lasted nine years, and to effectively monitor all results over the long term, Merck developed an internal infrastructure to evaluate all of the specimens collected during the trials. To ensure standardization of evaluation, a pathology panel of four independent pathologists were assembled and a diagnosis algorithm was applied (Bryan, 2007). Agreement by the pathologists was crucial to the integrity of the results, so Merck had a process in place where

All pathologists were blinded to the diagnoses results of the other members of the panel. If the diagnoses were in agreement, then that diagnosis was accepted. If there was disagreement, then the slides were sent to a third pathologist. If two of the three

diagnoses were in agreement, then that diagnosis was accepted. If there was disagreement between all three then the slides would be sent out for evaluation by the fourth pathologist. In very rare cases there was no overall agreement. In that situation, all four pathologists were brought together to simultaneously evaluate the slides and come to an agreement on diagnoses (Bryan, 2007, p. 3003)

All of the participating investigators were trained to use a standardized approach to collect the specimens, which was used in all of the clinical trials. A central pathology lab was used for all cytology and pathology work, and everything was processed through Merck's central lab. Merck had a dedicated pathology panel whose sole responsibility was to evaluate the specimens for the purpose of end point evaluation. A data safety monitoring board was used in all of the large clinical trials, and together Merck was able to ensure accuracy and provide a complete representation of the safety of the vaccine as well as the efficacy end points (VRBPAC, May 18, 2006). Merck is still watching women from the first trials, and according to one researcher at Merck, "women who received the placebo in those trials were given the vaccine as a 'thank you' since they exposed themselves to the virus because they were given the placebo, then they were given the vaccine at the end of their participation" (Interview #1).

The following section discusses each of the clinical trials in detail and summarizes each of the 12 trials.

### *Description of the Clinical Trials*

Gardasil was in development for over nine years. The clinical trials began in 1997 and ended in 2005 with a recombinant HPV virus-like particle (VLP) vaccine for the prevention of cervical cancer. It has been studied in over 27,000 subjects in 33 countries



on five continents in 12 separate clinical trials, which included both the monovalent immunogenicity studies and the quadrivalent efficacy studies (FDA, 2006; VRBPAC, May 18, 2006). Compensation for participation in the studies was subject to local rules and regulations; subjects in the US were compensated based on the centers in which the studies were held, but subjects in most other countries were not compensated (VRBPAC, May 18, 2006). There were 27,004 women in the overall study population, and roughly 5,500 of them received either monovalent or quadrivalent vaccine formulations, other than Gardasil; these data were reported separately to the FDA, and are not discussed in this chapter. The population receiving Gardasil itself was 21,400 (VRBPAC, May 18, 2006).

There were four phase I/II studies for the monovalent vaccines; protocol 001 for HPV 11, protocols 002 and 004 for HPV 16, and protocol 006 for HPV 18. These protocols studied the safety and immunogenicity of those monovalent vaccines. Merck conducted six clinical studies, some containing sub-studies, using the quadrivalent vaccine; protocols 005, 007, 013 (included protocol 011, 012), 015, 016, and 018.

Protocol 005 was a proof of concept phase II efficacy trial for HPV 16 study; the key strength of that study was that it involved a long term follow up (VRBPAC, May 18, 2006). Protocol 007 was a phase IIB study to assess the dose for the quadrivalent HPV vaccine to go forward into the phase III trials as well as to assess the efficacy for prevention of infection caused by the four vaccine types (VRBPAC, May 18, 2006). Two of the phase III trials were protocols 013 and 015. Protocol 013 was designed to assess the efficacy of the quadrivalent vaccine against CIN and genital warts. It included an intensive evaluation and genital inspection as well as an evaluation of frequent pap

testing (VRBPAC, May 18, 2006). Protocol 013 had two sub-studies, protocol 011, which was a hepatitis B concomitant use sub-study, and protocol 012, which bridged the immunogenicity results from HPV 16 from protocol 005 to the HPV component of the quadrivalent vaccine (VRBPAC, May 18, 2006, p. 92). Protocol 015 was designed to assess the efficacy of the quadrivalent vaccine for CIN 2/3 associated with HPV 16 and/or 18, and was designed to be a real world study to look at the impact of the vaccine on cancer. This study included a consistency lot sub-study, a non serious adverse event study, and a continuation of the registry study where women underwent yearly pap testing. Protocol 016 was designed to evaluate the safety and immunogenicity of the vaccine in preadolescents 10-15 years old and compared the immune response between that age group to women 16-23 years old. This protocol also included a sub-study to assess the immunogenicity of partial dose formulations. Protocol 018 provided additional safety and immunogenicity data for the preadolescent/adolescent age group with a comparison of a saline placebo (VRBPAC, May 18, 2006). Discontinuations in the studies, including those related to adverse events were rare (VRBPAC, May 18, 2006). Merck began their trials with monovalent formulations of the vaccine, which included protocols 001, 002, 004, 005, and 006.

Table 3 - Clinical Trial Data

Protocol #	Dates	Phase*	Study Participants	Objective	Endpoint(s)	Results
<b>Preliminary Trials</b>						
001	9/22/97-8/7/01	Phase 1	18-25 y.o healthy females	Safety and immunogenicity of 4 dose formulations of monovalent HPV11	1. The % of subjects achieving anti-HPV serum RIA levels $\geq 200$ mMU/mL at 4 weeks post dose 3 2. Anti-HPV 11 GMTs	Induced anti-HPV 11 antibody response at all doses tested

002	1/5/98 – 10/31/01	Phase 1	18-25 y.o. healthy females	Safety and immunogenicity of 3 dose formulations of monovalent HPV 16	1. % of subjects achieving anti-HPV 16 serum levels $\geq 20$ mMU/mL 4 weeks post dose 3 2. Incidence of serious adverse events	1. 40mcg and 80mcg doses immunogenic. 2. All dose formulations elicited and immune response. 3. Geometric mean titers persisted through month 36
004	10/12/98 -9/30/01	Phase 2a	18-25 y.o. healthy females	Determine the safety of 3 doses of pilot manufacturing material of HPV 16 vaccine in subjects either HPV 16 seronegative or seropositive prior to vaccination.	1. % of subjects who had anti-HPV 16 serum levels at 4 weeks post final dose. 2. occurrence of any severe local injection site reaction or SAE	1. all doses elicited acceptable immune response 2. Adverse events mild to moderate 3. No correlation between increased dose and % of Serious adverse events.
Trial #4 Protocol 005	10/22/08 -3/31/04	Phase 2a	16-25 y.o females	Demonstrate efficacy of the HPV 16 vaccine at 40 mcg in preventing persistent HPV 16 infection	1. Incidence of persistent HPV 16 infection/detection of infection. 2. HPV-related CIN (any grade), AIS, or cervical cancer	1. Persistent HPV 16 infection in 7 vaccine vs. 111 placebo groups cases. 2. Evidence of efficacy against persistent HPV infection and CIN infection
006	3/2/00-1/25/01	Phase 1	16-23 y.o. health females	1. Evaluate safety and tolerability of 3 doses of HPV 18 vaccine	1. Proportion of women achieved anti-HPV serum level $\geq 200$	HPV 18 vaccine induced acceptable

				2. Assess immunogenicity in women negative to HPV 18 3. Safety of vaccine in women positive to HPV 18	mMU/mL post dose 3 2. Any local injection site reaction and any SAE	immune response in protocol pop.
Protocol #	Dates	Type	Study Participants	Objective	Endpoint(s)	Results
Clinical Trials						
Trial #1, protocol 015 FUTURE II	6/02-5/03	Phase 3	15-26 y.o. healthy females	Evaluate safety and efficacy of Gardasil vaccine	1. demonstrate reduction in incidence of HPV 16 and 18 CIN2/3, AIS, cervical cancer when naïve to relevant strains at baseline 2. Evaluate persistence of vaccine-induced serum anti-HPV 6/11/16/18 in subjects naïve at baseline 3. Impact of Gardasil on incidence of all CIN 2/3 by any vaccine or non-vaccine type; incidence of HPV 6/11/16/18 related genital warts, VIN, VaIN, vulvar/vaginal cancer	1. Interim analysis - Protocol pop – 91% efficacy combined incidence of HPV 6/11/16/18 related CIN. ITT pop – 39% efficacy combined incidence of HPV 6/11/16/18 related CIN 2. Analysis from NEJM article – Protocol pop. – 95% overall efficacy. ITT pop. – 44% efficacy
Trial #2 Protocol 013 FUTURE I	12/28/01-11/4/05	Phase 3	16-23 y.o. healthy females	Evaluate safety and efficacy of Gardasil vaccine	1. Demonstrate that a 3 dose regimen of Gardasil reduced incidence of HPV 6/11/16/18 related genital warts, CIN, VIN, VaIN,	1. Protocol pop. – 100% efficacy against HPV 6/11/16/18 CIN and external genital lesions.

					AIS, vulvar/vaginal/ cervical dysplasia or cancer 2. demonstrate that 3 dose regimen was well tolerated	ITT pop. – 73% efficacy against external genital lesions; 55% efficacy against cervical lesions
Protocol 011 (sub- study of 013)	12/28/01 -6/11/04		16-23 y.o. healthy females	Evaluate concomitant admin. Of Gardasil and Hep. B vaccine	Demonstrate that concomitant admin. Of Gardasil and Hep B vaccine did not interfere with immune response to either vaccine	Concomitant admin. Of Gardasil and Hep. B vaccine id not interfere with immune response to either vaccine
Protocol 012 (sub- study of 013)	5/30/02- 6/30/04		16-23 y.o. healthy females	Compare FMP material to PMM HPV16 vaccine	Demonstrate that FMP material of vaccine induced a similar anti-HPV 16 response as those induced by PMM HPV 16 vaccine used in protocol 005	FMP material induced a similar anti- HPV response as the PMM
Trial # 3 Protocol 007	5/26/00- 5/10/04	Phase 2b	16-23 y.o. healthy females	Determine final dose to be used in phase III trials	1. Part A – investigate general tolerability of quadrivalent vaccine 2. Part B – identify the quadrivalent formulation that results in acceptable type specific anti-HPV responses; demonstrate tolerability of vaccine	Overall efficacy of vaccine formulation was 87.6%; Tolerability was demonstrated
Trial #5 Protocol 016	12/7/02- 9/20/04		10-15 y.o. healthy girls and boys;	Demonstrate tolerability and immunogenicity of	1. Demonstrate that the 3-dose regimen of the	1. Males had highest Geometric

			16-23 y.o. healthy females	quadrivalent vaccine in male and female preadolescents and adolescents to determine end-expiry specifications for the vaccine	quadrivalent vaccine resulted in similar anti-HPV 6/11/16/18 responses four weeks post dose 3 in girls and boys 10-15 as it did in women 16-23 2. Identify the minimum partial dose formulation of quadrivalent vaccine in 3-dose regimen that would induce a similar response as administration of full dose formulation in 3-dose regimen 3. Demonstrate that 3-dose regimen is generally well tolerated in adolescents and young adults.	mean titers followed by 10-15 y.o. girls, and 16-23 y.o. female adolescents 2. 20% formulation was the minimum acceptable end-expiry formulation 3. Vaccine generally well tolerated. Adverse events comparable among all groups
Trial #6 Protocol 018	10/8/03-1/19/05		9-15 y.o. healthy and not yet sexually active boys and girls	Determine the safety and immunogenicity of the quadrivalent vaccine. (was the only study to use a placebo without the aluminum adjuvant)	1. Demonstrate that a 3-dose regimen of the quadrivalent vaccine was generally well tolerated by evaluating the occurrence of any severe injection site reactions of vaccine related Serious adverse events 2. Demonstrate that the 4 week post dose 3 responses of	1. Boys had higher Geometric mean titers than girls, but seroconversion rates were nearly identical. 2. Higher proportion of Adverse events in vaccine group; 5 incidences of Serious adverse events in vaccine

					quadrivalent HPV vaccine in preadolescent and adolescent boys are non inferior to those observed in preadolescent and adolescent girls.	group vs. none in placebo group; girls reported a higher number of Adverse events than boys
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*Phase I-II studies with Monovalent HPV VLP Vaccines*

Protocol 001 ran from September 22, 1997 – August 7, 2001, and was called “The Safety/Tolerability and Immunogenicity of Research Lot HPV 11 Virus-Like Particle (VLP) Vaccine in College Age Women” (N. B. Miller, 2006, p. 19). The objective of the study was to determine the safety and immunogenicity of four dose formulations of monovalent HPV 11 L1 VLP vaccine (administered at 0, 2 and 6 months) in women 18-25 years of age. It was a phase I, randomized, double-blind, placebo-controlled trial. Subjects were enrolled in two locations in the United States. It was noted for all double blind studies that “all subjects, investigators and their staff, and laboratory personnel were blinded to treatment group” (N. B. Miller, 2006, p. 20). In any study that included a minor, parental/guardian consent was obtained in addition to the minor’s consent.

The subjects were healthy females 18-25 years of age, with a mean age of 20 years old, and were seronegative for anti-HPV 11. There were a total of 140 women enrolled in this study; 116 women completed the study. The subjects could not have a history of evidence of HPV related disease. As was the case for all of the trials conducted, subjects had to have a negative pregnancy test on the day of vaccination in order to be admitted to the study. The subjects were divided into four groups of 35; each

group was then subdivided into 28 in each vaccine group and seven in each placebo group. The vaccine preparation for this study was for the HPV 11 L1 VLP vaccine in the following amounts; 10 mcg/0.5 mL, 20 mcg/0.5 mL, 50 mcg/0.5 mL, 100 mcg/ 0.5 mL, with each group being assigned to one vaccine dosage. Both the placebo and the vaccine contained 225 mcg aluminum as amorphous aluminum hydroxide sulfate (AAHS) (N. B. Miller, 2006). The vaccine was given at 0, 2, and 6 months, with a booster given to half of each of the four cohorts at month twelve (N. B. Miller, 2006).

This was an immunogenicity study, not an efficacy study, so there were no efficacy endpoints that were looked at or measured. There were two immunogenicity endpoints, a primary and a secondary. The primary endpoint was “the percentage of subjects achieving anti-HPV 11 serum RIA levels  $\geq 200$  mMU/mL at 4 weeks postdose 3 with 95% CIs” (N. B. Miller, 2006, p. 22). The secondary endpoints include “anti-HPV 11 GMTs; evidence of generation of anti-HPV 11 neutralization in Mouse Xenograft Neutralizing test; antibody persistence at 2.5 years post dose 3; assessment of dose response; and anti-HPV 11 levels after a 4<sup>th</sup> dose of vaccine” (N. B. Miller, 2006, p.22).

There were also safety endpoints looking at local reactions within 5 days after vaccination and systemic reactions within 15 days after vaccination. Serious adverse events were looked at throughout the study period. One way of measuring any potential adverse events was to have the subjects take and record their oral temperature four hours after vaccination and daily for the next four days. They then met with study personnel at regular intervals over the course of the study to discuss any potential adverse events.

The results showed that the monovalent HPV 11 vaccine induced anti-HPV 11 antibody response at all doses tested. There was a “significant difference between



placebo and the 10 mcg dose in percentage of subjects with an anti-HPV 11 antibody level  $\geq 200$  mMU/mL” and the 20, 50, and 100-mcg dose levels of HPV 11 L1 VLP vaccine appear immunogenic (N. B. Miller, 2006, p. 23). There was evidence of persistence of anti-HPV 11 antibodies at Month 36. The results also showed that administration of the fourth (booster) dose did not appear to produce meaningful increases in the antibody levels at Month 36 (N. B. Miller, 2006). Safety data were available for all 140 subjects enrolled in the study. In general, there were a higher percentage of subjects reporting an adverse event after the 1st dose as compared to the 2nd and 3rd doses.

There was a dose response in the 3 higher doses for injection site reactions, most of which were mild to moderate. The overall incidences of systemic adverse events were higher in the 50 mcg and 100 mcg doses. The most common systemic adverse events were headache and upper respiratory infections. Merck scientists did not believe there were any safety issues identified from this Phase I trial, though they do note one serious adverse event of depression 75 days post dose 2 of the 100 mcg dose (N. B. Miller, 2006).

Protocol 002 ran from January 5, 1998 – October 31, 2001. The title of this study was the “Safety/Tolerability and Immunogenicity of a Research Lot of HPV 16 Virus-Like Particle (VLP) Vaccine in College Age Women.” The objective of this study was “to determine the safety and immunogenicity of three dose formulations of the monovalent HPV 16 L1 VLP vaccine in young women 18-25 years of age” (N. B. Miller, 2006, p. 25). This study was a phase I, randomized, double blind, placebo controlled trial which took place at just one location. There were a total of 109 participants who were

divided into three groups, with each group getting a different dosage of the vaccine; a portion of each group received the placebo. For the HPV 16 L1 VLP vaccine, the dose formulations were 10 mcg/0.5 mL, 40 mcg/0.5 mL, and 80 mcg/0.5 mL. Merck realized early on that “the 10 mcg dose showed decreased immunogenicity in mice. Therefore, subjects randomized to the 10 mcg dose were subsequently given the 40 mcg dose” (N. B. Miller, 2006, p. 25). Both the vaccine and placebo contained (225 mcg aluminum as amorphous aluminum hydroxide sulfate (AAHS)). The vaccine schedule was 0, 2, and 6 months.

The study was conducted at one center in the U.S, and the subjects were healthy 18-25 year old women with a mean age of 20 years old who were naïve for HPV 16 infection at baseline (women enrolled were to be HPV 16 seronegative and negative by polymerase chain reaction (PCR) at screening), had 0-5 lifetime sexual partners, and had no history of abnormal Pap (N. B. Miller, 2006). 109 women were enrolled in the study and 103 completed the vaccination phase, staying in the study through month 7.

The primary endpoint for this study was the percentage of subjects “achieving anti-HPV 16 serum RIA levels  $\geq 20$  mMU/mL 1 month following the third injection of vaccine/placebo” (N. B. Miller, 2006, p. 26). The primary safety endpoints were incidences of serious adverse events that were vaccine related, and severe injection site adverse events. Though not considered primary safety endpoints, local reactions and fevers within 5 days of vaccination and systemic reactions within 14 days of vaccination were also assessed. This was not an efficacy study, so there were no primary efficacy endpoints, but there were exploratory endpoints that “included the rate of incident HPV 16 infection, the rate of incident HPV 6, 11, and 18 infections, the incidence of HPV

related disease, and the association between PCR responses and Pap test results” (N. B. Miller, 2006, p. 26). Safety was assessed in the same way as it was in protocol 001, which was discussed earlier in this section.

The results of this study showed that the 40-mcg and 80-mcg dose levels of the HPV 16 L1 VLP vaccine appear immunogenic. All dose formulations elicited an immune response to anti-HPV 16, and geometric mean titers (GMTs) persisted through Month 36 for all doses. There was no discernible difference in the safety profile after doses 1, 2, and 3. In all of the treatment groups, the majority of adverse events were reported as being mild or moderate, and these rates were generally comparable among treatment groups. The most common injection site adverse events experienced were pain/tenderness/soreness, most of which were rated as mild. The most common systemic clinical adverse event was headache.

Protocol 004 ran from October 12, 1998-September 30, 2001. This study was titled, “A Study of the Immunogenicity of Pilot Manufacturing Material of HPV 16 Virus Like Particle (VLP) Vaccine in 18-25 year old Women.” The objective of this study was to “determine the safety of three doses of pilot manufacturing material of HPV 16 VLP vaccine in subjects who are either HPV 16 seronegative or seropositive prior to vaccination” (N. B. Miller, 2006, p. 31). The doses were given at zero, 2 and 6 months, with four doses of the vaccine, 10 mcg, 20 mcg, 40 mcg, and 80 mcg given to the four groups. Both the placebo and the vaccine contained 225 mcg aluminum as amorphous aluminum hydroxide sulfate (AAHS). This study was a phase IIa, randomized, double blind, placebo-controlled trial. It was conducted at 15 centers in the U.S. with healthy females 16-23 years of age who were not screened for HPV 16 disease prior to

enrollment. The subjects were followed for 14 days after each vaccination and checked for persistence of anti-HPV antibody through Month 24.

This study was also an immunogenicity study, not an efficacy study, so there were no efficacy endpoints. The immunogenicity endpoints were to check the proportions of subject who had anti-HPV 16 serum levels at four weeks after the final dose in month six. In terms of safety, this study was looking for the occurrence of any severe local injection site reactions and the incidence of any serious vaccine related adverse events. The subjects also took their temperature four hours after each dose and for the four days following each dose. This information along with any local injection site reactions or other perceived effects was recorded. Study staff contacted the participants at regular intervals to check on this information, and to ensure that 14 days post vaccination there were no systemic adverse events (N. B. Miller, 2006).

There were a total of 480 healthy females enrolled in this study with ages ranging from 18-26 years of age, with a median age of 22 years old. Of the 480, 384 subjects completed the vaccination. The remainder of the subjects were either lost to follow up or refused to participate further (N. B. Miller, 2006). The safety data showed that one subject in the placebo group discontinued the study due to an adverse event (headache). The majority of the other subjects who reported adverse events were graded as mild to moderate in severity, and were generally comparable across dose groups. This study did not show a clear correlation with increasing dose and the percentage with severe adverse events. The most common injection site adverse event was pain/tenderness/soreness, with rates ranging from 79.4% in the 10 mcg group to 87.8% in the 40 mcg group; the majority of these were rated as mild to moderate (N. B. Miller, 2006). The incidence of

injection site adverse events was generally comparable for all of the doses. The overall incidences of systemic adverse events from Days 0-14 were generally comparable in all 5 groups (with incidences ranging from 68.3% - 78.5%). The incidence of fever occurring between days 0-14 was somewhat higher in the vaccine groups as compared to the placebo group (with 6.7% with a fever in the 80 mcg dose group and 2.0% in the placebo group) (N. B. Miller, 2006).

The most common clinical adverse event was headache, which was present in 48% of placebo recipients and in 46.9 to 49.5% of vaccine recipients (N. B. Miller, 2006). Three serious adverse events, gastroenteritis, severe pneumonia, and suicide attempt were reported in the 10, 40, and 80 mcg groups respectively. All of these occurred after the 2<sup>nd</sup> dose and all three of these women went on to receive the 3<sup>rd</sup> dose. There were a total of 19 pregnancies, 2 in the placebo group and 17 in the vaccine group. Out of the 17 pregnancies, there were two miscarriages, 4 termination of pregnancies, 8 healthy infants, 1 infant with a congenital anomaly (tracheomalacia), and 2 with unknown outcomes (N. B. Miller, 2006). The two women in the placebo group delivered healthy babies.

The results showed that all dose levels elicited acceptable immune responses. At 18 months post dose 3, “anti-HPV 16 levels were detectable in the majority of women who were vaccinated and anti-HPV 16 geometric mean titers remained numerically higher than those in women who developed anti-HPV 16 responses to natural infection” (N. B. Miller, 2006, p. 38)

Protocol 005 ran from 10/22/98 – 3/31/04; the actual data were collected between October 1998 and November 1999 with the analysis continuing through March 2004 (Koutsky et al., 2002; N. B. Miller, 2006). This was one of the clinical studies and unlike

the other monovalent studies was an efficacy study. Its results were combined with studies 007, 013, 015 for an efficacy report. The title of this study was, “Study of Pilot Manufacturing Lot of HPV 16 Virus Like Particle (VLP) Vaccine in the Prevention of HPV 16 Infection in 16 to 23 year old Women.” The primary objective of this study was to demonstrate the efficacy of the HPV 16 L1 VLP vaccine at 40 mcg in preventing persistent HPV 16 infection compared with placebo, as well as to demonstrate its safety. There were three secondary objectives. The first was to evaluate the effect of HPV 16 L1 VLP vaccine on the incidence of CIN 1, CIN 2, or CIN 3 due to HPV 16 and on the incidence of CIN 2 or 3 due to HPV 16 as compared to placebo. The second was to evaluate the relationships among HPV 16 antibody levels, virologic measurements, disease endpoints, and if the data were available, anti-HPV 16 neutralization response. The third was to evaluate the antibody response to HPV 16 L1 VLP vaccine in polymerase chain reaction (PCR)-positive and seropositive subjects, and to investigate the natural history of the development of genital warts (N. B. Miller, 2006, p. 234). This study did not assess whether this formulation of the vaccine reduced the viral load of HPV 16 infection compared with placebo. In assessing safety, the study was looking for the occurrence of severe injection site reactions and/or the incidence of any serious vaccine related adverse events.

This study was a phase IIa, randomized, double blind, placebo-controlled trial that took place at 16 centers across the United States. The vaccine or placebo was given at zero, 2, and 6 months. There were a total of 2409 participants split evenly between the vaccine (1204) and placebo (1205) groups. The study participants ranged in age from 16-23, with a mean age of 20 years old. The primary efficacy endpoint was the incidence of

persistent HPV 16 infection, which included HPV 16 related CIN. The secondary endpoints were: the detection of HPV 16 on at least one visit post month 7; HPV 16-related CIN 1, CIN 2, CIN 3, AIS, or cervical cancer; CIN 1, CIN 2, CIN 3, AIS, or cervical cancer; or the incidence of invasive HPV related procedures - colposcopy with biopsy, definitive therapy, genital warts excision (N. B. Miller, 2006, p. 235). This study also had three exploratory endpoints which were; the rate of clearance of HPV 16 infection, the amount of time to clear the infection, and the rate of progression to clinically apparent HPV 16-related disease. To assess immunogenicity, the study looked at serum anti-HPV 16 geometric mean titers (GMTs) at Month 7, which was four weeks after the final dose. To assess safety, each participant took their temperature four hours after each injection and daily for the next four days. They also had to note any injection site or systemic reaction on day one or 14 days after each injection. All subjects were observed by study staff for 20-30 minutes following each injection.

Subjects were followed for efficacy through month 48 and were seen every 6 months from month 12 through month 48. An interim analysis was done in June 2001, in preparation of the phase 3 studies. This analysis showed that “there were zero cases of HPV sustained positivity identified in the vaccine group and 24 cases in the placebo group, and met the statistical criterion for success. The observed efficacy was 100%” (N. B. Miller, 2006, p. 244). A primary fixed case analysis was done in November 2001 and the final analysis was done in June 2004. At the time the final analysis was done, there were 111 cases of persistent HPV 16 infection in the placebo group and 7 cases in the vaccine group.

The results for the endpoints demonstrated efficacy of the monovalent HPV 16 vaccine (40 mcg) against persistent HPV 16 infection. The vaccine appeared immunogenic in a very high proportion of individuals. There was evidence of efficacy against both HPV 16 related CIN 2 or 3 and against any HPV related CIN 2 or 3. The exploratory endpoints showed that in clearing HPV16, there was a slightly higher clearance rate in the placebo group as compared to the vaccine group, 42.2% versus 35.7% per 100 person-years at risk. There was no difference between the two groups in “time to clearance” (N. B. Miller, 2006, p. 254). In terms of the rate of progression of HPV 16 to CIN or worse, the number of cases was small, with a few cases in each group. There was one more case of HPV 16 related CIN 1 or worse in the placebo group as compared to the vaccine group (N. B. Miller, 2006).

Adverse events, both systemic and injection site were somewhat comparable between the two groups, though there were slightly higher injection site adverse events in the vaccine group than the placebo group. Most adverse event reporting occurred after dose one, though reports continued with subsequent doses. Most adverse events were rated as mild to moderate in the 15 days following injection. There were nine people who discontinued the study due to adverse events; four in the vaccine group and five in the placebo group (N. B. Miller, 2006).

An article discussing the results of this study was published in the November 21, 2002 issue of the New England Journal of Medicine (Koutsky et al., 2002). It was noted at the end of the article that this article was “supported by Merck Research Laboratories, which funded all work,” and Drs. Koutsky, Ault, and Brown report having received consulting fees and research support from Merck during the past two years” (Koutsky et



al., 2002, p. 1650). The authors for this study confirmed the methods and results discussed in the clinical review. The authors also provided more detail about the study population. The women were recruited through advertisements on college campuses and in the surrounding communities and were paid in amounts that ranged from \$20-\$225 per visit; the amounts were determined independently by each center (Koutsky et al., 2002). The women were eligible if they were not pregnant, reported no prior abnormal pap smears, and reported no more than five male sex partners during their lifetime.

For analysis, the subjects had genital samples taken to test for HPV-16 DNA at enrollment, one month following the final injection (month 7), and every six months thereafter; some women were referred for colposcopy according to the protocol. Biopsy tissue was evaluated for cervical intraepithelial neoplasia (CIN) and analyzed for HPV-16 DNA with use of the polymerase chain reaction (PCR). The primary end point the study looked at was persistent HPV-16 infection, which was defined as the detection of HPV-16 DNA in samples obtained at two or more visits. The primary analysis was limited to women who were negative for HPV-16 DNA and HPV-16 antibodies at enrollment and negative for HPV-16 DNA at month 7 (Koutsky et al., 2002).

The authors also discussed the results in more detail in their discussion section. The incidence of persistent HPV-16 infection in the placebo versus vaccine group per 100 woman years was 3.8 and 0 respectively. All 41 cases of HPV-16 infection occurred in the placebo group; 31 were persistent HPV-16 infections without cervical intraepithelial neoplasia (CIN), 5 consisted of HPV-16–related cervical intraepithelial neoplasia grade 1, four consisted of HPV-16–related cervical intraepithelial neoplasia grade 2, and 1 occurred in a woman who was HPV-16–DNA positive for the first time on

the last visit before she was lost to follow-up. An additional 44 cases of cervical intraepithelial neoplasia that were not associated with HPV-16 infection were detected, 22 among placebo recipients and 22 among vaccine recipients (Koutsky et al., 2002). The authors stated that the fact that all nine cases of HPV-16–related cervical intraepithelial neoplasia occurred among the placebo recipients constitutes encouraging evidence of the efficacy of the vaccine, but they believe that a larger study is required to prove that clinical disease is prevented by vaccination (Koutsky et al., 2002).

Protocol 006 ran from March 2, 2000 – January 25, 2001 and was titled, “A Study of the Safety/Tolerability and Immunogenicity of HPV 18 Virus-Like Particle (VLP) Monovalent Vaccine in 16-23 year old Women.” The objective of this study was to evaluate the safety and tolerability of three doses of the HPV 18 L1 VLP vaccine in women, and to assess the immunogenicity of the vaccine in HPV 18 seronegative women and women who are shown to be negative by polymerase chain reaction (PCR) (N. B. Miller, 2006). An additional objective was to obtain preliminary safety data with the vaccine in women who are positive for HPV 18 (either by serology and/or DNA status) (N. B. Miller, 2006). There was only one group in this trial that got the vaccine and that was at the 80 mcg dose, which was given at zero, 2, and 6 months. Both the vaccine and the placebo contained 450 mcg aluminum as amorphous aluminum hydroxide sulfate (AAHS). This study was a phase I, double blind, placebo controlled, randomized trial that took place at three centers in the US. This was not an efficacy study, though specimens were collected so that vaccine efficacy might be evaluated a later time.

The subjects were healthy 17-23 year old females who did not have a history of prior Pap test abnormalities; the mean age of the women was 20 years old. There were a

total of 40 women in this study, with 27 in the vaccine group and 13 in the placebo group. Two women in the vaccine group did not finish the study because one refused further participation and one was lost to follow up. One woman in the placebo group discontinued due to the adverse event of moderate hives on days 2 and 3 after injection.

The primary immunogenicity endpoint was to see what proportion of the women achieved an anti-HPV 18 serum level  $\geq 200$  mMU/mL post dose 3, which would be at Month 7 (N. B. Miller, 2006). In terms of safety and tolerability, this study was looking for the occurrence of any local injection-site reactions and the incidence of any serious vaccine-related adverse events. The determination of the severity of any local site reaction was that the area of redness and swelling be more than two inches. At month 7, cervical and vaginal specimens were taken to determine the detection of HPV 18 in those women who had tested negative at enrollment, as well as checking for HPV related pap test abnormalities and/or cervical intraepithelial neoplasia (CIN) in women who had a negative pap test at enrollment (N. B. Miller, 2006).

To evaluate safety, all women were followed for 15 days following each injection. The placebo group had a higher incidence of adverse events than the vaccine group and their adverse events were reported as severe compared to the vaccine groups who reported their adverse events to be moderate. There was a high rate of injection site reactions in both the vaccine (96.3%) and placebo groups (84.6%), with the most common complaints being pain/soreness/tenderness (N. B. Miller, 2006, p. 43). There were also reports of systemic adverse events in both the vaccine (70.4%) and placebo groups (84.6%), the most common of which were headaches and pharyngitis, and were rated as mild to moderate. One woman in the vaccine group became pregnant during the

study and had a miscarriage 6 weeks into her pregnancy, which was 18 days after the final dose of the vaccine.

The results showed that there was significant statistical evidence to support that the HPV 18 L1 VLP vaccine induced an acceptable immune response in the per protocol population. The per protocol population included women who were naïve to HPV 18 at enrollment and did not acquire HPV 18 infection during the study, though the results show that no subjects who were initially HPV 18 negative at Day 0 became HPV 18 positive at Month 7, which was tested by polymerase chain reaction (PCR). Three doses of the 80 mcg dose of the HPV 18 L1 VLP vaccine which had a higher level of the adjuvant than in studies 001, 002, and 004 (450 mcg AAHS compared to 250 mcg) was noted to be immunogenic at 4 weeks post the 3<sup>rd</sup> dose, and the geometric mean titers (GMTs) of anti-HPV antibodies were highest at 1 month after the 3<sup>rd</sup> dose of vaccine (N. B. Miller, 2006, p. 43). The FDA felt that the results of the monovalent studies, 001, 002, 004, and 006 provided support for continued development of the quadrivalent HPV vaccine (N. B. Miller, 2006).

*Clinical Studies for Quadrivalent HPV 6, 11, 16, 18 L1 VLP Vaccine Phase IIb-III Trials (013 (incl. 011,012), 015, 016, 007, 018*

Trial #1, Protocol 015 was titled, “A Randomized, Worldwide, Placebo Controlled, Double Blind Study to Investigate the Safety, Immunogenicity, and Efficacy on the Incidence of HPV 16/18 Related CIN 2/3 or Worse of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus Like Particle (VLP) Vaccine in 16-23 Year Old Women – The FUTURE II Study (Females United to Unilaterally Reduce Endo/Ectocervical

Disease).” This study ran from June 2002 – May 2003 and is generally referred to as the FUTURE II study. This was a phase III, randomized, placebo-controlled trial that enrolled 12,167 healthy adult women 15-26 years of age with a mean age of 20 years old (Koutsky, 2007; N. B. Miller, 2006). This study was conducted at 90 centers in 13 countries; Brazil, Colombia, Denmark, Finland, Iceland, Mexico, Norway, Peru, Poland, Singapore, Sweden, United Kingdom, and the US (N. B. Miller, 2006). The primary overall objective of this study was to evaluate the safety and efficacy of Gardasil. There were three other objectives; efficacy, immunogenicity, and exploratory efficacy. The efficacy objective was to demonstrate that the vaccine reduced the incidence of HPV 16 and HPV 18-related cervical intraepithelial neoplasia (CIN) 2 or 3, adenocarcinoma in situ (AIS), or cervical cancer in subjects who were naïve to the relevant HPV types at baseline. Naïve at baseline was defined by being seronegative of those HPV types at day 1 and negative at day 1 and at month 7 by use of polymerase chain reaction (PCR). The immunogenicity objective was to evaluate “the persistence of vaccine-induced serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti- HPV 18 responses in subjects who were naïve to the relevant HPV types” (N. B. Miller, 2006, p. 48). The exploratory efficacy objective was to assess the impact of Gardasil on the incidence of all CIN 2 or 3 or invasive cervical carcinoma caused by any vaccine or non vaccine HPV type, as well on the incidence of HPV 6, 1, 16, 18-related external genital warts, Vulvar Intraepithelial Neoplasia (VIN), Vaginal Intraepithelial Neoplasia (VaIN), vulvar cancer, or vaginal cancer (N. B. Miller, 2006).

This study also included three sub-studies. The first was “The Nonserious Adverse Experience Substudy,” which took place in the US only, provided an assessment

of the safety of the vaccine in a group of subjects who completed a Vaccine Report Card (VRC). Subjects in this study recorded their oral temperature 4 hours after each injection and for 4 days after. Any systemic or injection site adverse event was recorded for 14 days after each injection. A ruler was provided to the subjects to measure any injection site adverse events (redness, swelling), which were then rated from mild to severe. The ratings were 0-1 inch was mild, 1-2 inches was moderate, and above 2 inches was severe. The second sub-study was “The Consistency Lot Substudy,” which was intended to demonstrate that the Final Manufacturing Process (FMP) resulted in a vaccine that induced consistent serum anti-HPV 6, 11, 16, and 18 responses four weeks following dose 3, and to evaluate the persistence of antibody levels out to month 48. Subjects in this sub-study received different lots of the vaccine than others in this study. The third sub-study was “The Registry Substudy,” which planned to complete ascertainment of cytology and pathology specimens and was to be conducted in countries in which Cervical Screening Registries already exist (N. B. Miller, 2006).

