Abstract

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Vaccine development represents a special case where historically, public health priorities are central. Trends of privatization have increased the role played by pharmaceutical and biotech companies in developing new biomedical technologies. As the innovative science behind new medical technologies moves into pharmaceutical laboratories and biotech companies, the "logics of action" that pattern knowledge production shift. This project explores how different logics of action based on commercial investment and public good shaped the development of Gardasil, a new vaccine to prevent cervical cancer. The study found that both the logics of public good and commercial profit significantly shaped the final product. The study also found that variations in the definition of public good allowed for the settlement of tensions between good and profit. The findings have implications for the future of vaccine development, as well as for the analysis of biomedical innovation in our contemporary political economy.

BIOMEDICAL INNOVATION AND THE POLITICS OF SCIENTIFIC KNOWLEDGE: A CASE STUDY OF GARDASIL

by

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Introduction

Innovation is often written into history as progress and vaccines are a great success story of modern medicine. Pediatric vaccines have spared millions from morbidity and death from the viruses and bacteria that cause polio, tuberculosis, diptheria, measles, mumps, rubella, chicken pox and others. In 2006 the Food and Drug Administration approved Gardasil, a vaccine designed to prevent cervical cancer, precancerous genital lesions, and genital warts. Cervical cancer is second only to breast cancer as the most prevalent cause of cancer related deaths for women worldwide.

As a health technology, vaccines retain an almost mythic status as the most successful and cost-effective way to promote health and eradicate disease. Richard Horton writes, "Today vaccines are largely an untouchable subject, their benefits too obvious to be questioned. Any hint of dissent concerning their clinical effectiveness and all-around social value is met with bitter rebuttal and resentment" (Horton 2003: 207). Yet, stories of medical success efface the socio-cultural and political-economic work that goes into vaccine development.

Behind the oft-told stories of disease reduction and eradication through vaccination are the structural realities in and through which these innovations are produced and used. The intersection of new potentialities made possible by advances in molecular and genetic science, with neoliberal shifts in the political economic organization of the fields of health and medicine have pushed vaccine innovation from state-funded apparatuses into the private sector (see Blume and Geesink 2000). This privatization of vaccine research and development (R & D) has also taken place in

vaccine development, stimulating fundamental changes in the networks in and through which vaccines are produced.

Unlike most of the vaccines of the past, Gardasil was developed by a pharmaceutical company rather than by state health agencies. Historically, it has been state apparatuses whose obligation to public health supported development of the vaccines that have saved so many lives. As the science of vaccines moves into the private sector, commercial commitments to profit create a tension with the goals of public health. The term vaccinology captures this shift to private sector innovation and points to specific issues concerning this shift. Blume and Geesink explain, "Vaccinology is a science of and for the pharmaceutical industry. Our response to its emergence, then, will reflect our sense of the *compatibility of industrial commitments with the earlier public health objectives* of vaccines research. It is here that reasons for concern arise" (2000: 70; emphasis added).

Research Questions

The central research question in this analysis takes up this concern with the compatibility of industrial commitments with public health goals. This inquiry into biomedical innovation asks how different logics of action (i.e. commercial profit versus public health good) are embedded in the process of biomedical innovation. As this analysis demonstrates, a clean separation between a logic of public or social good underlying medical innovation on the one hand, versus a drive for commercial profit on the other does not accurately characterize the relationship between the two logics. In the development of Gardasil, complex and continuing negotiations between public good and private profit are embedded throughout the process of innovation.

In showing how these logics are embedded in innovation, differing notions of public good that are mobilized in the development of Gardasil become a pivotal factor. It is not too long ago in historical memory that public health included not only public good but also the eugenic extermination of races, populations, and groups as well as human experimentations on "vulnerable" populations. As a sub-question this paper analyzes how the "public" of 'public health' is defined by the actors and institutions committed to and implicated by the development of Gardasil. The definition of such publics (whose health concerns feed into the logic of a general notion of public good) plays a key role in settling and unsettling the tension between commercial profit and public health. In the development of Gardasil, the complex category of woman and its intersections with class, race, and sexuality is bound up in what Nikolas Rose terms the "ethopolitics" of biomedical innovation (Rose 2006).

The concept of ethopolitics facilitates an analysis of the mechanisms of power that operate in and through *moral* justifications. Decision-making around the issue of public good versus commercial profit in the context of neo-liberal shifts towards privatization is a question of ethics. In the development of new vaccines, a clear narrative of public good as the sole motivation or justification for action can no longer be supported by assumptions concerning the role of the state in public health. The institutional logic of private sector R & D seeks to maximize profits but is also constrained by an ethical imperative to justify their actions (at least in part) through a logic of public health. The moral and ethical arguments and justifications deployed in the development of Gardasil are a central mechanism of power that both constrained and enabled the transfer of knowledge and resources that made Gardasil possible. The final

question in this project centers on this question of ethics and asks how an ethopolitics is written into the innovation of Gardasil.

The organization of this thesis is as follows: I begin by outlining the broad theoretical framework through which I investigate the development of Gardasil and clarify what constitutes biomedical innovation within the perspective of science and technology studies. Then I move on to specify the analytic framework that I employ in the analysis of the innovation of Gardasil. The next section presents the methodology used in this study. Finally, I move on to the findings and analysis.

Theoretical Framework

To understand the development of Gardasil I approach the innovation through the broader theoretical framework of Science and Technology Studies (STS). A sub-discipline, drawing together scholars from the humanities and social sciences, STS emerged (in part) from a more traditional sociology of knowledge. More specifically, this project works within *critical STS*, a branch that focuses explicitly on questions of power, analyzing science and technology from a perspective of social justice and democracy (Hess 1997:133). Research in the critical STS tradition opens the 'black boxes' of scientific knowledge to reveal the political content of a science once thought to be objective and unbiased. The science behind Gardasil was not an autonomous knowledge project, immune from the political, economic, social and cultural influences of the environment from which it emerged.

Technoscientific innovation in critical science and technology studies[1]

Sociological perspectives in STS that focus on technology in society have shown that technologies have to be built. That is, they are socially constructed. This perspective, commonly referred to as SCOT (social construction of technology), has its roots in the works of Bijker, Hughes and Pinch (1987). For this project, the SCOT perspective draws attention to the contingent nature of technological innovation. In contrast to narratives of evolutionary science, the development path of new medical technologies such as Gardasil, is not predetermined and as I will show in this analysis, possible alternative paths are 'lost' along the way as a matter of contingency.

An alternative STS perspective views technologies as outcomes of particular socio-technical networks, intended to capture the heterogeneous social, economic, technical and political processes involved (Oudshoorn 2003; 1994). This perspective has its roots in the works of Callon, Latour and Law and is commonly referred to as actor-network theory (or ANT) (Brown and Webster 2004). Traditionally, these networks included only human actors but the importance of non-human actors (or *actants*) such as available technologies and material resources has been found to play a significant role in shaping the direction and interactions of scientific innovation. Vaccines, like other medical innovations, are outcomes of particular socio-technical networks, which are comprised by a mosaic of institutions, actors (both human and non-human), materials, relationships and resources. Building the sociotechnical network for Gardasil meant the

[1] Technoscience, a concept introduced by Bruno Latour, emphasizes the collapse of the traditional distinction between science and its application –technology (Latour 1987). Traditionally this distinction supported the idea that 'basic science' was free of the politics that were inherent in the application of scientific discoveries. Following Latour and others, I adopt this term to emphasize the political nature of scientific discoveries and practices.

transfer of valuable knowledge to the institutions that controlled the necessary material resources that made the vaccine a possible outcome.

The sociotechnical networks that produce biomedical innovations only comprise part of the story. Alternative analytic approaches to technological innovation have brought cultural aspects forward along with sociotechnical networks (see especially Oudshoorn 2003). In *The Male Pill,* for example, Nelly Oudshoorn demonstrates the importance of the cultural context of biomedical innovation as both a constraining and enabling force. In her study, the innovation in male contraceptive technology has been stalled not only by a lack of industrial interest (and therefore a lack of available resources and networks of innovation), but also more significantly by norms of hegemonic masculinity that have prevented the configuration of an appropriate user (Oudshoorn 2003). Oudshoorn also shows how the importance of cultural context extends even into the science itself, demonstrating how cultural norms and beliefs about masculinity and reproduction shaped how scientists *could* design male contraceptives.

Drawing from both the SCOT and network approaches to STS, the *New Political Sociology of Science* (NPSS) draws attention to structural bases of power and inequality in knowledge politics and brings a critical perspective to traditional science and technology studies scholarship. This focus on structural bases of power extends SCOT and ANT, taking the perspective that an actor's position within a specific institution or network provides access to available resources, "NPSS demonstrates the ways in which institutions and networks shape the power to produce knowledge and the dynamics of resistance and accommodation that follow" (Frickel and Moore 2006: 5). Any analysis of large-scale structural relationships is subject to critiques of the deterministic nature of

such analysis. Following Frickel and Moore, I take the position that there are "sustained large-scale relationships that make some kinds of claims, outcomes and processes far more likely than others" (Frickel and Moore 2006: 9).

Biomedicalization and the potential of biovalue

While a technoscientific outcome of a particular sociotechnical network, contingent upon the cultural and structural context of its development, Gardasil is also a *biomedical* innovation. Clarke et al. (2003) argue that the political economic reconstitution of biomedicine along with its increasingly technological and scientific make-up represents a significant shift, "a second transformation of American medicine" (Clarke et al. 2003: 161). By 1985 this uneven but significant shift had coalesced into what the authors term biomedicalization. Though largely driven by technoscientific changes within health and medicine, theories of biomedicalization draw attention to "the realms and dynamics of the social *inside* scientific, technological, and biomedical domains [that] are too often rendered invisible" (Clarke et al. 2003: 166; original emphasis). Biomedicalization characterizes the sociocultural and political economic context of the wider arenas of health and medicine that circumscribed the innovation of Gardasil.

New transformative possibilities provided by advances in molecular and genetic biology are one of the major tenets of biomedicalization theory. These new capabilities have made possible what Catherine Waldby has termed biovalue. The author explains that "Biovalue is generated wherever the generative and transformative productivity of living entities can be instrumentalized along lines which make them useful for human projects –science, industry, medicine, agriculture or other arenas of technical culture"

(Waldby 2000: 33). In other words, biovalue is surplus value *extracted* from the vital capacities of living beings both human and non-human.

