Too Fast or Not Too Fast: The FDA's Approval of Merck's HPV Vaccine Gardasil

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Introduction

There are not many public health issues where views are as extremely polarized as those concerning vaccination policies. Ever since its *Fast Track* approval by the U.S. Food and Drug Administration (FDA) in 2006, Merck's human papilloma virus (HPV) vaccine Gardasil has been sparking controversy. Initially, the criticism has been focused at Merck, due to their overly aggressive marketing strategies and lobbying campaigns. According to a 2007 editorial in *Nature Biotechnology*,[1] "Surrounded by a chorus of disapproval, Merck cracked. As *Nature Biotechnology* went to press, the company announced a cessation of all efforts to lobby for US state laws requiring compulsory vaccination." Subsequently, questions have been raised whether it was appropriate for vaccine manufacturers to partake in public health policies when their conflicts of interests were so obvious. Some of their advertising campaign slogans, such as "cervical cancer kills x women per year" and "your daughter could become one less life affected by cervical cancer,"[2] seemed more designed to promote fear rather than evidence-based decision making about the potential benefits of the vaccine versus any risks. Although, conflicts of interests do not necessarily mean that the product itself is faulty, marketing claims should be carefully examined against factual science data. Currently, Gardasil vaccination is strongly recommended by the U.S. and other health authorities while public concerns about safety and efficacy of the vaccine appear to be increasing. This discrepancy leads to some important questions that need to be resolved. The current review examines key issues of this debate in light of currently available research evidence.

The HPV Vaccine Debate

In June 2006 the U.S. Food and Drug Administration (FDA) approved Gardasil, the first vaccine against the human papilloma virus (HPV).[3] The quadrivalent vaccine targeting four common HPV strains (6, 11, 16 and 18) was the first pharmaceutical product specifically developed to protect against cervical cancer.[4] Five years later, Gardasil became a key topic in the U.S. 2011 Republican presidential debate when Congresswoman Michelle Bachmann criticized Texas Governor Rick Perry over his prior executive order to make the vaccine mandatory.[5] Bachmann later expressed serious concerns about the safety of the vaccine which added even more heat to the already controversial subject.

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The American Academy of Pediatrics (AAP) responded promptly to Bachmann stating that there was "absolutely no scientific validity" behind her allegations. According to the AAP, "Since the vaccine has been introduced, more than 35 million doses have been administered, and it has an excellent safety record." The AAP further stated that "this is a life-saving vaccine that can protect girls from cervical cancer."[6] Yet, not every organization fully agreed. The Association of American Physicians and Surgeons (AAPS) opined, "…this HPV vaccine costs hundreds of dollars for something that most of the recipients do not even need protection against." "There was no public health justification for requiring this [vaccine] to attend school," stated the AAPS, elaborating that, "without adequate testing but with well-placed political funding and lobbyists, Merck pushed for requiring that the HPV vaccine, Gardasil, be given to young schoolgirls as a condition for entering sixth grade. But the disease it supposedly protects against is not even contagious in the school environment."[7] What are the reasons behind such polarized views, and why does the AAP statement fail to settle the debate on Gardasil? In view of future vaccination policies, these issues need to be carefully examined.

Promoting Gardasil: Too Much Too Soon?

According to the latest report by the U.S. Centers for Disease Control and Prevention (CDC), only 32% of girls aged 13 to 17 completed the full three-dose series for Gardasil in 2010. The CDC concluded that "stronger provider recommendations for HPV vaccination, implementing reminder-recall systems, eliminating missed opportunities, and educating parents of adolescents regarding the risk for HPV infection and the benefits of vaccination, are needed to effectively protect adolescent girls against cervical cancer."[8] In reference to the CDC report and the low HPV vaccine uptake rate, a recent article in *JAMA* stated that "if voluntary vaccination proves unsuccessful, states should seriously consider compulsory vaccination laws without generous exemptions."[9]