The vaccine contained HPV 6, 11, 16, 18 L1 VLP at a dosage of 20, 40, 40, 20 mcg respectively, and both the vaccine and placebo contained 225 mcg of the aluminum adjuvant (N. B. Miller, 2006). Subjects had a pregnancy test prior to enrollment and prior to each vaccination. If a subject became pregnant during the vaccination period, vaccination was postponed until at least 2 weeks after the resolution of the pregnancy. Subjects who became pregnant after completion of the vaccination series completed study procedures at the discretion of the investigator. Breast feeding was not a contra indication for enrollment or vaccination. Their temperature was also taken prior to each vaccination, and injection was postponed if there was a temperature above 100° F.

Subjects were also monitored for 30 minutes following each injection for any adverse events. Intensity of adverse events were graded as follows: Mild – awareness of sign or symptom; moderate – discomfort enough to cause interference with usual activities; severe – incapacitating with inability to work or do usual activity (N. B. Miller, 2006, p. 52). Visible external genital lesions noted during the study period, after Day 1 through Month 48, were biopsied (N. B. Miller, 2006).

An interim analysis occurred on August 15, 2005. The results were broken up into the per-protocol population and the intention to treat population. In the per protocol population, for the specific vaccine HPV type for which the subject was naïve (seronegative at baseline and PCR negative at baseline through Month 7), there was a high degree of efficacy against lesions related to that specific HPV type (N. B. Miller, 2006, p. 66). The vaccine efficacy for this population with respect to the combined incidence of HPV 6, 11, 16, or 18 related CIN was 91% (N. B. Miller, 2006).

The intention to treat population, which is referred to as MITT (modified intention to treat) included subjects who were protocol violators, and were assessed for vaccine efficacy regardless of HPV baseline status. The efficacy in this group was 39% (N. B. Miller, 2006). For subjects who were positive by polymerase chain reaction (PCR) and/or seropositive for the relevant HPV type at baseline, efficacy against vaccine HPV related CIN in this subgroup was low (18.9%), and did not reach statistical significance (N. B. Miller, 2006).

An article was published about this trial in the *New England Journal of Medicine* on May 10, 2007. It was noted that this work was supported by Merck. The individual authors were not listed as there were more than two dozen who were the primary

members of the FUTURE II study group. It is the study group that is listed as the author of the article, though Laura Koutsky, PhD, the chair of the FUTURE II study group is listed as the person from whom to request article reprints. All members of the FUTURE II study group were either current or former employees of Merck or had been paid consulting fees by Merck (Koutsky, 2007). The authors confirmed what was discussed in the clinical review, and went into more detail regarding the methods and the results. They confirmed that the study was “designed, managed, and analyzed by Merck in conjunction with external academic investigators and members of the external data safety monitoring board” (Koutsky, 2007, p. 1916). The article confirms that the academic authors had full access to the data, the analyses, that they approved the final manuscript, and that they all vouched for the completeness and accuracy of the data presented.

The article discussed the methods of the study, and confirmed the testing of the quadrivalent HPV-6, 11, 16, 18 VLP vaccine with amorphous aluminum hydroxyphosphate sulfate adjuvant and an aluminum-containing placebo. Subjects were randomly assigned to receive vaccine or placebo at day 1, month 2, and month 6 after having a negative result on a pregnancy test of the urine or blood. Subjects were observed for 30 minutes after receiving the injection and were asked to report serious adverse events occurring 1 to 15 days after each injection. A total of 916 subjects (all of the subjects at U.S. centers) were asked to use a vaccination report card to record all adverse events occurring 1 to 15 days after each injection. Throughout the trial, all serious adverse events that were potentially related to either the procedure or the vaccine, all deaths, and all pregnancy outcomes were reported (Koutsky, 2007). Following randomization, the first-day visit included a gynecologic examination, a medical history



with collection of cervical samples for Pap testing, and anogenital swabs (of the labial, vulvar, perineal, perianal, endocervical, and ectocervical areas) for HPV DNA testing. Follow-up visits were scheduled at month seven, and months 13, 24, 36, and 48 (Koutsky, 2007).

The results as discussed in this article noted that subjects were followed for an average of 3 years after the administration of the first dose of vaccine or placebo. In the per protocol population, which included 10,565 of 12,167 women who underwent randomization, the vaccine prevented 98% of HPV- 16, 18–related high-grade cervical lesions. In this population, 1 woman in the vaccine group and 42 women in the placebo group received the diagnosis of cervical intraepithelial neoplasia (CIN) grade 2 or 3 or cervical adenocarcinoma in situ (AIS) associated with HPV-16, HPV-18, or both. The single subject whose disease was counted as a case of HPV-16– related cervical intraepithelial neoplasia (CIN) grade 3 in the vaccine group was positive for HPV-52 at baseline as well as in five specimens collected at the time of diagnosis and treatment. HPV-16 DNA was detected in one of those specimens but not at any other time points. They concluded that vaccine efficacy remained high at 95%. In the overall population, cervical intraepithelial neoplasia (CIN) grade 2 or 3 or adenocarcinoma in situ (AIS) developed in 3 subjects in the vaccine group and in 62 in the placebo group. The authors noted that “to provide a preliminary assessment of the effect of quadrivalent vaccine on high-grade cervical disease related to HPV-16 or HPV-18 in a population that included women with and without prevalent cervical intraepithelial neoplasia and infection due to vaccine and non vaccine HPV types at baseline, we performed an intention-to treat analysis of all women who had undergone randomization” (Koutsky, 2007, p. 1921). In

that population, vaccine efficacy was 44%, and high-grade cervical disease related to HPV 16 or HPV 18 developed in 83 subjects in the vaccine group and 148 in the placebo group. Vaccination did not appear to alter the course of cervical lesions related to HPV 16 or HPV18 or of infection present at the time of randomization (Koutsky, 2007).

Trial #2, Protocol 013 ran from December 28, 2001 – November 4, 2005 and was titled, “A Study to Evaluate the Efficacy of Quadrivalent HPV (Types 6, 11, 16, and 18) L1 Virus-Like Particles (VLP) Vaccine in Reducing the Incidence of HPV 6, 11, 16, and 18 Related External Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer in 16-23 Year Old Women (FUTURE I)” This study is generally referred to as the FUTURE I study. This study was a phase III, randomized, double blind, placebo controlled trial that enrolled 5455 women between the ages of 16-24 years old, with a mean age of 20 years old. It was conducted in 62 centers in 16 countries; Austria, Australia, Brazil, Canada, Colombia, Czech Republic, Germany, Hong Kong, Italy, Mexico, New Zealand, Russian Federation, Thailand, United Kingdom, the US, and Puerto Rico. Each subject was also enrolled into one of the two immunogenicity sub studies.

The two sub-studies of protocol 013 were protocols 011 and 012. Protocol 011 ran from December 28, 2001 – June 11, 2004, and was titled, “Immunogenicity and Safety of Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine in 16-23 year old women when administered alone or concomitantly with Hepatitis B vaccine (Recombinant).” This study was conducted in 21 study sites in 5 countries in North America (US), Latin America (Brazil, Peru), and Europe (Germany, Czech Republic). Protocol 012 ran from May 30, 2002 – June 30, 2004, and was titled, “Immunogenicity and Safety of Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine in 16-23 Year

Old Women with an Immunogenicity Bridge Between the HPV 16 Component of the Quadrivalent Vaccine and the Monovalent HPV 16 Pilot Manufacturing Material.” It was conducted in 48 study sites in 14 countries in North America (US, Canada, Puerto Rico), Latin America (Colombia, Mexico), Europe (Germany, Austria, Italy, Russian Federation, and the United Kingdom), and Asia-Pacific (Australia, Hong Kong, New Zealand, and Thailand) (N. B. Miller, 2006). For all of the studies, the vaccine (including the Hepatitis B vaccine which was given along with the HPV vaccine) or placebo was given intramuscularly at zero, 2, and 6 months.

The primary efficacy objective of protocol 013 was to demonstrate that a three dose regimen of the quadrivalent HPV vaccine reduced the incidence of HPV 6, 11, 16, and 18 related external genital warts, Vulvar Intraepithelial Neoplasia (VIN), Vaginal Intraepithelial Neoplasia (VaIN), vulvar, vaginal, or cervical cancer, cervical dysplasia, Cervical Intraepithelial Neoplasia (CIN) of any grade, or Adenocarcinoma in Situ (AIS) compared with placebo. The primary safety objective was to demonstrate that a three dose regimen of the quadrivalent HPV vaccine was generally well tolerated. Subjects recorded their oral temp 4 hours after each injection and daily for the next 4 days. They also recorded any injection site or systemic reaction, which occurred on day 1 or 14 days after each injection. Pap testing was done on each subject at day 1, month 7, and every 6 months up to month 48; Pap test abnormalities were followed up. External genital lesions were checked at day 1, month 3, month 7, month 12, and every six months up to month 48, and whenever a subject presented with symptoms (N. B. Miller, 2006).

Protocols 011 and 012 each had a primary immunogenicity objective. The objective for 011 was to demonstrate that the concomitant administration of the

quadrivalent HPV vaccine and the Hepatitis B vaccine did not interfere with the immune response to either vaccine. It should be noted this is the only other vaccine that Gardasil was tested with. The objective for protocol 012 was to demonstrate that “the Final Manufacturing Process (FMP) material of the quadrivalent HPV vaccine induced a similar anti-HPV 16 response as those induced by administration of the Pilot Manufacturing Material (PMM) HPV 16 vaccine that was used in Protocol 005: “Study of PMM lot of HPV 16 VLP Vaccine in Prevention of HPV 16 infection in 16-23 year old women” (N. B. Miller, 2006, p. 125). The subjects in protocol 011 were given either the vaccines or the placebo. The HPV L1 VLP vaccine contained a dosage of 20, 40, 40, 20 mcg for the types 6, 11, 16, and 18 respectively, and both the vaccine and the placebo groups received 225 mcg of the aluminum adjuvant. The subjects receiving the Hepatitis B vaccine received a dosage of 10 mcg which included 500 mcg of the aluminum adjuvant; the placebo group received 420 mcg of the aluminum adjuvant. The Hepatitis B vaccine was given as 1.2 mL single dose compared to the .75 mL dose of the HPV vaccine (N. B. Miller, 2006). The subjects in protocol 012 received the same formulation of the quadrivalent HPV vaccine as those in protocol 011. The subjects randomized to receive the monovalent HPV were given a dosage of 40 mcg along with 225 mcg of the aluminum adjuvant; the placebo groups received the same amount of the adjuvant.

In terms of prophylactic efficacy, the results showed that the observed vaccine efficacy against both co-primary endpoints of 6, 11, 16, or 18 related CIN and 6, 11, 16, or 18 related external genital lesions (EGLS) was 100%, and there were no cases of cervical cancer. In the per protocol population, there was evidence of efficacy of Gardasil against CIN of different grades related to each of the vaccine HPV types. Findings were

also discussed in the modified intention to treat population (MITT), which included protocol violators and subjects who did not have to be naïve to the relevant HPV types.

The efficacy for those not naïve at baseline was 43%. In reviewing these trials, Dr.

Miller, the primary reviewer at the FDA noted that

Although administration of Gardasil to subjects who were seropositive and PCR positive at baseline in Study 015 did not appear to be associated with an increased incidence of cervical disease in the Gardasil group as compared to the placebo group, the results in Study 013 and the combined analyses raised a concern for the review team. In Study 013 and the combined analysis, there was a higher incidence of Gardasil recipients with squamous intraepithelial lesion as compared to placebo recipients in this subgroup. The findings in Study 013 may be related to the presence of an abnormal Pap test at baseline (N. B. Miller, 2006, p. 88).

An article about this study was published in the May 10, 2007 New England Journal of Medicine; the same issue that the FUTURE II article was published. The article was titled, “Quadrivalent vaccine against Human Papillomavirus to prevent anogenital diseases” (Garland et al., 2007). The authors stated that the study was designed, managed, and the results were analyzed by Merck in conjunction with external academic investigators and an external safety data monitoring board (Garland et al., 2007). Merck also collated the data, monitored the conduct of the study, and performed the statistical analyses; the authors had full access to the analyses. The manuscript was drafted by Merck employees, though all authors listed on this article approved the final manuscript and vouched for its completeness and accuracy of the data presented (Garland et al., 2007).

The article went into slightly more detail about the study population, which was primarily drawn from communities near universities and had to be comprised of healthy women who were not pregnant, were required to use contraception throughout the vaccination period, had a lifetime number of no more than four sexual partners, and did

not have a history of genital warts or abnormal results on cervical cytology testing (Garland et al., 2007). A total of 6463 women between the ages of 16-24 years old were screened between January 2002 and March 2003 at 62 study sites around the world. 5455 women were enrolled into the study and split evenly between the vaccine and placebo groups (Garland et al., 2007).

The statistical analysis of the data used a fixed event design, which required at least 38 cases of vaginal and cervical lesions associated with a vaccine type HPV for the “study to have 91% power to declare the vaccine efficacious against at least one of the primary composite end points with a one-sided alpha level of significance of 0.0125 (incorporating multiplicity adjustment), assuming a true vaccine efficacy of at least 80%” (Garland et al., 2007, p. 1930). The analysis occurred approximately 1½ years of follow up after the administration of the 3<sup>rd</sup> dose, and the primary analysis focused on women who at baseline were not infected with vaccine type HPV. All data collection occurred before July 15, 2005, and the analysis was included in the application for vaccine licensure, which was approved by the FDA on June 8, 2006 (Garland et al., 2007).

The results showed that in more than 95% of the subjects who were randomized and included in “one or more of the type-specific, per protocol unrestricted susceptible populations” the vaccine efficacy was 95% of all grades of external anogenital or vaginal lesions, 98% for all grades of cervical lesions, 91% for high grade vulvar or vaginal lesions, and 100% for adenocarcinoma in situ (Garland et al., 2007, p. 1932). The intention to treat population included women regardless of their baseline HPV status. The results from this group may more accurately reflect the efficacy in the population at large because girls and young women are not be tested for vaccine HPV types prior to

vaccination. The efficacy against vaccine HPV types was 73% when all grades of external anogenital or vaginal lesions were combined and 55% when all grades of cervical lesions were combined (Garland et al., 2007). The authors of this article do state that when evaluating effectiveness “against disease associated with the HPV types covered by the vaccine in the intention-to-treat population (as compared with the unrestricted susceptible population) all additional cases detected in the vaccine group occurred in subjects who were infected with vaccine type HPV before vaccination” (Garland et al., 2007, p. 1940). In the discussion section of the article, the authors state that “there appears to be no interference among the four HPV types covered by the vaccine, since 100% HPV type specific efficacy was observed in the per-protocol analysis” (Garland et al., 2007, pp. 1935, 1940). Limitations cited were lack of long term follow up, lack of knowledge about the duration of the vaccine and whether a booster is needed, and that no minimum protective anti-HPV antibody titers have been identified (Garland et al., 2007).

Trial #3, Protocol 007, ran from May 26, 2000 – May 10, 2004 and was titled, “A Placebo Controlled Dose-Ranging Study of Quadrivalent HPV Virus Like Particle (VLP) Vaccine in 16 to 23 Year Old Women.” Efficacy results for this study were combined with efficacy results from Protocols 013 and 015. This study helped to determine the final dose to be used in the phase III trials. The dose for Phase III (20/40/40/20 mcg) was selected in June 2001 based on an interim analysis of this data. The mean age of the women in this study was 20 years old. This trial was a phase IIb study with two parts. Part A was a randomized, double blind, placebo controlled trial. It took place in several centers across the US. Part B was a randomized, double-blind, placebo controlled trial.

It took place in 23 sites in 5 countries: US, Brazil, Finland, Norway, and Sweden. Both of these studies were dose escalating trials meaning that each group received a larger dosage of the vaccine than the previous group. The group that received the largest dose of the quadrivalent vaccine also received the largest dose of the aluminum adjuvant. Each study part had its own objective. The objective of Part A was to investigate the general tolerability of the quadrivalent HPV L1 VLP vaccine for types 6, 11, 16, 18 (N. B. Miller, 2006). The objective of part B was to identify the formulation with HPV 6, 11, 16, 18 that, when administered intra-muscularly in a 3 dose regimen, results in acceptable type specific anti-HPV responses, as well as to demonstrate that the administration of the quadrivalent HPV vaccine is well tolerated (N. B. Miller, 2006).

Part A had a total of 45 people enrolled and those people were broken out into five groups. Two of those groups (Ia and Ib) received a placebo with the aluminum adjuvant; group Ia received the adjuvant in a quantity of 225 mcg and group Ib received 450 mcgs. The three other groups (II, III, IV) received the quadrivalent vaccine in differing amounts, with each group receiving a higher dosage than the previous group. All three groups also received the aluminum adjuvant with group IV receiving a higher dosage of the adjuvant. For HPV types 6, 11, 16, and 18 plus placebo, each group received the following dosages respectively: group II – 20, 40, 40, 20, 225 mcg; group III – 40, 40, 40, 40, 225 mcg; group IV – 80, 80, 40, 80, 395 mcg (N. B. Miller, 2006). Part B had 1000 people enrolled and those people were also broken out into five groups. The groups received the same dosages and the groups in Part A.

The efficacy endpoints for this study were evaluated by polymerase chain reaction to detect persistent external genital and cervicovaginal infection with HPV 6, 11, 16,



and/or 18, and to also determine if this infection was still present when performing the same test four months apart. The secondary efficacy endpoint was to determine if there was HPV 6, 11, 16, or 18-related genital disease such as cervical, vaginal, or vulvar intraepithelial neoplasia or related cancers, adenocarcinoma in situ, or genital warts (N. B. Miller, 2006). Exploratory efficacy parameters included both the incidence of HPV-related procedures such as colposcopy with biopsy, definitive therapy, genital warts excision, as well as the rate of and time to clearance of HPV 6, 11, 16, or 18 infection (N. B. Miller, 2006).

The primary safety endpoints were the proportion of subjects with severe injection site adverse events, and the proportion of subjects with any vaccine related serious adverse events. To monitor safety, subjects took their temperature four hours after each injection and then daily for the four days following each injection (N. B. Miller, 2006). Subjects were also asked to record any injection site reaction for days 1-14 following each injection. The subjects in Part A were contacted four days after each injection to “establish the absence of vaccine attributable SAEs and assess general safety” (N. B. Miller, 2006, p. 208). After those subjects had been assessed and general safety information had been determined the study staff then proceeded to the subjects in Part B. Pregnancies which occurred through month seven were followed for outcome data.

In evaluating the results, Merck addressed how they compared the groups that received differing dosages of the aluminum placebo. Subjects who received the lower doses of quadrivalent vaccine formulation were primarily compared with subjects who received the placebo with 225 mcg aluminum per dose. Subjects who received the highest dose formulation were compared with subjects who received the placebo with 450 mcg

aluminum per dose. The safety profiles of the two placebo groups were then compared observationally, and if their safety profiles appeared similar, then the two placebo groups were combined and compared with each of the three quadrivalent HPV vaccine groups (N. B. Miller, 2006).

The study groups were further broken down into the per-protocol population and the modified intention to treat populations (MITT), which consisted of three groups. The results for these three groups showed varying rates of efficacy. The efficacy for the per-protocol population (N=235), which consisted of subjects who received all 3 vaccinations, were sero- and PCR negative at Day 1 and PCR negative through Month 7 for relevant HPV types, and did not deviate from the protocol was 89.5% (N. B. Miller, 2006). The three MITT populations included those who did deviate from the protocol though specific definitions of each group was not provided (N. B. Miller, 2006). The results for these groups were, MITT-1(N=249) was 89.7%, MITT-2 (N=266) 88.5%, MITT-3 (N=268) 64.5%.

The results showed that the estimate of vaccine efficacy at 2.5 years after completion of the three-dose regimen was 89.5%, and the “efficacy of the quadrivalent HPV vaccine appeared comparable with respect to the various vaccine components” (N. B. Miller, 2006, p. 18). The efficacy results were also broken down by region. The Nordic region had a total of 233 subjects and an efficacy rate of 100%. The US had a total of 501 subjects and an efficacy rate of 95.9%. Brazil had a total of 372 subjects and the lowest efficacy rate of 60.7%. Merck did not know how to explain this except to say, “it is unclear as to the reason for this finding, although the numbers of subjects are small. There does not appear to have been a greater exposure to vaccine HPV types in the

Brazilian population” (N. B. Miller, 2006, p. 219). The vaccine efficacy against vaccine HPV type related persistent infection and disease for all formulations used in this study was 87.6% (N. B. Miller, 2006).

Trial #5, Protocol 016 looked at the use of Gardasil in young adolescents. It ran from December 7, 2002 – September 20, 2004 and was titled, “A Study to Demonstrate Immunogenicity and Tolerability of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents, and to Determine End-Expiry Specifications for the Vaccine.” This trial was conducted in 61 centers in 19 countries including Australia, Brazil, Canada, Colombia, Costa Rica, France, Germany, Greece, Guatemala, Israel, Netherlands, Philippines, Portugal, Spain, Sweden, Taiwan, Thailand, United Kingdom, and the United States (N. B. Miller, 2006). This study was composed of two sub-studies; the adolescent immunogenicity sub-study and the end-expiry sub-study. The adolescent sub-study was a multicenter immunogenicity and tolerability study conducted in 3 groups; 16 – 23 year old females, 10 – 15 year old females, and 10 – 15 year old males. The mean age for the 10 – 15 year olds was 12 and the mean age for the 16 – 23 year old was 20. All subjects in this sub study received a 3-dose regimen of the quadrivalent HPV vaccine in a dosage of 20/40/40/20 mcg (N. B. Miller, 2006). The objective of this sub-study was to demonstrate that the 3-dose regimen of the quadrivalent HPV vaccine results in similar anti-HPV 6, 11, 16, and 18 responses four weeks post dose 3 in girls and boys 10 to 15 years old as it does in women 16 to 23 years old (N. B. Miller, 2006). The end expiry sub-study was a multicenter expiry dose and tolerability study conducted in two female groups; 10 – 15 and 16 – 23 year olds. Subjects from both groups were randomized to receive a 3-dose regimen of either 20%

(4/8/8/4 mcg), 40% (8/16/16/8 mcg), 60% (12/24/24/12 mcg), or 100% (20/40/40/20 mcg) of the dose formulation of the quadrivalent HPV vaccine (N. B. Miller, 2006). The objective of this sub-study was to identify the minimum partial dose formulation of quadrivalent HPV vaccine among the 20%, 40%, or 60% partial dose formulations, given in a 3-dose regimen that would induce a similar immune response as administration of the 3-dose regimen of the full dose quadrivalent HPV vaccine (N. B. Miller, 2006). The primary overall safety objective was to demonstrate that a 3-dose regimen of the quadrivalent HPV VLP vaccine is generally well tolerated in adolescents and young adults (N. B. Miller, 2006).

There were a total of 3000 subjects in this trial; 500 boys and 1500 females. All of the males participated in the adolescent sub-study and were therefore all given the full dosage of the vaccine. Regardless of the dosage given, all subjects in both sub studies received 225 mcg of the aluminum adjuvant. The subjects received the vaccine at zero, 2, and 6 months. There was no placebo in this trial. The primary immunogenicity endpoints for the adolescent sub-study were to detect, by geometric mean titers anti-HPV 6, 11, 16, or 18 at one month post dose 3 (month 7), and to identify the proportion of subjects who were naïve at baseline to the four HPV types who then became seropositive four weeks post dose 3 (month 7) (N. B. Miller, 2006). The primary safety endpoint was to identify any injection site or vaccine related adverse events. In the adolescent study, the overall proportion of subjects with at least one adverse event within 15 days of any vaccination was comparable between the three groups. The proportion of subjects who had at least one injection site or systemic adverse event was generally higher among the 16 – 23 year old females compared to the other groups (N. B. Miller, 2006). The 10 – 15

year old boys had the lower rates of injection site or systemic adverse events than both of the female groups (N. B. Miller, 2006). There were three serious adverse events in the adolescent study. One 13 year old female had vaginal bleeding 26 days following dose one and 42 and 125 days following dose three. The bleeding lasted for one month, 7 days, and 9 days respectively (N. B. Miller, 2006). One 15 year old female had an intentional overdose, though the results do not specify what she overdosed on, though she did recover. One 15 year old male had lower abdominal pain, vomiting, and diarrhea; he recovered (N. B. Miller, 2006). Five people discontinued the study due to adverse events which included, pain and redness at the injection site, diarrhea, swollen cervical lymph nodes, and rheumatoid arthritis (N. B. Miller, 2006).

In the end-expiry sub-study, the overall proportions of subjects with AEs were comparable among the 4 groups. The most common injection site adverse events were pain and swelling, and most of those occurred after the 2<sup>nd</sup> and 3<sup>rd</sup> dose. There was a slightly higher proportion of injection site adverse events reported by the 16 – 23 year old age group in the 20% and 100% formulations as compared to the 10 – 15 year old age group (N. B. Miller, 2006). The most common systemic adverse events were headache and fever and the proportions among the four groups were comparable. Systemic adverse events were reported less frequently following the 2<sup>nd</sup> and 3<sup>rd</sup> doses compared to the 1<sup>st</sup> dose. A higher proportion of the 16-23 year old subjects (60-64%) had reports of a systemic adverse event as compared to the 10-15 year old subjects (54-58%) (N. B. Miller, 2006). There were ten severe adverse events in this sub-study including, loss of consciousness, vaginal bleeding, convulsion (subject on psychiatric medication), pregnancy related problems, and exacerbation of preexisting case of anorexia. There

were also adverse events that caused some subjects to discontinue in the study, which included rheumatoid arthritis, skin reaction, injection site pain, nausea, and tonsillitis (N. B. Miller, 2006).

The results for the adolescent sub-study showed that the males had the highest numerical geometric mean titers followed by the 10 – 15 year old girls, and then the 16-23 year old females (N. B. Miller, 2006). The majority of the per-protocol population seroconverted by month 3, which was 4 weeks after the 2<sup>nd</sup> dose (N. B. Miller, 2006). Breaking that down by HPV type, 100% seroconverted for types 6, 11 and 16 four weeks post dose 3 (month 7). 100% of females 10 – 15 seroconverted for type 18 four weeks post dose 3 (month 7), while 99% seroconverted in the 10 – 15 year old boys and the 16 – 23 year old females (N. B. Miller, 2006). The 16 – 23 year old females who did not seroconvert to at least one HPV type by month 3 and/or month 7 were heavier than their overall cohort (170 lbs vs. 133 lbs) (N. B. Miller, 2006). The results for the end expiry study showed that for the 20%, 40%, 60%, and 100% dose formulations, the seroconversion rate at one month post dose 3 (month 7) was 99.7%, 99.3%, 99.0%, and 99.6% respectively (N. B. Miller, 2006). The conclusion was that the 20% formulation was the minimum acceptable end-expiry formulation (N. B. Miller, 2006).

Trial #6, Protocol 018 ran from October 8, 2003 – January 19, 2005 and was titled, “A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents.” This study was a randomized, double blind, placebo controlled trial in boys and girls 9-15 years old who were healthy and not yet sexually active. This is the only trial to use a placebo without the aluminum adjuvant. The dosage amount of the vaccine was also higher in this

trial than the others. For the HPV 6, 11, 16, and 18 VLP the dosage was 40 mcg, 80 mcg, 80 mcg, and 40 mcg respectively. This study took place in 47 sites in 10 countries in North America (US), Latin America (Colombia, Mexico), Europe (UK, Portugal, Norway, Denmark, Spain) and Asia (Thailand, Taiwan). The primary safety objective of this study was to demonstrate that a 3 dose regimen of quadrivalent HPV vaccine is generally well tolerated in adolescents and preadolescents (N. B. Miller, 2006). The primary immunogenicity objective was “to demonstrate that the 4-week post dose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV vaccine in preadolescent and adolescent boys are non inferior to the responses observed in preadolescent and adolescent girls” as well as to observe the persistence of the immune response of the quadrivalent vaccine (N. B. Miller, 2006, p. 300).

Enrollment in this study was stratified by age and gender, with two age groups per gender, 9-12 year old and 13-15 year olds. The primary immunogenicity endpoints were the anti HPV geometric mean titers for all four HPV types, and the percentage of subjects who seroconverted for the four HPV types; both of these were looked at four weeks post dose three (month 7). The primary safety endpoints were the occurrence of any severe injection site reactions or vaccine related severe adverse events (N. B. Miller, 2006). Overall, there were 696 subjects randomized, and 692 vaccinated with at least one dose of vaccine for the 9-12 year old age group, and 488 randomized and 487 vaccinated in the 13-15 year old age group. The immunogenicity results showed that the boys were noted to have higher geometric mean titers (GMTs) as compared to the girls, although seroconversion rates were nearly identical (N. B. Miller, 2006). Four subjects failed to

seroconvert at Month 7 to a vaccine HPV type. Two of those who received the vaccine did not seroconvert to any vaccine HPV type, and two others at the same site who received placebo, had very high anti-HPV antibody levels of the vaccine types. There was concern that labels for the two vaccines were accidentally switched with the two who received placebo and that accounted for the discrepancy (N. B. Miller, 2006). Overall, 18 subjects who were in the per protocol population who received the placebo were found to be seropositive to at least one vaccine HPV type at four weeks post dose three (month 7). Merck postulates that this could be due to issues around assay specificity, sample mislabeling, or failure to identify receipt of incorrect study material due to third party blinding. Dr. Miller the primary reviewer at the FDA commented that “there were 4 placebo recipients who may have incorrectly received vaccine (based on the levels of antibodies noted). 7 of the other subjects became seropositive to only one vaccine HPV type potentially were exposed to natural HPV infection with one of the vaccine HPV type (HPV 16). Seven others became seropositive to 2 or 3 of the vaccine HPV types” (N. B. Miller, 2006, p. 315).

The safety results for this study showed that there were a statistically higher proportion of adverse events in the vaccine group (5.0%) compared with the placebo group (0.7%) (N. B. Miller, 2006). There were five incidences of serious adverse events occurring in the vaccine groups within 14 days of injection; there were none in the placebo group. These serious adverse events included anemia and dysfunctional uterine bleeding, appendicitis, acute renal failure following surgery for a broken finger, and infected and painful toe. Three subjects in the vaccine group discontinued their participation in the study due to adverse events, which included the individual who went



into renal failure, one girl with severe swelling at the injection site, and one male with injection site pain (N. B. Miller, 2006). In each group, girls reported a higher number of adverse events than the boys. Significantly higher proportions of vaccine recipients reported injection site erythema, pain, and swelling as compared to placebo recipients (N. B. Miller, 2006). The injection site adverse events were reported more after the 1<sup>st</sup> dose than the 2<sup>nd</sup> or 3<sup>rd</sup> doses. The most common systemic adverse events occurring within 15 days of vaccination were headache, fever, and sore throat. In terms of immunogenicity, this trial concluded that the vaccine was immunogenic in both the girls and boys of this age group (N. B. Miller, 2006).

Two articles were published that discussed a combined analysis of the clinical trials to assess the effect of the vaccine. One article which was written by the FUTURE II study group and published in *The Lancet* looked at a combined analysis of four of the clinical trials, protocols 005, 007, 013, and 015 (The Future II Study Group, 2007). The other article which was written by Dr. Eliav Barr and colleagues, was published in the *American Journal of Obstetrics and Gynecology* and looked at a combined analysis of five of the clinical trials, protocols 005, 007, 013, 015, and 016 (Barr et al., 2008).

The article written by the FUTURE II study group restated the rationale for the use of CIN 2 or 3 and AIS as the end points for the studies as these are the immediate precursors to invasive cancer. It also restated that the studies were designed by Merck in collaboration with external investigators and an external safety and data monitoring board. Merck collated the data, monitored the study, did the statistical analysis, and coordinated the writing of the manuscript with all of the authors (The Future II Study Group, 2007). The authors were actively involved in the collection, analysis, and

interpretation of the data and the corresponding author had full access to the data and accepted full responsibility for the contents of the manuscripts and the decision to submit the article for publication (The Future II Study Group, 2007).

The participants were enrolled regardless of baseline HPV status or pap test results, so that the trial would more accurately reflect the efficacy and safety of the vaccine in the general population including in women who may already be infected with one or more of the vaccine HPV types (The Future II Study Group, 2007). Despite the inclusion of all women, the primary efficacy analyses were done in women who were naïve to the relevant HPV types before vaccination. Supplementary analyses were done to assess the effect of the vaccine on the general study population. The analysis done for this article was part of the application for vaccine licensure submitted to the FDA and approved after a priority review on June 8, 2006 (The Future II Study Group, 2007).

This article combined the four trials to look at a total of 20, 583 women who were enrolled and randomized into one of those four trials. Eligible were healthy women who were not pregnant, had no report of a previous abnormal pap smear, and had a lifetime history of less than four to five sex partners (The Future II Study Group, 2007). To perform their analysis, the authors “did an exact test of the homogeneity in relative risks between the four studies before the data were combined for an overall estimate of vaccine efficacy. Homogeneity between the studies allowed the common relative risk and hence the common vaccine efficacy to be estimated with an exact stratified approach” (The Future II Study Group, 2007, p. 1863). The primary efficacy hypothesis was that the administration of the vaccine would reduce the incidence of HPV 16 or 18 related CIN grades 2 or 3 or worse compared with placebo (The Future II Study Group, 2007).

The results from this article showed that the participants were followed for a mean of 3 years and in the type specific per protocol populations, 85 women developed histological confirmed HPV 16 or 18 related CIN 2 or 3 or AIS in the placebo group versus one case of HPV 16 related CIN 3 in the vaccine group. The authors noted that the women from the vaccine group had tested positive to HPV 52 at baseline and at the time of diagnosis and treatment as well as for HPV 16 at the time of diagnosis (The Future II Study Group, 2007). Vaccine efficacy for HPV 16 or 18 related CIN 2 or 3 or AIS for the unrestricted susceptible population, which included participants who became infected with HPV 16 or 18 before or within one month after receiving all three injections, was 98%. For the per protocol it was 98% and for the intention to treat population, it was 44% (The Future II Study Group, 2007). There was no clear evidence of protection against HPV 16 or 18 related disease in women who were positive by polymerase chain reaction at baseline. The findings supported that the vaccine is most efficacious as a prophylactic and does not protect against strains already present at the time of vaccination (The Future II Study Group, 2007). The vaccine showed efficacy with respect to HPV 16 and 18 related lesions that might progress to invasive cancer thus potentially reducing the incidence of those cancers (The Future II Study Group, 2007). In terms of populations to vaccinate, the authors state that the results show that there is strong evidence that the HPV vaccine should be targeted to adolescents before or immediately after sexual debut, which would likely reduce their overall risk for development of cervical cancer. Their data also suggested that vaccination of sexually active women provided benefit against HPV 16 and HPV 18 related high grade cervical

disease, though the benefits of the vaccine diminished as the numbers of lifetime sexual partners increases (The Future II Study Group, 2007).

The second article by Dr Eliav Barr and colleagues discussed the role that the HPV vaccine can play in the population in reducing the burden of HPV 6, 11, 16, and 18 related diseases. Ideally females should receive the vaccine prior to sexual debut, and with the median age of sexual debut in the US being 15 years of age, the ideal vaccination period would be younger than 15 years old (Barr et al., 2008). The effectiveness of catch up vaccinations in the 16-25 year age group was less clear as that group was likely to have already been exposed to and possibly contracted one or more of the vaccine HPV types. However, the authors found that 16-25 year old women in North America remained naïve to the four HPV types in the first 5-10 years after sexual debut. The evaluations done in this article were meant to help make informed policy decisions regarding this vaccine (Barr et al., 2008).

A total of 21, 954 women from the five studies were included in the evaluation for this article. The end points looked at were: the combined incidence of CIN 2 or 3 and AIS; CIN of any grade or AIS; and genital lesions including genital warts, VIN 1-3, and VaIN 1-3 (Barr et al., 2008). To perform the analysis, homogeneity of vaccine efficacy was assessed before data from the studies were combined. Women were enrolled into the study regardless of baseline HPV status, but the prophylactic efficacy analyses were conducted in an unrestricted susceptible population, which included subjects who were sero-negative and negative by polymerase chain reaction to the relevant HPV types at day one (Barr et al., 2008). An intention to treat population, which included all participants regardless of HPV status and who received at least one dose of the vaccine

and who had one visit after enrollment was analyzed to estimate the population impact of the vaccine (Barr et al., 2008).

The article stated that the results of the trials showed that the vaccine was observed to be highly effective in the prevention of cervical, vulvar, and vaginal precancers and genital warts that are caused by the vaccine HPV types. However, there was no evidence of protection from disease that was caused by the vaccine HPV types which the subject tested positive for before vaccination (Barr et al., 2008). As the vaccine covers four HPV types, women who are positive to one or more of the vaccine types can still be protected against the types for which she is naïve at the time of vaccination. Women who were positive to all four types received little benefit from the vaccination (Barr et al., 2008). Based on the analysis done, the authors concluded that vaccination before the age of 15 was most beneficial, and a catch up vaccination for sexually active 16-25 years old resulted “in substantial reductions in the burden of clinical HPV disease” (Barr et al., 2008, p. 261.e9).