Biovalue, by definition, implies a potential for use but not a specific end. As with the development of Gardasil, the production of biovalue did not determine its specific use. The deployment of biovalue, in the case of Gardasil, was (in part) determined by the logic of pharmaceutical and biotechnology companies which is focused on the production and *profitable* deployment of biovalue (Waldby 2000: 19).[2] Gardasil's development in these specific institutional settings was contingent on the sociotechnical network from which it emerged and the historical trajectory of vaccine R & D. In the next section, I return to the concept of vaccinology that describes the networks of vaccine R & D.

Vaccinology: An industrial science

The history of vaccine use and success makes a ready connection between vaccine research and public health. The "basic science" behind new medicines has traditionally been credited to university academics working on grants supplied by state health organizations. This organization of structures and resources supported the idea of an autonomous realm of objective science, purportedly free from the demands of industry. State funding allowed researchers the freedom to pursue technological and economic innovation for the advancement of society and the good of the public (Kleinman and Vallas 2006:39). This organization of vaccine research has changed. In the case of Gardasil, neoliberal political economic changes designed to support innovation, (along with technological necessities) have pushed vaccine research into the private sector.

[2] "'Biotechnology' is any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use" (UN Convention on Biological Diversity). A biotechnology (biotech) company specializes in the innovation of these types of technologies.

Privatization in vaccine development is supported by larger political economic changes associated with neoliberalism. Lisa Duggan writes, "The primary strategy of turn-of-the-millennium neoliberalism is *privatization*, the term that describes the transfer of wealth and decision-making from public, more-or-less accountable decision-making bodies to individual or corporate, unaccountable hands" (Duggan 2003: 12; original emphasis). The retreat of the state from direct responsibility for the population and increasing commercialization is characteristic of neoliberal trends. Critics of neoliberal privatization in health and medicine cite the increasing costs of medicines and health services that exacerbate existing health inequalities, the lack of efficiency in the United States (low health outcomes per dollar spent compared to other post-industrial nations), and the proliferation of expensive 'lifestyle' drugs (Fort et al. 2004).[3]

Also driving this privatization are technoscientific changes in biomedicine associated with biomedicalization (Clarke et al 2003). To work at the level of genes and molecules, scientists need expensive equipment, large quantities of biomaterials (that are often of limited availability), and extensive funding. These basic research necessities have spurred adjustments in sociotechnical networks as researchers and other interested parties (i.e. pharmaceutical and biotech companies) create new sets of relations to meet these needs. Vaccinology describes these new networks of scientists and organizations involved in the production of vaccines and profitable biovalue.

Identifying this shift to privatization, Blume and Geesink (2000) compare the innovation and application trajectories of the polio and hepatitis-B vaccines. While the polio vaccine was developed in an academic setting with state funding in response to a

[3] Lifestyle drugs are a class of pharmaceuticals that are designed to enhance the *lifestyle* of individuals rather than cure sickness. See Mamo and Foskett (forthcoming) and Mamo and Fishman (2002).

global public health crisis, the hepatitis-B vaccine was developed through collaborative agreements between biotech companies, pharmaceutical companies and academic researchers. Pharmaceutical companies funded the research and development behind the hepatitis-B vaccine. This privatization, the authors argue, has shifted the focus of innovation in vaccine research from a focus on public health priorities to a focus on potential profits from valuable intellectual property. “The focus, in other words, was not to be on the fight against a specific disease, but on knowledge potentially relevant to the development of a range of vaccines” (Blume and Geesink 2000: 59).

As the innovative science behind new medical technologies moves into pharmaceutical laboratories and biotechnology companies, the logics of action that pattern the production of knowledge in these settings shift (Frickel and Moore 2006; Knorr-Cetina 1999; Rabinow 1996; Kleinman and Vallas 2006). David Kleinman and Steven Vallas note,

> Amid rising fiscal constraints on public spending (and with social entitlements placing limits on public support for higher education), university administrators increasingly looked to market-based sources for much needed resources. The result, many suggested, involved a historically significant shift in the very logic that traditionally informed university research. [M]uch of this literature voiced concern over the ways in which joint ventures of various types between universities and corporations, or academic efforts to foster licensing arrangements or patent protection, threatened both the free flow of knowledge and the autonomy of scientific research (2006: 39).

The logics at stake in this formation are based in institutions; they are bound up with culture and serve to inspire and justify action (see Knorr-Cetina 1999 on epistemic cultures in scientific knowledge production). Through profit motives have gained ground due to privatization, complex and continuing negotiations between public good and private profit are embedded throughout the process of innovation.

The ethopolitics of biomedical innovation

Joan Fujimura (1987) argues that cancer research depends on the 'doability' of certain research problems. Doability not only depends on available technology, resources and networks, but also on the alignment of several levels of work organization. The three levels in which Fujimura describes this process of alignment are the level of (1) experiment, (2) laboratory, and (3) social world. Framing a problem in a way that can align these levels of organization makes a problem 'doable' (Fujimura 1987: 258). Extending this concept, I argue that a doable problem for vaccine development must also be ethically doable, as concerns public opinion.

Public opinion becomes crucial factor in the success or failure of biomedical technologies and pharmaceutical and biotech companies are constrained in their actions. Sarah Franklin, for example, describes how scientific objectives are directed by the necessity of avoiding ethical objection from public opinion (Franklin 2003: 98). 'Promissory components' of biocapital must take into account public opinion and ethics *before* a technology makes it to market.

Like all venture-capital-funded biotechnology companies, [one such company] is striving to avoid circumstances that might compromise its future profitability. By selecting a route forward that rids the company of one of the most potentially

compromising sources of public opposition in the United States… [this company] is charting a strategic course between what is practical and viable experimentally and what is commercially feasible as a means of shortcutting public opposition to research (Franklin 2003: 120).

This ethical component of biomedicine extends into the laboratory and into the science at the same time that biomedicine seeks to produce surplus out of vitality. A main goal of this project is to identify the spaces and practices where varying notions of public good and the search for commercial profit infuse each other and become an ethopolitics designed to work on the morality of consumers, working towards answering the question of why science works better for some rather than others.

Methodology

This project employs situational analysis to understand the innovation of the HPV vaccine Gardasil. Situational analysis, a method pioneered by Adele Clarke, is based on a framework of following three complementary cartographic approaches: (1) a situational map, (2) a social worlds/arenas map and (3) a positional map. In addition to these mappings, I created an innovation timeline to model process. Together these mappings provided the data necessary to answer the three research questions posed (see figures 1-5).

The first step was to build a situational map. The goal of a situational map is to "descriptively lay out as best one can all the most important human and nonhuman elements in the situation of concern of the research broadly conceived" (Clarke 2005:

86). This first approach to the data focused on analyzing the relations between the elements identified in the situation. Situational maps are messy representations of the situation and provide a preliminary picture of the important elements in the situation.

The second map, a social worlds/arenas approach, focused on the collective and sociological aspects of groups implicated in the development of Gardasil. Social worlds are defined as "universes of discourse" and "the focus of social worlds/arenas maps is on *collective social action*" (Clarke 2005: 109; 114). Individual actors were mapped into social worlds as representative of an arena. The boundaries between social worlds/arenas are porous and plastic rather than rigid and allowed a complex analysis of communities of commitment to action. To demonstrate the porosity of social worlds, the social worlds maps show overlapping categories bounded by lines that are not solid (see figure 1).

The timeline models the sequence of innovation and highlights important events. The three levels within the timeline show how the development of Gardasil progressed along the three analytic dimensions. Innovation is not a linear process, and so the timeline demonstrates the overlapping of the processes that eventually produced Gardasil (see figure 2).

The positional maps "lay out most of the major positions *taken in the data* on major discursive issues therein –topics of focus, concern, and often but not always contestation" (Clarke 2005: 126). The positions of interest in this paper are whether developments in the production of Gardasil follow a logic of public good or commercial profit. For each of the three moments in the narrative a positional map shows which events follow which logic as well as the relationship between the opposing logics of action (see figures 3-5).

To answer research question one, investigating how different logics of action are embedded in the development of Gardasil, I used the maps to identify groups committed to action based on the production of biovalue and/or groups operating with a logic based on maximizing public health good. Significantly, I found that at certain moments, these two logics were indistinguishable from one another (see figure 4). The critical question of how public health good is defined and by whom relied on the positional map to flesh out what public health or public good means coming from specific actors in certain social worlds. Question three involved a holistic analysis of all the maps, focusing on how commitments to action in the social worlds/arenas map articulated with the positions of those groups in the positional map and how these formations were able to control actions and resources.

The broader puzzle of this project is how biomedical innovation happens in the context of advanced technoscience and a neoliberal political economic environment. To capture process I construct an analytic narrative, specifying the mechanisms through which the vaccine was developed. To construct the narrative I began at the end, with the release of Gardasil. By tracing the process backwards through the scientific journal articles, I put together the pieces of the *scientific* story of innovation. The theoretical framework that grounds this analysis pushes the boundaries of scientific innovation towards the inclusion of the elements at work outside of the laboratory. To capture the political and economic elements of the situation data collection moved to the institutional aspects of innovation, relevant science policy, and FDA hearings, for example.

The story told here is only one of many narratives that could be told of the innovation of Gardasil. The focus on scientific innovation in this narrative reveals my

objective. The objective is to interrogate our notions of how science happens, opening the 'black box' of innovation. The relationship of the theory to the data is interpretative and validity relies on the internal consistency of the narrative and the power of the explanation offered. In this project I hope to offer a strong explanation of biomedical innovation in our contemporary social formation.

This project draws on a variety of data types and sources. The first major sources of data were scientific journal articles. From these scientific journal articles, I identified important scientist actors, crucial technological developments, and points of scientific emphasis, controversy or consensus. Medical journal commentary, and published stories, interviews, and biographies documenting the development trajectory of the HPV vaccine provided supporting evidence for social worlds, positional and situational maps. Narratives of the development of the HPV vaccine that have been published by various actors and institutions provided particularly crucial supporting evidence that allowed the research to extend beyond the laboratory. For example, the story of a decade long patent battle over technology relating to the discovery of the vaccine is a significant part of the process that is not found in the scientific literature.