Certainly, the medical profession has a responsibility to promote vaccinations with those vaccines whose safety and efficacy have been thoroughly demonstrated. Nonetheless, the fact that Merck waged an aggressive lobbying campaign with state governments to make Gardasil mandatory and funded educational programs for the U.S. professional medical associations (PMAs) as a marketing strategy to promote vaccine use, raised the question whether Gardasil vaccination was promoted by the medical community from an evidence-based medicine perspective.[10] Indeed, according to a 2007 editorial in *Nature Biotechnology*, "In its rush to market its human papillomavirus vaccine, Merck forgot to make a strong and compelling case for compulsory immunization."[11] Furthermore, a 2009 *Special Communication* in *JAMA*[12] revealed that much of the educational material delivered by the PMAs failed to address the full complexity of the issues surrounding the vaccine and did not provide balanced recommendations on potential risks and hoped-for benefits. Notably, Merck-sponsored educational programs delivered by the PMAs strongly promoting HPV vaccination began in 2006, more than a year before the clinical trials containing important safety and efficacy data were published.[13] What followed were Merck's aggressive advertising campaigns telling young women worldwide that they would be "one less" life affected by cervical cancer.[14] Merck's "one less" campaign was so successful that in 2006, Gardasil was named the pharmaceutical "brand of the year" for building "a market out of thin air."[15] The wider scientific community, however, was not so impressed by Merck's "one less" business success. In a telling 2007 editorial in the *American Journal of Bioethics,* Glenn McGee and Summer Johnson noted, "Just as pizza bearing cheerleader drug reps are a poor substitute for medical education, pharmaceutical company lobbying is a poor substitute for well-reasoned public health policymaking."[16]

Indeed, how could Merck and the FDA which approved Gardasil be so certain about the effects of the vaccine a year before final safety and efficacy data became available? The current public skepticism surrounding the HPV vaccine appears to indicate that this question has not yet been adequately answered. In order to do so, we examined the basis on which the FDA approved Gardasil.

Gardasil and the FDA: The Basis for Fast Track Approval

Gardasil received a *Fast Track* approval by the FDA following a six-month priority review process.[17] According to the FDA, to be fast-tracked the drug must target a serious disease and fill an *unmet medical need.*[18] The latter is defined as providing a therapy where none exists or, providing a therapy which may be potentially superior to an existing therapy. In order to gain approval, a *Fast Track* drug must demonstrate the following:[19]

1. Show superior effectiveness to existing treatments (if such are available)

2. Avoid serious side effects of an available treatment
3. Improving the diagnosis of a serious disease where early diagnosis results in an improved outcome
4. Decrease a clinically significant toxicity of an accepted treatment

Cervical cancer is a serious disease, affecting almost half a million women world-wide on an annual basis.[20] Nonetheless, almost 90% of cervical cancer deaths occur in developing countries where regular Papanicolaou (Pap) screening procedures are either non-existent or of very limited availability.[21] In contrast, in developed countries cervical cancer mortality rates are very low (1.4-1.7/100,000 women).[22] That Pap testing alone has decreased mortality from cervical cancer in the developed world by 70% in the last few decades is well established.[23] On the contrary, to date, clinical trial evidence has not demonstrated that Gardasil can actually prevent cervical cancer (let alone cervical cancer deaths because the follow-up period was too short (5 years,[24] while cervical cancer takes 20-40 years to develop from the time of acquisition of HPV infection).[25] What Gardasil has been demonstrated to prevent are infections with two out of 15 oncogenic HPV strains (HPV-16 and HPV-18) and pre-cancerous cervical intraepithelial neoplasia (CIN) 1-3 lesions,[26] both of which were used as surrogate endpoints to cervical cancer.

According to the FDA, a drug that receives *Fast Track* designation is eligible for *Accelerated Approval*, which is, "approval on an effect on a surrogate, or substitute endpoint reasonably likely to predict clinical benefit."[27] The *Accelerated Approval*, which is temporary, is expressly designed to get drugs on the market *before* they demonstrate any real benefit. Indeed the very reason why the FDA instituted the *Accelerated Approval* process is to expedite access to potentially important therapies while being mindful of the fact that obtaining data on clinical outcomes can take a long time.[28] Nonetheless, the *Accelerated Approval* based on a surrogate endpoint (i.e., CIN 1-3), is given on the condition that post-marketing clinical trials (otherwise known as phase 4 trials) verify the anticipated clinical benefit. If, however, the confirmatory phase 4 trials do not show that the drug provides real clinical benefit, then the "FDA has regulatory procedures in place that could lead to removing the drug from the market."[29]