In 2007, an article was published in the *Canadian Medical Association Journal* by Lisa Rambout and colleagues that performed a systematic review of the evidence from six randomized controlled trials of the HPV vaccine including monovalent and quadrivalent vaccines (Rambout et al., 2007). The study characteristics for this review were a total of 40, 323 women ranging in age from 15-25 years old who enrolled in the six studies. The greatest number of lifetime sexual partners was six, the women had to use contraception, and the majority of women had not had a prior abnormal pap smear. The authors also looked at the data from the per protocol population and the intention to

treat population; descriptions of each of these groups was discussed previously in this section (Rambout et al., 2007).

Their review concluded that HPV vaccination among women naïve to the vaccine HPV types is highly efficacious in preventing infection with the vaccine HPV type specific infections including precancerous cervical disease. This was particularly so among young women aged 15-25 years who received all three doses and had not had more than 6 lifetime sexual partners (Rambout et al., 2007). The per protocol analysis more accurately reflected the estimation of the effect of vaccinating young girls before they become sexually active. The intention to treat analysis provided a more accurate estimate of the effect on a more “heterogeneous and potentially less compliant populations” (Rambout et al., 2007, p. 475).

The following section discusses the efficacy of the vaccine. Included are articles that have been published regarding the efficacy of the vaccine, information from the two of the primary meetings about the recommendations for Gardasil and its use; the Advisory Committee on Immunization Practices (ACIP) and the Vaccines and Related Biological Products Advisory Committee Meeting (VRBPAC). Quotes from interviewees are also included where relevant.

### *Efficacy*

Dr. Eliav Barr, the head of Merck’s HPV vaccine clinical program presented the safety and efficacy findings for Gardasil at the Advisory Committee on Immunization Practices (ACIP) meeting in June 2006 as well as at the Vaccines and Related Biological Products Advisory Committee Meeting (VRBPAC) in May 2006. At the VRBPAC

meeting, Dr. Barr discussed two kinds of efficacy; prophylactic, which is the primary basis for licensure and addressed the impact of Gardasil to HPV naïve subjects, and population impact analyses that evaluated the efficacy of Gardasil in the overall incidences of HPV disease regardless of whether the individual was naïve to all HPV types at the time of vaccination. Since the vaccine is to be given to females without prior screening of HPV, the subjects were enrolled regardless of baseline HPV status. The design of the clinical trials was based on recommendations made by the FDA's Vaccines and Related Biologics Advisory Committee (VRBPAC) and the World Health Organization (Bryan, 2007; Pratt et al., 2001; Rambout et al., 2007; VRBPAC, May 18, 2006).

The evaluation of the vaccine was two-fold. The primary evaluation was focused on efficacy in subjects who at baseline were HPV-naïve. The secondary evaluation focused on the general impact of the vaccine regardless of baseline status. The endpoints for the studies of Gardasil were: cervical, vulvar, and vaginal cancers via surrogates; the overall incidence of cervical intraepithelial neoplasia (CIN) of any grade or adenocarcinoma *in situ* (AIS); and external genital lesions caused by HPV types 6, 11, 16, or 18. Immunobridging studies were also conducted as the vaccine is administered to pre-adolescent girls. The immunobridging studies were used because while impact studies of Gardasil could be conducted on pre-adolescents, efficacy studies would not be feasible on this population due to the difficulty in performing genital sampling. The immunobridging studies would therefore be used to demonstrate that anti-HPV levels induced in females 9-15 were comparable to those observed in the older populations where efficacy was demonstrated. According to the FDA, the overall efficacy rates of

Gardasil in preventing clinical HPV disease are: 100% effective against HPV 16/18-related cervical cancer by CIN 2/3 and AIS; 100% effective against HPV 16/18-related vulvar and vaginal cancers by precancerous lesions; 95% effective against HPV 6/11/16/18-related CIN or AIS; 99% effective against HPV 6/11/16/18-related external genital lesions (FDA, 2006).

Gardasil is most effective when given before exposure to infection with HPV. Gardasil is “immunogenic, it induces an immune response that's many-fold higher than natural infection and it has an excellent safety profile” (FDA, 2006, p. 15). The efficacy of Gardasil greatly depends on sexual activity and exposure to HPV, and is best used prior to any sexual activity and thus exposure to HPV (CDC, 2007). This was concurred by a Merck researcher,

It was shown that women needed to get all three shots in order to be protected. Some women in the clinical study encountered the virus after the first month and before completing the entire regimen – those women were not protected. The vaccine must be given to girls before they are sexually active. The problem is who is going to decide when a child is sexually active, so instead of trying to figure out when a child is sexually active, it is better to just have the children get vaccinated when they are still young. That way you can be sure of protection (Interview #3).

Gardasil does not prevent against an HPV type present at the time of vaccination, but still protects against the other HPV vaccine types. Merck's data show that efficacy in subjects already exposed to “the relevant HPV types” was -44.6% (VRBPAC, May 18, 2006). At five years follow up for one of the trials, protocol 007, a phase IIb quadrivalent dose ranging study and long-term efficacy evaluation, the prophylactic efficacy for Gardasil was high and no breakthroughs due to waning immunity were documented (CDC, 2007; VRBPAC, May 18, 2006). Merck did not feel that a booster would be needed based on the five year data, though it remained unknown if a booster would be



needed at some point (CDC, 2006, p.12; 2007; N. B. Miller, 2006). According to Merck's Dr. Brill Edwards, "efficacy was durable through at least 2.5 years post vaccination with respect to infection and disease caused by HPV6, HPV 11, and HPV 18, and at least 3.5 years post vaccination with respect to infection and disease caused by HPV 16. Because these subjects completed their vaccinations in 2003, the longer-term duration of efficacy of the vaccine will be known well in advance of the time needed to implement booster vaccinations in the general population (if such booster are required)" (Brill-Edwards, 2006). The need for a booster did not change the CDC's recommendation for this vaccine, though they did caution that it might change the cost effectiveness of the vaccine (CDC, 2007). Based on the current trial results, Gardasil should be very effective in preventing about 70% of cervical cancers.

To examine immune memory, Merck conducted an immune memory evaluation to determine whether Gardasil could "create the kind of memory that's a hall mark of long-term protected efficacy" (VRBPAC, May 18, 2006, p. 77). A fourth dose – a booster – was given at year five "among women who received Gardasil...to challenge whether we could demonstrate immune memory. And what you see can see is that anti-HPV responses for 16, 18, 6, and 11 was the same, much, much higher, even at one week and one month post dose – post fourth dose compared to the month seven results. So, we have very high boostability, long term efficacy through five years and obviously, a generation of robust immune memory" (VRBPAC, May 18, 2006, p. 77-78).

According to Merck's trial data, there were not any break-through infections due to waning immunity. While Merck was able to demonstrate that efficacy is associated with the development of high titer anti-HPV responses, they were unable to define a

minimum anti-HPV level that protected boys, girls, and women against infection and disease with HPV (VRBPAC, May 18, 2006). To fully evaluate efficacy, Merck evaluated for break through infections. The longest duration of follow up was in protocol 005, which was with the HPV 16 component of Gardasil (VRBPAC, May 18, 2006). In terms of the prophylactic populations at year four, there was 100% efficacy with respect to HPV 16 CIN. Merck was

comparing anti-HPV levels in the Gardasil group to a group of women who had been previously infected with HPV 16, had mounted an immune response to the infection, cleared the infection and what's left at day zero is the marker of that successful clearance, an anti-HPV level. And among the placebo recipients who were -- who met that criterion, this is the anti-HPV levels, very stable over a prolonged period of time...Vaccine induced immune responses were higher and they then reached a very stable plateau through month 48, and the same results were observed for the other types. The other types were actually closer to what we saw with the naturally infected women, but again, with a plateau. So, with 100 percent efficacy at year four and the plateauing of the anti-HPV responses, we're...very confident that this vaccine will...have long lasting immune protection. (VRBPAC, May 18, 2006, pp. 57-58).

In order to evaluate the full spectrum of cervical, vaginal, and vulvar disease in women, women were allowed in the trial with some variation in the management of abnormal pap tests. This allowed Merck to represent the diversity and approaches of physicians inside and out of the United States (VRBPAC, May 18, 2006). The trial population included some women who were infected with at least one HPV type at day one, and therefore some of the women in the clinical trials did develop pre-cancer lesions on their cervix within three years of vaccination, which is just 14% fewer than in the placebo group. Due to the inclusion of these women in the trial, Merck knew that that this was going to happen (VRBPAC, May 18, 2006). This included women who developed pre-cancer lesions caused by any HPV type, not just the types prevented by the vaccine (specifically, HPV types 6, 11, 16, and 18). There are over 40 types of sexually transmitted HPV types, and some of the pre-cancer lesions observed in the study may

have been from any of these types, though there were some women in this study who did develop pre-cancer lesions due to the HPV vaccine types. 27% of the women in the trials were already infected with an HPV type contained in the vaccine at the time of vaccination and the vaccine does not prevent against disease due to an HPV type already present (CDC, 2007).

Merck planned to combine some of the studies together to improve the precision of the efficacy estimates (VRBPAC, May 18, 2006). For the end points that involved all four HPV vaccine types, Merck combined three studies, protocol 005, 013, and 015. For the most important end point, which is HPV 16 and 18 related CIN 2 or 3 or AIS, Merck combined all four of the protocols together to evaluate the results. In the efficacy population, there were approximately 21,000 females with a median age of 20, the majority of which were sexually active. Of this population, 27% was positive to at least one of the four HPV types, meaning that 73% of the population was completely naïve to the four HPV types. Of the 27%, most were positive to only one of the vaccine HPV types, so Merck was able to determine whether the vaccine was efficacious in protecting against the other three in those women (VRBPAC, May 18, 2006). Merck's data was based on vaccination with all three doses. There was high study compliance and approximately 20-30 people who got less than three doses, so Merck did not measure efficacy in that population as there were not enough people (VRBPAC, May 18, 2006).

Merck had very precise and detailed means of analysis to look at all CIN and all genital lesions caused by the four HPV types. Merck trained all of the colposcopists in a precise way so that there was uniformity when taking a biopsy of suspect lesions (VRBPAC, May 18, 2006). The process went as follows

Every area of abnormality was biopsied and placed in a separate container. They were then sent to the central lab and fixed -- and processed and put into paraffin and then each biopsy was cut into 13 sections. The first two and the last two were put on slides, were then H & E stained and were read by the pathology panel. The intermediate pieces were sent to the PCR lab where DNA was extracted and typing was performed (VRBPAC, May 18, 2006, p. 38).

Merck conducted a different analysis for the women who were naïve to the relevant HPV types at baseline, which was about 73%. This allowed for Merck to have a clearer picture of how the vaccine worked in women who were naïve and women who were positive to at least one relevant HPV type at baseline. Since the vaccine is given to both populations, it was important for them to evaluate the vaccine in both instances. The results of the trials were based on the endpoints that were evaluated. The first endpoint is the cervical cancer endpoint; proof of prevention for this endpoint for HPV 16 and 18 used CIN grades 2 or 3 and AIS as the primary endpoint as these are the immediate precursors to cervical cancer (VRBPAC, May 18, 2006). These endpoints were observed in protocol 015, which was the CIN 2/3 efficacy study. In this study, there were 21 cases of HPV 16 and 18 related CIN2/3 or AIS, though this was all in the placebo group, showing 100% efficacy for those naïve to the relevant HPV types at vaccination (VRBPAC, May 18, 2006). Looking at the combined analysis of the phase 2 and 3 trials, there were 53 cases of primary CIN 2/3 and AIS, yet these were also all in the placebo group, again showing 100% efficacy in the population naïve to the relevant HPV types at vaccination. Looking at the broader HPV naïve population, the efficacy was 99%. Focusing just on CIN 3 and AIS, Merck saw 100% efficacy in this population.

The next endpoints that Merck looked at were the precursors to vulvar and vaginal cancer, which are VIN 2/3 and VaIN 2/3. These are rare cancers and these kind

of lesions are relatively uncommon (VRBPAC, May 18, 2006). The analysis for this endpoint was done in the broadest population possible, combining three out of the four trials; protocol 005 was excluded because of its sole focus on cervical disease. For these endpoints, there were 24 cases of HPV 16 and 18 related VIN 2/3 and VaIN 2/3, all of which were in the placebo group, showing 100% efficacy in the population naïve to the relevant HPV types at vaccination (VRBPAC, May 18, 2006). Based on these key endpoints, Merck showed that prophylactic vaccination with Gardasil “was highly effective in preventing cervical, vulvar, and vaginal cancers caused by the two HPV types in the vaccine using pre-specified surrogate markers” (VRBPAC, May 18, 2006, p. 46).

CIN of any grade and AIS were other endpoints that Merck looked at. The primary evaluation for these endpoints was protocol 013, which was designed for the detection of CIN of any grade (VRBPAC, May 18, 2006). There were 37 cases of the primary endpoints, though all were in the placebo group, showing 100% efficacy. There was efficacy for each one of the four HPV types and in the broader population, Merck saw a high efficacy, which was 97%, and in the combined analysis, efficacy was 95% (VRBPAC, May 18, 2006). There were four cases of CIN 1 lesions in the Gardasil group that were detected very early on after the end of the vaccination period, though they were none attributed to breakthroughs due to waning immunity.

The final endpoint reviewed by Dr. Barr at the VRBPAC meeting was the external genital lesion prophylactic efficacy, where the endpoint was the full spectrum of disease caused by the four vaccine types. This included genital warts and other lesions. The primary evaluation was in protocol 013, though Merck did a supplemental analysis in the combined data set, excluding protocol 005 because it did not evaluate genital lesions

(VRBPAC, May 18, 2006). In the per-protocol population, there were 40 cases of lesions in the placebo group (most of which were HPV 6 and 11 related), showing 100% efficacy. Looking at the broader population of external genital lesions, efficacy was 99%; in this population there were 113 cases in the placebo group and one in the Gardasil group. The one case in the Gardasil group was an HPV 6 related condyloma, and occurred shortly after completion of the vaccination regimen and was not due to waning immunity (VRBPAC, May 18, 2006).

There were women in the trial who were positive to one HPV type, but were free of infection with the other three relevant types and Merck also looked to see whether the vaccine was efficacious against the remaining three. The efficacy of the vaccine remained high against the three types that were not present at the time of vaccination (VRBPAC, May 18, 2006).

Dosing was another area that Merck wanted to try to make as realistic as possible. Understanding that it would be difficult to ensure that adolescents were vaccinated according to the exact scheduled recommended – at zero, two, and six months – Merck only required that people in the per-protocol population get vaccinated three times in a one year period (VRBPAC, May 18, 2006). Any kind of dosing regimen of three doses in a year was acceptable.

To evaluate the immunogenicity of the vaccine, Merck looked at a total of 14 genital HPV types, including the 4 vaccine types. The primary evaluation looked at women who were negative to the four vaccine HPV types; the results for the other 10 types were not yet available. As a substitute for the other HPV types, a negative pap test at day one was used. This is not a good substitute, is not as sensitive, and a negative pap

test only excludes 65% of CIN 2/3 and AIS present at day one caused by non-vaccine types (VRBPAC, May 18, 2006). It is also possible that a woman is infected, yet has not yet developed CIN 2/3, something a pap test does not pick up. The best that Merck was able to do at this stage, without the final phase 3 results, is a population of women who were predominantly HPV naïve (VRBPAC, May 18, 2006).

According to the statements made at the VRBPAC meeting, the data to date showed efficacy for at least three and a half years. The immunogenicity studies showed bridging from adults to children and the sentinel cohort allowed Merck to look at the long term efficacy. This is discussed in more detail in the section on post-marketing surveillance. All of this data was needed and used to make public health policy regarding the possibility of boosters if needed (VRBPAC, May 18, 2006).

Many articles were published regarding the efficacy of the Gardasil vaccine. Most of them supported the trial results' data in terms of efficacy, yet the majority of those articles still presented questions regarding the overall efficacy of the vaccine as well as its use and long term outcomes.

One article touted the efficacy of the HPV vaccine and did not really pose any questions regarding the trials or the data, but did support continued trials to assess long term outcomes. An article published in *Gynecologic Oncology* by Kevin Ault, who was also involved in the Gardasil trials and listed as an author or corresponding authors on some of the publications of the trials results. In this article, the author felt that the trials results demonstrated “up to 100% efficacy against persistent HPV and cervical lesion development” (Ault, 2007, p. S28). Using the Hepatitis B vaccine as a model, the author stated that an effective vaccine must be able to induce a strong humoral immune

response, and that the protection induced by the HPV vaccine appeared similar to the immunity induced by the Hepatitis B vaccine (Ault, 2007). The data for the clinical trials only goes out to five years, so the author used a mathematical modeling analysis to attempt to determine the long term antibody response to a three dose regimen for HPV 16 in females 16-23 years old. Using this model, “fitted to serum anti-HPV 16 levels measured over a 48-month period, estimated that in 50% of women anti HPV 16 levels would remain above those induced naturally by HPV infection for 12 years, and above detectable levels (>5.9 mMU/mL) for 32 years. A modified model (with a better data fit) predicted that 99% of women would have almost life-long detectable anti HPV 16 levels” (Ault, 2007, p. S28).

The long term outcomes are still being monitored in the long term efficacy studies that are being carried out in the Nordic countries (which are discussed later in this chapter), and the author believed these are necessary due to the lag time between exposure to HPV and the development of invasive cervical cancer (Ault, 2007). The author still maintained that the results from the phase III trials of the quadrivalent and monovalent HPV vaccine supported claims of efficacy and that the continued long term follow up is prudent to ensure that there is not waning immunity and that the vaccine does induce the strong memory response demonstrated in the trials (Ault, 2007).

An article published in the *Journal of Women's Health* by Kathleen Vetter and Stacie Geller also largely supported the vaccine and the data from the trials (Vetter & Geller, 2007). The authors discussed that the vaccine was shown to be highly effective in women 16-26 years of age and that the data showed “100% efficacy for disease and 88% efficacy for incident infection associated with the four strains” as well as the vaccine



being safe and well tolerated (Vetter & Geller, 2007, p. 1260). They did acknowledge that while no booster is recommended at this time, long term immunity remains unknown. The authors discussed that when modeling for the effect of the vaccine, researchers found that vaccinating girls before age 12 would reduce the incidence of the vaccine HPV types cervical warts and cancer by 78% (Vetter & Geller, 2007)

Since the vaccine only targeted two oncogenic HPV strains, Vetter and Geller felt continued pap smears and HPV testing when appropriate remained critical in cervical cancer prevention (Vetter & Geller, 2007). As the vaccine is prophylactic, the use of pap smears and HPV DNA testing in older women might be the only means for cervical cancer prevention in this group as the vaccine is not recommended for females older than 26 years old. They also believed that to change the course of cervical cancer, broad vaccination coverage must be realized (Vetter & Geller, 2007). In order to do this, Vetter and Geller believed that a comprehensive education program was necessary to elicit demand from the target population. As most of the educational efforts had been funded by the maker of the vaccine, the authors felt that this might make the public less inclined to believe the information as it came from a source that would financially benefit from widespread use of the vaccine. Therefore, they believed educational campaigns must be in the public realm (Vetter & Geller, 2007).

The following articles show support for the vaccine, yet still raise questions regarding the vaccine. An article written by Charlotte Haug and published in the *New England Journal of Medicine* discussed the fact that while the results of the clinical trials are promising, sufficient evidence is still lacking since the real impact of HPV vaccination on cervical cancer will not be observable for decades (Haug, 2008). The

vaccine was licensed in June 2006, yet the first results from the phase III trials were not reported until May 2007. This left the author concerned that while the vaccine was successful in reducing the incidence of precancerous cervical lesions caused by HPV 16 and 18, a number of unanswered questions remained (Haug, 2008). The primary question was what effect this will have on actual cases of cervical cancer and death, particularly how this vaccine will affect other oncogenic strains and whether protecting against these two strains will open the door to other oncogenic strains becoming more significant (Haug, 2008). Additional questions this author had were how the vaccine will affect preadolescent girls since the studies on this population were for immune response, not efficacy, and how will the vaccine affect screening practices since women still need to get regular pap smears even if vaccinated. Additionally, since most HPV infection is cleared by the body, how does the vaccine affect the natural immunity against HPV, and of course how long the vaccine lasts and what kind of booster, if any, will be necessary (Haug, 2008).

An article published by Margaret Stanley in the *British Medical Bulletin* discussed that prevention of infection by the strains of HPV covered by the vaccine are promising considering that efficacy rates for HPV 16 or 18 related CIN 2 or 3 was 99% and 100% for HPV 16 or 18 related AIS and that the vaccine is safe and well tolerated (Stanley, 2008). The author did also acknowledge that the efficacy rates for HPV 16 or 18 related CIN 2 or 3 or AIS in the intention to treat population was 44%. The author discussed the trial results and supported the use of CIN 2 and 3 as the surrogate endpoints for evaluation of efficacy. She agreed that cervical cancer is not an ethical endpoint due

to the long time it takes to develop and the fact that there are interventions available to prevent it (Stanley, 2008).

The author also felt that a number of factors remained (Stanley, 2008). The fact that this is a prophylactic vaccine meant that this vaccine should be targeted to preadolescent girls in the 9-13 year old range (Stanley, 2008). The expected benefits from the vaccine include a reduction in the burden of disease caused by the vaccine HPV types. Since the vaccine only includes two of the oncogenic HPV types, screening has to continue for the foreseeable future. Another factor discussed by the author was the effect of the vaccine in the developing world since that is where 80% of cervical cancer cases occur. The biggest challenge in her view will be the implementation of adolescent immunization programs since no platform for that currently exists (Stanley, 2008). Another factor is whether to immunize males. If herd immunity is to be achieved, then the author believed that boys should be included in immunization programs. However, she stated that in a heterosexual population, the spread of HPV infection can be stopped entirely by complete protection of one sex alone and “dynamic simulation models of HPV transmission show that if high coverage of females can be achieved, there is little to be gained in the additional reduction of cervical cancer by vaccinating males” (Stanley, 2008, p. 70). Overall, the author felt that the HPV vaccine has been shown to be immunogenic and well tolerated, but would like to see an evolution in this vaccine making it less expensive, delivered by a non-injectable method and provide sustained long term protection (Stanley, 2008).

An article published in the *American Journal of Managed Care* by Pamela Ann Hymel also discussed the trial results and the efficacy rates of 100% for the per protocol

population and that the vaccine was relatively well tolerated in clinical trials (Hymel, 2006). Despite this efficacy rate, the author acknowledged that the ultimate goal of preventing cervical cancer is still unknown because of the short trial duration. Long term efficacy trials are needed to fully assess the long term effects, though modeling techniques have predicted high efficacy (Hymel, 2006). The author expressed some concern that Gardasil is approved for use in young girls yet this was not based on clinical efficacy trials in this population. Rather, bridging immunogenicity and safety studies were conducted where efficacy is inferred from immunologic responses on girls ages 9-15 with young women ages 16-26 who had demonstrated efficacy against HPV disease. The duration of the vaccine is also unknown at this time and will be determined by long term follow up (Hymel, 2006).

The cost effectiveness of the vaccine was also discussed by the author. She felt that the true health care costs are unknown at this time since the lack of long term trial data precluded actual assessment of the vaccine's effects on cervical cancer morbidity and mortality (Hymel, 2006). She did discuss how simple estimates to complex mathematical models and cost benefit analyses have produced general consensus "that implementation of HPV vaccine programs with continuation of appropriate screening will significantly reduce the prevalence of precursor lesions and cervical cancer and will be significantly cost-effective" (Hymel, 2006, p. S477). Some concerns expressed in this article were to target vaccination to girls before the onset of sexual activity to receive the most benefit from the vaccine, whether or not males should be vaccinated, to ensure that women continue to receive pap smears, and to ensure that underserved population are given access to this vaccine. Additionally, an education program for the public was

viewed as mandatory for acceptance of the vaccine as is promotion by the medical community. Despite some unanswered questions, the author felt that the vaccine has demonstrated efficacy and is cost effective (Hymel, 2006)

Another article published in the *New England Journal of Medicine* by George Sawaya and Karen Smith-McCune had many of the same concerns (Sawaya & Smith-McCune, 2007). The authors began by stating that the vaccine appeared to be safe and showed “significant efficacy against anogenital and cervical lesions related to vaccine type in women with no evidence of previous exposure to vaccine-specific types” (Sawaya & Smith-McCune, 2007, p. 1991). They did question the use of the CIN 2 surrogate which was used as an endpoint because it is not an irrefutable cancer surrogate and up to 40% of such lesions spontaneously regress. CIN 3 was a more appropriate surrogate endpoint in their view because it has the lowest likelihood of regression and the strongest possibility of becoming invasive (Sawaya & Smith-McCune, 2007). The authors had questions from the FUTURE I trials and the efficacy among all subjects. They stated that “rates of grades 1 to 3 cervical intraepithelial neoplasia or adenocarcinoma in situ per 100 person-years were 4.7 in vaccinated women and 5.9 in unvaccinated women, and efficacy of 20%. Analyses by lesion type indicate that this reduction was largely attributable to a lower rate of grade 1 cervical intraepithelial neoplasia in vaccinated women; not efficacy was demonstrable for higher grade disease, but the trial may have lacked adequate power to detect a difference” (Sawaya & Smith-McCune, 2007, p. 1992). This was similar for the FUTURE II study where efficacy for rates of grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ was 17% (Sawaya & Smith-McCune, 2007). Analyzing the results by lesion type, the authors felt that efficacy only appeared to be

significant for grade 2 cervical intraepithelial neoplasia; they did not feel that efficacy was demonstrable for grade 3 cervical intraepithelial neoplasia or adenocarcinoma in situ (Sawaya & Smith-McCune, 2007). They also estimated that 129 women would have to be vaccinated in order to prevent one case of high grade CIN during an average of three years (Sawaya & Smith-McCune, 2007).

An explanation given for the modest efficacy that they discussed was that the vaccine does not have protection against vaccine HPV types already present at the time of vaccination, and that vaccination before the onset of sexual activity seems to be preferable to vaccination once sexual activity has been initiated (Sawaya & Smith-McCune, 2007). Another explanation they offered was that there are at least 15 oncogenic strains of HPV and this vaccine only covers two, HPV 16 and 18. Therefore only targeting two strains may not have a great effect on overall rates of preinvasive lesions (Sawaya & Smith-McCune, 2007). They also discussed that the findings from the FUTURE II study showed that “the contribution of nonvaccine HPV types to overall grade 2 or 3 cervical intraepithelial neoplasia or adenocarcinoma in situ was sizable...the overall disease incidence regardless of HPV type continued to increase, raising the possibility that other oncogenic HPV types eventually filled the biologic niche left behind after elimination of HPV types 16 and 18” (Sawaya & Smith-McCune, 2007, p. 1992). The authors also had concerns about the effect of the vaccine on preadolescent girls as they were not included in efficacy studies. Overall, they felt that the vaccine showed high efficacy against HPV 16 and 18, that the vaccine appears to be safe, and that delaying vaccination would mean that some women might miss an opportunity from protection against these strains. Yet, they do recommend that a cautious approach be

taken with the vaccine as there are still unanswered questions regarding efficacy (Sawaya & Smith-McCune, 2007).

An article published in the *Annals of Medicine* by Jorma Paavonen and Matti Letinen also raised some concerns about the vaccine (Paavonen & Lehtinen, 2008). The authors stated that the clinical trials showed that the vaccine is almost 100% effective in preventing infection and high grade pre-cancer associated with vaccine HPV types and that the vaccine appeared to be safe, well tolerated, and highly immunogenic when given in three doses within six months. The efficacy after 3 years in women who were not previously infected with HPV 16 or 18 was 98% (Paavonen & Lehtinen, 2008). The authors were concerned that the vaccine efficacy was 44% in the intention to treat population including all women with or without previous infection, and the vaccine efficacy against all high grade cervical lesions (CIN 2 or 3) regardless of causal HPV type was 17% (Paavonen & Lehtinen, 2008). For the endpoint of vulvar or vaginal lesions (VIN 2 or 3, VaIN 2 or 3), the authors were encouraged by the efficacy rate of 100%, though they felt similar concern that the efficacy rate in the intention to treat population was 71% and 49% irrespective of whether or not HPV DNA had been detected (Paavonen & Lehtinen, 2008).

The authors were concerned about the population impact of the vaccine since it is prophylactic and the efficacy therefore would be much lower for those already sexually active and exposed to HPV (Paavonen & Lehtinen, 2008). They felt that this made it difficult to infer the effectiveness of the vaccine as well as the role of non vaccine HPV types in the overall rates of pre-cancerous lesions. The authors agreed with Sawaya and Smith-McCune that CIN 2 was not a strong surrogate end point because its regression

rate is up to 40% (Paavonen & Lehtinen, 2008). They felt more comfortable with CIN 3 as a surrogate end point because spontaneous regression is less likely. They felt it was important to “understand that both CIN 2 and CIN 3 trigger treatment in clinical practice” (Paavonen & Lehtinen, 2008, p. 165).

The authors did have questions and concerns raised by the vaccine efficacy trials. The first was that not all cervical and vaginal cancers are caused by HPV 16 and 18 leaving women vulnerable to the other oncogenic HPV types. Second, the prophylactic nature of the vaccine makes it necessary to vaccinate women before they are infected with these HPV types in order to receive the full benefit of the vaccine. This makes preadolescents the primary target population. Third, they felt that more cost effectiveness studies are needed for the secondary target population which includes older females up to 26 years of age who have had their sexual debut. The authors felt that resources should not be diverted from the primary target group. Fourth, they questioned whether males should also be included in vaccination. They felt that a gender specific vaccine against a sexually transmitted infection was not necessarily a good idea and the “ethics of a gender-specific vaccination policy is a difficult concept” (Paavonen & Lehtinen, 2008, p. 165). Finally, the authors wondered what the effect on actual rates of cervical cancer morbidity and mortality would be, and thought it might be possible, though unlikely, that non vaccine HPV types might emerge as important oncogenic high risk HPV types. Overall, they felt that the data to date provided sufficient evidence to support policy recommendations for the introduction of the HPV vaccine (Paavonen & Lehtinen, 2008).

An article published by Gerd Gross in *Medical Microbiology and Immunology* stated that while the trials for Gardasil demonstrated 100% efficacy in preventing clinical



disease, questions still remained (Gross, 2007). Since the vaccine is prophylactic, the author agreed with others that to have the greatest public health benefit, the vaccine should be given before exposure to HPV. Therefore, he believed a successful vaccination program should be aimed at preadolescents and stress the importance of vaccination prior to sexual initiation (Gross, 2007). The author did have questions regarding the vaccine. One question was how this vaccine really affects the incidence of cervical cancer mortality since it will be decades before the effect of the vaccine on the actual cases of cervical cancer are known. He agreed with the endpoints of the study as CIN 2 and 3 are precursors to invasive cancer, yet still questioned the effect on actual cases of cervical cancer (Gross, 2007).

The duration of protection was also an issue as the trials only go out to 48 months, so it remains unknown how long people are protected. Along with this is whether the 3 doses are needed and whether 2 doses may provide the same level of immunity as well as whether another adjuvant might prove to prolong protection (Gross, 2007). The author also had questions about whether males should be vaccinated and how that would impact “herd immunity” and the effect that would have on the prevention of genital warts and anal and penile cancer in that population. Finally, the author stated that some data exist that the vaccine could generate cross immunity to other types of HPV and questioned whether this could potentially protect against an even larger number of cervical disease, yet if that cross protection did not occur, then the author believed that the vaccine should eventually include more oncogenic HPV types (Gross, 2007).

An article published in the *Current Opinion in Investigational Drugs* by Archana Monie and colleagues agreed that the trial for Gardasil had been successful in inducing

protection from persistent HPV infection with HPV types 6, 11, 16, and 18. The authors felt that broader protection might possibly be achieved by developing a multivalent vaccine including more HPV genotypes to include the other oncogenic types (Monie, Hung, & Wu, 2007). However, doing so might increase the cost and complexity of the manufacturing process which may decrease the rate of return, particularly since manufacturing the current vaccine is expensive and requires a number of facilities for large scale production and distribution (Monie et al., 2007). The authors also postulated that a different adjuvant might also influence the level and length of the immune response.

The authors did have some concerns about the existing vaccine. They were concerned that the prophylactic nature of the vaccine did nothing to relieve the considerable burden of HPV infections worldwide (Monie et al., 2007). Additionally, it will take decades to understand the impact the vaccine will have on actual rates of cervical cancer “because of the prevalence of a significant population with existing HPV infections and the slow process of carcinogenesis” (Monie et al., 2007, p. 1041). To deal with these issues the authors believed that it is important to continue the development of therapeutic vaccines against HPV, though an ideal vaccine in their view would prevent new infections while treating established HPV infections and HPV associated lesions (Monie et al., 2007).

An editorial published in the *New England Journal of Medicine* by Lindsey Baden and colleagues supported the efficacy claims of the clinical trials, yet also felt that the efficacy of the vaccine was limited by two main factors (Baden, Curfman, Morrissey, & Drazen, 2007). First, not all cervical cancer is caused by HPV 16 and 18, leaving women

unprotected by the remaining oncogenic strains. Second, this is a prophylactic vaccine, so it is necessary to vaccinate young women before they become sexually active and therefore exposed to HPV, something that may prove to be difficult (Baden et al., 2007). Both of these concerns are linked to the unanswered question of how this affects the rates of cervical cancer morbidity and mortality. Additional questions such as whether males should be vaccinated, the durability of immune protection, whether two doses could provide equal protection, and whether the “the potential exists of non-vaccine related strains to emerge as important oncogenic serotypes” were also raised (Baden et al., 2007, p. 1990). While the authors understood the use of CIN 2 and 3 as the surrogate endpoints for the trials, the ultimate outcome of cancer prevention requires long term observation of a large number of treated women (Baden et al., 2007).

Another editorial published in *Pediatric Research* by Paul Krogstad and James Cherry supported the efficacy results from the trials, yet acknowledged that the true efficacy will not be known for decades (Krogstad & Cherry, 2007). The authors felt that there is still much to learn about the vaccine and work to be done to lessen the burden of HPV related disease. They discussed the prophylactic nature of the vaccine and that it offers no benefit to those already infected with the vaccine HPV types. Additionally, they felt it was important that vaccination is not a substitute for routine cervical cancer screening, as well as the fact that the current vaccine strategy of only vaccinating females does not result in herd immunity (Krogstad & Cherry, 2007). Other concerns expressed were that the duration of protection is currently unknown, and that there is the possibility that less common oncogenic HPV types will replace those covered by the vaccine.

Overall, they felt that the current HPV vaccine is an excellent place to start (Krogstad & Cherry, 2007).

An article published in the *Journal of Midwifery and Women's Health* by Nancy Zonfrillo and Barbara Hackley, spoke similarly about the vaccine as the authors previously discussed in this section (Zonfrillo & Hackley, 2008). Overall, they felt that the trials demonstrated strong efficacy in preventing vaccine HPV type cervical, vaginal, and vulvar disease primary in females who were HPV naïve. The efficacy was less robust in females who had HPV infection (Zonfrillo & Hackley, 2008). The authors were concerned that since the vaccine is prophylactic and the efficacy analyses largely focused on participants who were completely naïve to the vaccine HPV types, it may not be a true reflection of efficacy in the total population. Participants who showed evidence of current or prior infection with vaccine related HPV types represented less than 30% of all of the participants in the phase II and II trials and were only included in a subset of efficacy analyses (Zonfrillo & Hackley, 2008).

The differing efficacy rates between the vaccine type HPV naïve females and the general population are not insignificant to the authors. They felt that strongly emphasized the need for females to be fully vaccinated prior to sexual initiation in order for them to receive the maximum benefit of the vaccine (Zonfrillo & Hackley, 2008). The authors felt that the long term efficacy of the vaccine is largely unknown, and therefore it is unclear how durable the protection is and whether a booster is needed. Efficacy studies were not done in girls ages 9-15; they were only included in immunogenicity studies. This led to the presumption that the vaccine had comparable clinical efficacy in younger females, however the authors felt this presumption should be

held with caution until formally studied (Zonfrillo & Hackley, 2008). Additional concerns by the authors include the effect of the vaccine on pregnant women despite the FDA's classification of the vaccine as pregnancy category B, meaning it is safe to use while pregnant. However, the ACIP does not recommend the use of this vaccine during pregnancy due to insufficient data (Zonfrillo & Hackley, 2008). The possibility that decreasing the prevalence of one HPV type may make other oncogenic strains more robust was also mentioned as a concern. They also discussed the variation in HPV prevalence between countries where some regions have higher rates of certain strains of HPV than others. This may affect the effectiveness of the vaccine if the vaccine HPV types are types that are not as prevalent in a certain part of the world where the vaccine is being used. Another concern is that receiving the vaccine would decrease the rates that women accessed pap smear which would remain necessary as infection could still occur with other HPV strains. The final concern expressed by the authors was cost effectiveness of the vaccine and whether and how the high cost of the vaccine would impact its use (Zonfrillo & Hackley, 2008).