Publicly traded companies such as Merck & Co Inc., have financial records that are available for analysis. The periodic reports that are published to inform shareholders of projects that are in various stages of Merck's research and development "pipeline" provided evidence to the development trajectory of Gardasil. Third party licensing agreements and settlements were documented in these reports (although not disclosed). Institutional histories, news releases, business news concerning these companies, rules and regulations from within or outside of organizations and corporate mission statements

provided supporting evidence for the analysis. Specific government documents such as transcripts from open FDA hearings concerning Gardasil were a rich source of data. The Biological License Application submitted by Merck to the FDA provided evidence for processes of innovation. Legal opinions and rulings relating to relevant patent disputes were analyzed as well.

This exploration of the innovation of the HPV vaccine can be seen as a response to Nikolas Rose's call for a "cartography of the present". A cartography of the present is a mapping of the range of paths not yet taken that may lead to potential futures. Towards identifying the grounds on which alternatives can be established, the mappings undertaken in this project also paid close attention to the spaces between and the discursive silences that represented the erasures and possibilities not explored.

Why Gardasil?

The human papillomavirus is the first and only *necessary* cause of any cancer that has been identified to date. HPV has been proven to be a necessary (but not sufficient) cause of cervical cancer. The ability to prevent infection of the human papillomavirus translates into the ability of medical science to eliminate its worst enemy. The enormity of the scientific breakthrough represented by Gardasil's release makes this particular vaccine a fascinating case study with implications for the future of one of the most deadly human diseases.

Unlike other vaccines, which are based on attenuated or inactivated forms of real viruses, Gardasil is comprised of what is most simply described as a clone of the real human papillomavirus. In contrast to other types of vaccines that introduce weak or

inactive forms of a virus or toxin, vaccines based on virus-like-particle (VLP) technology introduce a genetically engineered 'copy' of a real virus that is, in effect, good enough to elicit an immune response, yet artificial enough not to cause disease. The HPV vaccine is only the second vaccine to be based on recombinant DNA technology (cloning), but there are new vaccines are 'in the pipeline' based on this virus-like-particle technology.

The timing of the development of the HPV vaccine is also important. This time frame encapsulates both the shift to biomedicalization and the beginnings of the neoliberal backlash against the welfare state (see Clarke et al. 2003 and Duggan 2003). Vaccine research has seen a revival due to these changes and thus, the timing of Gardasil provides a lens through which to reveal how larger changes in the political and economic arena affect medical technologies.

Changes in vaccine development have implications for our present understanding of larger shifts in the political-economic arrangements of late capitalism as well as the future of public health in this context. Vaccines have long been in our arsenal of medical technologies and will continue to proliferate. Yet given shifts to privatization and away from public social goods, it is not only important but crucial, to understand the production of medical knowledges and innovation not as "discovery" but as socio-cultural and technical networks constitutive of larger political economic organization of US economies. Gardasil provides a lens through which to begin to understand these issues.

Findings and Analysis

The following presentation of findings and analysis tells the story of the innovation of Gardasil. I begin with how the HPV vaccine became a doable problem. Building scientific consensus around the idea of the link between HPV and cervical cancer was crucial to the technologies being taken up by pharmaceutical and biotech companies. The second section demonstrates how scientists were able to produce biovalue and shows how that production of biovalue became tied to a logic of commercial profit through the patenting and transfer of valuable scientific disclosures. In the third and last section, I detail the approval process of Gardasil demonstrating how ethical considerations play out in the final stage of development. At times I will tack back and forth from narrative to analysis, answering the research questions posed at the beginning of this analysis. Following this narrative, I synthesize the analysis in the discussion section and return to the research questions to summarize the key findings of this study.

A Doable Problem: Preventing Cervical Cancer

The human papillomavirus and its connection to cervical cancer is the only known *necessary* cause of any type of cancer. It took close to twenty years for a scientific consensus to be built around this idea, but in 1995 HPV type 16 was declared a human carcinogen by the International Agency for Research on Cancer (IARC; also see Bocsch et. al. 2002).

Ambivalent technology

Harald zur Hausen spent most of his career in universities between the United States and Germany as a microbiologist researching the infectious causes of cancer. Since the early 60's zur Hausen had been studying viral causes of cancer. At this time, cancer was mainly thought to be too multi-factorial for any necessary condition to be found. Harald zur Hausen hypothesized the link between human papillomavirus and cervical cancer in the early 1970s. The link between HPV and cervical cancer needed the advent of two important technologies before it could be confirmed. In 1973 Cohen and Boyer, building on years of genetic research found a way to recombine DNA. This is often attributed as the birth of what is now termed 'biotechnology'. For most readers, cloning is its most familiar name. Human papillomavirus cannot be grown in cell cultures like most viruses, therefore to do research, scientists were forced to look to other sources for HPV DNA. With the discovery of recombinant DNA technology, Mathis Durst, working in Germany, was able to clone the HPV virus type 16 and subsequently confirm its presence in almost 100 percent of cervical cancer tissue samples (Durst et al. 1993). Even this was not enough for a scientific consensus.

Kary Mullis developed polymerase chain reaction, a technique for quickly identifying and replicating portions of DNA chains, in 1983. This development was said to have 'democratized' genetic research, "making genetic testing available to almost all researchers with minimum tools" (see Rabinow 1996). This democratization proved to have deleterious effects on zur Hausen and Durst's work. The availability of PCR techniques (this was more of a conceptual discovery than a technical one) confused the etiological role of HPV in cervical cancer. "This period caused more confusion than

clarification because the tools were not used properly and people found HPV everywhere" (McIntyre 2005). The epidemiological evidence supported the theory that cervical cancer spread much like a sexually transmitted disease and at this time Herpes simplex virus was thought to be the cause of cervical cancer (ibid).

Despite being disbelieved by colleagues, zur Hausen was convinced of the role of HPV in cervical cancer (see zur Hausen 1976; zur Hausen 1978; zur Hausen 1989). He approached pharmaceutical companies in 1984 to see if they would work with his discovery to find a vaccine for cervical cancer (McIntyre 2005). He was unable to enroll the pharmaceutical industry. The incidence of cervical cancer had been decreasing for some time due to increased use of Pap smear screenings. Scientific consensus around the idea was not yet strong, and vaccine research was not a popular area of investment at this time either. Without pharmaceutical buy-in, a cure for cervical cancer is not a doable problem. Human subjects protections and increased FDA regulations have made pharmaceutical development safer, but the trade off is increased dependence on pharmaceutical companies to buy-in to a new idea or technology (i.e., see a potential for profit). Before federal regulations were put in place, academic researchers could take their own concepts all the way through what is now referred to as Phase II clinical trials.

Technological advances in biomedicine were ambivalent yet necessary for the development of Gardasil. A clear logic of public good that would support the idea of a linear progression from crucial scientific advances to a life-saving vaccine was not the only logic at work in making an HPV vaccine a doable problem. The technological advances that eventually contributed to making Gardasil doable were not hailed as the all-important breakthroughs in an ongoing process that was continually frustrated by lack

of scientific capacity. Rather than a problem of the progression of science, the doability of Gardasil was simultaneously a political, cultural and scientific project.

Institutional Scientific Consensus and Vaccine Priorities

The International Papillomavirus Society (IPV) provided the infrastructure for the extension of HPV cancer research outside of the discipline of microbiology. On the website the mission of the organization states, "The International Papillomavirus Society is a not-for-profit organization of biomedical scientists who are investigating human and animal papillomaviruses and their associated diseases. [T]he purposes of the IPVS are primarily educational" (International Human Papillomavirus Society 2007). The IPV has held annual conferences since 1982 in different venues, connecting scientists and ideas from all over the world. In 1983 zur Hausen (with others) hosted the second annual IPV conference in Sweden.

Scientific consensus around this link was official only two years prior to the submission of the first Investigational New Drug Application to the FDA from Merck. In 1995, the International Agency for Research on Cancer officially categorized human papillomavirus types 16 and 18 as Group One, known human carcinogens. Part of the World Health Organization, The International Agency for Research on Cancer (IARC) is based in Lyon, France and is dedicated to conducting research on the causes of human cancer and to developing scientific strategies for cancer control (IARC 2006). The domestic version of this list is called the "Report on Carcinogens" and is compiled by the U.S. Department of Health and Human Services National Toxicology Program. Human papillomaviruses were not added to this list until 2004.

Although certain HPV types became "known human carcinogens", a vaccine for human papillomaviruses was not on the high priority list for needed vaccines when development began. [4] At the request of the NAID and the NIH, the Institute of Medicine (a non-profit organization chartered in 1970 as a component of the National Academy of Sciences) issued two lists of vaccine priorities; one for United States priorities and another for health priorities in developing countries. The human papillomavirus did not make the 1985 list of priority diseases for domestic vaccine development but did make second tier on a 1999 update of the 1985 list. The IOM also created the model through which vaccine priorities were decided. The addition of a target disease as a candidate for vaccine development rested on the current "state of knowledge" concerning the development of a particular vaccine. Regardless of the lack of need for this vaccine target established in 1985, by 1999, microbiologists were well on their way to developing a working HPV vaccine. The model for adding a vaccine to the IOM list also utilizes a reductive cost-benefit analysis. The 'benefits' of a potential vaccine must outweigh the 'costs'. The addition of HPV in 1999 as a "more favorable" vaccine candidate (versus "most favorable") is calculated based on how much money an HPV vaccine could save society (Chapter 2: Priority setting for health-related investments: a review of methods; see also Galambos 1995: 148).

To make an HPV vaccine a doable problem, zur Hausen had to build consensus around the connection between HPV and cancer to establish potential public good. The scientific "bandwagon" at this time was focused on herpes as a cause of cervical cancer

[4] See Committee on Issues and Practices for New Vaccine Development. 1985. *New Vaccine Development: Establishing Priorities, vol. 1, Diseases of Importance in the United States;* vol. 2, *Diseases of Importance in Developing Countries*. Institute of Medicine: Washington D. C.

and not HPV (see Fujimura's 1988 work on scientific bandwagons). Technological advances alone were not enough to provide consensus. Consensus emerged when the technological advances were stabilized enough to produce consistent results and when the political economic environment was suitable for investment in this particular vaccine. The stabilization of experimental techniques is a requirement for a new scientific bandwagon to take hold but it would take more than science to get pharmaceutical buy-in, a necessity for biomedical innovation (Fujimura 1988). The professional organizations that held conferences played a significant role in transferring scientifically legitimated knowledge outside the discipline of virology and to pharmaceutical companies. The need for pharmaceutical buy-in for medicines and vaccines to be made available to the public has not always been the case. We have already explored the technoscientific doability of the HPV vaccine. Next, we turn to the historical development of the political economic situation to complete the explanation of how the HPV vaccine became a doable problem.