During the longest reported follow-up of Gardasil trial participants (5 years), the vaccine was found to be highly efficacious against persistent HPV infections and CIN 1-3 lesions.[30] However, the reported combined efficacy pertaining to the reduction of HPV-16/18 related CIN 1-3 is of little value in determining the true long-term prophylactic potential of the vaccine. The reason for this is that in the natural course of cervical cancer, only a small fraction of CIN 1 lesions will progress to CIN 2 lesions and likewise, only a small fraction of CIN 3 lesions will eventually progress to cervical cancer. Specifically, long-term research data show that as much as 60% of CIN 1 lesions spontaneously regress, 30% persist, 10% progress to CIN 3, and only 1% eventually progress to invasive cancer.[31] Therefore, in any female population, there will be many more CIN 1 lesions than all CIN 2s, CIN 3s and cervical cancers put together. CIN 1, however, is neither an adequate marker of cervical cancer progression nor an adequate surrogate endpoint for assessing long-term clinical benefits in HPV vaccine trials (due to their benign nature and high frequency of regression).[32] Thus, the reported pooled efficacy against CIN 1-3 in Gardasil post-licensure trial[33] gave a highly misleading impression about the true clinical value of the vaccine, given that the vast majority of the lesions within the trial population would have comprised of CIN 1 lesions.

Although the results from the 3-year follow-up pre-licensure trials inspired much confidence in Gardasil's prophylactic potential as they showed >97% vaccine effectiveness against HPV-16/18 related CIN 2/3+ lesions, the corresponding figures against CIN 2/3+ caused by all HPV types were well below 40%.[34] This information is frequently overlooked even though it is crucial for assessing the long-term protective efficacy of the vaccine. Indeed, because of the possibility of infections with HPV types not covered by the vaccine and/or multiple infections including these types, any meaningful assessment of a true prophylactic value from Gardasil vaccination, which would likely result in a real clinical benefit (i.e., a global reduction of the cervical cancer burden), must take into consideration analysis of vaccine efficacy against CIN 2/3+ caused by *all* relevant (high risk) HPV types.[35] When taken together, the results from pre-clinical trials that the true HPV vaccine efficacy lies anywhere between 16.9% and 70%.[36] Given the demonstrable success of Pap screening programs in achieving a 70% reduction in cervical cancer mortality in developed countries, it is unlikely that vaccination with Gardasil would have a notable impact in reducing further the global cervical cancer burden beyond that accomplished by Pap screening.

Thus, with regard to efficacy, although Gardasil partially satisfies the FDA's criteria for *Accelerated Approval* (as prevention of high-risk HPV infection and precancerous lesions perfectly fits the FDA's defi-

nition of a surrogate endpoint),[37] ultimately it does not satisfy the criteria for *Fast Track* approval as the vaccine fails to show superior efficacy to Pap screening. In spite of this, the vaccine manufacturer as well as the U.S. medical authorities continue to promote Gardasil as if indeed it already had post-phase 4 confirmatory trial approval (i.e., demonstrated efficacy against cervical cancer). For example, Merck states that "Gardasil does more than help prevent cervical cancer"[38] while the AAP describes Gardasil as a "life-saving vaccine."[39] Similarly, the FDA and the CDC maintain that Gardasil is "an important cervical cancer prevention tool that will potentially benefit the health of millions of women"[40] and that thus, stronger provider recommendations for HPV vaccination "are needed to effectively protect adolescent girls against cervical cancer."[41] However, in light of Merck's limited 5-year follow-up data, these claims are demonstrably inaccurate. In other words, in the absence of adequate phase 4 confirmatory trials, the notion that Gardasil prevents cervical cancer remains speculative. In this context, it is worth noting that the existing clinical trials show that antibodies against HPV-18 from Gardasil fall rapidly, with 35% of women having no measurable antibody titers at 5 years.[42] This outcome suggests that rather than preventing future cases of cervical cancer cases, Gardasil may only be effective in postponing them.