Many of my interviewees spoke to some of the efficacy issue raised in these articles. First is the theoretical issue of whether or not protecting against the two oncogenic strains of HPV would open the door to other strains thus making them more potentially harmful, or spoke to the fact that the strains covered by Gardasil are not necessarily the most common in other parts of the world. One physician-researcher who had many unanswered questions, spoke to this point when asked what her thoughts were about the inclusion of strains 6 and 11, which cause genital warts. She stated that

The reason these are all open questions is there are other types and they're not that common in this country but in other parts of the world 6 and 11

aren't necessarily the most common types. So will we see replacement with other types with the results that there's no change in disease? Possibly. I think that some of the early efficacy data from the interim results of the phase III trials suggest that that's happening which is why the efficacy is so much less than what you've predict. We may not be seeing a difference in CIN3 at all. Maybe the drop in 6 and 11 - 16 and 18 CIN3s has been replaced by other types. Don't know, right? (Interview #7)

Another physician researcher also discussed the inclusion of strains 6 and 11. He thought that "it's actually a very good idea. But the reason is that we have many ways to combat cervical cancer in this country, many really well-proven ways, through screening, for example. We have absolutely no ways to prevent genital warts, just none. We have no primary prevention strategy for genital warts" (Interview #8).

Another problem that was discussed was that the vaccine is given preadolescent girls. There was some concern about that particularly since the trials for the younger girls did not include efficacy studies. One physician researcher discussed her concerns, even though she felt that they may just be theoretical concerns at this point. She discussed

The transformation zone, which is the area on the cervix between the squamous and the columnar epithelium - there are two cell types that meet on the cervix. That's a fairly unusual situation... So that junction between the two cell types on the cervix is very wide in young girls and as we undergo puberty and mature it starts to travel up towards the opening of the cervix and then into the canal. So when we vaccinate young girls we're populating this huge area now with memory T cells that are primed to recognize those types of HPV and protect against that and that's good. This theoretical worry that I have is that those T - there are so many more of them because of vaccination than a natural immune response from a normally acquired infection so now we have a whole new situation we've never had before. Many, many more T cells maybe with a much broader antigenic repertoire maybe that can cross-react against types that normally you wouldn't get protection against. I don't know what that's going to do to, again, the infections that come in later from other types stimulating this

new population of T cells and maybe not invoking a protective response but more of an inflammatory response. And there's a lot of literature linking inflammation to cancer. So I'm not sure what's going to happen to these girls as they age and as they then get exposed to the non-vaccine types (Interview #7)

Another researcher who worked on the clinical trials was not concerned about vaccinating this age group. She felt the best age was still younger because "it is well known that the younger you give it, the better the immunological response. The body is more primed at a younger age to make antibodies" (Interview # 5).

The following section addresses the safety of the vaccine as discussed by Merck scientists at the approval meetings for the vaccine, as well as quotes from my interviews. Safety was also discussed in the clinical trial section as part of the description of each of the trials.

### *Safety*

Dr. Eliav Barr from Merck discussed the safety record of Gardasil at the VRBPAC meeting in May 2006. Safety was evaluated in a structured approach that was uniform in all of the studies (VRBPAC, May 18, 2006). Non serious adverse events were collected between day one and day fifteen using vaccine report cards, a process which was done in all of the studies. Serious adverse events were also collected from day one through day fifteen and any serious adverse events that occurred at any time during any of the studies was reported. There was a mandatory worksheet that was completed at every visit to ensure that no serious adverse events went unreported. A medical history was also collected at every visit to capture any event that may not have fit with the pre defined adverse events categories. A data safety monitoring board was used to supervise

the phase III studies (Brill-Edwards, 2006; FDA, 2006; N. B. Miller, 2006; VRBPAC, May 18, 2006).

While over 27,000 subjects were enrolled in the trial, the population that received Gardasil itself was 21,400. Serious adverse events, pregnancy outcomes, and new medical histories were recorded for each of these subjects. For a subset of the population called the “detailed safety population” vaccine report cards were used. Certain sites in protocol 015 used spontaneous reporting rather than the vaccine report cards (VRBPAC, May 18, 2006). In discussing the safety of Gardasil, Dr. Barr explained that there were more subjects in the Gardasil group than the placebo group so the comparisons between the two were done on a percentage basis (VRBPAC, May 18, 2006).

According to Dr. Barr, there were slightly more adverse events in the Gardasil group than the placebo group, due to injection site adverse event experiences, which were generally mild to moderate in intensity and generally short-lived (VRBPAC, May 18, 2006). The incidents of serious adverse events were comparable between the two groups, and those thought to be vaccine related were rare. A few women died and the most common cause of death was a motor vehicle accident. There were very rare discontinuations due to adverse events (VRBPAC, May 18, 2006).

A typical worry for the Merck investigators was allergic reaction. Dr. Barr mentioned that there were seven serious adverse events that were judged by investigators to be possibly, probably, or definitely vaccine related, though at this meeting, he did not go into detail of what these were except to say that there was one broncho-spasm in the Gardasil group and one case of hypersensitivity in the placebo group (VRBPAC, May 18,



2006). Beyond that, Dr. Barr stated that there were a variety of different experiences that women reported. (VRBPAC, May 18, 2006).

In order to evaluate these events, subjects were required to take their temperature four hours after receiving the vaccine and then continued that over the next four days. In the detailed safety population, subjects who received Gardasil had a slightly higher rate of fever, mostly low-grade (VRBPAC, May 18, 2006). The rates were comparable between the two groups when it came to a high grade fever. Looking at the children (9-15 year olds) versus adults (16-26 year olds), there were slightly less adverse events in the children compared to the adults (VRBPAC, May 18, 2006).

Another feature of the safety monitoring of the studies was the focus on pregnancy outcomes since this vaccine is given to women of child bearing potential. In the trials, women were required to undergo urine pregnancy testing because the vaccine had not been tested in pregnant women, so if they tested positive, they were not vaccinated (VRBPAC, May 18, 2006). It was not possible to entirely prevent women already enrolled in the study (who had a negative pregnancy test prior to entering the study) from getting pregnant during the study, so all pregnancy outcomes were carefully evaluated (VRBPAC, May 18, 2006). Women were instructed to use contraception during the trial. Medical histories were taken during pregnancy in all women and outcomes were evaluated in both mother and child through the neonatal period. Infants were followed over the course of the years of the trials because Merck wanted to make sure that anything that was not picked up during the neonatal period could be picked up later on. Included in the evaluations were causes of spontaneous abortions to obtain the reason why this occurred (VRBPAC, May 18, 2006).

The pregnancy outcomes as of November 2005, which were reported at the VRBPAC meeting were based on a total of 1,115 women who had a pregnancy, some of which had multiple pregnancies or twins, meaning there were more pregnancies than there were women with pregnancies (VRBPAC, May 18, 2006). There were approximately 2,000 pregnancies whose outcomes were known. The Data Safety Monitoring Board asked Merck to divide the pregnancies by the onset of the pregnancy and its proximity to vaccination using a 30 day number; estimated onset of pregnancy within 30 days of vaccination or beyond 30 days of vaccination (VRBPAC, May 18, 2006).

Looking at the Gardasil and placebo groups within 30 days of vaccination, there was slightly less spontaneous loss in the Gardasil group compared to the placebo group, and slightly higher live birth rates compared to placebo. Beyond the 30 days, there were comparable rates of spontaneous loss, slightly lower elective terminations, and slightly higher live birth rates (VRBPAC, May 18, 2006). Congenital anomalies between the two groups were also comparable; there were fifteen cases in the Gardasil group versus sixteen cases in the placebo group. When breaking down by proximity to vaccination, there was a difference in the patterns. In the group within 30 days of vaccination, there were five congenital anomalies all in the Gardasil group. These five congenital anomalies were all different and occurred at different times in the woman's pregnancy (VRBPAC, May 18, 2006). Beyond 30 days, there were six fewer anomalies in the Gardasil group compared to the placebo group, but at the VRBPAC meeting, Dr. Barr did not give specific numbers of these anomalies (VRBPAC, May 18, 2006). Based on the Gardasil package insert, there were 10 cases of abnormalities in the Gardasil group and

16 in the placebo group (Merck & Co., 2006). The types of anomalies observed in both of these groups are “generally observed in pregnancies in women aged 16-26”, and Merck’s teratology experts looked at all of the cases and determined that they were highly unlikely to be related to Gardasil (Merck & Co., 2006).

Merck does not know if Gardasil antigens or antibodies are excreted in human milk, though they do say that caution should be exercised when Gardasil is administered to a lactating woman nursing her baby. 995 nursing mothers (500, vaccine, 495, placebo) were given Gardasil or placebo during the trial. Seventeen infants of subjects who received Gardasil and 9 infants of subjects who received placebo experienced a serious adverse event, though Merck’s investigators in the trial did not determine these to be vaccine related (Merck & Co., 2006).

Based on minutes from the ACIP meeting held in June 2006, side effects were reported in the trials, and Gardasil did show slight increases in injection site adverse events than in the placebo group. The rates of serious adverse events were extremely low. The most common adverse events were headache, dysmenorrhea and related symptoms, sore throat, nasopharyngitis and other flu-like symptoms. Based on the data so far, Gardasil has an excellent safety profile; the vaccine contains components that are well known and are understood to be safe and effective. Merck believed that Gardasil would have a strong public health impact (CDC, 2006).

The CDC released a document in June 2007 with answers to some of the most common questions about Gardasil including addressing concerns about the safety of this vaccine (CDC, 2007). They stated that the clinical trials found no increased number of serious adverse events in girls/women who received the vaccine compared with those

who received placebo. Like all vaccines, Gardasil has some side effects, but the Advisory Committee on Immunization Practices (ACIP), which recommends use of vaccines, determined that the benefits of Gardasil outweigh the risks. Since the vaccine has been licensed, the most common reports to the Vaccine Adverse Events Reporting System (VAERS) have been reactions at the site of injection, which was also seen in the clinical trials. There were also some cases of fainting after vaccination (MMWR, 2008). Since the vaccine was licensed, there have been 13 reports of Guillain-Barre Syndrome (GBS) among persons who received Gardasil. Guillain-Barre Syndrome (GBS) occurs at a rate of 1-2/100,000 person per year during the second decade of life, some cases occur coincidentally following vaccination, but not necessarily due to vaccination. Since the vaccine was licensed, there have been three deaths reported among persons who received Gardasil: One involving a pulmonary embolism; one involving myocarditis due to influenza A infection; and one from a blood clot. These deaths are being fully investigated by the CDC. Since more than 5 million doses have been distributed thus far, some deaths occurred coincidentally following vaccination, but not necessarily due to vaccination (CDC, 2007).

Safety was discussed by some of my interviewees. One issue that was brought up was how safety is ensured, particularly in the youngest age groups. Despite the immunogenicity studies that involved children as young as 9, there was still some concern about the long term safety of this vaccine on girls so young and who had not yet gone through puberty. One researcher had concerns about the immunobridging studies and felt that they did not adequately address issues of safety. She said

Immunobridging studies just showed same antibody titers between younger and older girls who received the vaccine. There were no studies

that ever said it was safe to do in infancy - just that it showed the same efficacy and assumed same safety. The primary aim is to show an antibody response - there was nothing done to show it was safe in that age group. This is common in vaccines - in different age groups they are worried about antibody titers, they are not worried about differences in safety. They don't know the difference in safety if the vaccine is given to 12 year olds for HPV

One physician researcher when asked if there were more safety concerns for the girls 9-15 than for older females, she replied,

I think there are theoretical concerns. The transformation zone, which is the area on the cervix between the squamous and the columnar epithelium - there are two cell types that meet on the cervix. That's a fairly unusual situation. We have the same situation in our esophagus going into the stomach, two cell types meet, in the lungs two cell types meet and those are all sites where cancer can occur pretty regularly. So that junction between the two cell types on the cervix is very wide in young girls and as we undergo puberty and mature it starts to travel up towards the opening of the cervix and then into the canal. So a 50-year-old woman, that juncture is way up high and in young girls way out here. So when we vaccinate young girls we're populating this huge area now with memory T cells that are primed to recognize those types of HPV and protect against that and that's good. This theoretical worry that I have is that those T - there are so many more of them because of vaccination than a natural immune response from a normally acquired infection so now we have a whole new situation we've never had before. Many, many more T cells maybe with a much broader antigenic repertoire maybe that can cross-react against types that normally you wouldn't get protection against. I don't know what that's going to do to, again, the infections that come in later from other types stimulating this new population of T cells and maybe not invoking a protective response but more of an inflammatory response. And there's a lot of literature linking inflammation to cancer. So I'm not sure what's going to happen to these girls as they age and as they then get exposed to the non-vaccine types (Interview #7).

She also had safety concerns about the clinical trial results, with one particular incident that troubled her.

The other issue about safety that I'm really concerned about is that there was one vulvar cancer in a 23-year-old woman who got vaccinated and that just doesn't happen. So again it raises the question about whether there's some tweaking of immune response that is really unpredictable and potentially not beneficial but deleterious against other HPV types. This

cancer did not have 6, 11, 16, or 18, so it - that's what you would expect. But it is an HPV-associated cancer so what is it and why did it happen in this 22-year-old? Maybe it's just a fluke, that would be good, but to me it kind of has hints of potential harm that we just don't know yet and that we're setting up a natural history experiment to find out probably.

She was not the only one to mention this case of vulvar cancer. Another physician researcher mentioned this during our interview. He named three concerns he had about the vaccine before seeing it given to large numbers of girls and women. First, he was concerned that

There is one woman in the trial who got the vaccine and she developed vulvar cancer at the age of 22, which is so rare. That usually occurs in women in their seventies and it's 2.2 per 100,000, mainly with women in the older age groups and it's almost unheard of in that age group. So when that occurred that was the sentinel event that made me be very cautious and that's when I said, 'We need to make sure that this is just a one-off very odd chance occurrence before we start doing this to everyone' (Interview #8).

Following this, I asked subsequent interviewees whether there should be concern about this. A member of the HPV working group at the CDC was not concerned about it. Noting that it was a single case, she thought it was "of note but it's not...something that needs to be followed up on but it's not that we're particularly concerned about that one case right now" (Interview #10). A physician researcher was also not concerned because

It's just one case. First of all...only 50% of vulvar cancers are associated with HPV, not 100%. I mean obviously vulvar cancer in a young woman is odd to begin with but it does happen, it's rare. They were very big trials. If there was maybe five cases of vulvar cancer you'd get me concerned but I think one case is totally kind of shooting from the hip when you're talking about a disease that's not 100% associated with HPV. I think one case - I have a very hard time finding it troublesome (Interview #9).

The following section addresses how Merck and the government are continuing to monitor the reported side effects. As vaccination with Gardasil continues, it remained

important to continue monitoring reported side effects and to see which if any are serious and are shown to be causally related to the vaccine.

### *Side Effects - Monitoring*

Before any vaccine is licensed and made available to the American public, the Food and Drug Administration (FDA) must approve it as safe and effective. With the vaccine in general use, the CDC and the FDA worked together to closely monitor the safety of the HPV vaccine (CDC, 2007). One tool that was used in monitoring vaccine safety is the Vaccine Adverse Event Reporting System (VAERS). VAERS serves as an early-warning system to detect problems that may be related to vaccines. It is a national reporting system that accepts and monitors approximately 18,000 reports of adverse events submitted annually by a variety of sources, including healthcare providers, patients and family members. Because of this, VAERS is subject to several limitations including underreporting and incomplete information. CDC and FDA physicians and scientists review all VAERS reports of serious side effects in order to identify potential safety concerns that may need further study. It is important to know that many adverse events reported to VAERS may not be caused by vaccine (J. S. Abramson, 2006; CDC, 2006, 2007).

There have been a total of 8,864 reports filed related to Gardasil (Millspaw, 2008). VAERS reports show that 18 people have died after receiving Gardasil and there have been some other serious adverse events including Guillain-Barre Syndrome. The most commonly reported side effects have been fainting, dizziness, and pain at the injection site. Side effects have also been reported in Australia where Gardasil was

widely being used (Sikora & Bissett, 2007). A scientist at Merck stated “that when given to a lot of people, there are going to be side effects and physicians report to VAERS. Physicians report any effect that is shown after the vaccine, so it may seem like there are a lot, but one cannot be sure if it’s the vaccine or not. There have been some cases there of deaths, but there is no way to know for sure if it’s connected to Gardasil” (Interview # 1). One physician researcher stated, “There will be some side effects, some will be serious and it will kill some people, but you can never prove that number statistically because in general, the vaccine has been proven to be safe. It is difficult to know for sure if it is the result of the vaccine or of something else. Bad things can happen, they just happen in small numbers” (Interview #6). A member of the Advisory Committee on Immunization Practices echoed these sentiments, when he stated that

when vaccinating large numbers of people, there are going to be reactions. The associations are almost meaningless because of the reporting. With the vaccine reporting system, any reaction is reported and there is no real way to know if that was a result of the vaccine or something else. As soon as vaccines come out, side effects are reported. It depends on the age and the issue. There may be an association between the vaccine and what is perceived as a side effect, but that is not the same as causation. There is no way to know if the vaccine caused it (Interview #4)

Another area of monitoring is how Gardasil interacts with other childhood vaccines. Gardasil was only tested with the Hepatitis B vaccine (N. B. Miller, 2006; VRBPAC, May 18, 2006). VAERS reports show that Gardasil and Menactra (the meningitis vaccine) do not react well together and there were 220 cases of adverse events reports from July 2007-March 2008, most commonly fainting, nausea, and dizziness (Millspaw, 2008).



There were side effects reported in the clinical trials. Some of them were mild reactions at the injection site such as redness or swelling (N. B. Miller, 2006). There were also more severe adverse events that in some cases caused the subject to discontinue participation in the study. In protocol 007, there were six cases of serious adverse events, with four in the vaccine group and two in the placebo group. These included one case of renal colic, appendicitis, and two cases each of worsening depression and pyelonephritis. All of these subjects continued their participation in the study. In that same study there were three people who discontinued their participation due to adverse events at the injection site. In the vaccine group, one person experienced swelling at the injection site with flu-like symptoms, and another experienced erythema and severe pain. In the placebo group, one of the subjects that received the 450 mcg dose of the aluminum adjuvant had numbness in her extremities, nausea, and stomach cramps (N. B. Miller, 2006).

Side effects and general reactions to the vaccine were to be expected. Neither the documentation nor the people who I interviewed expressed concern that adverse event experiences after vaccination with Gardasil were severe or out of the ordinary. When asked whether they felt the reported side effects could be attributed to Gardasil, one researcher who worked on the clinical trials and was one of the publishing authors on one of the FUTURE studies said,

local side effects are only things that have shown to be a direct result of the vaccine. The placebo groups...looking at all outcomes, there have been deaths, but that is also a part of life, so have to look to see what are the possibilities that this is connected to vaccine. So, need to look at the cases and see if there is a real connection to the vaccine. People who do not have as much knowledge about the issue, might read it wrong and wrongly attribute this to the vaccine, when it may be unrelated (Interview #5).

The following section discusses the Human Papillomavirus and its connection to cervical cancer.

### *HPV and Cervical Cancer*

The connection between the human papillomavirus and cervical cancer is well established (Brill-Edwards, 2006; Paavonen & Lehtinen, 2008; VRBPAC, May 18, 2006; zur Hausen, Gissman, Steiner, Dippold, & Dreger, 1975). In the 1970's Dr. Harald zur Hausen established the link between HPV and cervical cancer (zur Hausen et al., 1975). The Nobel Prize in Medicine was awarded to Dr. zur Hausen in 2008 for his discovery (Altman, 2008). One physician researcher discussed this discovery and how it paved the way for the HPV vaccine in the following quote,

...in the Seventies they thought it might be a virus and then they thought it was actually herpes simplex virus. Then they got a little more information and they honed in on HPV as being the likely source. And, as you probably know, this year the Nobel Prize in Medicine was awarded to Harold zur Hausen. He is the one who made this link between the Seventies and the present between HPV and cancers in general. So this whole story is kind of a Nobel Prize-winning story that has really strong, strong epidemiologic links implicating HPV as being the causative agent in cervical cancer. Then, of course, in this decade we started getting good HPV testing – “good” meaning it seems to – we can detect the virus to some degree of accuracy and then find women who have pre-cancerous lesions, etc. So, of course, the next step is – the most obvious step is this is great because we know how to avoid viral infections through vaccination. So it's this totally synthesis of an incredible amount of gratuitous information to some degree to come up with kind of a novel strategy to try to avert cancer through vaccination (Interview #8)

Dr. Brill-Edwards and Dr. Eliav Barr each discussed both HPV and cervical cancer, reinforcing the fact that HPV is the most common sexually transmitted infection world-wide and is the cause of cervical cancer (FDA, 2006). In Americans, the lifetime risk for infection with at least one strain of HPV is 50%, and the lifetime risk for adults for developing Cervical Intraepithelial Neoplasia (CIN) or genital warts is 25% and >10% respectively (VRBPAC, May 18, 2006). A smaller portion of women develop CIN 2 or 3 or adenocarcinoma in situ (AIS). Without any cervical cancer screening, the lifetime risk of developing cervical cancer is roughly 1/30. Pap testing and regular screening can drop risk down to roughly 1/120 (VRBPAC, May 18, 2006).

Dr. Barr also went on to discuss HPV's culpability in other cancers as well as other areas of morbidity. As mentioned, HPV infection is necessary for the development of cervical cancer; it is also a contributor to cancers in the genital tract for both men and women as well as certain head and neck cancers (VRBPAC, May 18, 2006). HPV types 16 and 18 are thought to be responsible for more than 50% of cervical cancer, but more than 15 different types of HPV are considered to be oncogenic and are associated with the development of cervical cancer (N. B. Miller, 2006).

In females, HPV can cause vulvar and vaginal cancers, which accounts for roughly 3500 cases a year and while these forms of cancer tend to occur in women older than 50, the incidences of these cancers have increased in women younger than 50 (VRBPAC, May 18, 2006). Dr. Barr associated this increase to an overall increase in HPV infection (VRBPAC, May 18, 2006). HPV also causes cancers in men, generally in the head and neck, anal canal, and the penis, affecting approximately 10,000 American men a year. Men are also the primary means of transmission of HPV to women, and

infection in men is generally the cause of the acquisition of HPV in women (VRBPAC, May 18, 2006). HPV can also cause benign tumors including genital warts, and while not malignant do cause large amounts of morbidity, can be psychologically damaging to the young people who get them, and do increase health care costs (VRBPAC, May 18, 2006). Another outcome of infection with HPV is recurrent respiratory papillomatosis, which affects the vocal folds in the larynx, which causes hoarseness and airway obstruction, and requires regular surgery to treat (VRBPAC, May 18, 2006).

#### *Summary of Aim I*

The first aim of this study followed the trajectory of Gardasil to understand the origins of the vaccine and its development. This information laid the foundation for the project and was necessary to understanding the rest of the story. This aim included looking at the clinical trials, the safety and efficacy of Gardasil, and the background, incidence and prevalence of HPV and HPV related diseases.

Gardasil was approved by the Food and Drug Administration on June 8, 2006 through an expedited review. This process is also referred to as fast-tracking and shortens the review time from a minimum of 12 months to six months. This process is generally reserved for novel innovations that address life threatening conditions or meet unmet medical needs. This shortens the time that the public would otherwise have to wait for treatments, though one potential problem can be that not enough time has been allotted to ensure safety and efficacy of the product. Drugs have been pulled off the market due to serious adverse events or have had black box warnings attached to them, so it is vital to ensure that any product that comes to market has a solid safety profile.

Gardasil does meet part of the criteria for an expedited review in that it is novel as it is the first vaccine to address the issue of cancer, specifically cervical cancer. While this is an important step in women's health, it is also important to understand that cervical cancer is a slowly progressing disease that has been mitigated to a large extent by preventive care in the form of pap smears. Pap smears have consistently lowered the rates of cervical cancer in this country (eHealth MD, 2004).

The technology for Gardasil was obtained by Merck in 1995 from an Australian biotechnology company called CSL. Australian researchers developed the technology that led to the development of the vaccine. They had an existing research agreement with CSL, and CSL negotiated the deal with Merck. Merck immediately began development on the vaccine and the Gardasil name was licensed to Merck in 1996. In order to begin the process with the FDA, Merck submitted an investigational new drug application (IND) to the FDA in 1997, the same year that their phase 1 trials began. Phase I trials are the preliminary trials that test for the safety and tolerability of the vaccine and determine what type of immune response the vaccine elicits.

The clinical trial program ran from 1997-2005. It has been studied in over 27,000 subjects in 33 countries on five continents in 12 separate trials (FDA, 2006; VRBPAC, May 18, 2006). Women were enrolled in the clinical trials regardless of baseline HPV status, though they were tested at baseline to determine their status and upon analysis were broken out into two groups, the per protocol population and the modified intention to treat population (MITT). The per protocol population were the ideal subjects in that they had not been exposed to the relevant strains of HPV and had not had an abnormal pap smear. The modified intention to treat population was a more accurate reflection of

the general population and those in that group may have been exposed to one or more of the relevant strains of HPV and/or may have had a previous abnormal pap smear. This allowed Merck to obtain a more accurate picture of how the vaccine affected those who had not been exposed to the relevant HPV types and those who had. All females were randomized into the trials because there was an understanding that the vaccine would be administered to females without prescreening, so there would be no definitive way to know whether some of the females being vaccinated had been exposed to HPV. This allowed Merck to get information on how this vaccine would work in the general population. Enrolling females in this fashion was also a recommendation that came out of a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held in 2001, where the committee felt strongly that women who were infected at baseline be included in the trials to evaluate the safety of the vaccine in this population (VRBPAC, May 18, 2006, November 28-29, 2001). The initial trials for Gardasil began in 1997 and looked specifically at safety and immunogenicity - whether the vaccine elicited an immune response.

The efficacy trials began in 2001, and those trials measured whether or not the vaccine met the clinical endpoints that were set, which were that Gardasil protected against the development of high grade cervical dysplasia caused by HPV 16 and 18. The clinical endpoints are an interesting aspect of this story and tie into the label claim that Merck made about Gardasil. Merck wanted to make the claim that Gardasil protected against cervical cancer though the FDA was initially hesitant to allow that. According to a Merck scientist, Merck felt it was important to make the label claim that Gardasil protected against cervical cancer because if not, they might risk lower sales and therefore

lower profits. The claim that it protected against cervical cancer would not only make it a more attractive vaccine, but would position it as a breakthrough in the area of vaccines as it would be the only one to address the issue of cancer (Interview # 1).

During a meeting with an advisory committee at the FDA in 2001, the clinical endpoints that would serve as the basis for licensure of Gardasil were discussed. Merck made the case that studying cancer itself was not feasible because cervical cancer can take decades to develop and allowing women to develop cancer would be unethical when there are treatments out there to manage precancerous lesions. Even though cervical cancer can be traced to HPV infection, most HPV infections clear on their own. Since cervical cancer begins with cervical dysplasia, showing that Gardasil could prevent the development of high grade cervical dysplasia, specifically cervical intraepithelial neoplasia (CIN) grades 2 and 3 caused by HPV strains 16 and 18, would show that Gardasil could protect against cervical cancer. Theoretically, if the high grades of cervical intraepithelial neoplasia could not develop, then neither could cervical cancer. This allowed Merck to make the claim that Gardasil protects against cervical cancer, when it actually protects against strains of the Human Papillomavirus that lead to CIN, which can eventually lead to cervical cancer if left unchecked and untreated. It is still possible for women who are vaccinated with Gardasil to develop cervical cancer, so it remains important that women continue to receive regular pap smears even after being vaccinated. This is something that the Gardasil ads are clear about. The real impact on actual cases of cervical cancer will not be known for decades since cervical cancer takes decades to develop.

## *Aim II: Approval of the Gardasil Vaccine*

The previous discussion spoke to aim 1 of this study and covered the process of the development and testing of the Gardasil vaccine covering the areas of the clinical trials, effectiveness, and side effects. The following section addresses the issues associated with aim 2 of this study, which describes the process of the approval of Gardasil. This includes an overview of the core meetings that took place between Merck and the FDA and CDC to discuss the recommendations for Gardasil's use. The following section also addresses the issues of the expedited review process, the cost of the vaccine and the post marketing surveillance plans for Gardasil to ensure continued safety of the vaccine.

The approval process for Gardasil began with meetings between Merck and the Food and Drug Administration (FDA), and included meeting with the CDC's HPV vaccine working group, the Advisory Committee on Immunization Practices (ACIP). The two agencies work in tandem where the FDA determines whether or not a drug or vaccine can be approved for use, and the CDC sets the guidelines for use. Throughout the process, Merck submitted data to the FDA, which was how determinations such as whether to fast track the product were made. The ACIP working group received data from Merck, when approval was imminent and guidelines for use needed to be set.

Following the submission of its data to the FDA, a meeting was held on May 18, 2006 to discuss the data. The meeting was the Vaccines and Related Biological Products Advisory Committee meeting, referred to as VRBPAC. This committee is made up of people from the FDA's Center for Biologics Evaluation and Research. After the FDA



approved Gardasil in early June 2006, the ACIP met later that month to discuss the guidelines for its use. These two meetings were the two necessary steps to getting Gardasil into the market place and into widespread use. The following section discusses the steps taken for the approval of Gardasil as well as related issues such as cost effectiveness, plans for post marketing surveillance, and how the decisions was made to fast track the review of Gardasil.

### *Regulatory History*

In order to begin the process with the FDA, Merck submitted an investigational new drug application (IND) to the FDA in 1997. An IND is required for any new drug or vaccine that is being developed. Dr. Nancy Miller of the FDA discussed the regulatory history of Gardasil at the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting in May 2006. The first IND for the monovalent HPV 11 vaccine was submitted in 1997, with the other INDs for the monovalent product HPV 16 and HPV 18 following shortly thereafter (VRBPAC, May 18, 2006). The IND for Gardasil became effective on May 17, 2000 (Axelrod, May 7, 2007; VRBPAC, May 18, 2006). In November of 2001, VRBPAC held a meeting to discuss the endpoints that would be appropriate for phase III development of a preventive HPV vaccine (VRBPAC, November 28-29, 2001). In 2002, the product development program was granted fast-track status and phase III trials began. The FDA met in May of 2005 to discuss the Biologics License Application (BLA), and agreed to allow the submission of the BLA for Gardasil as well as grant it a priority review (Axelrod, May 7, 2007; VRBPAC, May 18, 2006). The BLA application for Gardasil was submitted on December 7, 2005, which

included phase III study data; that also served as the start of the expedited review. Overall, approximately 60,000 pages of clinical review materials were submitted electronically for review, and the review was completed in a six-month regulatory time frame. Standard product reviews take a minimum of a year. The application for Gardasil was approved on June 8, 2006 (Axelrod, May 7, 2007).

*Expedited Review (Fast-Tracking)*

The Gardasil vaccine received a priority review (also referred to as an expedited review or as fast-tracking) because of its potential to meet an unmet medical need (FDA, 2006). The decision to grant Gardasil an expedited review was made in 2002 after the FDA received preliminary data from the clinical trials. The expedited review actually began in May of 2005. One researcher at Merck discussed the issue of fast tracking and why it would be used in this case. He said that “one reason why a drug would get fast-tracked would be because if FDA thinks that you have gotten to something first, they will do an accelerated review. If they think you have something really innovative and lifesaving that’s not out there yet, then ‘In a sense, it’s a race to save lives’. They were able to get approval in 6 months time, instead of the usual 12+ months. The FDA is its own body, there is no congressional input, so if they don’t approve it, there is no going over them” (Interview #1).

*Vaccines and Related Biological Products Advisory Committee and Advisory Committee on Immunization Practices Meetings*

Following the submission of all of the data and the review of that data, formal meetings began with the FDA and CDC to approve Gardasil and set the guidelines for its use. The first of the two core meetings was with The Vaccines and Related Biological Products Advisory Committee (VRBPAC), through the Center for Biologics Evaluation, which is part of the FDA. They held a meeting on May 18, 2006, which involved a discussion regarding the safety and efficacy of the Gardasil vaccine, and culminating in the recommendation for its use. This was a public meeting and in attendance were members of the advisory committee, six FDA staff members, speakers from various professional organizations, and seven sponsor representatives including two of Merck's senior directors; Dr. Eliav Barr, Senior Director, Vaccines/Biologics Clinical Research, and Dr. Patrick Brill-Edwards, Director, Worldwide vaccines Regulatory Affairs. This meeting was held to discuss and make recommendations on the safety and efficacy of the human papillomavirus vaccine, Gardasil (FDA, 2006; VRBPAC, May 18, 2006).

The meeting opened with introductions, and Dr. Brill Edwards gave a brief overview of Gardasil, its status in the review process, and some general results (Brill-Edwards, 2006). His statement was followed by Dr. Barr who spoke at length about the clinical trial and the safety and efficacy of the vaccine. There was a question and answer session open to the committee members, which was a chance to have Dr. Barr clarify anything said during his statement. Dr. Nancy Miller of the FDA, who was the primary author of the clinical review for Gardasil also spoke at the meeting, providing the FDA review of the vaccine. Information from both of these meetings is discussed throughout this chapter in the relevant sections (VRBPAC, May 18, 2006).

Following the approval of Gardasil, the Advisory Committee on Immunization Practices (ACIP), through the Department of Health and Human Services Centers, for the Centers for Disease Control and Prevention National Immunization Program, held a meeting from June 29-30 2006. The meeting minutes are available online through the CDCs website (CDC, 2006). At this meeting Gardasil, the HPV vaccine was discussed along with the Varicella and Influenza vaccines. I just discuss the proceeding related to Gardasil. There were many participants at this meeting including the 15 members of ACIP, the ACIP executive secretary, dozens of people from various governmental and professional organizations, dozens of CDC representatives, and over a hundred more guest presenters (including 48 Merck employees), press, and members of the public. During the meetings, formal comment periods were scheduled, and time was allotted for public comments. A Merck researcher described this meeting during our interview.

When it was close to licensure, representatives from Merck went to DC for the advisory committee meeting, which is sponsored by the FDA. This is an open meeting and anyone can come. They did not know what to expect because some people from Merck had already met with religious groups who were concerned about the vaccine causing promiscuity. Merck presented all of their clinical data. Many people spoke, including an Oncologist from the Mayo clinic who came and talked about cervical cancer, leaving people in tears. She spoke about the horrors of the disease and how it can rob families of young mothers, taking women in the prime of their lives. Many groups were there to support Gardasil. No one spoke in opposition of Gardasil at that meeting (Interview #1).

The CDC appointed the members of ACIP, and the goal was to appoint members with the greatest level of expertise while minimizing any actual or perceived conflicts of interest. When considering guidelines for a specific vaccine, ACIP members were required to vote only on the safety, efficacy, and cost effectiveness of the vaccine. They were instructed not to take into consideration how federal or state government would pay for the vaccine (CDC, 2006). Information discussed at the meeting was addressed in the

relevant sections of this chapter. One area that was discussed at both meetings and was deemed very important was how Gardasil would be monitored after its approval and release. With five years of trial data to support claims of safety and effectiveness, it was important that monitoring of the vaccine continued so that any potential adverse events would be captured. The post-marketing plans for Gardasil are discussed in the following section.

#### *Post Marketing – Surveillance Studies*

There are several post marketing plans for Gardasil, which began following the conclusion of the clinical trials, and include both short term and long term follow up studies. The post marketing surveillance plan was discussed at both the VRBPAC and ACIP meetings (CDC, 2006; VRBPAC, May 18, 2006). Following his formal presentation, Dr. Eliav Barr from Merck confirmed that even after licensure, Merck planned to continue with supplemental analyses at the end of the phase three trials to look at the impact of the vaccine on type-specific disease as well as to obtain a clearer picture of the impact of Gardasil on the overall burden of clinical HPV disease (VRBPAC, May 18, 2006).

Dr. John Iskander of the CDC Immunization Safety Office described the CDC's vaccine safety monitoring plan for Gardasil at the ACIP meeting. The Vaccine Adverse Event Reporting System (VAERS), which is a national passive surveillance system for reporting adverse events and is co-managed by the CDC and the FDA, is used in monitoring the safety of Gardasil. VAERS has under-reported data and an inability to determine causal relationships between vaccines in most reports, yet maintains a solid

track record as a hypothesis-generating system. VAERS can be helpful at identifying adverse events in populations that may have been excluded from the clinical trials. There was also a focus on cardiovascular, allergic, and clinical issues (CDC, 2006; N. B. Miller, 2006; VRBPAC, May 18, 2006).