Favorable Political Environment

Although, vaccines had recently achieved unrivaled medical success with the eradication of small pox in 1979, pharmaceutical investment in vaccine research and development had been on the decline. Many of the private firms that participated in vaccine innovation and production began leaving the business in 1968 and over half had left by 1979 (Galambos 1997:178). Companies involved in private sector vaccine development had every reason to abandon this domain of health research. Lawsuits claiming injury from vaccines were on the rise, R & D costs had been steadily increasing, and government contracts demanded low cost vaccines that undercut profits (Galambos 1997: 145-148).

The U.S. federal government began to express concern about the lack of private investment in the sector of vaccine R & D. In 1985, Congress passed the National Vaccine Injury Compensation Act (VICP). This act made investment in vaccines more profitable for pharmaceutical companies. Previously, pharmaceutical companies could be held liable for injuries caused by vaccines. The National Vaccine Injury Compensation Act legislates that the federal government will compensate children and parents for injuries that result from immunizations on the compensation list (Department of Health and Human Services 2006). The act is designed to serve as a catalyst for increased private investment in vaccine R & D: "Since its inception, the VICP has been a key component in stabilizing the U.S. vaccine market by providing liability protection to both vaccine companies and health care providers. Not only does it provide a more streamlined and less adversarial alternative to the traditional tort system for resolving claims, the VICP encourages research and development of new and safer vaccines" (Division of Vaccine Injury Compensation 2006).[5]

The Bayh-Dole Act of 1980 allowed university researchers to patent technologies that they discovered while working on government contracts. Previously, university researchers were not entitled to property rights concerning the work done in state-funded research projects. Along with the Vaccine Injury Compensation Act, the Bayh-Dole act stimulated private sector investment in research and development. The ability to patent

[5] The following vaccines are covered by the VICP: Diphtheria, tetanus, pertussis (DTP, DTaP, Tdap, DT, Td, or TT); Haemophilus influenzae type b (Hib); Hepatitis A (HAV); Hepatitis B (HBV); Human papillomavirus (HPV); Influenza (TIV, LAIV) [given each year during the flu season]; Measles, mumps, rubella (MMR, MR, M, R); Meningococcal (MCV4, MPSV4); Polio (OPV or IPV); Pneumococcal conjugate (PCV); Rotavirus (RV); Varicella (VZV); Any combination of the vaccines above; Additional vaccines may be added in the future (National Vaccine Injury Compensation Program).

technology, it is believed, has opened up pathways for the transfer of technology from laboratories to pharmaceutical companies to the public.

Pharmaceutical companies became more interested in vaccine research and development after the implementation of these policies. As of 1997, taxpayers cover 36% ($500 million) of funding in the field of vaccine research and development, large pharmaceutical and biotech companies provide 46% ($650 million) and risk capital provides 18% ($250 million) (National Vaccine Advisory Committee 1997:3). Now, private companies fund almost half of all vaccine R&D, but the retreat of the private sector from vaccine development in the previous period left only a few major firms who now hold a significant monopoly over the production and distribution of vaccines.

In the early 1970s Merck's R & D pipeline for new drugs did not look promising, "Merck's growth had been sustained by a series of new products discovered through screening, assays, chemical isolation and chemical synthesis. [B]ut in the early 1970's the pace of innovation was slowing at Merck…" (Galambos 1995: 120-121). Shortly after this lull, success with the vaccine for Hepatitis-B positioned Merck as a leader in the new cycle of vaccine innovation based on recombinant DNA technology. Capitalizing on this success, Merck decided to further invest in its vaccine research infrastructure. In 1993 Merck hired Katherin Jansen, a yeast expert, whose work was crucial to the development of the HPV vaccine that eventually became Gardasil. In 1995 Merck purchased rights to use certain patented technologies that were necessary to even begin research on an HPV vaccine.

The path to the doability of Gardasil could have been different. Various scientific, social political and economic developments littered the path of Gardasil's innovation.

Had vaccine research remained doable within the state or university apparatus and did not need the investment of pharmaceutical companies it is possible that an HPV vaccine would have been made available sooner or not at all. In the next section we move to the production of biovalue, where public good becomes potential commercial profit.

Producing Biovalue: Public Good becomes Potential Commercial Profit

The most important breakthrough in the development of the HPV vaccine was less of a single breakthrough than a process. This process revolved around the production of biovalue and the transfer of that (patented) knowledge from the publicly funded domain of university research to biotech companies and then to pharmaceutical companies. Over the course of four years scientists on opposite sides of the globe figured out how to clone only the outer shell of the HPV virus to produce virus-like-particles. These virus-like particles (VLPs) can create an immune response that blocks the major protein forming the outer layer of the real virus, thus preventing infection. But the VLPs do not hold the infectious genetic material contained in the human papillomavirus and cannot cause infection. Claiming “discovery” of this crucial HPV virus-like-particle, four institutions engaged in a patent battle over property rights to this technology: the University of Queensland, Australia, the University of Rochester, the National Institutes of Health’s National Cancer Institutes and Georgetown University (McNeil 2006). The inventors are microbiologists or virologists and most had been working with human papillomaviruses for some time. Between the years of 1991 and 1994 each team made a substantial scientific contribution to the development of HPV vaccines.

Patents and Interference

Ian Frazer, a microbiologist at the University of Queensland at Brisbane (Australia), began working with human papillomaviruses in the early 1980s. Jian Zhou, who had also been working with HPV for almost a decade, joined Frazer at the University of Queensland in Brisbane in 1989. The team's research was funded by grants from the federal government in Australia (Zhou et. al 1991:256). [6] They realized they had a breakthrough when they discovered that two of the proteins on the outer shell of the HPV 16 virus would self-assemble into a virus-like-particle when correctly expressed in a host (Zhou et. al 1991). They quickly patented this discovery. This biotechnology was licensed to Commonwealth Serum Laboratories, Ltd. (CSL) a few months later.

At Georgetown University in 1992, a year after Frazer and Zhou presented their discovery at the 10th International Papilloma Virus conference in Seattle, Ghim, Jenson and Schlegel expanded on the discovery. Ghim et. al found that for the VLPs to produce *effective* antibodies, they have to fold correctly (Ghim et. al 1992). Initially, the Georgetown University team was awarded the U.S. patent because the VLPs made by Zhou and Frazer did not fold correctly. The U.S. Court of Appeals overturned this decision in August of 2007. They found that the PCT (Patent Cooperation Treaty)

[6] The funding agencies include: The National Health and Medical Research Council of Australia, the Queensland Cancer fund, the Mayne bequest, and the Princess Alexandra Hospital Research and Development Foundation

application that Frazer and Zhou had filed in 1991 qualified as an "enabling disclosure" in the making of the VLPs (U.S. Court of Appeals 2007).[7]

At the University of Rochester, the team of virologists did not start out looking for a prophylactic vaccine. The group was trying to develop a quick and accurate method for identifying whether high-risk HPV types are associated with abnormal Pap smear results (Ireland 2006). Robert Rose, a member of the Rochester team, learned at an HIV conference how to make virus-like-particles in 1990 (Ireland 2006). Along with his team in 1993, Rose et. al produced VLPs that folded correctly and demonstrated that these VLPs provoked an antibody response in animals (Rose et. al 1993). This research was funded by U.S. federal grants from the National Institute of Allergy and Infectious Diseases (NIAD) and the DHHS (ibid). Rose et. al patented this discovery and licensed it to a biotechnology company called MedImmune.

Also in 1993 Douglas Lowy, John Schiller and Reinhard Kirnbaueer discovered that researchers could produce better assembling VLPs by using a different strain of HPV-16 from which to clone the major shell protein (Lowy et. al 1993). This group was also able to patent this enabling disclosure, although as research scientists working for the NIH's National Cancer Institute the United States Federal Government automatically licenses their discovery.

Biotechnology Companies and Early Phase Trials

There were two biotechnology companies involved in the production of Gardasil: Commonwealth Serum Laboratories (CSL) and MedImmune. Post-patenting, biotech

[7] The Patent Cooperation Treaty is an international agreement involving 117 countries. The agreement respects priority dates for patents submitted in other countries.

companies take the role of mediator and serve to transfer valuable scientific knowledge from 'bench to bedside.' After the crucial VLP technologies were licensed to the biotech firms, these firms provided the test vaccine so that university scientists could conduct more extensive animal trials (and in some cases preliminary human trials). Only after these early trials had provided proof of concept, did Merck and GSK on-license the patented technology from CSL and MedImmune respectively. Biotechnology companies began sprouting up after the Bayh-Dole Act opened up patent rights to universities and the individual scientists at those universities (Zucker and Darby 1996). The ability to patent biotechnological products encouraged investment in start-up biotech companies that serve to facilitate transfer of innovative technologies to larger pharmaceutical companies.

Medimmune founded by Wayne T. Hockmeyer in 1988, is based in Gaithersburg, Maryland and has approximately 2000 employees worldwide. In 2005, the company reported over $1 billion U. S. dollars in annual revenues and investments of more than $384 million in research and development (Medimmune Annual Report 2005). CSL is an Australian biotech company that began as a state agency in charge of vaccine manufacture (Galambos 1995). It was privatized in 1994. According to their annual report, CSL received $86 million from Merck & Co. Inc. in royalty payments on global sales of Gardasil (CSL Annual Report).

Phase I trials for the vaccine that was eventually approved as Gardasil began in 1997. After extensive animal trials, preliminary human trials tested the safety and immunogenicity (whether or not the vaccine produces antibodies) of the VLP vaccine concept. These trials were conducted under the Investigational New Drug Application

submitted by Merck to the Food and Drug Administration's Vaccines and Related Biological Products Committee. Merck completed six phase I and II trials and two phase III trials for Gardasil (VRPBAC 2006).

The results of the first trials of the HPV vaccine that was licensed to MedImmune and GlaxoSmithKline, were presented at the 18th International Papillomavirus Conference in Barcelona, Spain in 2000. The 19th IPV conference, held in Brazil in 2001, brought together results from phase one and two trials, as well as results from early phase trials conducted by the National Cancer Institute. Although early phase trials had shown the safety and immunogenicity of the HPV-VLP vaccine, clinical efficacy data was largely missing. Researchers from the National Cancer Institute (NCI) conducted the very first large double blind phase II clinical trial in Costa Rica (Berry and Palefsky 2003:5). In this study the endpoints were persistence of HPV infection and development of cervical lesions.

When Medimmune licensed technologies relating to the HPV vaccine from Rochester University, the company was convinced that it had obtained exclusive licensure for the technology. The company history reads: "October 1995: MedImmune acquires exclusive worldwide rights to human papillomavirus technology developed at the University of Rochester" (Medimmune Company History 1995). The ensuing patent battle resulted in a loss of this exclusivity. The patent rights that come along with vaccine R & D and guarantee a market monopoly for the life of the patent. During this monopoly period companies make the majority of their profits. Since 1979, the vaccine industry has been aware "that without a high rate of sustained innovation, the vaccine business could not be conducted on a profitable basis…" (Galambos 1995: 147). Without exclusive

property rights to enabling disclosures, other companies and/or governments can make cheaper generics, cutting into profits.

In 1993, Merck hired Katherin Jansen, a microbiologist and a yeast expert as the Executive Director of Microbial Vaccine Research for Merck Research Laboratories. In 1995, Merck on-licensed Frazer's HPV VLP discovery and Jansen began work on the HPV vaccine that would soon become Gardasil (Grady 2003). After licensing the necessary technologies and hiring Jansen, Merck was able to produce Gardasil. The vaccine technologies licensed to GlaxoSmithKline eventually became Cervarix, which was released after Merck's Gardasil had already enjoyed almost a year of complete monopoly on the HPV vaccine market.

The production of biovalue happened in university and state health agency settings. That knowledge was transferred through patents and licensing mechanisms to the private sector where profit logics reign. The prospect of preventing a deadly human disease such as cancer stimulated both a logic of profit and a logic of public good. That both of these logics were able to justify the development of an HPV vaccine, following the production of biovalue potential, meant that the state (through NCI), Merck and biotech companies were involved in these early phase trials. After this period, researchers had proved that they had a vaccine that could stimulate anti-bodies against HPV, but proving that the vaccine was efficacious in preventing cervical cancer proved problematic.

An ethopolitics on trial: accelerated approval and phase III trials

Before final approval Merck had to prove the efficacy of Gardasil in phase III clinical trials. Decisions concerning vaccine indications (the specific disease that a medicine prevents or cures) and which HPV types to include needed to be made. These decisions highlight the ethopolitics of the development of Gardasil. A committee in the FDA approval process subsequently evaluates these decisions before releasing the vaccine to the public.

Vaccine indications: cervical cancer, anogenital cancer or HPV

The target disease of the vaccine was not a forgone conclusion. The vaccine could be described as prevention for cervical cancer, making it a women's health issue; as anogenital (genital and anal) cancer prevention; or as protection from the sexually transmitted disease HPV. A status report on the development of HPV vaccines made for the Bill and Melinda Gates Foundation reports:

> Considerable attention is being paid to how to best position the vaccine (i.e., for cancer prevention or for sexually transmitted infection [STI] prevention). There is concern that in some settings, presenting the vaccine as an STI-prevention measure could have a negative impact on acceptance rates. However, other experts posit that ensuring that women (or the parents of minors) fully understand all implications of the intervention is a fundamental right and not providing complete information would be unethical. The tension between these two positions makes this issue particularly sensitive. The two vaccine companies differ in their positioning on this issue. GSK will promote its vaccine as one to prevent cervical cancer by reducing susceptibility to the STI that causes it. Merck will position its vaccine to protect against both cancer and genital warts (PATH 2005).

For pharmaceutical companies, the 'tension' referred to in the above quote is of the utmost importance. A lack of immediate vaccine acceptance would put the profitability of their patent monopoly in jeopardy and thereby most of the profitability of Gardasil more generally. Merck has marketed Gardasil exclusively as a vaccine for cervical cancer. This decision shows how profit motives shaped innovation.

As the science progressed from microbiology to other disciplines, preventing "anogenital cancers" mysteriously shifted to preventing "cervical cancer". The reasoning behind this move is less clear than that of an underlying logic of profit, but a clue lies in the methods used to test the efficacy of the vaccine. Young women, a category denoting "females 16 to 23 years of age" were randomly assigned to either a placebo group or a vaccine group in a classic double-blind study design (Koutsky et al. 2002:1645).[8] Genital samples were obtained from participants to assess their HPV status upon enrollment in the trial and multiple times thereafter. This reasoning was used to exclude men from clinical trials in the VRBPAC meeting. FDA consultant Dr. Karen Goldenthal comments, "Now, in women, the cervix is the sample that is most commonly used, and that is the site where the pathology is. And the appropriate sample in males is not at all clear" (VRBPAC 2006).

The female body has long been a site for medical intervention, especially when reproductive organs are concerned (Oudshoorn 2003). The inability of researchers to devise a way to test men for HPV and its related diseases reifies the female body as an object to be intervened upon. Men do not get cervical cancer, but zur Hausen's discovery did not include only cervical cancer but anal and penile cancers were also associated with

[8] In a double-blind study neither the clinicians nor the 'subjects' know who received a placebo and who received the vaccine.

the same high-risk HPV types. This points to the power of women's health advocacy in the United States as an issue that compels actions based on a broad moral imperative to promote and protect women's health. In this case, the promotion of women's health is to the exclusion and even the intentional elision of the possibility of promoting and protecting men's health. The assumption of heteronormativity also does this work of effacing men's risk by ignoring the health needs of homosexual men who have higher rates of anogenital cancer.

The search for Clinical Endpoints: Making "good" profit possible

Clinical endpoints are the necessarily well-specified goals of phase III clinical trials. For example, the best (theoretical) endpoint for a vaccine to prevent cervical cancer would be invasive cervical cancer. If researchers did not see a significant drop in cervical cancer (the endpoint) after administration of a vaccine, then the FDA would not approve the product. This search for clinical endpoints was also a search for the scientific justification for Merck's decision to market the vaccine as cervical cancer prevention. The development of clinical endpoints for phase III efficacy trials proved problematic and logic of profit again delayed the progress of Gardasil.

The human papillomavirus is a necessary cause of cervical cancer but not a sufficient cause. Microbiologists largely agree that HPV must be present for cervical cancer to develop but ninety percent of cases of HPV infection clear the body without intervention. What science has yet to discover are the conditions under which HPV does in fact progress to cancer. Although HPV can cause cervical cancer, there is another mechanism that enables HPV to become cancer. The success of Pap smear screening is based on identification of lesions caused by HPV infection, followed by evaluation of the

persistence and type of lesion and (possibly) their subsequent removal (Clarke and Casper 1998). Despite the conceptual consensus, questions and uncertainties concerning the link between HPV and cancer remain.

The time lag between HPV infection and the development of cervical cancer is disputed. Most women are not considered at risk for cervical cancer until 15 to 20 years after infection with HPV. A major stumbling block in the development of Gardasil was the lack of clear clinical endpoints with which to analyze the efficacy of a vaccine (Pagliusi 2004). Obvious ethical considerations preclude using cervical cancer itself as a clinical endpoint, especially because early detection through cytological screening is a successful, pre-existing method. Finding the appropriate clinical endpoints is a necessary step for beginning the all-important Phase III trials that are designed to test the efficacy of a product as concerns its "official" indications.

Clinical trials are about statistics and Merck needed a null hypothesis. To conduct efficacy trials, researchers had to be able to falsify the inefficacy of the vaccine. In other words, they needed to know how many cases of cervical neosplasia[9] would "naturally" occur in the population in order to determine if the vaccine had prevented a significant amount of those natural occurrences. To establish clear clinical endpoints, vaccine developers needed to understand the "natural history" of the human papillomavirus. In the mid-1990s Katherin Jansen met Laura Koutsky, an epidemiologist from the University of Washington at Seattle.[10] Koutsky had been studying the natural history of

[9] A precancerous lesion on the cervix

[10] Where and how these two met would tell an important story about how Merck was able to gain access to Koutsky's valuable knowledge, but I have found conflicting stories of their meeting, although the time frame of 1994-1995 has been consistent.

the human papillomavirus since the late 1980s (Bock 2007). Koutsky's epidemiological work was the key to moving into the crucial phase III trials.

Koutsky's role in the development of Gardasil is undeniable; it earned her first authorship on the proof-of-concept trial publications (Koutsky 2002). Koutsky's natural history data solved the problem of the uncertainties concerning the time lag between HPV and cervical cancer. Nine hundred female volunteers on the University of Washington campus participated in Koutsky's research starting in the late-1980s. For three years, the women were followed up with pelvic exams and detailed questionnaires about their sex lives. These data provided evidence of the temporal relationship between HPV types-16 and -18 and the high-grade lesions of the cervix that are the precursors of invasive cervical cancer. Koutsky found that it takes only months to go from infection with HPV to the development of pre-cancerous legions (Koutsky 1992). In 2001 at the 19th Papillomavirus Conference in Brazil, Laura Koutsky presented preliminary efficacy results based on her earlier epidemiological findings.

In November of 2001, the Vaccines and Related Biological Products Advisory Committee (VRBPAC : a branch of the FDA) held an open session to discuss the possible surrogate endpoints for the accelerated approval of Gardasil. For two days, a committee made up of scientists and researchers from various disciplines listened to presenters and discussed the appropriate clinical endpoints for the Gardasil trials. By the end of the session, the committee had come to a consensus. Cervical cancer could not be used as an endpoint, so the committee decided that the clinical endpoints would be cervical intraepithelial neosplasia (CIN) grades 2/3, and CIN 3. These endpoints line up with the standard of care in Pap smear screening. When clinicians identify CIN 2/3 or

CIN3, women are immediately followed up with biopsy of the lesions. This decision standardized the identification of abnormal pap smear results that have been locally controlled and manipulated since the advent of cytological screening (see Casper and Clarke 1998).