At the Advisory Committee on Immunization Practices (ACIP) meeting in June 2006, as well as the Vaccines and Related Biological Products Advisory Committee meeting in May 2006, the long term follow up plan for Gardasil was presented. A long term follow up study was to be conducted in the Nordic region of the world because of the extraordinary public healthcare infrastructure that allows for all Pap tests and biopsy results to be reported to the national database by identification number. Mass screening programs for cervical cancer have been underway in this region for the last four decades and cervical cancer mortality has been reduced over the last thirty years by 59% (Denmark) and 76% (Sweden) (Ault, 2007). Pap tests and biopsy results can be retrieved, followed and tested for HPV types. There were 5,500 subjects who had been enrolled, and they had given their permission to Merck to follow them for the remainder of their lives for evaluation of long term efficacy as well as for impact on other cancers. (CDC, 2006; VRBPAC, May 18, 2006).

The women involved in that study are who Merck discussed in the meetings as a “sentinel cohort” because they were vaccinated in 2002 and 2003, 3-4 years before anyone in the general population in the US would be vaccinated, so there was already years of follow up on them by the time Gardasil was released for general use in the United States (VRBPAC, May 18, 2006). That cohort of women would be followed every two years and evaluated for break through infections by testing any and all of their

biopsy lesions to determine if they are connected to the vaccine HPV types. This would help Merck determine long term safety and efficacy, as well as to determine whether or not a booster is needed; there was no evidence from the clinical trial data that a booster would be needed (VRBPAC, May 18, 2006).

Another long term follow up study was being conducted in adolescents to better understand the immune response in this age group. This study (protocol 018) included approximately 1,800 girls and boys ages 9-15 who were vaccinated in 2003 with a mean age of 12 years at enrollment. Beginning in 2007, girls in this study who reach age 16 would begin efficacy studies which included genital sampling (CDC, 2006; N. B. Miller, 2006).

There was a short term safety surveillance study that was planned to be conducted in a US managed care organization in 2009, which would include approximately 44,000 vaccinated subjects who would be followed for 60 days following immunization for assessment of general short-term safety (i.e., emergency room visits, hospitalization, and deaths). The subjects would also be followed for 6 months subsequent to vaccination for new autoimmune disorders, rheumatologic conditions, or thyroiditis. Also included in the study would be “a sufficient number of children 11-12 years of age” to analyze safety outcomes. The study would be conducted in 2009 and was expected to be completed by June 30, 2009. The final study report was scheduled for submission by September 30, 2009 (Baylor, 2006).

Another post marketing study was a collaboration with the cancer registries in Sweden, Norway, Iceland, and Denmark to assess the long-term outcomes following vaccination with Gardasil. This study began in 2003 and concludes in 2017. Subjects in

this study would be followed for 14 years, with the study concluding at the end of 2017. The two goals of this study are: To assess the long-term effectiveness of Gardasil and evaluate for the presence of HPV related oncogenic cancers; to assess whether vaccination with Gardasil results in replacement of these diseases with non-vaccine HPV types (Brill-Edwards, 2006). Since Gardasil covers the two strains that account for 70% of cervical cancer cases, it is possible that women who were vaccinated would still develop cervical cancer due to the other oncogenic strains (Brill-Edwards, 2006; VRBPAC, May 18, 2006).

Two others studies will also be conducted in the Nordic region looking at long term safety and effectiveness. In these studies, females were vaccinated in 2002 and the studies would be followed “over time” (CDC, 2006, p. 21). It is likely that these studies would run for longer than five years to measure whether or not a booster is necessary. The studies are being conducted in this region because it “has an extraordinary public healthcare infrastructure that allows for all Pap tests and biopsy results to be reported to the national database by identification number. Pap tests and biopsy results can be retrieved, followed and tested for HPV types” (CDC, 2006, p. 21). This infrastructure also captures every HPV vaccination in the country and they are going to mandate that everyone who gets a vaccination must register in order to be followed (VRBPAC, May 18, 2006).

A pregnancy evaluation was incorporated into the clinical trial program due to the vaccine being administered to girls and women of child-bearing age (Baylor, 2006). To further evaluate general safety and pregnancy outcomes, Merck also has a large post licensure study in 35,000 subjects. 11% of the clinical trial population became pregnant



during the course of the trials and follow-up (N. B. Miller, 2006). In November 11, 2005, data showed outcomes for approximately 2,000 pregnancies (N. B. Miller, 2006). The differences between the Gardasil and placebo groups was small, however the Gardasil group had a lower incidence of spontaneous miscarriage, lower incidence of elective termination, and higher incidence of live births; the two groups had comparable rates of congenital anomalies. Further analyses were done among two strata of pregnancies: those with an estimated onset within 30 days of vaccination and those with an estimated onset beyond 30 days of vaccination. Five cases of congenital anomalies occurred in the first group only among those that received Gardasil as opposed to placebo. In the second group, fewer congenital anomalies occurred in the group that received Gardasil as opposed to placebo (no numbers were given for this group). The conclusion was that the congenital anomalies were unlikely to be associated with Gardasil. The FDA gave Gardasil a category B label because animal studies showed no adverse effects. There have not been any controlled trials performed on pregnant women. Merck recommended discontinuing vaccination with Gardasil if pregnancy occurred (VRBPAC, May 18, 2006). One researcher who was an author on one of the main articles published on the trial results said that there was nothing to show that this vaccine is unsafe for pregnant women (Interview #5). Another physician researcher expressed concern about the vaccine being given to pregnant women and cited the FUTURE II study and how

women who became pregnant within 30 days of being vaccinated had a higher risk of congenital anomalies and that has never been mentioned, talked about, or anything but it's in black-and-white in the New England Journal paper. I personally - again I think it's a statistical fluke. I think it's absolutely no reason to believe that that would be a sustained effect mainly because in the placebo group there were no anomalies and you would expect at least some because there is an anomaly rate that we can always look at as being kind of a baseline background rate anomalies. So

I would say that until we know whether or not there is that effect - because it was shown and it was statistically significant. Until we know that we need to think about whether we should be counseling women who are sexually active and getting vaccinated to use contraception because if it ends up that that is the true effect I'm not quite sure how in the world we could have justified that unless we knew it and we just ignored it (Interview #8).

This was echoed by another physician researcher as a cause for concern. She said

the issue of the group that was vaccinated and got pregnant within 30 days of vaccination and they had five congenital anomalies in that group versus 0 in the placebo group. That difference was statistically significant - They did report that in the interim analysis with the effective vaccination. If conception occurred within 30 days it shows significant deleterious effect (Interview #7).

#### *Risk Management Plan*

In addition to the post marketing surveillance studies, Merck developed a risk management plan to effectively monitor and address any safety issues that may arise following use of Gardasil in the larger population. Dr. Adriana Dana from Merck presented Gardasil's risk management plan at the VRBPAC meeting (VRBPAC, May 18, 2006). There are three major areas of the risk management plan: The safety specification summarized the safety database, safety knowledge, data gaps and known risks for Gardasil; the pharmacovigilance plan outlined approaches to be taken to follow the safety of Gardasil in the future and described routine pharmacovigilance practices, and delineated action plans for specific safety concerns of Gardasil; and a risk minimization plan was developed if necessary, though that was not expected to be needed for Gardasil (VRBPAC, May 18, 2006).

Exposures during pregnancy would continue to be monitored. Monitoring will be conducted in the Nordic regions where long term studies would be conducted, as well as in the United States, France, and Canada where pregnancy registries are being developed

for surveillance of spontaneously reported pregnancy exposures. Merck conducted an observational post-marketing safety surveillance trial in a managed care organization setting, focusing on pregnancy exposures that occurred during the trial to provide a descriptive epidemiology of exposures. The government of Norway committed to establishing an HPV vaccine registry for the entire country, and Merck will use data from the HPV vaccine registry and existing birth registries in Norway to analyze pregnancy exposures and outcomes. Additionally, a short term safety study would be conducted in the United States with 44,000 subjects to monitor safety issues that occurred 60 days following vaccination with Gardasil (VRBPAC, May 18, 2006).

Monitoring would also be conducted on women to determine infection with non-vaccine HPV types due to the theoretical concern that vaccination against some types will leave a niche for other types to emerge. Merck would continue communication with the FDA and regularly submit their monitoring data. None of the documents that I had access to gave specific dates or timeframes for when this would occur. There is no biologic data yet to support this theory and no evidence of replacement has been seen in clinical trials to date. Infection with one HPV type can be a risk factor for infection with other types. Long-term effectiveness and immunogenicity would also be monitored. The five-year data on Gardasil demonstrated that the vaccine has the ability to induce long-lasting immune memory and did not show breakthroughs due to waning immunity. However, the duration of protection and the need for a booster remained unknown (VRBPAC, May 18, 2006).

Following the presentations by the Merck scientists at the ACIP meeting time was allotted for public comment. The comments made were from people representing national organizations connected to this issue.

*Public Comments at the ACIP meeting*

There were public comments from nine people representing the following groups; National Coalition for Cancer Survivorship (NCCS), Planned Parenthood Federation of America (PPFA), AmeriChoice, Women's Health at The Balm in Gilead (BIG), American Social Health Association (ASHA), American Society for Clinical Oncology (ASCO), Celebrate Life Foundation (CLF), Women in Government (WIG), and the International Recurrent Respiratory Papillomatosis (RRP) Information, Support and Advocacy Center (ISA) (CDC, 2006). All of the speakers expressed broad support for Gardasil with strong recommendations to make it available to as a wide a population as possible. There was the desire to have this included in the Vaccines for Children program, so that all eligible females could have access to the vaccine. Each speaker stressed the importance of this vaccine and felt it was a breakthrough in the area of women's health. One person, on behalf of his organization, expressed the organization's desire to see males included in the vaccination plan because of other non-cervical/genital HPV related diseases that also effect males (CDC, 2006).

Each of the speakers spoke highly of Gardasil and no concerns were raised about the vaccine. Each of the speakers was connected to an organization and there was not anyone who spoke independently of such an organization.

Following shortly after the CDC's Advisory Committee on Immunization Practices meeting held June 29-30, 2006, which occurred after the June 8, 2006 approval of Gardasil by the FDA, the CDC made their recommendations for the use of Gardasil. One of the issues the committee took into consideration was the cost effectiveness of the vaccine.

*Cost-effectiveness of HPV vaccination in the United States*

After determining the cost of the vaccine, the next step was to determine whether or not this was cost effective. Dr. Harrell Chesson, of the CDC Division of STD Prevention, presented data at the ACIP meeting in June 2006 to demonstrate the potential cost-effectiveness of Gardasil in the United States (CDC, 2006). Independent studies with different models –sensitivity and dynamic - were used to estimate the cost effectiveness of the vaccine in terms of cost per quality-adjusted life year (QALY). Quality adjusted life years “measures both the quality and the quantity of life lived as a means of quantifying the benefit of a medical intervention. QALYs are based on the number of years of life that would be added by a specific intervention” (Stanley, 2007, p. S21). The studies discussed used estimates of vaccine efficacy, age of vaccination (12 years old), estimated coverage of the vaccine, and estimated cost of the vaccine plus a potential booster. In these scenarios, the range of cost per QALY ranged from \$14,600 - \$24,300 (CDC, 2006). Merck also conducted its own study with the assumption that initial vaccination would provide lifetime coverage. Vaccination age would ideally be 12 years old, but there would be an additional catch-up strategy for females ages 12-24. This would be cost-saving at \$0 per QALY. Even in models where Merck incorporated

the cost of adding a catch-up strategy, their findings demonstrated that the HPV vaccine would be a long-term investment with benefits increasing over time (CDC, 2006). An ACIP member discussed this issue and said “the issue of cost-effectiveness varies because it depends which formula you use. It is based on estimates of the cost per quality-adjusted life year (QALY). There is a difference between cost savings and cost effectiveness. The Varicella vaccine provides cost savings, and well as the Pneumococcal. They are not necessarily cost effective. Vaccines have not all provided cost savings. Depends on the amount of money per quality-adjusted life year (QALY)” (Interview #4).

Other physicians at the ACIP meeting in June 2006 discussed this issue in terms of the importance of the failure of some adolescents to not complete the three dose regimen, which left them unprotected (J. S. Abramson, 2006). Without the three doses, lower vaccine efficacy and decreased cost effectiveness can be assumed. The issue of herd immunity was discussed as it factors into cost effectiveness. At the time, the ability to achieve high coverage rates to obtain herd immunity was unknown. Merck does plan to conduct studies on infants at some point in the future, but vaccinating babies at this time is thought to be premature (CDC, 2006).

Gardasil was not expected to divert tax dollars away from pap testing (CDC, 2006). Pap testing remains one of the main public health measures to prevent cervical cancer. ACIP recommendations state that vaccinated women should continue to have regular Pap testing. There are many reasons why women still need regular cervical cancer screening.

- The vaccine does not protect against all HPV types that cause cancer. Approximately 30% of cervical cancers are caused by types not covered

by the vaccine, so vaccinated women would still be at risk for some cancers.

- Women may not get the full benefit of the vaccine if they receive it after they have already acquired one or more of the four HPV types covered by the vaccine.
- The vaccine does not treat existing HPV infections, nor does it prevent the development of diseases caused by existing infections (CDC, 2006).

Several articles have been written that addressed the issue of cost effectiveness.

Harrell Chesson, who presented at the ACIP meeting in June 2006, published an article in 2008 in *Emerging Infectious Diseases*, which is published by the CDC, along with other colleagues from the CDC regarding the cost effectiveness of Gardasil. One area of saving would be the screening and treatment costs for HPV related genital warts and cervical disease which are estimated to be at least \$4 billion annually in the US (Chesson, Ekwueme, Saraiya, & Markowitz, 2008). To complement the existing models which estimated cost effectiveness, the authors developed a simplified model to estimate the cost effectiveness of adding HPV vaccination of 12 year old girls to existing cervical cancer screening practices in the US. Their approach “estimated the potential benefits of HPV vaccination based on current, age specific incidence rates of HPV-related outcomes...to reflect a more current understanding of the vaccine’s characteristics and to include the potential benefits of preventing HPV-related anal, vaginal, vulvar, and oropharyngeal cancers” (Chesson et al., 2008, p. 244).

The results of the model by Chesson et al showed that the estimated cost per QALY gained by adding vaccination of 12 year old girls to existing cervical cancer screening ranged from \$3,906 - \$14,723 (Chesson et al., 2008). The range was due to variables such as whether herd immunity effects were taken into account, whether the

benefits of preventing cancers other than cervical cancer, and whether bivalent or quadrivalent vaccine types of HPV were targeted. Identifying the limitations to their model, the authors stated that overall, the prevention of HPV related health problems resulted in averted treatment costs and QALYs saved (Chesson et al., 2008).

Another article was published in 2007 in *Emerging Infectious Diseases*, this one written by Merck researchers in an effort to assist policymakers in formulating guidelines, provided the epidemiologic and economic impact assessment of the HPV vaccination based on their transmission dynamic model (Elbasha, Dasbach, & Insinga, 2007). Their model took into account the issue of vaccine derived immunity as well as herd immunity, which many of the models done by other researchers were unable to address (Elbasha et al., 2007). Routine vaccination of 12 year old girls was used as the defined reference vaccination strategy. To perform the analyses, the authors assumed the degree of protection from infection was 90% and 100% for associated diseases, the duration of protection was 10 years, up to 70% of 12 year olds received the 3 dose vaccine, coverage increased linearly during the first 5 years of the vaccination program remaining at 70% thereafter, and that cost for the 3 dose vaccine would be \$360 (Elbasha et al., 2007).

The results from this model predicted that 20% of all cervical cancer cases occurred among women who were never screened, which is similar to what has been observed in the US population (Elbasha et al., 2007). The model did predict lower cervical cancer incidence among older cohorts, which was expected because as more young people get vaccinated, less older people will theoretically develop cervical cancer. The HPV prevalence rates were higher among boys and men than girls and women due to



males' exclusion from vaccination. However, overall HPV 16 and 18 prevalence was higher for girls over 12 than for boys and men, and increased with level of sexual activity (Elbasha et al., 2007). For both sexes, prevalence increased, reaching a peak between 20-24 years and declining thereafter. Their model showed that with 10 years of protection, vaccination reduced disease incidences steadily until 10-15 years after vaccination. Their findings were consistent with other cohort based cost effectiveness analyses including the illustration of the herd immunity benefits provided by the vaccine. Overall, their results suggested that a "quadrivalent HPV vaccine program that targets female adolescents and women, ages 12-24 years, can be cost effective (\$4,666/QALY) when compared with other commonly accepted medical interventions" (Elbasha et al., 2007, p. 32)

An article published in 2007 in *The Journal of Women's Health* discussed the modeling that was done to determine the cost effectiveness of Gardasil. The authors confirmed the work of other researchers and felt that vaccinating girls before age 12 would be cost effective provided it was "in the context of an organized cervical cancer screening program" (Vetter & Geller, 2007, p. 1261). Adding catch up vaccination for women up to 24 years of age would also prove to be cost effective in this context. Vaccinating males was also discussed as being cost effective and based on the modeling done would reduce the incidence of vaccine HPV type genital warts and cervical cancer by 97% and 91% respectively (Vetter & Geller, 2007).

Margaret Stanley published an article in 2007 in *Gynecologic Oncology* that addressed, in part, the issue of cost effectiveness. While the long term data prevent us from knowing the true cost effectiveness of the vaccine, the author believed that the pharmacoeconomic data indicated that the introduction of the HPV vaccine may be more

cost effective than current clinical practices (Stanley, 2007). There were still issues that needed to be resolved in order to confirm this aim such as who should be vaccinated and at what age, and what the impact of vaccination would be on current screening programs. The models that have predicted cost effectiveness in terms of QALYs have limitation that include a failure to take herd immunity into account, vaccinating males, and the possibility of the reactivation of latent infections (Stanley, 2007). The author felt that a dynamic transmission model was needed to “assess the epidemiological changes in type-specific HPV prevalence over time, estimate the impact of herd immunity and determine the relative value of vaccinating females only” (Stanley, 2007, p. S22).

Cost effectiveness was also measured by Stanley in its impact on the use of health care resources. She referred to data from 2000 and 2005 based on the US National Health Interview Surveys that indicated that there could be a reduction in the 65 million pap tests that are performed annually as a result of the introduction of the HPV vaccine (Stanley, 2007). Based on this data, Stanley felt that biennial pap screening from age 24, as opposed to annual screening, was predicted to reduce the annual total pap test volume by 43%, thus increasing the cost effectiveness of the vaccine (Stanley, 2007). In addition to pap test reduction, the vaccine may also reduce the workload at STD clinics. A reduction in HPV related morbidity in regard to STDs would likely result in a lower workload for STD clinics for those STDs that are related to HPV, thus opening more resources for the treatment of other STDs (Stanley, 2007). Finally, Stanley felt that across all age groups, vaccination also predicted a 95% reduction in the prevalence of lesions associated with HPV 16 and 18, thus reducing screening and treatment for these lesions (Stanley, 2007).

An article published in 2008 in the *New England Journal of Medicine* built upon previous studies and models to evaluate the cost effectiveness of vaccinating 12 year old girls as well as catch up programs that vaccinate girls up to the age of 26 (Kim & Goldie, 2008). The authors took into consideration “the dynamics of HPV transmission, the duration of vaccine efficacy, the potential benefits of preventing noncervical HPV-related conditions, the anticipated changes in screening practice, and potential disparities in access to care” (Kim & Goldie, 2008, p. 822). Included in the analysis was also the assumption of lifelong, complete protection, though they did evaluate the effect of waning immunity with and without a booster. Adopting a societal perspective, they discounted costs and benefits by 3% annually and expressed the benefits as QALYs gained (Kim & Goldie, 2008).

The results of the study by Kim and Goldie found that vaccination against HPV 16 and 18 was expected to be economically attractive at approximately <\$50,000/QALY, if high coverage can be achieved in the primary target population of 12 year old girls and if vaccine immunity is lifelong (Kim & Goldie, 2008). Catch up programs for girls between 13 and 18 were shown to be cost effective, though extending the catch up to girls 21 years and older proved to be less cost effective. Extending coverage to women up to 26 years old was the least cost effective since most women that age have engaged in sexual activity and up to 30% of women may be exposed to HPV in the first year of being sexually active (Kim & Goldie, 2008). The cost per QALY continued to rise when boosters were needed, when there were disparities in screening and vaccination coverage and when vaccinated girls underwent frequent screening in adulthood. Overall, their findings were consistent with other studies and showed that “high vaccination coverage

warranted modification of screening protocols and that the cost-effectiveness of vaccination was enhanced with less frequent screening with more sensitive tests and beginning at later stages” (Kim & Goldie, 2008, p. 829).

Among the article previously discussed in this section, there seemed to be agreement that the lack of long term data precluded the actual assessment of the impact of the vaccine on the disease burden of the vaccine HPV types and their true cost effectiveness. There was consensus, according to Hymel that the implementation of HPV vaccine programs along with the continuation of appropriate screening would be both significantly cost effective and successful at reducing the prevalence of precursor lesions and cervical cancer (Hymel, 2006). The optimal age for vaccination in these models was 12 years old and estimates showed that the short term impact in the US would be a 33% - 50% reduction in overall CIN 2 and 3 cases for those who were vaccinated (Hymel, 2006). In terms of policy, one author, based on the various studies regarding cost effectiveness, stated that successful implementation of the HPV vaccine, “must be country-driven and well planned, with full support and involvement of policymakers, parents, district and hospital managers, medical personnel, and community groups” (Hymel, 2006, p. S478).

*Proposed recommendations for the use of Gardasil*

Based on all of the data that the CDC’s HPV working groups and the Advisory Committee on Immunization Practices reviewed about Gardasil, the CDC proposed their recommendation for its use after the meeting held from June 29-30, 2006. The HPV working group received the data approximately 2 ½ years before Gardasil’s approval

(Herskovits, 2007a). Dr. Laurie Markowitz of the CDC was the head of the HPV vaccine workgroup, which was part of the Advisory Committee on Immunization Practices, and presented the workgroup’s proposed language, supporting data, and rationale in formulating recommendations for Gardasil, and solicited ACIP’s votes on four recommendations (CDC, 2006). The FDA licensed Gardasil on June 8, 2006 for use in females 9-26 years of age for prevention of certain diseases caused by HPV 6, 11, 16, 18, and it was the responsibility of the CDC and the ACIP to set the guidelines for use following the approval. According to one of the HPV working group members, the rationale for targeting females 11-12 years old is “because there's a strong movement afoot to establish adolescent visits [to the physician] at a time of life when people aren't going to the physician for routine care” (Herskovits, 2007a). Below is a table of the four recommendations made by the CDC, the ACIP’s comments and how the members voted (CDC, 2006).

Table 4 – CDC Recommendations

<b>Recommendation</b>	<b>ACIP’s suggestions/Comments</b>	<b>ACIP’s Vote (15 members)</b>
1. Routine vaccination of females 11-12, yet the vaccine can be started on girls as young as 9. Data show that there is a better outcome vaccinating on a routine basis rather than a risk-based strategy. The target age allows for the vaccination of most females before sexual debut. Five year data for duration of protection shows no evidence of waning immunity.	Add language to: <ul style="list-style-type: none"> <li>• Emphasize the rationale for the recommendation to target females 11-12 years old.</li> <li>• Explicitly state that ACIP’s intention is for health insurance plans to cover the cost of vaccination for girls as young as 9.</li> <li>• Clearly delineate the minimum amount of time between the three doses.</li> </ul>	Passed by a majority vote. 13 - in favor 2 - with conflicts did not vote.
2. Catch-up vaccination of children 13-26 years old. Vaccination should ideally	There was strong support for catch-up vaccinations.	Passed by a majority vote. 13 - in favor

<p>occur before sexual initiation, females who are sexually active should still be vaccinated, though they may not fully benefit from the vaccine due to pre-existing infection with HPV vaccine types. The benefit of vaccination will decrease with increasing age because more females will have been infected with HPV vaccine types. They propose that the following statement about cervical screening is included in their recommendation: “There is no change in the recommendations for cervical cancer screening. Vaccinated females could be subsequently infected with non-HPV vaccine types. Sexually active females could have been infected prior to vaccination. The decision to vaccinate should not be based on Pap testing, HPV DNA testing or HPV serologic testing.”</p>		<p>2 - with conflicts did not vote.</p>
<p>3. Gardasil can be administered in the following 5 special situations.</p> <ul style="list-style-type: none"> <li>a. Females with an equivocal or abnormal Pap test. They should be advised that they may already have one or more strains that Gardasil covers. Gardasil does not protect against the strain(s) if already present.</li> <li>b. Females with a positive HPV tests using the Digene Hybrid Capture II® (HCII) assay. A</li> </ul>	<p>None</p>	<p>Passed by a majority vote. 13 - in favor 2 - with conflicts did not vote.</p>

<p>positive test indicates infection with any of 13 high-risk types, but the test does not identify specific HPV types. Testing for specific types is not currently available in routine clinical practice.</p> <ul style="list-style-type: none"> <li>c. Females with genital warts or a history of genital warts. Data do not indicate the vaccine will have any effect on existing genital warts or HPV infection.</li> <li>d. To females who are immunosuppressed, though it may not protect as well as in other females.</li> <li>e. To lactating women</li> </ul>		
<p>4. Precautions and contraindications for Gardasil.  Precaution - Vaccination should be deferred until after moderate or severe acute illnesses improve.  Contraindication - A history of hypersensitivity or severe allergic reaction to yeast or any other vaccine component should be classified as a contraindication. Pregnancy is also a contraindication and vaccination should be delayed until after completion of pregnancy, and if a pregnancy is identified after initiating the vaccine series, completion of the vaccine series should be delayed until after the pregnancy.</p>	<p>There were also several suggestions made to strengthen the recommendation:  Language should be changed from hypersensitivity to “immediate hypersensitivity”  Pregnancy – language should be changed to make this a precaution, not a contraindication to avoid the need to include language on pregnancy tests and similar issues. Pregnancy should be included in a special section rather than in the precautions and contraindications section. There should be an explicit statement that pregnancy testing before vaccination is not necessary. Providers should be advised to ask their patient if she is pregnant, make a note in her chart and proceed with the vaccination. Do not include a statement about pregnancy testing because this language will complicate the</p>	<p>Passed by a majority vote.  13 - in favor  2 - with conflicts did not vote.</p>

	<p>recommendation. Add language that vaccination should not be based on pregnancy testing or screening.</p> <p>There was acknowledgement from the ACIP chair that the use of vaccines in pregnancy would continue to be a challenge.</p>	
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(CDC, 2006)

The American Cancer Society (ACS) also put out their own set of guidelines for use of Gardasil following a review of the existing data by an expert panel put together by the ACS (Saslow et al., 2007). This panel worked independently from, but parallel to, the ACIP working group. The American Cancer Society’s “Guidelines for the Early Detection of Cervical Cancer” was last updated in 2002 while clinical trials for the HPV vaccine were ongoing and before any of the data had been published. Their updated recommendations are that routine vaccination of females 11 – 12 years old is recommended, and females as young as 9 may also receive the vaccine. Catch up vaccination is recommended for females up to age 18; there was insufficient evidence to recommend for or against vaccination of females 19-26, and decisions for this age group should be made individually. Vaccination is currently not recommended for females over the age of 26 (Saslow et al., 2007).

There were also supporting recommendations made by the American Cancer Society in four areas; screening, vaccine implementation and utilization, education, and research (Saslow et al., 2007). They felt continued screening was needed whether vaccinated or not, and that HPV testing prior to vaccination was not recommended. Pap tests should still be performed and health care visits should be used to discuss and offer both the vaccine and a pap test (Saslow et al., 2007). For effective implementation,



public health and policy efforts are needed to ensure access and encourage high HPV vaccine coverage for all racial, ethnic and socioeconomic groups. For harder to reach populations, strategies should be implemented to maximize adherence to vaccine recommendations including co-administration with other vaccines (where proven safe), and the use of alternative vaccination sites as well as non-related health visits (Saslow et al., 2007). Examples of alternative vaccination sites could be anywhere where children gather such as sporting events, schools, Girl Scout meetings, and the like. Non related health visits occur outside of the normal schedule for children to visit their physician, which would include situations where a child comes in for a minor injury, an allergy, a cold, or some other minor condition.

According to the American Cancer Society, the need for education about cervical cancer prevention and early detection remained critical among providers, policymakers, parents, adolescents, and young women. Research and surveillance should continue to assess the duration of protection, population and lesion based changes in type specific prevalence of HPV infection, changes in pap testing and screening, and for safety and long term efficacy (Saslow et al., 2007).

*Post-Marketing - Requests for patent extension/expanded use of Gardasil*

Following the release of Gardasil in June 2006 and having observed the use of Gardasil following that approval, Merck submitted paperwork to the FDA to extend its patent on Gardasil. The FDA, which is under the jurisdiction of the Department of Health and Human Services put out a notice (docket number 2006E-0501) on May 22, 2007 titled, "Determination of Regulatory Review Period for Purposes of Patent

Extension; Gardasil” relating to Merck’s request to extend their patent on Gardasil (Axelrod, May 7, 2007). Merck was seeking 1,200 days of patent extension. The patent for Gardasil is set to expire in 2026 (Merck & Co., 2008). Under the Drug Price and Competition and Patent Term Restoration Act of 1984 (public law 98-417) and the Generic Animal Drug and Patent Term Restoration Act (public law 100-670) a patent may be extended for a period of up to five years as long as the patented item was subject to regulatory review by the FDA before the product was marketed. The regulatory review period for the product helps determine the amount of extension the product may receive (Axelrod, May 7, 2007).

The regulatory review period consisted of both the testing phase and the approval phase. For human biological products, the area where Gardasil falls, the testing phase began when the company received permission to begin clinical investigation, and ran until the approval phase began. For Gardasil, the clinical testing phase began on May 17, 2000, even though the preliminary phase I trials began in 1997. The approval phase began with the initial application to market the product and continued until the FDA granted permission to market that product. Merck submitted their biologics license application (BLA) for Gardasil (BLA 125126/0) on December 7, 2005. The application was approved on June 8, 2006, which is when Merck was able to start marketing Gardasil (Axelrod, May 7, 2007, Docket Number 2006E-0501).

Merck was also interested in expanding the use of Gardasil to include males, and wanted the public health authorities to begin considering this from the beginning of the post-licensure period. Merck believed there was a strong public health rationale for vaccinating boys as well as there being a cost to delaying the vaccination of boys

(VRBPAC, May 18, 2006). The FDA and CDC both expressed the fact that vaccine coverage in girls was likely to be incomplete in the years following the release of Gardasil, as it would take several years to not only vaccinate girls in the targeted age group of 11-12 years olds, but to also capture girls 13 and older for catch up vaccinations (CDC, 2006, 2008; VRBPAC, May 18, 2006). The most common route of transmission to women is from men; therefore including males would address the issue of herd immunity that has been discussed in some publications. However, one concern about that was cost effectiveness, which is discussed later in this chapter (CDC, 2006; Chesson et al., 2008; Elbasha et al., 2007; Stanley, 2007). In its modeling work, Merck showed that delayed vaccination of boys would reduce the overall population efficacy of the vaccine, as well as the time until maximum reduction in cervical cancer. Merck has not yet received approval for use in boys, which may be due to concerns about cost effectiveness (VRBPAC, May 18, 2006).

### *Cost*

The high cost of Gardasil has been discussed as a major factor in its widespread use. Cost, however is not taken into account during either the approval process or in setting the guidelines for its use. The CDC's Advisory Committee on Immunization Practices was specifically told not to take cost into account when making recommendations for its use. One member of the Advisory Committee on Immunization Practices discussed this issue and said that "The ACIP members are told explicitly that they are not worry about whether or not there is money in the budget to afford the

vaccines. They are strictly concerned with issues of safety, efficacy, and cost-effectiveness” (Interview #4).

Not only was Gardasil costly, but implementation of a vaccine program and the integration of Gardasil into the federal program to vaccinate children required analysis to determine the cost effectiveness of doing so. In April 2007, the CDC reported to Congress on the Section 317 immunization program (Gerberding, 2007b). The Section 317 program is a discretionary federal grant that can provide any ACIP recommended vaccine to persons of any age, though most funding is used to vaccinate children in health department clinics (Gerberding, 2007b). This program is the main source of funding for state and jurisdictional immunization programs. Most children served through Section 317 are under-insured or their parents are working poor who cannot afford the high deductibles or copayments required to fully vaccinate their children. This program is a complement to the vaccines for children (VFC) programs, which serves children and adolescents through age 18 who do not have insurance, are eligible for Medicaid, are American Indian/Alaska natives, and children who are underinsured and receive care through Federally Qualified Health Centers (FQHCs) and Rural Health Clinics (RHCs) (Gerberding, 2007b). In this program, federally purchased vaccines are distributed to public health clinics and private providers enrolled in this program. Gardasil was added to the vaccines for children on November 1, 2006 (Merck & Co., 2007a). Section 317 is a discretionary federal grant program to 64 state and local grantees providing a safety net for the vaccination of underinsured children and adolescents not served by the VFC program. In recent years, additional vaccines have come to market, and with them

recommendations for their use. This has increased the amount of money necessary to fully immunize each child (Gerberding, 2007b).

Reporting to the Senate Appropriations Committee, Dr. Julie Gerberding, the head of the CDC discussed this issue, and made recommendations for the fiscal year 2008. Vaccine costs for the groups targeted by this program were estimated to be approximately \$456.4 million annually (Gerberding, 2007b). The estimated costs in 2008 to fully vaccinate a male and female would be \$936.05 and \$1,240.28 respectively; the cost difference was reportedly due to the HPV vaccine only being recommended for females (Gerberding, 2007b). 78% and 71% of the cost to vaccinate females and males respectively are due to new vaccinations or expanded recommendations (Gerberding, 2007a).

In this report, the CDC broke out the costs of vaccinating eligible females up to 18 years of age, and females ages 19-26. The recommendation stated that routine vaccination should be targeted at females 11-12 years old, with a catch-up vaccination recommendation for females 13-26 (J. S. Abramson, 2006). If individuals are routinely vaccinated at age 11, that leaves seven cohorts of adolescents, up to age 18, to be included in a catch-up vaccination program. For 2008, the estimate was that there would be approximately 140,000 individuals who met eligibility for the vaccination program and who would ultimately be vaccinated (Gerberding, 2007b). This accounts for about 20% of the total cohort. The remainder would be vaccinated through insurance or other means, or may not be vaccinated at all. The estimated costs for vaccinating this cohort of 140,000 was approximately \$42.6 million (Gerberding, 2007b). There were approximately 1,450,512 women ages 19-26 who met eligibility for the section 317

program, and it was estimated that of this group, 290,102 women would be vaccinated annually, with a total cost of \$88.3 million (Gerberding, 2007b). These costs were at the federal contract price of \$304.23 for the three dose series, which was less than the standard price of \$360 (Gerberding, 2007b).

One of the researchers from Merck discussed the cost of the vaccine, how pricing was determined, and Merck's sales expectations. He stated that while Gardasil was being developed, "it was understood to be a blockbuster drug...but it hasn't taken off as hoped. It has not made as much money as Merck or Wall Street expected. It is expensive to do the studies, and so the vaccines had to be priced accordingly. Another factor in the pricing is for what it does" (Interview #1). Even with this brief explanation, it remained difficult to understand precisely how pricing was determined, though as discussed, this is one of the most expensive vaccines on the market.

#### *Summary of aim II*

The second aim of this study looked at the process for the approval of Gardasil. This involved looking at the meetings that were held between Merck and the FDA and the CDC, the cost of the vaccine and Merck's post marketing plans for Gardasil. The approval process for Gardasil began with meetings between Merck and the Food and Drug Administration (FDA), and included a meeting with the CDC's HPV vaccine working group, the Advisory Committee on Immunization Practices (ACIP). The two agencies work in tandem where the FDA determines whether or not a drug or vaccine can be approved for use, and the CDC sets the guidelines for use. Throughout the process, Merck submitted data to the FDA, which was how determinations such as whether to grant Gardasil an expedited review were made. The ACIP working group received data

from Merck approximately 2 ½ years prior to its approval, so that it could review the data in order to set the guidelines for its use. The guidelines were not set until after the vaccine was approved on June 8, 2006.

Following the submission of its data to the FDA, a meeting was held on May 18, 2006 to discuss the data prior to final approval. The meeting was the Vaccines and Related Biological Products Advisory Committee meeting, referred to as VRBPAC. This committee is made up of people from the FDA's Center for Biologics Evaluation and Research. After the FDA approved Gardasil on June 8, 2006, the CDC's Advisory Committee on Immunization Practices met for a meeting which was held June 29-30, 2006 to discuss the guidelines for its use. These two meetings were the two necessary steps to getting Gardasil into the market place and into widespread use.