HPV types, cervical cancer, and the distribution of risk

The first proof of concept study showed that Gardasil was 100 percent effective in preventing CIN2/3 and CIN3 (Koutsky et al. 2002). These results were astonishing; most vaccines have a success rate between 70 and 90 percent. The next decision concerned which types of HPV should be included in the vaccine. HPV type 16 was the original carcinogenic type of HPV discovered by zur Hausen and confirmed by Durst. But subsequently, over 40 "high-risk" strains of HPV have been identified. Choosing which types to include in the vaccine was a decision to be made by Merck. HPV types 16 and 18 are the most prevalent causes of cases of cervical cancer, and preventing infection from these types would theoretically prevent 71 percent of cases worldwide. But the geographical distribution of HPV types is varied. HPV 16 and 18 have the highest prevalence in Europe and North America, while non-vaccine types 45 and 31 have been shown to cause significant amounts of disease in Africa and Latin America (Munoz et al. 2004).

Global rates of cervical cancer were quoted by Merck to justify the public good of their vaccine during the final presentation to the FDA for the approval of Gardasil. Missing from the presentation was an analysis of the global geographical distribution of this risk. A logic of public good would justify saving the maximum amount of lives, but

profit requires users that can afford Gardasil.[11] The population that can afford Gardasil is not the population that has the greatest need for a vaccine against cervical cancer. The population that has the greatest need and therefore justifies a logic of good is not compatible with a logic of profit. This logic of profit is written into the innovation itself. In addition, due to the patenting of "enabling disclosures" it is unlikely that another vaccine with different types will become available in the near future.[12] This demonstrates how a logic of profit is indistinguishable from a logic of public good depending on the reference category of that good. If we interrogate that reference category, we see that a logic of profit had the upper hand in the final outcome.

The declines in the rates of cervical cancer in the United States have not received much attention in this process. Since the 1950's cervical cancer rates have been decreasing due to increased Pap smear use. This reduction in disease burden follows patterns of stratification common to other diseases and cancers. Poor women and women of color suffer a disproportionate number of what cases still occur of treatable and preventable diseases (Shi and Stevens 2004). Middle class women in the United States get regular pap smears and thus, are able to intercept and get rid of any HPV related disease that might lead to cervical cancer. Women in the United States have a 0.9 percent chance of developing cervical cancer and a 0.3 percent chance of death from cervical cancer (VRBPAC 2001:69). These rates are higher for low-income women, and African

[11] "National vaccine markets are usually two-tiered: with a large public sector and a smaller private sector in which prices and margins were higher. Only in the United States was the private portion of the market large enough to enable a producer to make profits that would justify continued investment in vaccines over the long run" (Galambos 1995: 208).

[12] It is worthwhile to note that Cervarix, the vaccine being developed by GlaxoSmithKline does protect against HPV types 16, 18, 45, and 31 but epidemiologists suggest a vaccine that could protect against the seven most prevalent high-risk types would be the best-case scenario (Munoz et al. 2004).

American women. Recent Asian immigrant women have the highest rates of cervical cancer in the United States (ibid).

In an open meeting of the Vaccines and Related Biological Products Advisory Committee Cindy Pearson, a representative from the Women's Health Network, addressed this very issue.

> So even though overall we look at cases of cancer and likelihood of death from cervical cancer that are very small in, and you might say low on the priority list for women in the U.S. But as a broad-based consumer group, we are aware that for certain groups of women in the United States that it is much higher on the priority list (VRBPAC 2001: 109).

The complexities and tensions between public good, commercial profit and how public good is defined are revealed in Pearson's statements. This use of the at-risk situation of poor and minority populations in the United States extracts the potential of public good from these women's at-risk bodies and instrumentalizes that corporeal risk as a justification for a vaccine that may not be made practically available or useful to these specific groups for decades. This type of argument wields immense power in a contemporary political formation of identity politics where inequality is rhetorically condemned but tolerated in practice.

Pearson continues, "But I would still put forth the perspective from our consumer group that a vaccine that is either approved preliminarily through accelerated approval, or finally through final approval based on its ability to prevent either infinite infection or persistent infection, isn't really making that much of a difference in women's lives"

(VRBPAC 2001: 109). This quote, juxtaposed to her last comment reveals an intersectional tension within the category of woman. The "broad based consumer group" of her first comment includes those "certain groups of women in the United States" that are at substantial risk for cervical cancer and thus justify the need for the vaccine. In the second comment, the approval of the vaccine is not an urgent need based on the at-risk status of these groups, but becomes inconsequential as it concerns for "women's lives". Preventing cervical cancer is preventing a women's cancer, but cervical cancer is not simply a women's cancer; it does not affect *all* women with equal opportunity.

Choosing the indication of cervical cancer, as opposed to preventing infection from HPV, was an ethopolitical move designed to harness this logic of public good (defined as preventing a women's cancer), push the approval process and guarantee vaccine acceptance to the end of commercial profit. Due to intense AIDS activism, the clinical trial process had been reshaped since the early 1990s to push drugs through the FDA system as quick as possible (see Epstein's work on Impure Science). This accelerated approval process was available to Merck.

Accelerated Approval

The Food and Drug Administration's accelerated approval process was formalized under the FDA Modernization Act of 1997. Accelerated approval is "intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic benefit compared to existing treatment" (FDA 1992: 58942). The FDA will consider accelerated approval if appropriate surrogate clinical endpoints can "reasonably suggest" the drug's effect on the real clinical endpoints (ibid). The accelerated approval process was the FDA response to pressure of

civil society organizations that were pushing for quicker and freer access to experimental therapies for HIV/AIDS and cancer and most of the drugs approved under this process had those diseases as their target (Roberts and Chabner 2004).

Gardasil is the first prophylactic vaccine to be approved under the guidelines of this accelerated approval process. The Biological License Application for Gardasil (submitted to the FDA after phase III trials) received priority review status. Priority review status reduces the time frame in which the FDA reviews and approves a new drug from ten months to only six months. It is clear from these two actions that the FDA was convinced that preventing cervical cancer with Gardasil represented a meaningful benefit as compared to existing therapies and needed to be released to women as soon as possible. This is a logic of public good that justifies the quick approval of Gardasil. Reiterating this point, FDA consultant Dr. Karen Goldenthal warns, "The original and current purpose of accelerated approval is to serve the best interests of the *public* and I did want to note that presented vaccines have not been previously approved using accelerated approval regulations (VRBPAC 2001:85; emphasis added). At the same time, accelerated approval follows a logic of profit. The patent monopolies that are crucial to the profitability of vaccines only last for 14 years and Merck knew that GSK was following closely behind Gardasil with another HPV vaccine, Cervarix.

Gardasil was approved on June 6, 2006 with a unanimous decision from the VRBPAC committee. As one of the final indications, Gardasil was proven to prevent cervical cancer.

Discussion

The potential for public good represented by the discovery of the etiological role of HPV in cervical cancer was not enough to spur pharmaceutical interest in 1984. Though rates of cervical had been steadily decreasing in Western countries, less developed nations still had high rates of cervical cancer deaths. Commercial profit potential was not recognized in zur Hausen's discovery in the eighties, and pharmaceutical companies were simply not interested in creating a vaccine for cervical cancer despite high death rates in developing countries. Whether or nor zur Hausen himself was motivated by profit or pubic good, by providing a necessary cause, the path to prevention was opened. Despite this opening of potential for public good in 1984, Gardasil did not become available for another 22 years. The lack of potential commercial profit delayed the emergence of this technology. At this moment in the development of Gardasil public good and commercial profit were easily distinguishable (see figure 3). Without pharmaceutical buy-in an HPV vaccine could not be brought to market and the potential for profit (a prerequisite for pharmaceutical buy-in) was not yet apparent.

The Bayh-Dole Act of 1980 made it possible for university scientists to patent technologies discovered while working under government contracts. The Vaccine Compensation Act spurred increased interest in these patentable technologies and their potential use in commercial vaccine development. Funding for the university scientists often comes largely from federal health research grants. This research money, which is doled out based on public health service research, becomes connected to the forces of commercial profit through this patenting of enabling disclosures. Patents and licensing enable the transfer of knowledge to the end of individual profit *and* public good. At this

moment during the development of Gardasil, the production of biovalue, the logic of profit is indistinguishable from the logic of public good. The logic of profit is subsumed under the more salient rubric of public good and the two logics are apparently compatible (see figure 4).

Discovering HPV VLPs was the biomedical breakthrough that signaled to pharmaceutical companies the potential for a profitable deployment of biovalue. To instrumentalize that potential Merck first had to on-license the necessarily patented technology needed to work on a vaccine. Next, they had to find the necessary expertise, which was outside the field of microbiology and in the discipline of epidemiology.

Hailed by some as one of the most significant medical breakthroughs, Gardasil proved 100 percent effective and an ethics committee stopped the trials in order to administer the vaccine to the placebo participants. Gardasil was seen by some as the perfect example of how public good and commercial profit can, should, and do successfully work together. A closer look at the notion of public good, however, reveals the tensions that reside within. The public, we discover, is not an all-encompassing notion that refuses to distinguish between populations. The logic of public good is revealed in the last instance as multiple and contingent on who is defining ‘public’ (see figure 5).

Conclusion

New biomedical possibilities in conjunction with neo-liberal policies designed to increase the potential for commercial profit (and thereby provide for the public good) provided the avenues through which Gardasil was made possible. The transfer of valuable scientific knowledge within a neo-liberal political economy allows potential

biovalue to become attached to logics of profit. The sheer cost of equipment and materials in addition to patent laws that create monopolies on scientific knowledge, dramatically increase the costs associated with moving a potential vaccine even beyond animal trials. Patent laws also impede competition from rival companies by granting monopoly rights to patent holders of new vaccines. Policies designed to stimulate pharmaceutical interest in vaccine development encourage companies to watch and wait for suitable patents with which to engineer a product with a built-in insurance policy.

In biomedical innovation the politics of scientific knowledge are ethopolitical. The ethopolitical argument that insists preventing cervical cancer with a vaccine is an undeniable public good, *needs* the risky bodies of those groups whose lack of access to pap smears puts them at risk of cervical cancer. Without these at-risk bodies there the need for Gardasil is questionable. These bodies support the ethically grounded political argument that we *should* support the uneasy marriage between science, government, and industry because it resolves the tension between public good and private profit. But these bodies are not those that will make Gardasil profitable

The development of Gardasil depended on both logics of commercial profit and logics of public good. Though Gardasil emerged with the appearance of satisfying both, the definition of public good varied by actor and institution. Varying notions of who constitutes this public reveal the continuing tension between good and profit in the final vaccine. Gardasil appears to collapse the logics of good and profit. Merck's focus on young girls supports this conceptual collapse by eliding the reality that only for specific publics does HPV even get the chance to progress to cervical cancer.

The question of good versus profit in this inquiry gets to the heart of a neoliberalism that encourages privatization in the name of public good. Although these profit logics were constrained by the need for an ethical biomedicine, in the end logics of profit had the upper hand. Our shared fear of cancer as the disease that science cannot beat provides Gardasil with an almost ready-made market for its medical benefits. This market though, does not include those women whose risk for cervical cancer supported arguments in favor of the vaccine's development. Both inside and outside of the United States, these women are least likely to have access to Gardasil.

Figure 1 Social Worlds/Arenas Map

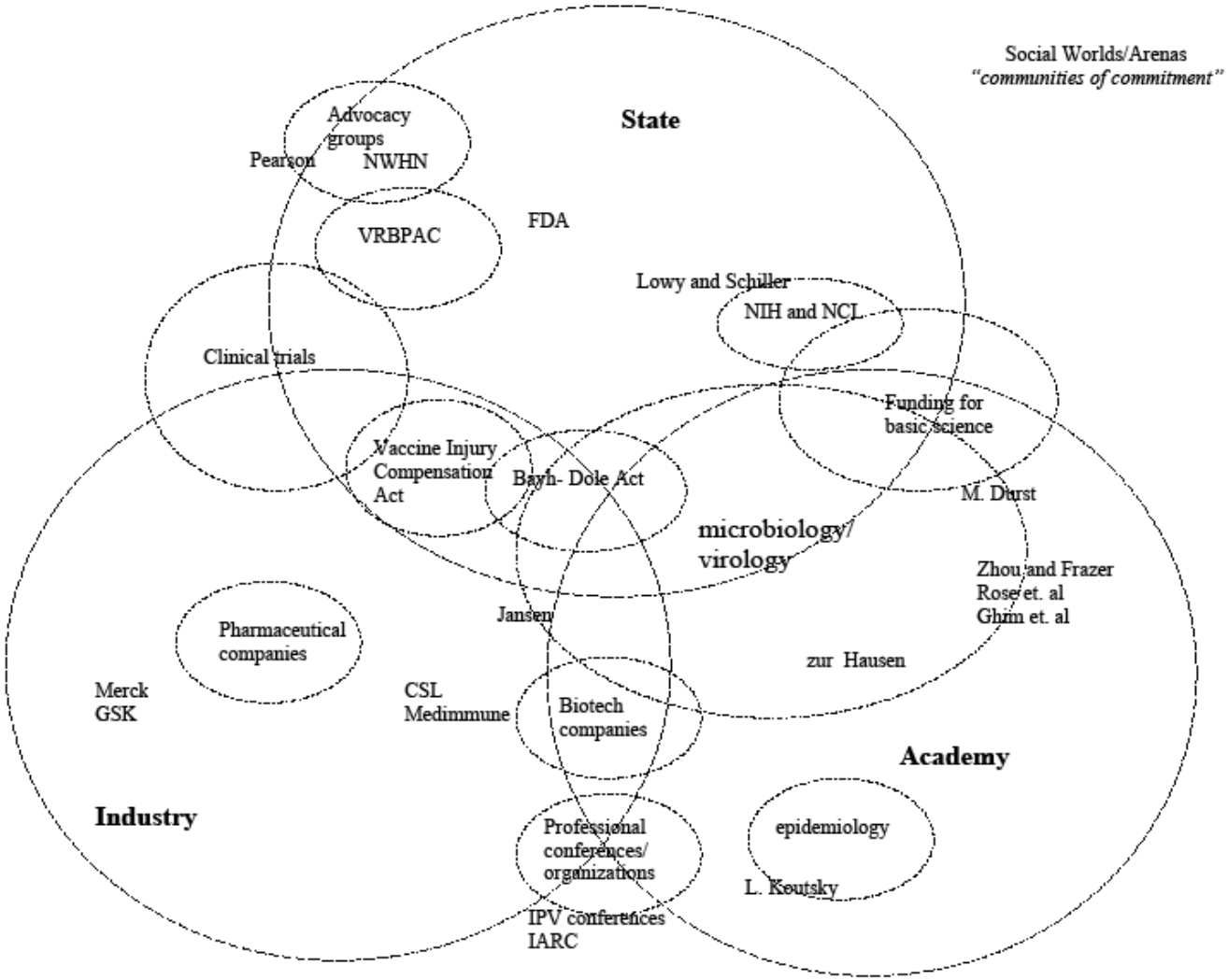
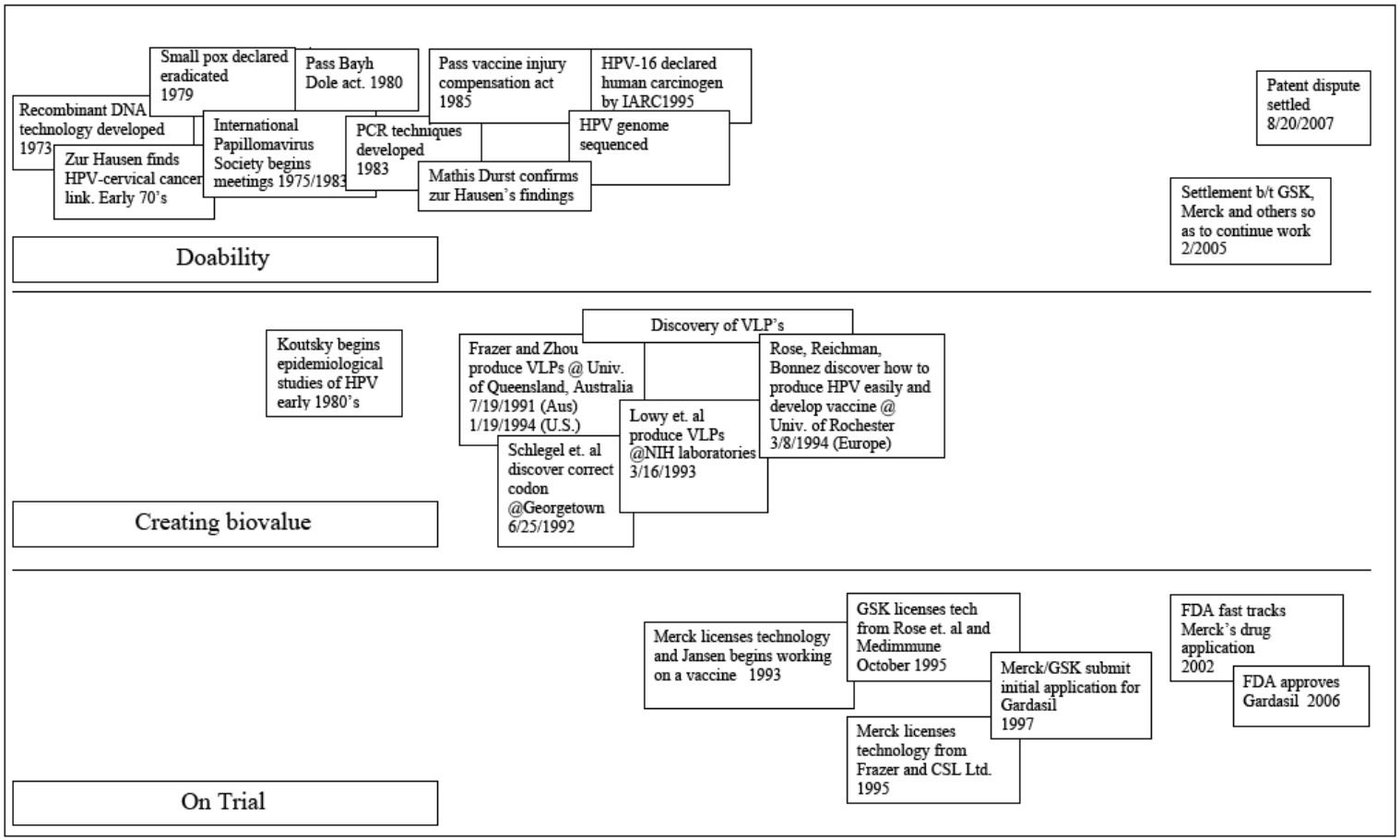