In order to begin the process with the FDA, Merck submitted an investigational new drug application (IND) to the FDA in 1997. An IND is required for any new drug or vaccine that is being developed. The first IND for the monovalent HPV 11 vaccine was submitted in 1997, with the other INDs for the monovalent product HPV 16 and HPV 18 following shortly thereafter (VRBPAC, May 18, 2006). The IND for Gardasil became effective on May 17, 2000 (Axelrod, May 7, 2007; VRBPAC, May 18, 2006). In November of 2001, the Vaccines and Related Biological Products Advisory Committee held a meeting to discuss the endpoints that would be appropriate for phase III development of a preventive HPV vaccine (VRBPAC, November 28-29, 2001). In 2002, the product development program was granted fast-track status and phase III trials began. The FDA met in May of 2005 to discuss the Biologics License Application (BLA), and agreed to allow the submission of the BLA for Gardasil as well as grant it a priority

review (Axelrod, May 7, 2007; VRBPAC, May 18, 2006). The BLA application for Gardasil was submitted on December 7, 2005, which included phase III study data; that also served as the start of the expedited review. Overall, approximately 60,000 pages of clinical review materials were submitted electronically for review, and the review was completed in a six-month regulatory time frame. Standard product reviews take a minimum of a year. The application for Gardasil was approved on June 8, 2006 (Axelrod, May 7, 2007).

The Gardasil vaccine received an expedited review (also referred to as fast-tracking) because of its potential to meet an unmet medical need (FDA, 2006). The decision to grant Gardasil an expedited review was made in 2002 after the FDA received preliminary data from the clinical trials. The expedited review actually began in May of 2005. According to a scientist at Merck, the reason the FDA would fast track a drug or vaccine is if they thought that drug or vaccine was really innovative and lifesaving and if there is not another comparable product like it currently on the market (Interview #1).

Following the submission and review of all of the data, formal meetings began with the FDA and CDC to approve Gardasil and set the guidelines for its use. The first of the two core meetings was with The Vaccines and Related Biological Products Advisory Committee (VRBPAC), through the Center for Biologics Evaluation, which is part of the FDA. They held a meeting on May 18, 2006, which involved a discussion regarding the safety and efficacy of the Gardasil vaccine, which culminated in the recommendation for its use. This meeting was held to discuss and make recommendations on the safety and efficacy of the human papillomavirus vaccine, Gardasil (FDA, 2006; VRBPAC, May 18,



2006). This was a public meeting and in attendance were members of the advisory committee, six FDA staff members, speakers from various professional organizations, and seven sponsor representatives including two of Merck's senior directors; Dr. Eliav Barr, Senior Director, Vaccines/Biologics Clinical Research, and Dr. Patrick Brill-Edwards, Director, Worldwide vaccines Regulatory Affairs.

Subsequent to the approval of Gardasil, the Advisory Committee on Immunization Practices (ACIP), through the Department of Health and Human Services Centers, for the Centers for Disease Control and Prevention National Immunization Program, held a meeting from June 29-30 2006 (CDC, 2006). There were many participants at this meeting including the 15 members of ACIP, the ACIP executive secretary, dozens of people from various governmental and professional organizations, dozens of CDC representatives, and over a hundred more guest presenters (including 48 Merck employees), press, and members of the public. The CDC appointed the members of ACIP, and the goal was to appoint members with the greatest level of expertise while minimizing any actual or perceived conflicts of interest. When considering guidelines for a specific vaccine, ACIP members were required to vote only on the safety, efficacy, and cost effectiveness of the vaccine. They were instructed not to take into consideration how federal or state government would pay for the vaccine (CDC, 2006). One area that was discussed at both meetings and was deemed very important was how Gardasil would be monitored after its approval and release. With five years of trial data to support claims of safety and effectiveness, it was important that monitoring of the vaccine continued so that any potential adverse events would be captured.

*Aim III: To describe How Merck constructed HPV to be a social problem needing treatment and how Gardasil was promoted and marketed*

The previous section addressed the second aim of this study, which mapped out the approval process for Gardasil and the recommendations for its use. Included were the core issues related to its approval and the guidelines for its use such as cost and cost effectiveness and post marketing plans to evaluate safety and effectiveness over the long term. The final section addresses the third aim of this study which is how Gardasil was promoted and marketed by Merck and how those campaigns successfully constructed HPV to be a social problem needing treatment, which led to the widespread acceptance and use of the Gardasil vaccine.

The following section addresses the promotional and marketing campaigns for Gardasil including how messaging was used to influence the acceptance and use of the vaccine. This includes the label claim which is the description that the company gives about its product. Attempts to mandate the vaccine were also part of Merck's efforts to increase the use of the vaccine. Finally, this section addresses the rates of use of Gardasil and concludes with my interviewees' comments on their perceptions of Merck as a company and in the context of the pharmaceutical industry.

### *Label Claim*

Following the approval and release of any product, the makers of that product must market it so that the public becomes aware of its existence, understands what the product does, and can begin to use it. The label claim is the claim that the company makes about its product. In the case of a drug or vaccine, the label claim must be approved by the FDA and must reflect what the product does.

Upon the release of Gardasil, Merck made the label claim that Gardasil prevents cervical cancer. At the VRBPAC meeting in May 2006, Dr. Brill-Edwards from Merck spoke about the vaccine in terms of preventing cancer when he said that “this is the first vaccine to prevent cervical cancer” (FDA, 2006, p. 12). One of the researchers at Merck discussed how Merck was able to make the label claim that Gardasil protects against cervical cancer, as opposed to the claim that Gardasil protects against infection with the four strains of HPV; 6, 11, 16, and 18. Along with describing the issue of the label claim, he also discussed the rationale behind the inclusion of HPV types 6 and 11, and Merck’s desire to broaden the use of Gardasil to include boys. The biggest question for Merck was what the label claim for Gardasil would be. Since the label claim is the claim that the company makes about its product, it is important that the label claim be sufficient to spark public interest and drive sales.

Merck initially wanted the label claim to be that Gardasil protects against cancer, though the FDA initially responded that Merck could not make that claim, but could only say that Gardasil protects against infection with the four strains of HPV. According to one scientist at Merck, they had to find a way to make the label claim that it protected against cancer because “if not then it would be a harder sell” to the public (Interview # 1).

He went on to say that

Merck could not wait the number of years it might take to follow women long enough to see whether or not they developed cervical cancer because that generally happens when women are in their 30’s. A big breakthrough came around the checking for abnormal cells, CIN1, CIN2, and CIN3. If Merck could show the prevention of CIN3 lesions, then they could get a claim of protection against cancer. In the final study before approval, they needed enough women, to have enough frequency to get results. Placebo was given to half the cases, and 30 women in that group developed CIN3, and the other group did not, so the other group showed that there was protection against cervical cancer. This allowed Merck to make the label claim that Gardasil prevents cancer (Interview #1)

He also discussed the inclusion of strains 6 and 11, which cause genital warts. The decision to include those strains was a “marketing decision...Merck wanted to do that because if they could prevent warts, they could broaden the use of the vaccine and then have it also be for boys” (Interview #1).

One physician researcher disagreed with that label claim and stated she was surprised the first time she heard it on a televised direct-to-consumer ad. Considering the CIN surrogates that were used as end points in the trials, she felt that those endpoints would be more appropriate to use when making claims of prevention. She stated:

I think at the time of that sound bite, ‘100% effective against cervical cancer,’ the data that was being released was that it was protective against CIN not cancer and there was 0 outcomes in the vaccine group and 7 in the placebo arm of the trials and that was the data that generated the sound bite that it’s 100 % effective against cervical cancer. The real surrogate is CIN3 and according to the interim analysis that was released last year we’re still not seeing efficacy for that particular outcome...So – that seems like an important surrogate that you’d want to have show that it’s effective against to make any claims about efficacy against cervical cancer. So that’s why I’m questioning it still. Because whether there is actually going to be efficacy against the immediate surrogate against – proximal to cervical cancer” (Interview #7).

I asked a member of the Gardasil working group at the CDC about the label claim. This individual was an integral part of the working group and played a large role in making the recommendations for Gardasil’s use. The decision and use of CIN as surrogate end points was also discussed in the context of the label claim. When asked about the label claim, she stated,

I think that from what we know about the natural history of HPV – and this was carefully considered by the Food and Drug Administration when the trials were being planned. I think there was initially some people in the HPV community that wanted the endpoints for the vaccine trials just to be HPV infection, not any of these pathologic endpoints. This was

discussed both at FDA and the World Health Organization and a decision was made using input from a lot of different experts to have the CIN2, 3 be the endpoint for the trials and that that would be the surrogate for cervical cancer. So I feel very comfortable that that is – based on that CIN2, 3 endpoint, I think that it is a surrogate for cervical cancer (Interview #10).

Once the label claim has been decided, the marketing campaigns can be fitted around that claim and can serve as the basis for the marketing of the product. The following section discusses the marketing of Gardasil and the media publicity surrounding it.

### *Media Publicity*

A pharmaceutical company cannot promote its specific product before it is approved and licensed. It can, however, begin an educational campaign that addresses the issues that the product may deal with without actually mentioning the name of the product. A company can begin planning the promotional campaign for their product long before it is approved so that it is ready to launch once approval is gained. In light of this, one Merck scientist said that “the first step was to build public awareness... Merck tried to be very creative and to target its potential audience” (Interview #1). Merck’s marketing team therefore had to divide the campaign into two parts; the unbranded, disease awareness part, and the post-approval, branded part, which finally urged women to go to their physicians and ultimately to get the vaccine (Herskovits, 2007a).

In 2006, as part of a five year cost cutting measure, Merck unveiled a new commercialization model “to win” major product launches, which meant that the Gardasil team at Merck was comprised of a diverse group of people from various departments

including marketing, regulatory, clinical, and policy, with one executive in charge of the whole team. (Herskovits, 2007a). In December 2006, Merck's president of global human health outlined four company objectives for the vaccine's debut: support global policy recommendations, secure broad public and private funding, encourage strong uptake among healthcare providers, and motivate women in the target age group (or their parents) to ask for the vaccine. Another hurdle was to gain the support of policymakers because in order to gain the broad coverage that it hoped for, Gardasil had to be integrated into the children's vaccine schedule (Herskovits, 2007a).

Merck worked with advertising agency DDB and public relations firm Edelman on both pieces of its campaign (Herskovits, 2007a). I was unable to obtain exact dates as to when Merck began working with these companies. I was also unable to speak directly with anyone in Merck's marketing department, though I did receive an e-mail response to my questions in this area. One of those questions was how far in advance these campaigns are crafted and who is involved and the response was "we do not disclose specifics" (Interview # 12). DDB was founded in 1949, is a multinational advertising agency with over 14,000 employees in nearly 100 countries, has won awards for its work, and used an approach to marketing that "relied on insight into human nature, respect for the consumer, and the power of creativity" (<http://www.ddb.com/>). They list many multinational companies as their clients; however, Merck is not listed.

Edelman is a PR firm and is over 50 years old, has 3,100 employees in 51 offices worldwide, and was described on its website as "the leading independent global PR firm." It was also "the first firm to apply public relations to building consumer brands. We invented the media tour; created litigation and environmental PR; were the first to use

a toll-free consumer hotline, and the first to employ the Web in crisis management” ([http://www.edelman.com/about\\_us/welcome](http://www.edelman.com/about_us/welcome)).

Both the unbranded and branded campaigns for Gardasil were primarily comprised of direct-to-consumer ads, along with print ads and accompanying websites. The unbranded campaign began in 2005 prior to the approval of Gardasil in June 2006. The ads were shown on TV, are available through YouTube, and were even shown in movie theaters along with movie previews (Rosenthal, 2008). YouTube was shown to be increasingly popular as a place to obtain health related information, and all of the Gardasil ads are available on YouTube as well commentary by professionals and the public about the vaccine (Ache & Wallace, 2008). In a study that rated the portrayal of HPV vaccination by doing a search on YouTube on one day in 2008, the researchers found that the Gardasil commercial had been viewed over 41,000 times and had been received positively, based on viewer comments (Ache & Wallace, 2008).

One Merck executive who answered questions via e-mail responded to how decisions were made about the promotional campaign for Gardasil, saying “We make decisions regarding our direct-to-consumer education efforts based on the need to educate parents and patients about the impact of disease. Most cervical cancers are preventable, yet approximately 11,000 women in the U.S. are diagnosed with the disease each year. As the makers of a vaccine that can help protect against 70 percent of cervical cancer, Merck believes it is responsible and appropriate to inform parents and women about the availability of this important preventative option” (Interview #12).

I also asked him how many people were involved in crafting the campaign to which he responded, “It’s difficult to say exactly how many people are involved in

bringing a communications program from conception to launch. We work with a large variety of internal and external stakeholders in developing campaign materials, as well as other awareness activities, so that we may help increase knowledge of HPV and its consequences” (Interview #12). He did not mention the work of DDB or Edelman in crafting their campaigns, not even when I asked how far in advance or at what point in the development of Gardasil these campaigns are crafted as well as who has to approve these campaigns and whether the FDA or other governmental organizations have any say in this process. He responded by stating that

We do not disclose these specifics; but, in deciding when to initiate DTC advertising for a new medicine, Merck considers both the need for physicians to have sufficient information to engage in an informed discussion with their patients and the need for patients to get timely information on the availability of new treatment options... Merck is committed to complying with the letter and spirit of the PhRMA Guiding Principles – Direct to Consumer Advertisements About Prescription Medicine. These are voluntary guidelines intended to reflect the commitment of PhRMA member companies to ensure that, in addition to meeting all applicable legal requirements, DTC communications contribute to public health by fostering an informed conversation about health, disease and treatments between patients and their health care practitioners. Additionally, we regularly submit our communications materials to the U.S. Food and Drug Administration’s (FDA) Center for Biologics Evaluation and Research (CBER) Advertising and Promotional Labeling Branch (APLB) for review and feedback prior to launching our campaigns (Interview #12).

The PhRMA guiding principles are a voluntary set of guidelines for direct to consumer advertising put out by the Pharmaceutical Research and Manufacturers of America that comply with the regulations of the Food and Drug Administration (PhRMA, 2005).

The unbranded educational campaign began in 2005, continued into 2006, and helped to lay the groundwork for the release of Gardasil by making the connection between HPV and cervical cancer (J. Schwartz, 2006). There were two campaigns



launched called “Make the Connection” (Merck & Co., 2005b) and “Tell Someone” (Merck & Co., 2005a). The “Make the Connection” campaign was the first of the campaigns and was launched in the fall of 2005, and was focused on spreading the word about the link between cervical cancer and HPV. It asked women to make the commitment to visit their physician to discuss HPV and cervical cancer and to assess their risk. Part of that campaign was beaded bracelet kits that could be ordered online; the idea was that as girls were stringing together the beads they were stringing together the facts about HPV and cervical cancer, which were included in the accompanying educational packet. The campaign was run by the industry-backed not-for-profit *Cancer Research and Prevention Foundation* and celebrity charity *Step Up Women's Network* (Medical News Today, 2006). The campaign included publicity events, a television public service announcement and cameos by celebrities, such as Maria Shriver and Jessica Alba, wearing beaded bracelets to highlight the link between cervical cancer and HPV (Medical News Today, 2006). Celebrities were also seen at public events wearing the bracelets and Merck pledged \$1 (up to \$100,000) to the Cancer Research and Prevention Foundation for every bracelet kit ordered. (Herskovits, 2007a; Merck & Co., 2005b).

The “Tell Someone” campaign was launched in April 2006, and tapped into “women’s natural inclinations as talkers and sharers” according to a Merck executive in charge of the marketing campaign (Herskovits, 2007a). This campaign focused on having women reach out to other women they knew to tell them about what they just learned regarding the connection between HPV and cervical cancer. Each woman that they told was one more woman who could be educated and potentially saved from

developing cervical cancer. Women were told not to ignore this information, and not to be shy about sharing it (Herskovits, 2007a). The website had images of women with the caption, “Did you know cervical cancer is caused by certain types of a common virus? Neither did we” (Merck & Co., 2005a). From this site, girls could send out personalized “tell someone” e-cards. Television ads showed actresses talking directly to the camera as if they were talking to each girl or woman personally. The disease awareness efforts drew on themes of safeguarding your children (for mothers) and empowerment (for girls). According to a Merck executive, “We learned early on that moms really wanted to protect their daughters—that protective insight is important. For young women, they want to empower themselves to take control of their own destiny” (Herskovits, 2007a). The campaign was effective and showed an increase in the percentage of females who could make the link between HPV and cervical cancer (Herskovits, 2007a; Rosenthal, 2008).

These two campaigns worked synergistically, where first women were informed about the issue, were asked to tell other women they knew, and then finally to visit their physician to discuss their risk of contracting HPV and possibly developing cervical cancer. These campaigns' linked learning about the issue, sharing it with friends and family, and seeing a physician with empowerment. The underlying message was about taking control of your health, about being a knowledgeable woman and doing what is necessary to prevent disease (Merck & Co., 2005b). Once the connection was made between HPV and cervical cancer, and Gardasil was approved, the next stage of the campaign could begin.

Once Gardasil was released in June 2006, their branded “One Less” campaign was launched November 13, 2006. This campaign involved images of vibrant young women and the catch phrase of “one less” as in you and the other women in your life could be one less woman to get cervical cancer. This campaign followed up on the themes of the previous campaigns and “the idea was really to deliver on the strong and powerful message of empowerment” (Herskovits, 2007a). The accompanying website had information, FAQs, quizzes to test ones' knowledge on the subject, and e-cards to send to friends/family in order to impart this information <http://www.gardasil.com/>. Each page on the website had a video that took up the top 1/3 of the page. The video had the same four women; 3 young women of diverse ethnicities (white, Asian, African-American) and one white older woman representing a motherly figure. Each video featured each of the women talking directly into the camera discussing the importance of getting vaccinated and encouraging viewers to get vaccinated as well. The remaining women are sitting on a couch in what looks like a living room interacting with each other. Below the video were four tabs to navigate the site; get the facts about HPV, learn about Gardasil, make an impact, and more for parents. The bottom section of the site had important facts about Gardasil, which gave a brief description about the vaccine, what it does, and what the reported side effects are. The site stressed the importance of continuing to receive pap tests, reminding women that a pap test can detect abnormal cells not limited to issues of cervical cancer (Merck & Co., 2005a).

The website not only contained information about HPV and Gardasil, but had resources for girls, young women, and their parents. The “make an impact” area of the site had three areas to choose from; tools to share, watch real life stories, and have some

fun. The “tools to share” section had an HPV information sheet as well as a PowerPoint presentation that could be downloaded. There was also an event planner for girls to plan a social gathering to “get the word out about HPV and cervical cancer.” The “watch real life stories” had videos of young women discussing HPV and cervical cancer and the importance of getting vaccinated. The “have some fun section” had wallpaper and screensavers, t-shirt designs, icons that could be used for instant messaging, as well as a banner that could be added to a blog; all of these are available to download for free. Girls can also sign up to get both mail and e-mail reminders for their remaining shots. The catch phrase used for this is “3 is key” <http://www.gardasil.com/what-is-gardasil/3-is-Key/three-is-key/index.html>. Additionally, items such as bags, pens, button, and posters were also available and had the Gardasil name and the slogan “one less” printed on them.

The Gardasil television ads that have been shown since 2006 and are still airing in 2009, stressed that the target population for the vaccine was young girls who had not yet become sexually active, yet the ads tended to show teenagers, who statistically are more likely to have engaged in sexual activity. The “one less” ads showed vital young women usually in their mid-late teens engaging in physical activity such as playing sports, skateboarding, riding horses, and dancing. The girl in each scene would speak straight into the camera saying that she could be one less women infected with HPV and at risk for cervical cancer. The girls would incorporate the slogan “one less” into their activity, where the skateboarder had “one less” written on her skateboard, the soccer player wrote “one less” on her shoe, and a girl sewed the word onto her sweatshirt. Other girls in the commercial held up signs saying “one less”

<http://www.youtube.com/watch?v=hJ8x3KR75fA&feature=related>.

Another commercial launched in 2008 used the slogan “I chose” and had the same type of young women talking straight into the camera and telling the reason why they chose to be vaccinated. In these commercials, the girls were in their bedrooms, in their living rooms, and at the kitchen table. It ends with a young woman saying she chose to get vaccinated because “my dreams don’t include cervical cancer”

<http://www.youtube.com/watch?v=gd4ypCXusrI&NR=1>. The ad is also available for viewing on the Gardasil website, <http://www.gardasil.com/i-chose-tv/>. In both of these ads, the young women are ethnically diverse, and portray different personality types; the athlete, the artist, the rebel, the intellectual, and even the girl next door. The ads do mention the reported side effects and the population it is intended for. Girls are encouraged to speak to their physicians and find out if Gardasil is right for them.

This girls depicted in the ads are from an older age group than the 11-12 year old girls that are the target population to vaccinate. This was brought up by a physician-researcher who was on the board for Merck and GSK, “so because their commercials were targeted so much at the semi-older woman, who’s already sexually active, the message they gave was very clear. It was like ‘oh, and it’s good for you too.’ So I have said to Merck – I said, ‘Well, if you say it’s okay for her then what’s the hurry in immunizing a young woman if it’s okay when she’s older?’ I said, ‘You really gave permission the way that you advertised it for young women to wait to get this vaccine.’”

(Interview #9). A Merck executive responded to this issue and said,

The perceived age of the girls/women in any type of advertising is subjective. We attempt to cast people in our commercials who represent those eligible for vaccination with Gardasil, which means incorporating a wide variety of females aged pre-teen to mid-20s. We have two different advertising campaigns ongoing - one that communicates HPV and vaccination messaging to moms

and another that communicates to young adult females. You'll notice that the age of the girls and women in these two different commercials does vary (Interview #12).

There have been some concerns that despite the valuable resources the sites and ads may have been, Merck's sponsorship of them might have sent the message that the purpose was less about educating women and more about selling Gardasil (J. Schwartz, 2006). An additional concern was that the frequency of the ads may leave viewers thinking that cervical cancer is more prevalent than it is (Norsigian & Stephenson, 2008).

Prior to the release of these ads, few women had heard of HPV (Grant, Kravitz-Wirtz, Breen, Tiro, & Tsui, 2009; National Cancer Institute, 2007). According to the National Cancer Institute, in 2005 61% of American women had never heard of HPV, and of those who had heard of HPV, 44% did not know of its connection to cervical cancer (National Cancer Institute, 2007). A Health Information National Trends Survey (HINTS) brief put out by the National Cancer Institute examined how variables such as sociodemographics, access to health care, cervical cancer screening history, cancer history, and attention to and trust of health information were associated with accurate knowledge of HPV and its connection to cervical cancer. They found that awareness of HPV was significantly lower among women who are older, less educated, and less exposed to health information. The research brief did not elaborate on what forms or sources of health information they examined. Factors associated with knowledge of HPV were being non-Hispanic White, getting regular Pap tests, and being aware of the change in cervical cancer screening guidelines. Among those women who had heard of HPV, the study found that the only factors positively associated with knowing that HPV causes

cervical cancer were having had an abnormal Pap or a positive HPV test result (National Cancer Institute, 2007).

A study done by Jasmine Tiro and colleagues used the HINTS data to assess the factors associated with US women's awareness of HPV and knowledge of its connection to cervical cancer (Tiro, Meissner, Kobrin, & Chollette, 2007). Accurate knowledge of this link is necessary in order to make appropriate, evidence-based health care choices. The authors believed it was important for health communication researchers to know which group(s) of women would benefit from educational messages about HPV and its link to cervical cancer, particularly as "HPV-based technologies diffuse into the general population" (Tiro et al., 2007, p. 288). While knowledge is not a direct predictor of health behavior, it is a key first step to the success of a health education intervention.

Their study showed that awareness of HPV has increased over the past decade, but knowledge of its link to cervical cancer still remained low. They found that from the national sample of women ages 18-75 years old, less than 40% of women had heard of HPV and less than half of those women also knew it caused cervical cancer. Their primary finding was that "factors associated with HPV awareness differed substantially from those associated with HPV-cervical cancer knowledge" (Tiro et al., 2007, p. 292). Women who had tested positive for HPV had heard of it and were 3.5 times more likely to know of its link to cervical cancer. Their findings suggested that education is more likely to occur after a woman had experienced an adverse consequence from HPV infection. Additionally, familiarity with HPV does not guarantee accurate knowledge about its link to cervical cancer. Therefore, the authors felt that it was important to identify women least likely to have accurate knowledge of HPV and to develop clear and

appropriate messages for them. Understanding among women about this issue is essential if “HPV testing and vaccination are the future for cervical cancer control” (Tiro et al., 2007, p. 294). This research was conducted prior to the release of the ads for Gardasil.

An article published in *Gynecologic Oncology* by Thomas Herzog and colleagues also discussed the fact that knowledge about HPV infection and cervical cancer as well as the need to vaccinate are still lacking among both women and physicians (Herzog, Huh, Downs, Smith, & Monk, 2008). Looking at recent studies, Herzog et al addressed both the awareness and attitudes about HPV vaccination among two groups; patients and parents, and physicians. In terms of awareness, they found that women who were the most knowledgeable about HPV were those previously tested or diagnosed with a cervical abnormality. Among the general population, awareness varied greatly, with approximately 44% knowing that HPV caused cervical cancer. The physicians included pediatricians, primary care physicians, and obstetricians/gynecologists. The majority of pediatricians were aware that low risk types of HPV caused genital warts, yet 2/3 knew that high-risk oncogenic types caused cervical cancer. Obstetricians/gynecologists were the most knowledgeable, while primary care physicians were the least knowledgeable (Herzog et al., 2008)

The attitudes among these groups were also analyzed (Herzog et al., 2008). The majority of parents surveyed reported they would be willing to vaccinate their adolescent daughters; vaccine acceptability appeared to be high despite generally low levels of knowledge of HPV. Vaccine acceptance seemed to vary based on ethnic, religious, and socioeconomic backgrounds. Therefore, strategies to increase awareness need to be



tailored to these various groups because what may work for one group may not necessarily be successful with another group (Herzog et al., 2008). Physicians' attitudes continue to be a crucial factor in their patients' and parents' views on HPV vaccination. The most important attributes for acceptance among physicians was efficacy and long term safety. One issue among pediatricians was that they do not generally discuss issues of sex or sexuality with their patients or their patients' parents unless asked directly. The vast majority of pediatricians also did not believe their current knowledge of the HPV vaccine was sufficient enough to properly explain the vaccine. For family care physicians and obstetricians/gynecologist, an influencing factor was recommendations by their respective professional organizations. Overall, the authors concluded that education and communication efforts to the public need to be increased, and that targeting these physicians in this education campaign is crucial (Herzog et al., 2008).

In 2007, following the release of these ads, 74% of girls 13-17, 79% of young women ages 18-26, and 76% of women ages 27-64 had heard of HPV (Grant et al., 2009). In a policy brief put out by the UCLA Center for Health Policy Research, which tracked females in California, television advertisements were cited as the most common source among women ages 18-26 (61%) and 27-64 (53%). The numbers were slightly lower for younger girls ages 13-17 (42%). For this younger age group, school was the most frequently cited source of HPV information, followed by health care providers and family members (Grant et al., 2009). Merck also did their own studies and found that awareness increased significantly following their campaigns (Herskovits, 2007a).

The advertising campaigns for Gardasil were successful and in 2007 and 2008 Merck won awards for them (Herskovits, 2007a; Koroneos, 2008; Rosenthal, 2008). In

2007, *Pharmaceutical Executive* gave its first “brand of the year” honor to Merck for its Gardasil campaign, and praised the campaign saying, “by combining innovative science, strategic commercialization, and savvy disease education, Team Gardasil created a campaign that evoked Merck in its prime—and made strides toward stamping out cervical cancer” (Herskovits, 2007a). Merck and its campaign for Gardasil were also applauded not just for their scientific achievement, but for their success at creating a successful brand. According to *Pharmaceutical Executive*, a great brand tells a story “about fulfilling a lifesaving need, overcoming obstacles both scientific and social, and teaching people a health lesson that lasts” (Herskovits, 2007a). In this instance Gardasil was viewed as a pharmaceutical breakthrough and not only “turned a medical success story into a campaign of empowerment for a generation of girls and young women” but also “made a market out of thin air” (Herskovits, 2007a). Another reason for awarding Merck for its Gardasil campaign was “Merck's researchers used visionary science to produce a vaccine...while marketers taught girls and young women how to talk about sensitive issues in a forthright, unapologetic way” (Herskovits, 2007a).

Gardasil also won six first place awards in 2008 at the 10th Annual Pharmaceutical Advertising and Marketing Excellence Awards (PhAME) (Koroneos, 2008). Merck’s campaign for Gardasil was an example of new marketing strategies that “focus on how consumers process information in complex disease categories” where “consumers have longer periods of time to acquire information before the initial steps in seeking therapy” (Koroneos, 2008). Along with their ad company DDB, Merck won first place awards for Gardasil in the following categories; best branded TV, best branded

print, best integrated campaign, and best multicultural campaign. Merck and DDB each won for marketer of the year and agency of the year respectively (Koroneos, 2008).

It was not only important to market the vaccine to the public, but to the medical community who would be providing the vaccine to the girls and women now aware of the vaccine. Physicians not only need to be aware of new innovations in medicine, but how to speak to their patients about them.

### *Marketing to Physicians*

In 2001, after the first clinical trial results for the monovalent HPV 16 vaccine were known and shown to be effective, Dr. Richard Haupt, executive director of medical affairs at Merck was asked to start thinking about the policy issues surrounding Gardasil particularly because professional society and ACIP recommendations are what drive the standards of care for providers (Herskovits, 2007a). Following the launch of the vaccine in 2006, Merck unveiled its educational campaign for physicians. Having capped the head count of its sales force for financial reasons, Merck redeployed members of its sales force to cover this growing area. Merck tailored its educational efforts to three specialties: pediatricians, who knew how to give vaccines but were less versed on HPV; gynecologists, who were familiar with the disease, but whose offices were not set up for vaccination; and family practitioners who were somewhere in the middle (Herskovits, 2007a). Merck also provided unrestricted educational grants to professional societies to help physicians address issues including vaccine inventory, legally required patient forms, and reimbursement. Those specializing in continuing medical education also

identified experts who could communicate with other physicians about the vaccine (Herskovits, 2007a).

Physicians were recruited and trained to give talks about Gardasil, making anywhere from \$1000 - \$4500 per talk (Rosenthal, 2008). Merck also partnered with the company Digene who make the HPV DNA test for the “educate the educator” program, which provided physicians with a CD with all of the information and tools needed to talk about Gardasil and its effectiveness in preventing HPV and cervical cancer. A physician-researcher discussed this and said

I think Merck has been very effective at their marketing and has given the tools to physicians to go out and spread their messaging in this ‘Educate the Educator.’ Merck underwrote the cost - and Digene underwrote the cost of producing this very slick CD tools...They gave it out to everybody and then they - these physicians who received the training for ‘Educate the Educator’ were paid by Merck to go and give the talk to groups of physicians in their community, paid a lot, \$1000 a pop. And who doesn't like to think that they're a local expert that has expertise in an area (Interview #7).

### *Lobbying*

Lobbying is widely practiced by the pharmaceutical industry and therefore was a potential factor in the promotional campaign for Gardasil. It was important to understand how lobbying factored into Gardasil's timeline. The following section discusses this issue and what role if any lobbying played in this process. The pharmaceutical industry has one of the biggest lobbies in Washington (Angell, 2004; Ismail, 2005, 2006). There is no evidence that lobbyists were involved in the promotional campaigns for Gardasil, though there was acknowledgement by one of my interviewees that lobbying played a role in the attempts to mandate the vaccine. One physician-researcher confirmed the involvement of lobbyists in attempts to make the vaccine mandatory. This individual stated, “I met with

the lobbyist who worked with Women in Government. That lobbyist wrote all the legislative material for WIG to take back to legislatures” (Interview #6).

In a 2008 article in the New York Times, the chairman of the ACIP was quoted as saying there “was incredible pressure from industry and politics” (Rosenthal, 2008). That same article quoted a prominent physician researcher who said “Merck lobbied every opinion leader, women’s group, medical society, politicians, and went directly to the people – it created a sense of panic that says you have to have this vaccine now” (Rosenthal, 2008). According to one researcher at Merck, “there is no participation from lobbyists in the approval process or meeting with the FDA” (Interview #1). He did not say if there was participation from lobbyists at other times.

Articles written in the mainstream press have confirmed the use of lobbyists in this process. Merck was financially backing efforts to pass state laws requiring girls to be vaccinated, and they have also paid into a program run by a Washington DC lobbying firm to lobby the CDC and Congress for increased federal funds for vaccines (Associated Press, 2007; Austin Peterson, 2007; Norsigian & Stephenson, 2008; Rosenthal, 2008). Much of their lobbying was done through the organization Women in Government which has received substantial donations from Merck, and a top official from Merck’s vaccine divisions sits on Women in Government’s business council (Associated Press, 2007; Austin Peterson, 2007). A Merck spokeswoman confirmed a donation to the organization, but would not disclose the amount given to Women in Government, and it was unclear exactly when that donation was given. She was quoted as saying “we disclosed the fact that we provide funding to this organization. We’re not in any way trying to obscure that” (Associated Press, 2007). In the state of Texas alone, Merck increased lobbying

spending to between \$150,000 - \$250,000 as lawmakers were considering mandating the vaccine in that state (Associated Press, 2007)

I asked one of the physicians at Merck to what extent lobbyists had been involved in any aspect of Gardasil's marketing or promotional campaign. This interview included an employee from Merck's public relations department who facilitated the interview.

They both spoke to this. First, the physician responded that

actually right now there's no active lobbying at all going on...I mean there is no lobbying – at least since I've been here... I was in practice up until I came here in August of 2007 and when I came here there was no lobbying going on right now and that was really a choice, you know, just to make sure that – we wanted to make sure that people external to Merck were making decisions that they thought were best for their constituents with the data that was publicly available and so to my knowledge there's been no lobbying going on (Interview #11).

At that point the public relations contact entered the conversation and stated

Let me make a clarification as well that when we're talking about lobbying, if at all, it's certainly more in the rollout type impact. How are people in the communities whether it be local city's governments, state assembly, how is that going to actually become available to people. But certainly when we're talking about a conversation like that with the CDC of what [name] mentioned, that's a scientific exchange that's not – that's not by any means you know, kind of what you're categorizing or what others categorize as lobbying" (Interview #11).

Arguably the most controversial aspect of the discussions around Gardasil were the attempts to make it mandatory so soon after its release. These attempts generated a lot of discussion about the vaccine itself as well as about Merck. The following section addresses this issue.

### *Mandating the Vaccine*

Mandating vaccination as a condition for school entry began in the early 1800s and is currently required by all 50 states for many childhood infectious diseases (Javitt, Berkowitz, & Gostin, 2008). Vaccines are generally on the market for several years before mandates are considered, so that public health officials have ample time to evaluate issues of safety and effectiveness (Saul & Pollack, 2007; Unlisted, 2007). Mandates are also a financial issue since issuing a mandate requires states to buy the vaccine and make it available to those who cannot afford it or whose insurance does not cover it. There are estimates that mandating the Gardasil vaccine could double the cost of vaccine programs in some states (Harris, 2006a, 2006b). The cost to the federal government to make this vaccine available to low income girls and young women would be approximately \$2 billion (Harris, 2006a, 2006b).

The efforts to make Gardasil mandatory, which have since stopped, caused controversy and generated a lot of discussion on the subject. One concern was that Merck pushed “too far too fast, potentially undermining eventual prospects for the broadest possible immunization” (Saul & Pollack, 2007, p. 1). An argument in favor of mandating the vaccine is that it helps to ensure more equal vaccination among the recommended group, thus helping to mitigate economic disparities that might prevent some groups from receiving the vaccine (Saul & Pollack, 2007). Vaccine requirements can ensure that the vaccine reaches those who need it most and who often have limited access to health care (JL Schwartz, Caplan, Faden, & Sugarman, 2007). Additionally, vaccination requirements are often viewed as the only proven means of ensuring high vaccination rates among children (JL Schwartz et al., 2007).

The possibility of mandatory vaccination brought unlikely groups together in opposition beginning in late 2006, early 2007 when the mandate issue was publicly being discussed. Those opposing mandatory vaccination included social and religious conservatives and civil libertarians who were concerned with government interference with parental decision making, as well as vaccine safety groups who were concerned about possible health effects from vaccines in general (JL Schwartz et al., 2007). There were also prominent people in the areas of infectious disease, vaccine policy, and public health who felt that the proposed mandates were occurring too soon after the vaccine's release, and that there was value in a gradual development of vaccination programs to ensure safety and efficacy of the vaccine (Saul & Pollack, 2007; JL Schwartz et al., 2007). In addition to the arguments mentioned above, there was also concern that there had not been enough public education or discussion on the topic, and that the sexual transmission of the virus did not warrant the kind of school mandate generally used for casually communicable diseases (Javitt et al., 2008; JL Schwartz et al., 2007). It would also be the first vaccine to be mandated for use exclusively in one gender. The role of Merck in this process also drew negative criticism as these attempts occurred less than 3 years after the Vioxx situation, which left many responding negatively to "what appeared to be a company overly interested in influencing the opinions of policymakers, physicians, and the public regarding the new vaccine" (JL Schwartz et al., 2007, p. 762).

An article published in the *Journal of Law, Medicine and Ethics* argued that mandatory HPV vaccination at this time is both unwarranted and unwise (Javitt et al., 2008). According to Javitt et al, the vaccine raised significant concerns. First, the long terms safety and efficacy had not been established, therefore the vaccine should be rolled



out slowly with risks and benefits carefully assessed. Only after the vaccine has been used in a larger number of females will the true incidence of adverse events be known. Additionally, the length of immunity remained unclear, and after the vaccine is used for a longer period of time, it may turn out that another vaccine schedule is determined to be more effective (Javitt et al., 2008). Second, HPV does not threaten an imminent and significant risk to the health of others, and does not meet the legal and ethical justifications that have historically supported vaccine requirements. In this case, mandating this vaccine would constitute an expansion of the state's authority thus interfering with individual and parental autonomy (Javitt et al., 2008). Third, there were constitutional concerns due to the requirement to only vaccinate girls. Finally, the mandate would likely place an economic burden on federal and state governments as well as individual practitioners which might impact the provision of other health services (Javitt et al., 2008).

Mandates are effective to protect the public health, and in the view of Javitt et al, HPV infection presents no public health necessity (Javitt et al., 2008). HPV is a sexually transmitted disease and infection with HPV is not immediately life threatening. Cervical cancer or other HPV related conditions take many years to develop, leaving ample time for medical intervention. Many women will also never be exposed to the cancer causing strains of HPV, and furthermore, not all women exposed to those strains develop cervical cancer (Javitt et al., 2008). Therefore, the authors felt that “conditioning school attendance on HPV vaccination serves only to coerce compliance in the absence of a public health emergency” (Javitt et al., 2008, p. 389).

In 2007, *The American Journal for Maternal/Child Nursing* presented a pro and con position by two different nurses about whether the HPV vaccine should be mandatory. The pro argument cited the efficacy results from the clinical trials, which showed 100% efficacy in the per protocol population, which the author said should be reason enough to support a mandate (Cruise, 2007). The high rates of HPV were also cited as a reason, and vaccinating girls before they become sexually active could help to significantly reduce the rates of HPV infection. Since statistics show that approximately half of high school aged people are sexually active, immunizing girls before they become sexually active could significantly reduce infection. While opponents often cite the high cost of instituting a vaccine mandate, this author felt that those costs would be offset by the reduction in costs associated with cervical cancer treatment and time lost from work by women who are ill (Cruise, 2007). Finally, immunization mandates in general have been shown to increase overall immunization rates, and since girls receive other vaccinations between the ages of 11-12, adding the HPV vaccine should not result in an inconvenience to families (Cruise, 2007).

The con argument presented several reasons against mandating the vaccine (T. Anderson, 2007). First, the author was concerned about the long term safety of the vaccine. The safety should be evaluated after being used in a real world context, not simply in the controlled environment of the clinical trials. She cited the Rotavirus vaccine that was shown to be safe in the trials, but after being used in hundreds of thousands of infants was pulled from the market due to serious adverse events (T. Anderson, 2007). Second, not all women are at risk for infection with the vaccine HPV types; most women who acquire HPV infection clear it naturally in a relatively short

period of time. Third, mandating the vaccine would violate the autonomy of women who choose abstinence. The fourth reason countered the argument that adding another vaccine to the existing schedule would not be problematic. In the author's view this did not take into account that most of the other childhood vaccines prevent casually communicable diseases, which differs from HPV transmission. Finally, the economic cost was a concern since there are families without private health insurance and who do not qualify for state or federal programs leaving them unable to afford the vaccine (T. Anderson, 2007).

A 2007 article published in *The Journal of the American Medical Association* also discussed this issue (Gostin & DeAngelis, 2007). One concern of the author was the limited safety and effectiveness data; the vaccine was not evaluated for efficacy among girls ages 9-15 years old. Allowing the vaccine to be widely used in the population without mandating its use would provide the opportunity to more fully evaluate the safety and effectiveness in all populations for whom the vaccine is recommended. The overall prevalence of HPV is relatively low, therefore, it seemed unwise to the authors that a female would need to be vaccinated against something for which she was at a low risk of contracting (Gostin & DeAngelis, 2007). Additionally, HPV is not an airborne disease, is not casually communicable, and there is no immediate risk of rapid transmission of HPV in schools. Another consideration was how people would be compensated if they incurred serious adverse events, which may complicate tort claims. The authors felt that if the state mandates an intervention, then it should also provide a compensation system in the event of serious adverse events. The fact that Merck spearheaded efforts to make the vaccine mandatory was also problematic for the authors who felt that such efforts should

be led by public health authorities, pediatricians, and infectious disease specialists (Gostin & DeAngelis, 2007). Their final concern was the cost of the vaccine, who would pay for it, and what other public health services may have to be sacrificed as a result. The authors felt it was more prudent to wait to see the data for the vaccine after it has been in use for a longer period of time in the general public (Gostin & DeAngelis, 2007).

A 2009 article published in *American Journal of Public Health* presented a view in favor of mandatory vaccination (Balog, 2009). The author began by comparing this to the issue of mandatory Polio vaccination that occurred in the early part of the 20<sup>th</sup> century. That vaccine effort helped to effectively eradicate Polio and the author felt that a similar situation currently exists with HPV, and that we have the ability to significantly reduce the incidence of this virus and thus maintain health (Balog, 2009). One important argument that this author refutes is that many parents are concerned that this would encourage children to engage in sexual activity and would interfere with their efforts to teach their children abstinence. In his view, this dismissed a focus on the prevention of a physical harm with “a social desire to uphold deeply rooted moral values about how the young should sexually behave” (Balog, 2009, p. 618). In terms of mandatory vaccination interfering with parental rights, this author felt that preventing a child from acquiring this virus should override respect for the parents’ autonomy. Mandatory vaccination makes the vaccine available to everyone and reduces disparities by providing universal access, which is an issue of justice (Balog, 2009). The final point the author made related to scientific concerns that have been raised regarding the relatively low incidence rates of cervical cancer, the lack of long term safety and effectiveness data, and cost effectiveness. Despite these concerns, the author still felt that mandatory vaccination is a

valuable tool in fighting cervical cancer and that ethical principles of protection against disease justify mandatory vaccination (Balog, 2009).

A researcher from Merck stated that he supported attempts to make the vaccine mandatory. He did not elaborate on the reasons why he felt mandating the vaccine would be beneficial, he just simply responded that he supported the attempts to make it mandatory, and then proceeded to another issue relating to Gardasil (Interview #1). In discussing the role of Women in Government in Merck's attempts to make Gardasil mandatory, one prominent physician researcher discussed the issue of mandating the vaccine and the role that Women in Government played in the process.

WIG group is made up of elected officials from all states at federal and state level. They willingly tell you they take money from anyone and everyone, which is what many organizations do because they need to stay afloat. Their job is to help make sure legislation that helps women will get introduced in the proper legislatures, so their reason for being is valid. They took on the issue of the HPV vaccine and cervical cancer with the misunderstanding that the vaccine will eliminate cervical cancer – they had the “let's get on the bandwagon” attitude. Was contacted by WIG because of her work, and gave them some primers about the issue and an understanding of what this vaccine could and could not do. Went to some of their meetings, and the message ended up getting contorted by saying that they want to eliminate cervical cancer and they want to mandate. They argued that this is the way to reduce health disparities by mandating the vaccine. The problem is that even if a mandate goes through it does not mean that there is not enough money to ensure everyone gets vaccinated (Interview #6).

Most of the people I interviewed did not approve of mandating this vaccine so quickly, and felt that the attempts to mandate the vaccine undermined the potential benefits of the vaccine. One physician researcher felt caution needed to be utilized before mandating the vaccine or even before vaccinating large groups of females. He questioned the urgency, particularly since cervical cancer is not a big problem in this country. He stated

So there is some urgency from a cohort effect for individual women but the question is is there urgency in the United States to get this done and get everyone vaccinated before the Phase III trials are known - results? I'm not sure where that's coming from because cervical cancer is not common. It mainly occurs amongst unscreened women and if we put as much time, energy, and resources into screening unscreened women than vaccinating - especially sexually active women, the risks and benefits really quite tenuous - we would really do a big service in terms of cervical cancer prevention because that's where most of it occurs in the U.S. (Interview #8)

When Merck's funding of this process was exposed, there was widespread criticism and in February 2007, Merck ceased its efforts to make Gardasil mandatory (Herskovits, 2007b; Norsigian & Stephenson, 2008)

#### *State Efforts to Mandate the Vaccine*

Since approval of Gardasil in June 2006, 41 states and the District of Columbia have introduced legislation regarding HPV vaccination and mandating the use of the vaccine (Javitt et al., 2008; Vetter & Geller, 2007). Only Virginia and the District of Columbia have passed laws requiring HPV vaccination, and an executive order mandating vaccination in Texas was quickly overridden by the legislature. The legislation introduced has focused on four main areas: mandating HPV vaccination of minor girls as a condition for school entrance; mandating insurance coverage for HPV vaccination or providing state funding to mitigate the cost of the vaccination; educating the public about the HPV vaccine; establishing committees to make recommendations about the vaccine (Javitt et al., 2008). The legislation also included opt out provisions that would have allowed parents to obtain an exemption from vaccinating their child for medical, religious, or philosophical beliefs (JL Schwartz et al., 2007; Vetter & Geller, 2007).

The legislation included establishing vaccination guidelines in the states' departments of public health, requiring vaccination for entry into the 6<sup>th</sup> grade, requiring insurance companies to cover the vaccine, and creating awareness campaigns for the vaccine. In the 2007-2008 year, four state legislatures passed laws about Gardasil (National Conference of State Legislatures, 2009). California passed a law through the legislature that would have required insurance coverage for HPV screening, HPV vaccine coverage, and cervical cancer treatment. It was vetoed by the governor in September 2008. Iowa successfully passed legislation that would require insurance companies to cover HPV vaccinations; it was signed by the governor in April 2008. Louisiana passed legislation through its legislature that would require schools to provide HPV information and vaccines in certain circumstances, though they do not elucidate what those circumstances are. In 2009, Louisiana had a bill in committee to require insurance companies to cover the vaccine. Finally, Michigan passed a law in 2008 that would require schools to provide HPV information and vaccines under certain circumstances, though they also do not elucidate what those circumstances are (Javitt et al., 2008; Millspaw, 2008; National Conference of State Legislatures, 2009).

Much of the legislation that was introduced into state legislatures was done with the help of the organization Women in Government. Women in Government introduced bills in 20 states, and in Florida; Merck helped write the legislation (Allen, 2008). In 2007 the governor of Texas issued an executive order mandating the vaccine before it was revealed that the Texas state director for Women in Government was the mother-in-law of the governor's chief of staff at the time, his former chief of staff left his office to work as a lobbyist for Merck in Texas, and the governor received \$6,000 from Merck's

political action committee (Allen, 2008; Saul & Pollack, 2007). One physician-researcher discussed her experience with and knowledge of this organization as well as the role that Merck's lobbyist played in those efforts.

That lobbyist wrote all the legislative material for Women in Government to take back to legislatures. Women in Government is made up of elected officials from all states at federal and state level. They willingly tell you they take money from anyone and everyone, which is what many organizations do because they need to stay afloat. Their job is to help make sure legislation that helps women will get introduced in the proper legislatures, so their reason for being is valid. They took on the issue of the HPV vaccine and cervical cancer with the misunderstanding that the vaccine will eliminate cervical cancer – they had the 'let's get on the bandwagon' attitude...the message ended up getting contorted by saying that they want to eliminate cervical cancer and they want to mandate this vaccine. They argued that this is the way to reduce health disparities by mandating the vaccine (Interview #6).

The promotion and marketing of Gardasil not only brought about awareness of this new vaccine, but influenced its use. The following section discusses the use of Gardasil and the rates of uptake for the vaccine. The first step in this process is ensuring acceptance of the vaccine because if it is not accepted, then it is unlikely to be used.

#### *Acceptance of the vaccine*

Ensuring acceptance of Gardasil is a key element in creating sustained widespread use of the vaccine. One of the first steps by Merck was to increase the public's knowledge about HPV infection and its relationship to cervical cancer, (Vetter & Geller, 2007), which began in 2005 with their unbranded marketing campaign. A lack of assurance from a trusted source that the vaccine is safe and effective can hinder development of a positive image of the vaccine. Comprehensive education programs are essential, yet since much of those efforts have been funded by Merck, the general public may be less inclined to believe the information from that source (Vetter & Geller, 2007).



Vetter and Geller believed that educational campaigns must be moved into the public realm such as state agencies, non-profit organizations, health care providers and schools (Vetter & Geller, 2007). There seemed to be more public acceptance for vaccinating females 13 and older as opposed to preadolescent girls 11 – 12 years old, therefore, effective communication should emphasize the importance of vaccination before a girl becomes sexually active (Vetter & Geller, 2007).

#### *Access to Gardasil*

As Merck pushed for increased use of Gardasil from the time of its approval in 2006, financial constraints had to be addressed because even though the Vaccines for Children program vaccinated eligible females 9-18 years old, the high cost of the HPV vaccine still placed an extra burden on the program (Vetter & Geller, 2007). States have taken on much of the responsibility when those issues might be better addressed at the federal level. Vaccination for females 19-26 is more uncertain for those with and without insurance, and may not be cost effective (Kim & Goldie, 2008; Vetter & Geller, 2007). As of February 2007, 64% of immunization programs reported that Medicaid covered or intended to cover HPV catch up vaccination, though coverage among private insurers was inconsistent (Vetter & Geller, 2007). Merck created a new patient assistance program for vaccines which made Gardasil available for free for females ages 19 and older who are uninsured or unable to afford vaccines (Merck & Co., 2007a). This program was available in private physicians' offices and private clinics, therefore women seeking care in public clinics would not be eligible for this program (Vetter & Geller, 2007).

### *Use of Gardasil*

A recent study by David Grant and associates at the UCLA Center for Health Policy Research presented the first HPV vaccination estimates for the state of California (Grant et al., 2009). Using data from the 2007 California Health Interview Survey, which ran from June 2007 – March 2008 this research brief looked at the uptake of Gardasil among females ages 13-26 since the ACIP recommendations were published in March 2007. It also looked at the knowledge and awareness of HPV and Gardasil as well as vaccine acceptability among females ages 13-64 and parents of eligible females ages 9-17 (Grant et al., 2009). Approximately 26% (378,000/ 1,468,000) of teen girls in California ages 13-17 reported receiving at least one dose of Gardasil in 2007, and 11% of teen girls reported receiving all three doses by the interview dates (Grant et al., 2009).

The percentages of uptake in California among the 13-17 year old age group appear to be higher than the numbers nationwide. A CDC report in the October 10<sup>th</sup> issue of the Morbidity and Mortality Weekly Report (MMWR) discussed the rates of vaccination nationwide (CDC, 2008). The CDC report used numbers from the National Immunization Survey – Teen (NIS-T), which estimated vaccine coverage from a national sample of teens ages 13 -17 years. The NIS-T has been conducted since 2006, and this particular survey was conducted during the fourth quarter of 2007. The NIS-T collected vaccination information on age-eligible adolescents, aged 13-17 years using a random digit dialing sample of household telephone numbers. They were interested in vaccine coverage for all vaccines recommended for adolescents, not just the HPV vaccine. This particular survey was the first time that information about the HPV vaccine was

collected. After receiving permission from the parent/guardian, surveys are then mailed to the adolescents' vaccination provider(s) to obtain the vaccination histories (CDC, 2008).

Among the households identified by telephone in NIS-T, 81.5% were screened for an age-eligible adolescent. Among the 9.5% in which an age-eligible adolescent lived, 83.3% (5,474) completed the household interview. Provider-reported vaccination records were obtained from 2,947 adolescents, representing 53.8% of adolescents with completed household interviews (CDC, 2008). According to this survey, approximately 25% of adolescents in this age group received at least one dose of the Gardasil vaccine (CDC, 2008). This showed that within one year after ACIP recommendations were made, approximately one in four adolescent females had initiated the vaccination series. It is unknown from this data how many of those completed the 3 dose vaccination series (Grant et al., 2009).

According to the Grant study, the vaccine uptake for the 18-26 year old group in California was lower than for the adolescents. In California, approximately 12% (262,000/2,273,000) of females in this age group reported receiving at least one dose of the vaccine, and 4% had completed the vaccine series, which was 38% of vaccine initiators (Grant et al., 2009). The CDC does not have vaccine information on this age group.

Vaccine acceptability is another area that the UCLA research brief discussed, as that may provide an indicator of those likely to be vaccinated in the future (Grant et al., 2009). When asked if they would be interested in receiving the HPV vaccine, 76% of 13-17 year olds and 60% of 18-26 year old reported that they would be. A slightly lower

percentage (57%) of parents of age eligible girls said they would be interested in vaccinating their daughters. In both the parent and young female groups who said they were not interested in either vaccinating their daughters or being vaccinated themselves, not knowing enough about the vaccine was the primary reason (Grant et al., 2009). Concerns about the safety and effectiveness of the vaccine were other frequently cited reasons for not wanting to vaccine or be vaccinated (Grant et al., 2009).

Vaccine acceptability was also discussed by The American Cancer Society who reported that based on studies, that overall acceptance of the HPV vaccine is high (Saslow et al., 2007). Acceptability is important in that it indicates who is likely to use the vaccine. Several factors influence people's attitudes about the vaccine. The most salient issues for the public included safety, high efficacy, severity of the infection, perceived risk, and physician recommendations (Saslow et al., 2007). For providers, professional society recommendations were also deemed important (M. Miller, Wilson, & Waldrop, 2008; Saslow et al., 2007). The level of knowledge that people had about HPV and its association with cancer was related to their level of acceptability; the more they knew, the more accepting they were about the vaccine. Messaging was also a factor, and there was a higher level of acceptability when the vaccine was perceived to prevent cervical cancer as opposed to a sexually transmitted disease (Saslow et al., 2007)

An article published in *The Nurse Practitioner* also discussed findings from studies regarding the level of and factors influencing acceptability (M. Miller et al., 2008). Factors positively influencing acceptability were the recommendation of either a parent, partner, or provider, and low cost, safety, and health beliefs (M. Miller et al., 2008). Safety was the biggest concern for parents. There were also concerns related to

sexual activity. Some thought that the vaccine would promote promiscuous behavior, and there was less urgency to vaccinate young girls due to their perceived low risk of being sexually active. A majority of adults aged 25-45 were not aware of the link between HPV and cervical cancer, but after an educational discussion, over 80% would accept the vaccine for either themselves or their daughter (M. Miller et al., 2008).

One study published in the *Journal of Adolescent Health* surveyed parents in California households to examine the likelihood of and reasons for parental acceptance of the HPV vaccine for young adolescent girls as well as any potential racial/ethnic disparities in acceptance rates (Constantine & Jerman, 2007). A total of 522 parents with one or more daughters living at home were included in the analysis and interviews were conducted in either English or Spanish depending on the respondents' native language. The respondents were asked a total of three questions; two closed ended and one open ended. The two closed ended were how likely they would be to have their daughter vaccinated before her 13<sup>th</sup> birthday, if the vaccine were available. The second question was dependent on the first because if they were unlikely to vaccinate, then they were asked how likely they would be to vaccinate her before her 16<sup>th</sup> birthday. The open ended question was why they felt that way about vaccinating their daughter (Constantine & Jerman, 2007).

The results from this study showed that overall, 75% of the sample reported they would be likely to vaccinate a daughter before age 13. 6% reported that they would be likely to vaccinate before age 16, but not before age 13, while 18% reported they would be unlikely to vaccinate before age 16 (Constantine & Jerman, 2007). In terms of race/ethnicity, Hispanic parents were more likely than others to endorse vaccination

before age 13, while Asian-American and African-American parent were less likely to do so. Parents who were likely to vaccinate had specific health and safety reasons for doing so such as keeping their child safe. Among those unlikely to vaccinate, the reasons included effects on sexual behavior, safety concerns about the vaccine, concerns about vaccines in general, and a feeling that vaccination was unnecessary (Constantine & Jerman, 2007). The acceptability level has direct implications for policy and social marketing decisions in this area (Constantine & Jerman, 2007).

Acceptability and use of the vaccine for some people might also be connected to their feelings or perceptions about the company that makes the vaccine. There were not any published studies that discussed the public's views about Merck and what effect if any that had on their intentions to use Gardasil, though that might be an issue discussed in the future. The view of Merck by professionals may affect their decision to recommend or use the vaccine on their patients or affect their view of the vaccine in general. I asked all of my interviewees about their views about Merck as a company and in the context of the pharmaceutical industry.

### *Sales and Revenue*

Worldwide sales for Merck increased 3% during the year 2006, which was helped in part by the release of Gardasil (Merck & Co., 2007b). Domestic sales particularly benefitted from the launch of three new vaccines, which included Gardasil. For 2006, sales of Merck's five vaccines totaled almost \$1.9 billion, which was an increase of approximately \$756 million from 2005 (Merck & Co., 2007b). In terms of revenue, the vaccine segment generated approximately \$1.7 billion, which included Merck's five

vaccines. In 2006, total sales of Gardasil recorded by Merck were \$234.8 million (Merck & Co., 2007b).

Worldwide and domestic sales both increased 7% over the sales for 2006. During 2007, “Merck began realizing benefits from its multi-year strategic plan designed to reengineer the way the Company develops and distributes medicines and vaccines worldwide” (Merck & Co., 2008, p. 2). Merck benefitted from the evolution of its new commercial model, which was designed to align its product research, development and marketing efforts by utilizing “the latest technologies and broadening its engagement with customers, physicians and scientific leaders to get needed medicines and vaccines through the development pipeline and to patients sooner” (Merck & Co., 2008, p. 2). The progress of Merck’s efforts is due in part to the continued market penetration of Gardasil (Merck & Co., 2008).

In 2007, Gardasil was Merck’s highest selling vaccine and generated \$1.5 billion in domestic sales, which included initial purchases by many states through the U.S. Centers for Disease Control and Prevention Vaccines for Children program (Merck & Co., 2008). Sales for Merck’s vaccine segment were \$4.3 billion, which was an increase from the \$1.9 billion from 2006. The vaccine segment, which includes five vaccines, generated \$3.8 billion in revenues for Merck. This increase was due in large part to Gardasil (Merck & Co., 2008). 2007 was also the year that Merck settled its lawsuits related to Vioxx, and agreed to pay \$4.85 billion into two funds that would then be distributed to those people who qualified for claims.

In 2008, Gardasil continued to be Merck’s top selling vaccine (Merck & Co., 2009). Gardasil generated \$1.4 billion in domestic sales, which was a slight decrease

from 2007, but that may be because many states had already made their initial purchases of the vaccine through their vaccines for Children program. Sales for Merck's vaccine segment for 2008 were \$4.2 billion, which was a slight decrease from the \$4.3 billion in 2007 (Merck & Co., 2009). Merck was a party to certain third party license agreements with respect to *Gardasil*, which included a cross-license and settlement agreement with GlaxoSmithKline. Merck's deal with CSL also provided CSL with a percentage of the money that Gardasil generates worldwide (Merck & Co., 2007b, 2008, 2009). As a result of these agreements, Merck pays royalties on worldwide Gardasil sales of approximately 24% to 26% in the aggregate, which are included in Materials and production costs (Merck & Co., 2007b, 2008, 2009).

Table 2 - Sales (in millions)

	<b>Sales</b>		
	<b>2006</b>	<b>2007</b>	<b>2008</b>
Gardasil	\$234.8	\$1,480.6	\$1,402.8
Vaccines and Biologicals	2,244.7	4,321.5	4,237.0
Total for all Products	22,636.0	24,197.7	23,850.3

Table 3 - Costs, Expenses and Other (in millions)

	<b>2006</b>	<b>2007</b>	<b>2008</b>
Materials and production	\$6,001.1	\$ 6,140.7	\$ 5,582.5
Marketing and administration	8,165.4	7,556.7	7,377.0
Research and development	4,782.9	4,882.8	4,805.3
Restructuring costs	142.3	327.1	1,032.5
Equity income from affiliates	(2,294.4)	(2,976.5)	(2,560.6)
U.S Vioxx settlement agreement charge	-	4,850.0	-
Other (income) expense, net	(382.7)	46.2	(2,194.2)



Totals	\$16,414.6	\$20,827.0	\$14,
042.5			

*Merck as a Company*

I asked all of the study participants about their thoughts of Merck as a company and how it compares to other pharmaceutical companies. Participants tended to have positive reactions to Merck, however some expressed that their feelings about Merck had changed as a result of Gardasil. One member of ACIP who I spoke to, but was not able to record the interview stated that he once considered Merck one of the most ethical companies until Merck's attempts to mandate Gardasil. He told the president of vaccines at Merck that he was disappointed that they were pushing for a mandate. He said there were many people who were very upset about the Merck mandate, and made their feelings known. He believed that Merck backed off the mandate because of the public pressure, not because of his or others' statements. The amount Merck was charging for the vaccine was also a concern of his and while he believed that the company is entitled to make a profit, he felt the product was too expensive. When he started out, there were about 12 vaccines companies, now there are four, and many are not in business anymore because it is not as profitable. So he felt it was important to allow them to make a reasonable profit, though he did say that the word "reasonable" was up to debate.

(Interview #4).

One physician researcher also discussed how his feelings towards Merck had changed due to Gardasil. He stated that Merck is the smaller company against GlaxoSmithKline (GSK). He viewed Merck as a scrappy company, and believed that

they have a good vaccine. He believed they were very regulated during the phase III trials, and that they went through the hoops that they were required to go through. All the people involved in trials are now in other areas of the company and working on different projects. He said that is when the marketing people took over. He believed Merck has gone from an efficiently good science company to a pushy marketing company that pushed the message down your throat, and were afraid of competition coming online. He thought the people involved in the marketing stage of Gardasil's process were "totally different than the people pre-launch". He believed that it was easy messaging to include the warts issue, and said that if people did not push that angle when talking about Gardasil, Merck got mad. He mentioned that the genital warts are the difference between Gardasil and Cervarix, which is a bivalent HPV vaccine manufactured by GlaxoSmithKline. He said they were pushing because there was a competitor right on their tails. As of 2009, Cervarix is not approved in the US, therefore Merck had a monopoly on this and they wanted to keep it (Interview #3).

One of the primary authors for one of the articles published on the trial data, who is herself a physician researcher, said that Merck had been fine to work with. She got answers to the questions she asked. She felt they were open to debate on things that she did not agree with and were open to providing the data that she wanted. She said that she does not go along with things that she does not agree with and did not get any pressure from Merck. She had not had any negative experience with Merck (Interview #5).

Another physician researcher felt more negatively towards Merck. She had been vocal in her opposition towards the rollout of Gardasil and Merck's behavior during that

time. Based on her opposition to their messages about Gardasil, Merck severed its relationship with her. She said

They have been incredibly aggressive. Their goal is to make money for their shareholders. They want to sell doses of their vaccine and want to aggressively market and push to get their product out there. There is nothing wrong with that, but they are a for-profit company trying to sell their vaccine, and are not necessarily a substitute for a person's physician. They are a business not a health care provider. Merck pushed too hard and in the wrong age group with their focus on 12 year olds. They came at it from so many aspects, but it was not appropriate. Their campaign was massive, and Merck treated the campaign as more cavalier and insensitive to the topics they were dealing with (Interview #6).

Another physician researcher who was not involved with the trials, but has spent her career studying HPV and has published articles discussing Gardasil had a generally positive attitude toward the company. When asked about Merck as a company and in relation to other pharmaceutical companies, she said

I can't compare. I don't know what I would compare it to. But I think they have a job to do and they've done a good job. I love my Merck rep, she's very responsive. I write to her with all these questions and comments, she sends these questions in to Merck, tries to get information back to me. They're very, what do I want to say, receptive to my questions. They've shown a willingness to entertain them. I don't always get all the answers I want but they do listen and share and respond – not always directly to the question I'm asking but something close often. So I really - I don't have that many issues with them (Interview #7).

Another physician researcher who does consulting work for both Merck and GlaxoSmithKline (GSK) was able to speak more comparatively about Merck. She also discussed them as not so much of a company, but as a collection of people when she stated that,

I don't know, they're run by people and I like some of the people and the other people I don't. I have found actually in my dealings with like the advisory boards that they're very professional, they seem to listen to their consultants. Every time I've seen them they've taken criticism to heart and they haven't turned back. So I personally think the people I've worked with I actually respect. I really have had a respect for, I would say, 90% of the individuals I have interacted with. There's

always 10% that you think “Whoa, where did this person get that ego?” or where they're going (Interview #9).

She also discussed Merck as a company and in comparison to GSK

I personally haven't found them doing things that I thought were terribly, you know, sleazy. They're trying to sell their product, they don't hide that fact. Again, in my working with them I haven't found them where they're trying to like hide things or I haven't found them where they're like ‘Well, you know you can't tell anybody that.’ I mean I speak for them and I very clearly say I don't think this vaccine should be done in older women. They continue having me speak for them. Obviously they had me speak to pediatricians, they're much more comfortable with that. I'm sure every time I show this slide I can always hear them in the back going ‘Ah, she's showing that one again.’ But they haven't like said, ‘No, we don't want you to be talk.’ To be honest with you, GSK – they asked me ‘Would you be a speaker’ and I said, ‘Sure,’ and they said, ‘Well, here's your slide set.’ I said, ‘Nuh-uh [no], I use my own slides.’ ‘Well, you can't do it then.’ I said, ‘Fine. I don't need to talk for you, I use my own slides period.’ Merck has never once asked to approve my slides, they don't look at them, I mean there is nothing. Whereas I find GSK more controlling. It's like ‘No, we want to know exactly what you're going to say, these are the slides you're going to use.’ So I found that much more controlling than Merck so I don't give talks for GSK, I give talks for Merck (Interview #9).

### *Summary of Aim III*

The third aim of this study looked at the promotional and marketing campaign of Gardasil, which helped to understand how Merck constructed HPV to be a social problem needing treatment and how Gardasil was positioned as the solution to that problem. The first step in this process was determining what the label claim would be for the product. The label claim is the claim that the company makes about what its product does. In the case of drugs or vaccines, the FDA must approve the label claim to ensure that claim accurately reflects the product's utility. Merck wanted to make the label claim that Gardasil prevents cervical cancer because it felt that claim would increase sales and would make the vaccine more attractive to the public. The FDA initially told Merck that it could not make that claim, but could only claim that the vaccine protected against HPV

infection with the four strains that are covered by the vaccine. Merck found a way to make the label claim that Gardasil prevents cervical cancer by showing that the vaccine prevented the development of cervical intraepithelial neoplasia (CIN) lesions of the highest grade, grade 3. CIN 3 is believed to be a precursor to cancer, so if the trials could show that Gardasil prevented these lesions from developing, then theoretically, cervical cancer would be prevented as well. When Merck presented this data, the FDA allowed Merck to make the label claim that it prevents cervical cancer.

The inclusion of strains 6 and 11 in the Gardasil vaccine was also discussed in this context. Gardasil carries four strains of HPV, yet only 16 and 18 are oncogenic and can lead to cancer. Strains 6 and 11 are responsible for genital warts. When asked about the inclusion of these two strains, a Merck scientist reported that it was a marketing decision because if the trials could show that the vaccine prevented genital warts, then it would make it more attractive and easier to market to males (Interview #1). In terms of the marketing and promotion of Gardasil the prevention of cervical cancer is what is most often heard; the prevention of genital warts was not a part of the overall marketing campaign for Gardasil, but it merely an added perk to receiving the vaccine.

### *Conclusion*

This chapter laid out the history of Gardasil starting from the technology that led to the development of Gardasil through the trials, the promotion and marketing campaigns, and ultimately to the acceptance and use of the vaccine. The findings were presented along with salient quotes from my interviewees to provide a detailed picture of how this vaccine came to become one of Merck's latest and biggest products and how

Merck attempted to ensure widespread use of this vaccine through a comprehensive marketing campaign which included attempts to make the vaccine mandatory. It was this attempt that affected some views and perceptions about Merck both among the public and among my interviewees. Surveillance of the vaccine continues and while side effects do continue to be reported, none have been serious enough to alarm any government agency, Merck, or any of the people I spoke with. States continue to debate how widespread the use of this vaccine should be with legislation being introduced, which ranged from having public insurance companies cover the vaccine to actually making the vaccine mandatory.

## Chapter Five - Discussion

This study's objective was to understand the origin, development, and promotion of the Gardasil vaccine to analyze how Merck persuaded the public – and the medical community - that HPV is a social problem and that Gardasil is its solution. Examining the origin and development of Gardasil entailed a review of the pharmaceutical technology that led to its creation, the vaccine's clinical trials, and its safety and efficacy. Assessing HPV's prevalence in the United States and the rates of preventive care helped to determine the morbidity and mortality of cervical cancer and other HPV-related diseases.

This research study had three aims:

Aim 1 – To describe the development and testing of the Gardasil vaccine

Aim 2 – To describe the approval process for the Gardasil vaccine

Aim 3 – To describe how Merck constructed HPV to be a social problem

needing treatment and how Gardasil was promoted and marketed

This chapter contextualizes and analyzes the study's findings, discusses its limitations, and suggests areas for future research.

### *Aim 1 – To Describe the Development and Testing of the Gardasil Vaccine*

The study's first aim was to provide a foundation for the project by examining Gardasil's origins and development, which included how Merck obtained the technology to develop the vaccine; the clinical trial program; the vaccine's safety and efficacy; and the background, incidence, and prevalence of HPV and HPV-related diseases.

This project used two frameworks to analyze its data: C. Wright Mills' power elite and Jill Quadagno's analysis of stakeholder mobilization. Mills' (1956) framework

posits that societal power is structural and institutional: those at the top of military, political, and corporate institutions exercise power and have access not afforded to others. Mills calls those at the top of society's institutions the power elite. These men and women wield power and exert their influence over one another to ensure the best outcome for their respective institutions. This study showed that Merck's top management team, which worked closely with its FDA counterparts, ensured that Merck received the outcomes for Gardasil that it requested and anticipated.

Jill Quadagno (2004) analyzed the process of stakeholder mobilization, concluding that those in power use strategies as a means of advancing their institutions' agendas. This complements Mills' analysis because it is not just about position but how those in positions of power mobilize and use their resources to shape public perception to ultimately reach their goals. Quadagno suggests that access alone is not enough to make change; there must be a strategy for the effective use of resources. This chapter demonstrates how Merck's position, its strategy, and skillful use of its resources enabled it to achieve its goals for Gardasil.

### *The Development of Gardasil*

In 1995, Merck, one of the top 10 pharmaceutical companies in the world, acquired technology from CSL Limited, an Australian biotechnology company, to begin its development of Gardasil. Although the details of the agreement between Merck and CSL were confidential, it was known that other companies had expressed interest in CSL's technology. Yet, Merck ultimately prevailed. The contract between Merck and CSL provided that the latter was entitled to a percentage of the worldwide sales of Gardasil (Merck & Co., 2007b, 2008, 2009), a financial arrangement that other



companies may not have been willing or able to offer. And, Merck's prodigious marketing and distribution capabilities may have overwhelmed rival pharmaceutical companies.

Merck also had the resources to develop the vaccine and to conduct a large clinical trial program (1997 to 2005) that consisted of 12 clinical trials with over 27,000 subjects in 33 countries (N. B. Miller, 2006). Coordinating such an effort required not only a large financial commitment but also highly trained personnel who could work with indigenous institutions to arrange sites, hire employees, enroll subjects, and understand and adhere to each country's rules and regulations.

#### *The Clinical Trial Program*

Throughout the course of its research program, Merck controlled the design and management of its clinical trials and the analysis of its data. Two factors influenced the trials' design: clinical endpoints and Gardasil's label claim. Clinical endpoints, what the vaccine actually tested for in the trials, were the most important factor in the trials' design. In the case of Gardasil, the primary clinical endpoint which led to the label claim that Gardasil protects against cervical cancer, was proving that the vaccine prevented advanced cervical dysplasia, called cervical intraepithelial neoplasia (CIN) grade 3, which is considered a precursor to cervical cancer. If this were proved, Merck argued that it could make the label claim that the vaccine prevented cervical cancer. The compelling appeal of vaccination would be obvious.

In designing the trials, Merck convinced the FDA to let it determine the clinical endpoints. In its initial meeting with the FDA, Merck stated categorically that it wanted Gardasil's label claim to state that it prevented cervical cancer, thereby enhancing its

appeal to women, increasing its marketability, and guaranteeing higher profits (Interview #1). If Gardasil could claim that it protected women against cervical cancer, the vaccine would break new ground, being the first vaccine of any kind to prevent the disease.

Initially, the FDA was reluctant to allow Merck's label claim because that would entail withholding treatment for cervical cancer from women to see if cervical cancer developed after being vaccinated with Gardasil. This would not only be unethical but also time consuming because cervical cancer takes many years to develop.