Figure 2 Analytic Timeline



Positional Map: A Doable Problem

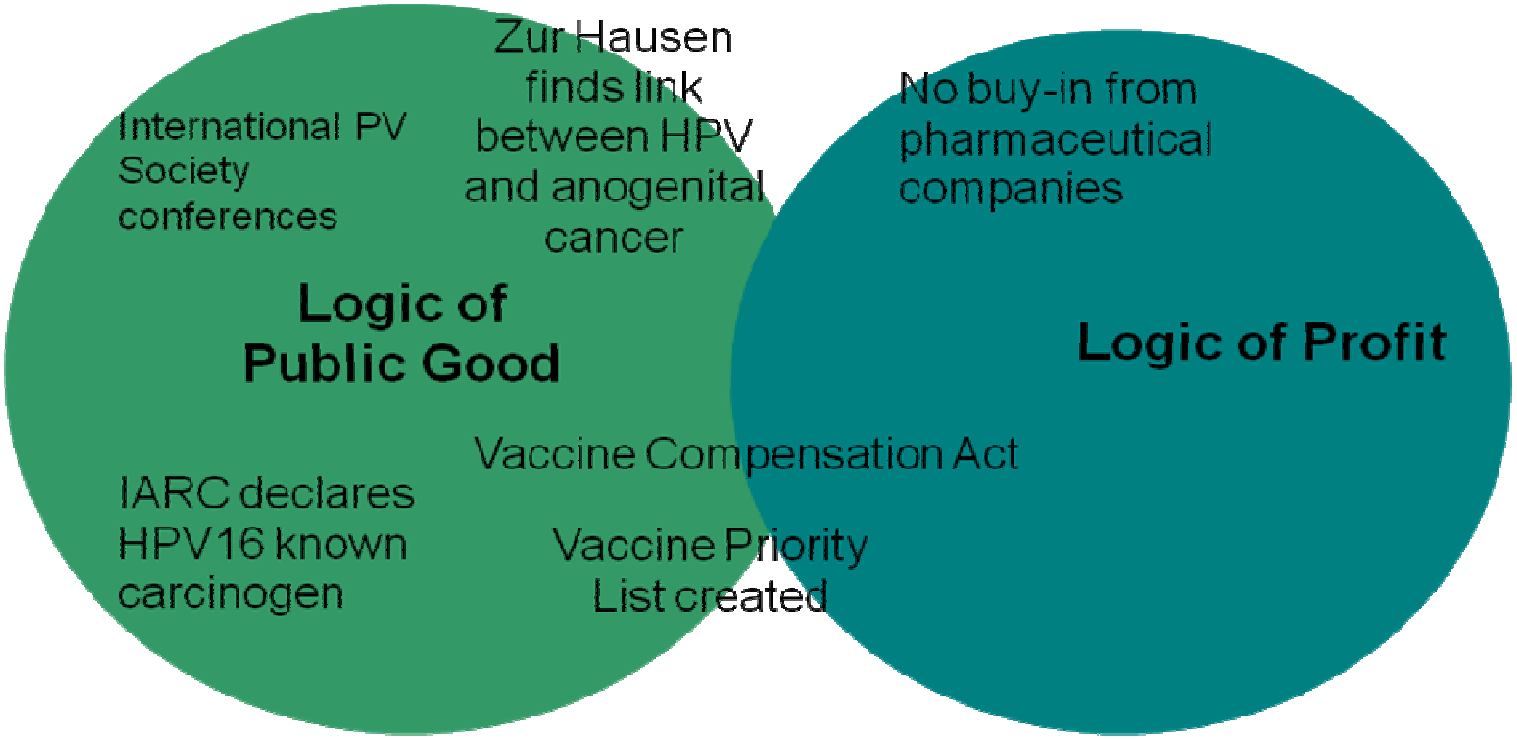


Figure 3

Positional Map: Producing Biovalue

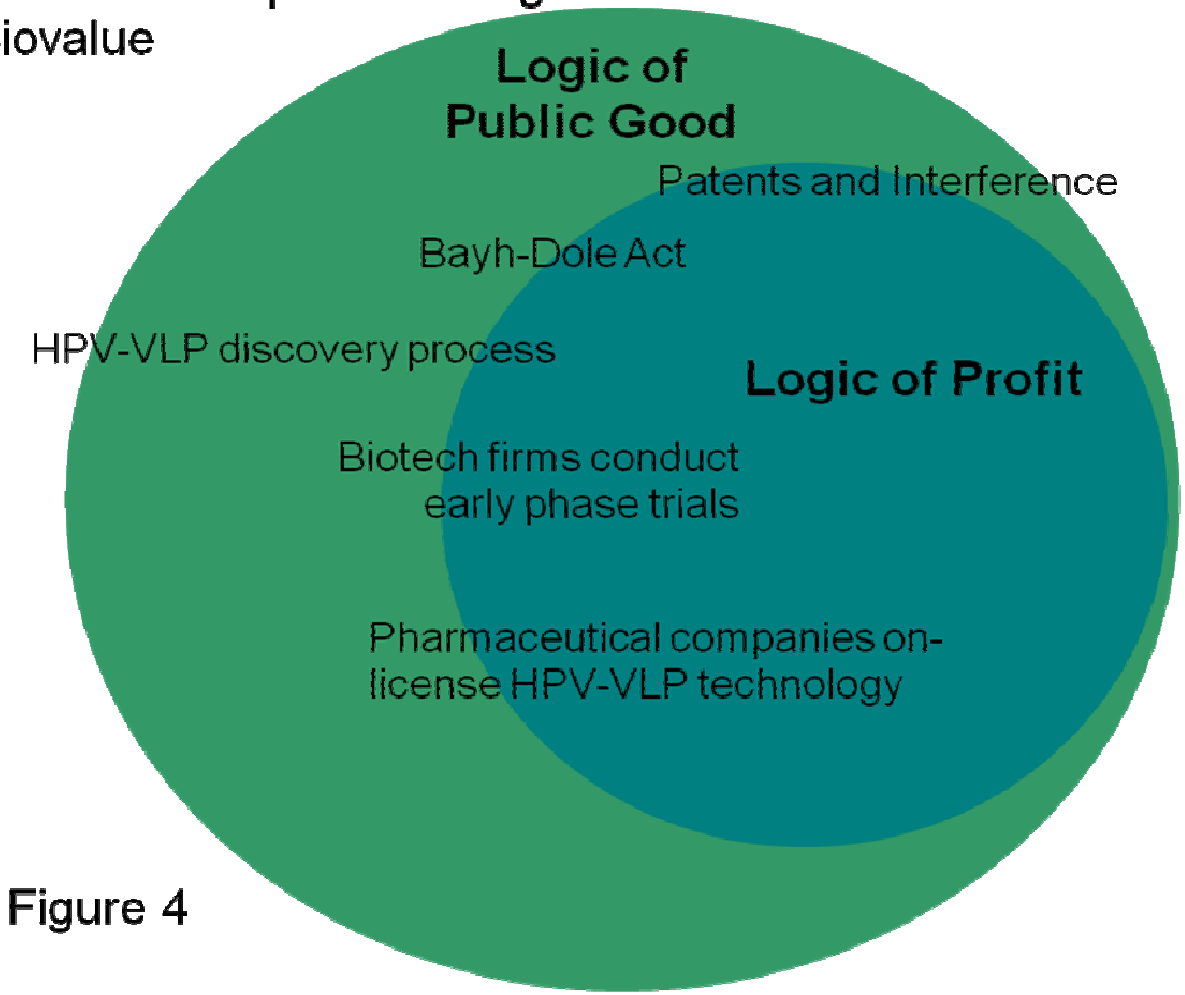


Figure 4

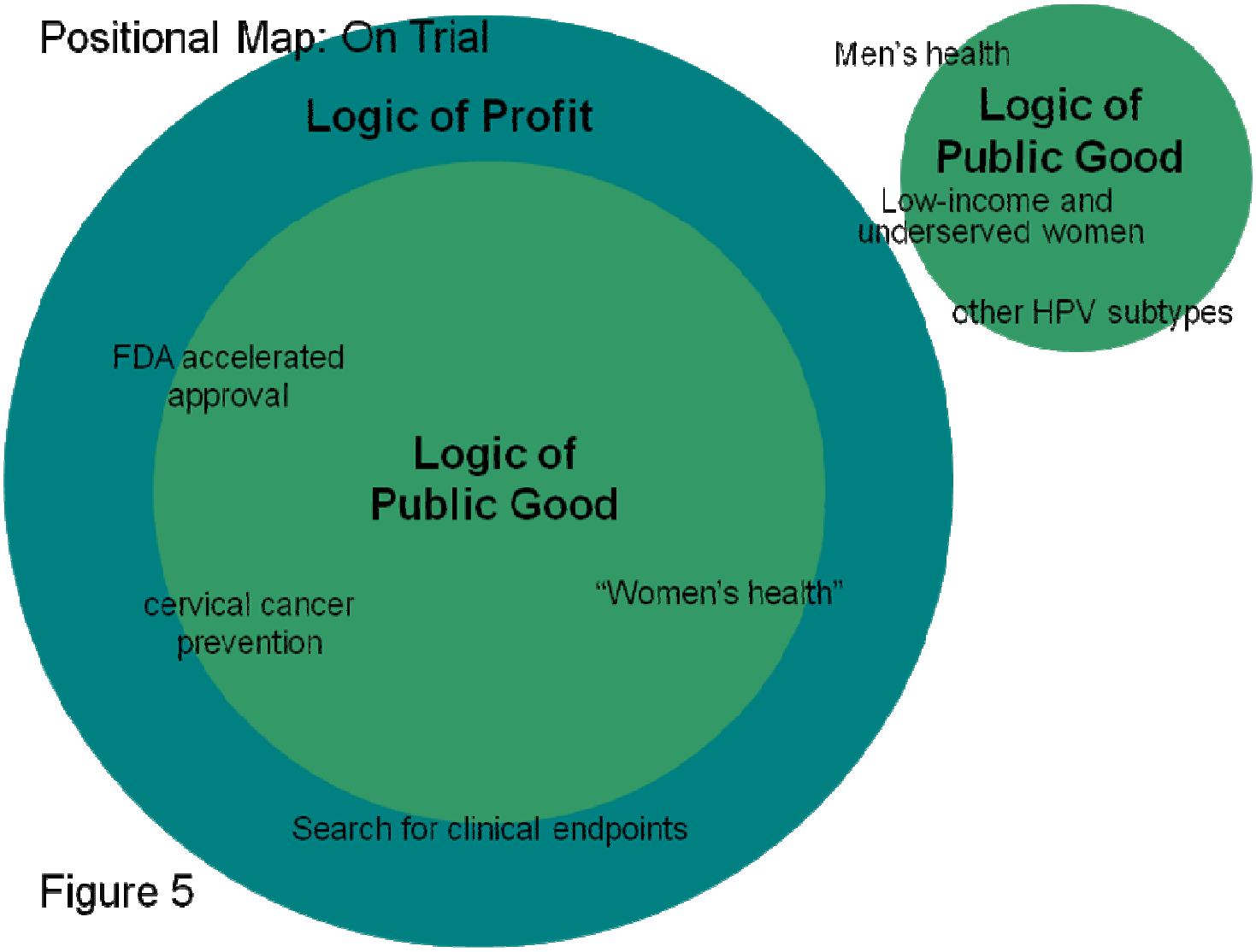

Positional Map: On Trial
Logic of Profit
Men's health
Logic of Public Good
Low-income and underserved women
other HPV subtypes
FDA accelerated approval
Logic of Public Good
cervical cancer prevention
"Women's health"
Search for clinical endpoints

Figure 5

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