Following the FDA's initial rejection of Merck's request to claim that Gardasil prevents cancer, Merck developed a strategy to make the claim through the construction of clinical endpoints. The clinical endpoint that Merck proposed, and which the FDA ultimately agreed to, was the development of CIN grade 3 (Bryan, 2007; Pratt et al., 2001; Rambout et al., 2007; VRBPAC, May 18, 2006). CIN grade 3 is often considered to be a precursor to cancer. Thus, if the trials could show protection against the development of CIN 3, protection against cervical cancer could be inferred (CDC, 2007; VRBPAC, May 18, 2006).

Merck's strategy successfully convinced, if not manipulated, those at the FDA that preventing CIN 3 legitimately demonstrated prevention of cervical cancer. Merck argued that testing for actual cases of cervical cancer would be unethical because that would deny women access to preventive care that could mitigate early infection before it became cancerous. This is a legitimate argument, the same one that the FDA made to Merck when it initially refused to accept its label claim. But, Merck turned the argument to its advantage, claiming that preventing CIN 3 was analogous to preventing cervical cancer. However, preventing CIN 3 does not mean preventing cervical cancer, yet that is

precisely what the FDA allowed Merck to claim. Gardasil's effect on real cases of cervical cancer cannot be known for several years, possibly decades, because it will take that long to see how the cases of those vaccinated progress. Regardless, Merck successfully changed the minds of the FDA decision makers and received its desired outcome.

Even after the clinical endpoints were established, Merck maintained rigid control over the clinical trial program, including data analysis. The FDA had directed that all women who met the broad inclusion criteria should be admitted into the studies (Bryan, 2007; Pratt et al., 2001; Rambout et al., 2007; VRBPAC, May 18, 2006); yet, when the data were analyzed, Merck divided the participants into two groups: the protocol group and the intention-to-treat group. The former reflected the most positive trial results because it had not been exposed to the vaccine strains of HPV or had an abnormal Papanicolaou Test result. The intention-to-treat group more accurately reflected the general population because it had either been exposed to one or more of the vaccine strains of HPV or had a previous abnormal Papanicolaou Test result.

Although Merck followed the FDA guidelines on inclusion criteria, its data analysis ignored the findings of the combined study participants on the trial results. By singling out the protocol group for the analysis, Merck cherry picked the data it presented. There was a marked difference in efficacy between the two groups, yet only the results for the protocol group were publicly presented. Disturbingly, the FDA did not object. Merck was allowed to present its results as it saw fit, thus highlighting the most flattering results.

Because the results for the protocol group showed close to 100% efficacy, those who are vaccinated and do not fit the protocol group's criteria may likely believe that the 100% efficacy applies to them. Underlying these findings is the obvious message: If this vaccine is 100% effective, women would be remiss in not being vaccinated because it would leave them vulnerable to cervical cancer. The findings show that the results are not strong for the intention-to-treat population, which likely represents a good portion of the general population that is or will be vaccinated. Even in preeminent peer-reviewed journals, like the *New England Journal of Medicine* and the *Lancet*, Merck managed to control the presentation of its findings to highlight the best outcomes of its trials, while downplaying outcomes that did not support its desired message (Garland et al., 2007; The Future II Study Group, 2007). Not publicly stated was the fact that the long-term outcomes are unknown and that it will be years before the real effect of this vaccine on the morbidity and mortality of cervical cancer is known.

#### *The Efficacy and Safety of Gardasil*

Although Gardasil protects women against four strains of HPV, only two (16 and 18) are oncogenic. However, there are roughly 15 oncogenic strains of HPV. Although sufficient data claim that Gardasil prevents the development of CIN grade 3 from strains 16 and 18 (N. B. Miller, 2006; VRBPAC, May 18, 2006), it does not obviate the need for Papanicolaou Tests, a fact that may not be clear to all women. Because women can still be infected with other HPV strains that can potentially lead to cervical cancer, the need for regular Papanicolaou Tests remains. This alone counters Merck's claim that Gardasil prevents cervical cancer.

The vaccine is most effective if given before exposure to any of the HPV strains Gardasil was developed to counter (VRBPAC, May 18, 2006). However, this message is not being adequately publicized, and women are not being tested for HPV before vaccination. Thus, some women who are vaccinated may already be infected with one of the oncogenic vaccine strains of HPV that Gardasil protects against. If a woman has HPV 16 and 18, she may not receive any oncogenic protection from the vaccine, making regular Papanicolaou Tests even more necessary and the value of the vaccine questionable.

Based on the trials' results, the vaccine appeared to be relatively well-tolerated and few discontinuations were recorded due to serious adverse events (VRBPAC, May 18, 2006). However, the trials only observed approximately 27,000 people; as the vaccine's use has widened, more adverse events have been reported (Millspaw, 2008). Since Gardasil's release, serious adverse events and deaths have been reported in addition to more common side effects, such as dizziness, fainting, and pain at the injection site (Millspaw, 2008). The number of reported side effects, from minor to serious, is likely to increase as the number of girls and women receiving vaccination increases.

The side effects that were publicly discussed included those that were observed during the clinical trials, such as dizziness, fainting, and pain at the injection site. The few serious adverse events, such as autoimmune disorders, were not mentioned or discussed publicly. Since Gardasil's release, however, many scientists and public health officials, who were aware of the reported serious adverse events and deaths, have questioned the causal nature of those events (J. S. Abramson, 2006). Nonetheless, an

unsuspecting public has been led to believe that any potential side effects are relatively innocuous, which leaves women less informed.

Interaction with childhood vaccines is another potential risk of Gardasil vaccination that has not been well-publicized. Children are often given multiple vaccines at once. If parents are not alerted to this potential interaction, they may unintentionally put their daughter at risk. Physicians too may be unaware of Gardasil's potential interactions, unwittingly putting their patients at risk. It has been established that Gardasil does not interact well with Menactra, the meningitis vaccine manufactured by Sanofi Pasteur Inc. (Millspaw, 2008). Gardasil was tested with the Hepatitis B vaccine, a Merck product (N. B. Miller, 2006; VRBPAC, May 18, 2006), but it is questionable why Merck would not test Gardasil with its other vaccines. Gardasil therefore is not a risk-free vaccine.

#### *The Necessity for Gardasil*

The necessity for Gardasil has been questioned for several reasons. First, Gardasil is most effective when given before any exposure to the HPV strains contained in the vaccine. Second, since Gardasil's release, serious adverse events and deaths have been reported. Third, continued Papanicolaou Tests are needed after vaccination. And, fourth, the populations in the United States that are most affected by cervical cancer are women who either do not or cannot access preventive care, specifically regular checkups and Papanicolaou Tests. Data show that most women who are diagnosed with cervical cancer have not had a Papanicolaou Test in the 5 years before diagnosis (eHealth MD, 2004). If women have been unable to obtain a Papanicolaou Test, how will they access the Gardasil vaccine, which requires three visits, one for each injection? And, without

the three injections, Merck cannot guarantee protection. As a result, women with less access to preventive and primary care may be at risk of developing high grade cervical dysplasia, and potentially cervical cancer. Merck has not addressed how Gardasil can be administered to this population of women.

Papanicolaou Tests, which have effectively reduced the incidence of cervical cancer, remain necessary even after vaccination with Gardasil. If women then still need to access preventive care to receive regular Papanicolaou Tests, what real protection does Gardasil offer? Although Merck's Gardasil advertisements and website state that Papanicolaou Tests remain necessary, women may still be unclear about this requirement. Equally unclear from the research data is the extent to which physicians have been and are reinforcing that message to their patients. For those women who are vaccinated but do not understand the need to continue regular Papanicolaou Tests, what will be their long-term health outcomes? Years or decades may elapse before the answers to those questions are known. Meanwhile, women will continue to be vaccinated.

In the light of Gardasil's demand, understanding the vaccine's efficacy and safety is necessary in determining its appropriateness for all of the girls and women who wish to be vaccinated. As for efficacy, Gardasil is only useful if given before a person is exposed to any of the relevant HPV strains. However, this message has not been and is not being strongly promulgated, and women are not being tested for HPV before vaccination. For those women who have been sexually active, therefore, their prior exposure to the vaccine's HPV strains will not be detected, limiting or negating any protection from the vaccine. In such cases, women may be receiving the vaccination unnecessarily. These women could make an informed decision about the pros and cons of vaccination if they

knew Gardasil's prophylactic capability. However, women hear that they must protect themselves from cervical cancer and be vaccinated. Consequently, many women may be vaccinated without fully understanding what protection they may or may not be receiving.

### *Merck's Corporate Influence and Product Strategy*

From the time Merck acquired CSL's technology, its strategy was to position Gardasil as a vaccine to prevent cervical cancer. That strategy, confirmed by a Merck scientist, would make the vaccine more attractive and thus more marketable. Merck's management expected Gardasil to be a blockbuster product, capable of generating huge profits.

A large, well-established pharmaceutical company, Merck was well-positioned in the powerful pharmaceutical industry. As such, it had the resources to purchase CSL's technology and to access the FDA's senior management. But, it was Merck's carefully crafted strategy in designing its clinical endpoints that secured the label claim it wanted. Merck's strategy was well-planned, beginning even before its agreement with CSL was completed. Merck understood the financial potential of having the first cancer vaccine and likely would not have developed it without the conviction that it could persuade the FDA to accept its desired label claim, a claim that would yield maximum profits.

Acquiring the technology to develop Gardasil and designing clinical trials to prove its effectiveness were the first steps in getting the vaccine to market. The next step was the approval process and developing guidelines to determine the vaccine's target population, how the vaccine would be monitored once approved, its cost, and cost-effectiveness on a national scale.



*Aim 2 - To Describe the Approval Process for the Gardasil Vaccine*

This study's second aim examined the process of approving Gardasil, which involved reviewing the meetings between Merck, the FDA, and the CDC; Merck's postmarketing plans, the vaccine's cost; and its cost-effectiveness.

*FDA Approval and CDC Guidelines*

In 2002, the FDA granted Gardasil *fast track status* just as Gardasil's preliminary trials were ending and phase III clinical trials were beginning. Gardasil was granted fast track status, which shortened the FDA's review time from 12 to 6 months, because the FDA agreed with Merck that the vaccine met an unmet medical need, being the first vaccine of its kind to protect women from a virus that leads to cancer. The FDA took this course of action even though cervical cancer is neither an uncontrolled problem in the United States nor does it progress quickly.

The FDA granted Gardasil an expedited review without final phase III trial data to support its decision; the expedited review began in 2005 based only on preliminary data. Twelve studies were conducted, two of which, the so-called FUTURE I and FUTURE II studies, provided the core data that was published in the *New England Journal of Medicine*. Data from these studies provided the efficacy rates that have been publicly accepted as the basis for and use of Gardasil. The FUTURE I study ended in May 2003; the FUTURE II study ended in November 2005. The FDA's expedited review began in January 2005 at the urging of Merck who successfully lobbied that the vaccine needed to get to market quickly.

The expedited review and approval illustrate the influence Merck exerted over the FDA. Despite the 60,000 pages of data that Merck submitted to the FDA, the expedited review was completed in 6 months. How effectively such a voluminous

amount of data was reviewed in such a short time is questionable. Troubling questions arise. Was FDA's decision to approve Gardasil *a fait accompli*, raising ethical concerns about the approval process? Or did the FDA want to share the limelight in making available the first vaccine to prevent cervical cancer?

More importantly, is Gardasil meeting an unmet medical need? Because cervical cancer takes years to develop, women who receive regular preventive care can largely forestall the disease. There was no medical or public health reason for Gardasil to be approved and released in the United States so quickly. Cervical cancer, however, is a problem in the developing world, where roughly 80% of cervical cancer cases occur (Laurance, 2006; Stanley, 2007). Worldwide, more than 200,000 women die each year from cervical cancer, compared with about 4,000 women in the United States. Although vaccine programs are now using Gardasil in some developing countries, it is not being promoted in those regions where cervical cancer is a major cause of morbidity and mortality. The promotion and availability of Gardasil has had less to do with need than profit.

In May 2006, the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) met to approve Gardasil. Following the vaccine's approval, the CDC convened its Advisory Committee on Immunization Practices (ACIP) in June 2006. At both meetings, the vaccine's trial results, cost-effectiveness, and postmarketing plans were discussed, another example of Merck's ability to dictate its corporate agenda. Transcripts of the meeting reveal how Merck scientists selectively presented results from the protocol group that showed Gardasil's high efficacy. The scientists did not explain that the rates for the protocol group did not accurately reflect the overall efficacy rates.

The efficacy rates for the intention-to-treat group were omitted from the public presentation of the findings.

A comment period was provided for committee members and the general public. The committee members were not particularly critical of the findings and did not question the efficacy rates. Ignoring the issue of potential adverse results, the committee members tended to ask for clarification of the scientists' presentations. Further, none of the public comments were critical of Gardasil. And, all of the public comments were submitted by people who were affiliated with organizations that worked in the areas of cancer, HPV, or women's health. What information these people and organizations had before the meetings is unclear, but they had supported Merck's message. It might have been expected that some people would have raised concerns about Gardasil, but none did.

#### *Postmarketing Plans*

Merck's postmarketing plans for Gardasil involved government agencies in foreign countries. Merck has several long-term studies planned or in process in several Nordic countries. Studies are being conducted there because of the extraordinary public health infrastructure, which will allow the results of Papanicolaou Tests and biopsies to be housed in a central database (VRBPAC, May 18, 2006). In organizing these studies, Merck had to clear its plans with the FDA and negotiate the specifics with the governments of the respective countries. To what extent the FDA and the Nordic governmental agencies will communicate with each other or if Merck will serve as an intermediary between the two is unclear. Regardless, this again exemplifies Merck's access not only to high-ranking individuals in U.S. governmental agencies but also those in other industrialized countries as well.

If monetary exchange was involved with the Nordic countries and how that may have affected Merck's access to their governments or their decisions to participate in these postmarketing studies is unknown. It remains to be seen how the data from these planned studies will be reported to the FDA and to the public and what benefits will accrue to the Nordic citizens who participated.

In addition to the studies in the Nordic countries, the Vaccine Adverse Events Report System (VAERS) will continue to monitor reported adverse events for Gardasil in the United States (VRBPAC, May 18, 2006). This reporting system is monitored by the FDA and CDC and is open to the general public, which means that the public does not have to rely solely on Merck to disclose adverse events. However, the public must rely on the FDA and CDC to accurately and publicly disclose the reports that it receives from this system. Unknown is the extent to which Merck has discussed these reports with the FDA and CDC and what level of control Merck had or will continue to have on how these data were or will continue to be reported to the public.

Many of the VAERS reports examined for this project were only made available after the organization Judicial Watch filed a Freedom of Information Act request (Millspaw, 2008). Finding the same data on the VAERS's website, which is not user friendly, proved far more challenging. For those who may be unaware of the VAERS site and the adverse event information available there or those who are not technically savvy enough to navigate the site to find that information, the VAERS website may thwart rather than enhance public access to this important information.

### *Cost and Cost-effectiveness*

Priced at \$360 for a series of three injections, the Gardasil vaccine is one of the most expensive vaccines (Harris, 2006a, 2006b). Merck alone determined the vaccine's cost, based in part to recoup the expense of conducting the clinical trials. Another factor in pricing was the expected benefit. As is standard practice for pharmaceutical companies (Angell, 2004), Merck determined the price for Gardasil without any regulation or input from the government or the public.

Merck promotes Gardasil as a necessary vaccine for girls and young women. Regardless of the vaccine's questionable "necessity", many girls and young women will want to be vaccinated. Although Gardasil's high cost may be prohibitive for federal vaccine programs, insurance companies, and people who must pay out of pocket, Merck did not account for this issue when determining the vaccine's price. Merck based the vaccine's cost on its business plan and profit expectations, not the public's needs or ability to pay.

The CDC's Advisory Committee on Immunization Practices (ACIP) determined the guidelines for Gardasil's use in 2006. When setting these guidelines, the ACIP was instructed to examine issues of safety, efficacy, and cost-effectiveness. The committee was specifically instructed not to take cost into account, which means that it could not discuss how federal and state governments, insurance companies, or individuals would pay for this vaccine. Despite this prohibition, it was expected to determine Gardasil's cost-effectiveness. This brings up the obvious question, how can cost-effectiveness be accurately determined without factoring in cost? If the vaccine were inexpensive, it would be quite cost-effective to vaccinate large numbers of people. Conversely, if the cost is high, cost-effectiveness would be marginal.

Women who are vaccinated must continue receiving Papanicolaou Tests. Therefore, state and federal programs as well as private insurance companies must now factor in the costs of both vaccination and Papanicolaou Tests. This may skew how these various groups interpret cost-effectiveness. Government programs and insurance companies may determine that providing the vaccine and continued Papanicolaou Tests is not cost-effective for them, which may result in reducing care for women.

If the ACIP had factored in cost, it may have determined that the cost was prohibitively high, which would have affected Gardasil's profitability. Excluding cost in this process insured Merck's ability to solely determine the cost of Gardasil without affecting the vaccine's approval or the guidelines for its use.

Independent studies, those without Merck's apparent financial support, were conducted to determine Gardasil's cost-effectiveness (Elbasha et al., 2007; Hymel, 2006; Kim & Goldie, 2008; Stanley, 2007; Vetter & Geller, 2007). In modeling these studies, assumptions had to be made, many of which gave Gardasil the benefit of the doubt in certain areas. Assumptions were made that girls would be vaccinated at 12 years old and the coverage would be lifelong, two core assumptions in Merck's own studies. Even if these studies were independent, it is likely that the researchers were influenced by Merck's data or by its promotion.

The studies were in agreement that the lack of long-term data precluded one's ability to assess the vaccine's true cost effectiveness (Elbasha et al., 2007; Hymel, 2006; Kim & Goldie, 2008; Stanley, 2007; Vetter & Geller, 2007). It is impossible to know the vaccine's true cost-effectiveness without knowing how long its protection will last and what its long-term effects will be. If long-term data show increased adverse events, the

vaccine's cost-effectiveness will be offset by the resources be needed to address those events.

### *Limits to Merck's Influence*

Despite the favorable approval it received from the FDA and the CDC, which allowed it to market Gardasil quickly, Merck could not convince those agencies to approve Gardasil's use in women over 26 years old and in men. Those requests have been denied for now. The FDA instructed Merck to submit more data, allowing that those approvals might be forthcoming in the future. Nonetheless, Merck can still profit because Gardasil can be used in those populations off label; it cannot promote the vaccine to those populations directly.

The final step in the process was promoting and marketing Gardasil to ensure that the target populations were made aware of the link between HPV and cervical cancer and convinced that they should be vaccinated.

### *Aim 3 - To Describe how Merck Constructed HPV to be a Social Problem Needing Treatment and how Gardasil was Promoted and Marketed*

This study's third aim examined Merck's promotional and marketing campaign for Gardasil, which revealed how the company constructed HPV to be a social problem needing treatment and how Gardasil was positioned as its solution. In addition to the theoretical frameworks discussed earlier, the theories of social construction and social control were also incorporated into this analysis.

Social construction (Berger & Luckmann, 1966) is a process that is based on the role of knowledge formation. The process of knowledge formation begins with the dissemination of information, which leads to the internalization of that information, and results in the habitualization of that information. The internalization of knowledge

occurs when members of society accept that information as their own. Habitualization results when people act in accord with that internalized knowledge, which tends to channel behavior in the direction that most benefits those who have promoted that information (Berger & Luckmann, 1966).

Another aspect of social construction is how social problems are constructed (Kitsuse & Spector, 1973). A social problem is a deviation from a social norm. People must be convinced that an issue is a problem before they will believe that it is and address the problem (Kitsuse & Spector, 1973).

Social control results from this process. After a problem has been constructed and people have internalized that the issue is a problem, habitualization follows. Fear is often used because it can effectively control people's actions (Altheide, 2002; Chomsky, 2002; Schattenberg, 1981; Seale, 2002; Thomas, 1978). This tactic targets people on an emotional level, which makes them more susceptible to manipulation, internalization of the message, and ultimately habitualization.

Language and messaging are the tools of the powerful who promote these ideas. One aspect of this messaging is the concept of prevention, which places the onus on the individual to avoid illness or disease (Howson, 1998; Zola, 1971). The promotion of Gardasil has focused on the prevention of cervical cancer. The implicit message has been that HPV is a social problem and Gardasil is its solution.

#### *Promotional and Marketing Campaigns*

Merck's label claim, which describes Gardasil's purpose and utility, was the basis for its promotional and marketing campaign and was the first step in constructing the problem. As discussed earlier, Merck claimed that Gardasil protects against cervical



cancer even though this does not accurately reflect what it does. Gardasil protects against four strains of HPV, two of which cause most cases of cervical cancer. The actual effects on cervical cancer will not be known for years. Despite the FDA's initial hesitation to allow Merck's label claim, Merck prevailed. It convinced the FDA that preventing CIN 3 was tantamount to preventing cervical cancer. Beyond that, Merck convinced the FDA that cervical cancer was the kind of health problem that could be treated by a vaccine even though it has been well-contained in the United States by Papanicolaou Tests (eHealth MD, 2004). That the FDA granted Gardasil an expedited review also bolsters the argument that Merck successfully constructed cervical cancer as a problem common enough that this vaccine was addressing an unmet medical need. Claiming that Gardasil could protect women from cervical cancer would successfully position it as the only cancer vaccine. This made Gardasil a more attractive vaccine and increased its marketability.

From the earliest stages of Gardasil's development, Merck planned to include HPV strains 6 and 11 in the vaccine to enhance its marketability (Interview #1). HPV 6 and 11 are responsible for roughly 90% of genital warts cases (FDA, 2006), a common affliction but not a pressing public health problem in the United States. It appears that Merck had always intended to market Gardasil to men but understood that men needed a more specific reason for vaccination than protecting future female sexual partners from contracting the two oncogenic HPV strains. It would also be difficult to convince the parents of young men to have their sons vaccinated for this reason. Thus, including these two strains was designed to broaden the vaccine's appeal and increase the number of people who could be vaccinated.

### *Marketing Gardasil*

Merck used fear in constructing HPV as a social problem. It successfully informed women of the link between HPV and cervical cancer, suggesting that those who may have contracted HPV were at risk of developing cervical cancer (Herskovits, 2007a; Rosenthal, 2008). The advertisements also reinforced the cancer threat, which likely led many women to conclude that HPV and cervical cancer were uncontained and growing problems for women in the United States. Although Merck's advertisements and website stated that women needed to continue receiving Papanicolaou Tests, they did not mention that Papanicolaou Tests alone reduce the incidence of cervical cancer, a fact that might lead some women to question the necessity of being vaccinated. The advertisements also successfully promoted the concept of empowerment through vaccination: Once informed of the threat of cervical cancer and given the tools to help themselves (medical advice and vaccination), women and girls (and their parents) would be empowered to take control of their lives.

To make women aware of the link between HPV and cervical cancer, Merck's marketing campaign used a broad demographic of young women to capture the widest audience (Herskovits, 2007a). Anticipating that girl-to-girl promotion would have a strong impact, the advertisements also used actresses of different ethnic backgrounds. The advertisements not only informed young girls and women of the link between HPV and cervical cancer but also urged them to share that information with the girls and women in their lives. Spreading the message in this way ensured that even those women who had not seen the Gardasil advertisements would be made aware of their risk of contracting HPV and possibly developing cervical cancer. Gardasil was an obvious and compelling option.

Although the advertisements targeted young women and their parents, cervical cancer is an older woman's health problem; cervical cancer is diagnosed most often in women between 50 and 55 years old (eHealth MD, 2004). Gardasil was approved for girls as young as 9, yet cervical cancer does not generally affect young women (eHealth MD, 2004). Because cervical cancer takes many years to develop, Merck had to convince young women, and their parents, that this was health problem they needed to address now. Because HPV is sexually transmitted and can lead to cervical cancer, Merck had to craft its message artfully to account for these issues.

Merck decided not to include very young girls in its Gardasil campaign, even though they were the target population. Using pubescent teenage girls in the advertisements made the sexual component more socially tolerable because they likely would have engaged in some sexual activity and been exposed to HPV. Merck did not want to use preadolescents in its advertisements because that could have been construed as sexualizing young girls. And, teenagers may not have been able to identify with younger girls, muting the effect of the advertisements.

Because young girls often emulate older girls, seeing teenage girls in the Gardasil advertisements may have led younger girls to discuss vaccination with their parents. By using older teenage girls, Merck targeted girls who would or could make health care decisions for themselves. On viewing the advertisements, the parents of younger daughters might be persuaded to consider Gardasil vaccination for their daughters. The images in the ads reinforced the concept of power and female empowerment.

Merck's marketing campaign had two components: motivating young women to ask her physician for Gardasil, and ensuring that those physicians reinforced Merck's

promotional message. Merck's marketing campaign targeted the three groups of physicians that girls and young women might visit (Herskovits, 2007a): pediatricians for young girls and family practitioners and gynecologists for older girls. Merck had to be sure that these physicians would reinforce its message and the need for vaccination. Each physician group was "educated" about the issue differently so that they could appropriately discuss the issue with their patients (Herskovits, 2007a; Rosenthal, 2008). Merck carefully crafted messages for those who should be vaccinated and those who would administer the vaccine. It understood what was necessary for physicians to internalize and act on the message that girls should be vaccinated.

#### *Mandating the Vaccine and the Role of Lobbying*

Following the Gardasil advertisements, Merck mounted a campaign to mandate the use of Gardasil, which demonstrated its powerful influence and prodigious resources in the process. To advance its agenda, Merck used its lobbyists and Women in Government, an organization comprised of female legislators at the local, state, and federal level. Following meetings with Merck and its lobbyists, Women in Government worked in their respective legislatures to promote legislation that would mandate the use of Gardasil. In working with just this one organization, Merck gained access to most of the state legislatures in the country. To further its control of the process, Merck used its lobbyists to craft the legislation and the messaging that legislators used in promoting that agenda.

Although Merck had publicly admitted to giving money to Women in Government, it had stopped short of admitting that its lobbyists drafted the legislation (Associated Press, 2007). Paying Women in Government to promote this legislation was

consistent with Merck's attempts to construct the issue of HPV and cervical cancer as a social problem and ensure widespread use of Gardasil. Using Women in Government was also a blatant attempt to control public discourse on this issue.

With members of Women in Government on point advancing its agenda, Merck also used government officials to promote its message, which may have undermined the public's trust in them. Ostensibly, publically elected officials serve to advance the welfare of their constituents not corporate interests. When the public realizes that their elected officials have placed industry over the public good, trust in government at any level suffers.

Although contributing funds to politicians is not new, the public expects, perhaps naively, that protecting the public health trumps political considerations. The push to mandate Gardasil so soon after its release demonstrates Merck's power because very few companies have the connections, resources, and political savvy to mount such a national campaign.

Merck encountered an unexpected backlash to its efforts to mandate the use of Gardasil. Once the campaign reached the state of Texas, the collusion of Merck, its lobbyists, Women in Government, and state governments was obvious and soon publicly disclosed, causing disparate civic groups to oppose attempts to mandate Gardasil. Aware that Gardasil was designed to protect young women from sexually transmitted strains of HPV, socially conservative and religious groups feared that the broad use of the vaccine would promote sexual activity among young girls. Parental rights groups were concerned that mandating this vaccine would infringe on their parental rights, pre-empting their role in deciding how best to care for their children. Some people had more general

reservations about Gardasil, seeing it as yet one more obligatory vaccine, particularly one that had been rushed to market. Other people saw in Merck's Gardasil campaign a devious motive: to recoup financial losses caused by the Vioxx debacle. The collective opposition of these groups effectively stifled Merck's ability to advance its agenda to mandate the use of Gardasil. Even so, Merck was successful in motivating many eligible women to be vaccinated.

Although citizen groups were vocally opposed to mandating Gardasil, consumer advocacy groups and physician groups were mute. For example, the Public Citizen's Health Research Group, the premier consumer advocacy group, has never issued any public statement about Gardasil. Its director stated that Public Citizen focused on drugs, not vaccines. In the light of the many vaccines that have been released in recent years and public concern about vaccines in general, Public Citizen's silence on this issue is puzzling.

Physician groups too have been silent on this issue; no vocal objections to Gardasil or Merck's attempts to mandate its use have been forthcoming. Although some physician researchers have publicly stated that they would like to see more data before widespread use occurs, most physicians still praise the vaccine. Professional medical societies have been very supportive of Gardasil and of its use, suggesting that Merck's physician-specific educational campaigns have been successful. Merck underwrote many physician speakers at medical meetings (Rosenthal, 2008), whose efforts may have defused potential criticism of Merck's Gardasil campaign. Finally, because physicians generally follow the recommendations of their professional societies, many physicians may have tacitly agreed with their society's endorsement of Gardasil. In the current

model of medical care, most physicians do not have time to research issues in depth. Thus, they trust their professional societies to promulgate recommendations that are in the best interest of their patients.

#### *Acceptance, Use, and Sales of Gardasil*

Before the Gardasil advertisements were released, data show that few women had heard of HPV or its relationship to cervical cancer (Grant et al., 2009; National Cancer Institute, 2007). By 2007, after the advertisements were publicly disseminated, the percentage of women who had heard of HPV and could make the connection between it and cervical cancer had significantly increased (Grant et al., 2009).

Released in June 2006, Gardasil became Merck's top selling vaccine and fourth highest selling product by 2007; its extraordinary profitability continued into 2008 (Merck & Co., 2008, 2009). In 2008, Gardasil generated \$1.4 billion in domestic sales. As of October 2008, roughly 25% of teenage girls aged 13 to 17 years old nationwide had received at least one Gardasil injection (CDC, 2008).

These findings show that Merck was ultimately successful in constructing HPV to be a social problem needing treatment and successfully positioned Gardasil as its solution. Gardasil's advertising campaigns targeted young women and their parents, playing on their fears and values. For girls, the fear of contracting HPV heightened the necessity for Gardasil vaccination. For parents, the fear of not protecting their children from a potentially life threatening disease condition reinforced Gardasil's appeal. The advertisements also targeted the values of girls and their parents. For girls, empowerment was the overriding theme of the advertising campaigns. Girls were encouraged to discuss Gardasil with their physicians and to take control of their health.

For parents, the Gardasil advertisements drew on the theme of safeguarding and protecting their daughters. The advertisements were successful.

Despite some opposition to mandate Gardasil, the vaccine's use has consistently grown and is likely to increase. Data show that the more aware people become about the links between HPV and cervical cancer, the more likely they are to seek vaccination for themselves or their daughters (Grant et al., 2009). Groups that once opposed attempts to mandate Gardasil have not pursued their campaigns, eliminating any vestige of public opposition.

Merck's successful promotional and educational campaigns convinced government agencies, physicians, and the public of Gardasil's value and paved the way for the vaccine's rapid and extraordinary success. Public opposition proved to be inconsequential. Gardasil's usage continues at a steady pace, reaping billions in profits. Gardasil remains Merck's top selling vaccine and fourth highest selling product.

### *Limitations*

There were limitations to this study. First, many of the documents that would have been helpful were proprietary. This researcher was not able to access any internal Merck documents. The documents related to Gardasil and the clinical trials were all obtained through the FDA as were the clinical reviews that the FDA conducted. While these documents contained pertinent information, certainly there was information contained in Merck's own documents that would have been helpful, and would have likely shed light on their development and promotional efforts. Additionally, notes from non public meetings held between Merck and the FDA and the CDC would have also been helpful and enlightening. This would have helped shed light on how Merck constructed



the issue for the heads of these organizations and how the messaging may have differed between agencies. I was able to obtain several documents through the organization Judicial Watch, which filed a Freedom of Information Act. These included several reports from the Vaccine Adverse Events Reporting System and Merck's application to the FDA to patent Gardasil.

Another limitation was with the interviews. I was not able to interview all of the people I would have liked, including a representative at the FDA. The few people whose contact information I obtained did not return repeated requests to speak with them. I was able to speak with a few people at the CDC, as well as members of the Advisory Committee on Immunization Practices. Employees at Merck proved to be much more difficult to contact. Although I had contact information for individuals at Merck, either I did not receive replies after repeated contacts or I was told that they were not interested in talking to me. Many of the researchers who worked with Gardasil have since moved onto other projects at Merck. One Merck representative who initially told me that she would coordinate an interview between me and a high ranking employee at Merck, but this was cancelled the day before our interview, and the representative stated that Merck had a policy that prevented representatives from speaking to me unless they were with the Merck's Public Relations department. Eventually, I was able to coordinate an interview between me and a Merck physician, but this individual was not directly involved in the development or testing of Gardasil. I was unable to interview Merck representatives about the marketing and promotion of Gardasil, although I did receive an e-mail response to questions I had in that area.

I was also unable to speak with any journalists who had covered Gardasil, Merck, or the pharmaceutical industry. Having their input would have been helpful and they have access to the internal working of organizations that most others do not. Journalists are also meant to be impartial reporters, so having that perspective may have helped shed light on certain aspects of this story.

Most of the people that I did interview were out of state and two were out of the country, so having to do most of the interviews by phone also proved to be a limitation. It is much easier to develop a rapport when you are speaking to someone face to face, so having to do many of the interviews over the phone likely limited the type and amount of information I was given. Some of the interviewees were only able to allot 30 minutes to speak with me, which obviously limited what could be discussed and in how much detail. Had those interviews occurred in person, I may have been given extra time. Additionally, I was not able to record some of the phone interviews due either to the interviewee's preference or to technology issues. In those cases, detailed notes had to be taken, and while I believe I captured all of the necessary information, there are likely smaller details that may not have been captured.

#### *Future Research*

This project laid the foundation for future sociological research about Gardasil as well as the pharmaceutical industry. One area of study would be to examine how the marketing campaign affected the perception of the Gardasil target audience and the vaccination rates. This would involve speaking with young women and their parents, including those who have been vaccinated and those who chose not to.

Gardasil marketing was also geared towards physicians, so that a study of physician knowledge and physicians practices about Gardasil would be interesting along with how they speak with patients and patients' parents about Gardasil, and whether they chose to stock and administer it in their offices. It would be interesting to assess how Gardasil sales representatives differ from sales representatives for other drugs.

Looking at how both consumer and physician groups were marketed to would also open the area for research looking at patient demand versus physician suggestion for the vaccine. This would help to understand how marketing affects both groups, by seeing how they have internalized and acted on the messages regarding the vaccine.

Merck also had to sell Gardasil to its investors and shareholders. Studying the relationship between Merck and its shareholders would shed light on some of the internal workings of the company. This would help to understand how decisions are made at the highest levels and how decisions are sold to investors and shareholders. This would be difficult because corporations are generally secretive, but it would shed light on how corporations bring new innovations from concept to product and how they gain support of shareholders and investors who ultimately make those innovations a reality.

The lobbying process is another area that would be useful to study. Many states initiated legislation related to Gardasil. Interviewing state and federal legislators to assess the process and effect of lobbying efforts would be useful. Women in Government played a large role in attempts to mandate the vaccine, therefore speaking to legislators who have worked with or within that organization would be useful. Speaking with lobbyists themselves would help to understand the process of how lobbyists work with legislators and how legislation was initiated and drafted for Gardasil.

The pharmaceutical industry has one of the largest lobbies, therefore, it would be useful to compare the lobbying efforts for Gardasil with other lobbying efforts on behalf of the industry. This would help to understand the process of lobbying and where and how resources are directed to understand how resources are dispersed between pharmaceutical companies or products.

Vaccines differ from drugs and the FDA has two separate offices for each. Therefore, it would be valuable to study and analyze the differences between the vaccine and drug development and approval processes at the FDA. Studying the internal processes at the FDA and the CDC would also expand knowledge about these agencies along with their relationships with the drug industry.

Gardasil's attempts to mandate the vaccine brought many disparate groups together in opposition including religious groups, parent's rights groups, anti-vaccine groups, and others. Because it is rare that these groups are on the same side of an issue, it would be useful to analyze how these groups worked together and whether these groups worked together on other issues. Additionally, it would be important to look at the issue of vaccine mandates in general to help place Gardasil in the larger context of when and how vaccines are generally mandated.

The construction of the efficacy results for Gardasil shed light on how clinical trials can be controlled by the pharmaceutical company that ran the trials. Looking at this trend among pharmaceutical companies would help to contextualize how Merck was able to present its findings without criticism from the FDA or CDC. It is important to understand how bias is allowed in the presentation of trial results and how that impacts the use and perceptions of pharmaceuticals.

Following the trajectory of Gardasil opened up many avenues of sociological study in the areas of vaccines, the pharmaceutical industry, and the impact on the public. The theories that were engaged in this study can be applied more broadly to this industry to understand many of the issues that were discussed in relation to Gardasil. This study of Gardasil addressed how a pharmaceutical company took its product through the development and approval process and how it ultimately sold that product to the public. Selling Gardasil to the public meant that Merck had to construct the problem that Gardasil was meant to solve. This was an example of a process that occurs regularly within the pharmaceutical industry; convincing the public they have a problem and that the pharmaceutical is the solution. This is an area not studied enough among sociologists and my intent is to continue to build on this study to bring a sociological analysis to the areas of vaccines and pharmaceuticals and their effect on the public.

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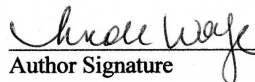
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