Also of note is that Gardasil is a prophylactic vaccine and will not treat pre-existing HPV infections and pre-existing pre-cancerous lesions, nor cervical cancer.[43] Notably, the opposite is true, at least according to Merck's pre-licensure trial data, which show that in such cases the vaccine may exacerbate the very disease it is designed to prevent.[44]

Adverse Reactions from Gardasil

As of September 2012, a total of 21,265 adverse reactions (ADRs) have been reported from Gardasil in the U.S. alone, including 78 deaths, 363 life-threatening ADRs, and 609 events which resulted in permanent disability (Table 1). Compared with all other vaccines, Gardasil alone was associated with >60% of all serious ADRs (including 61.9% of all deaths, 64.9% of all life-threatening reactions and 81.8% cases of permanent disability) in females younger than 30 years (Table 2).

Table 1

Summary of Adverse Reactions (ADRs) Following Vaccination with Gardasil in the U.S. Reported to VAERS in the Post-Licensure Period (June 2006-September 2012).

VAERS Internet Database[66] was searched using the following criteria: 1) Vaccine Products: HPV4 (Human Papilloma Virus Types 6, 11, 16, 18); 2) Gender (all genders); 3) Age (all ages); 4) Territory (the United States); 5) Date Vaccinated (2006-2012; Gardasil post-licensure period).

Total	21,265
Deaths	78
Life-threatening	363
Permanently disabled Serious	609 1669
Prolonged hospitalization	212
Emergency room visit	9565

Table 2

Age-Adjusted Rate of Adverse Reactions (ADRs) Related to Gardasil Compared with All Other Vaccines in the U.S. Reported to the Vaccine Adverse Event Reporting System (VAERS) as of September 11, 2012.

VAERS Internet Database[67] was searched using the following criteria: 1) Vaccine Products: HPV4 (Human Papilloma Virus Types 6, 11, 16, 18) and All Vaccine Products; 2) Gender (female); 3) Age (6 to 29 years; target age group for HPV vaccines); 4) Territory (the United States); 5) Date Vaccinated (2006-2012; Gardasil post-licensure period).

Events	Gardasil	All vaccines	% ADRs from Gardasil
All Serious	14,991 1313	79,657 2157	18.8 60.9
Deaths	39	63	61.9
Life-threatening	296	456	64.9
Permanently disabled	482	589	81.8
Prolonged hospitalization	175	236	74.2
Emergency room visit	7015	13,295	52.8

A report to a passive vaccine surveillance system such as U.S. VAERS does not by itself prove that the vaccine caused an ADR. However, the unusually high frequency of ADRs related to HPV vaccines reported worldwide, as well as their consistent pattern (i.e. nervous system-related disorders rank the highest in frequency),[45] point to a potentially causal relationship. Furthermore, matching the data vaccine surveillance databases, is an increasing number of case reports documenting similar serious ADRs associated with Gardasil administration, with nervous system disorders being the most frequently reported ADRs.[46] Cumulatively, these data suggest that the risks of HPV vaccination may not have been fully evaluated in pre-licensure clinical trials. A careful review of pre-licensure safety data on Gardasil confirms this concern.

For example, like many other vaccine trials, Gardasil trials used an aluminum-containing placebo.[47] Although historically aluminum adjuvants have been portrayed as inherently safe, studies in animal models and humans have demonstrated their ability to inflict immuno-inflammatory conditions by themselves.[48] Cumulatively this research has led to the identification of an "autoimmune/inflammatory syndrome induced by adjuvants" (coined "ASIA"), that encompasses several adjuvant-triggered medical conditions which are characterized by a misregulated immune response.[49] For this reason, Exley notes, "it is necessary to make a very strong scientific case for using a placebo which is itself known to result in side effects and I have not found any scientific vindication for such in the recent human vaccination literature."[50]

According to Merck, the number of girls aged 9-26 years who reported a serious ADR from Gardasil indicative of an autoimmune disorder during pre-licensure clinical trials was 245, compared to the 218 in the aluminum "placebo" group.[51] Thus at best, Gardasil was shown to be as safe as its potentially neuro-immunotoxic constituent aluminum.

In contrast to Gardasil vaccination, a procedure which uses a speculum to take cells from the cervix does not carry a risk of death, or neurological or autoimmune complications. Neither is the loop electrosurgical excision procedure (LEEP), which is used to remove high-grade CIN 2/3 lesions in women who test positive on a Pap screen, a risk for such serious ADRs.

The poor design of existing vaccine safety and efficacy trials may be reflective of the fact that in the past two decades the pharmaceutical industry has gained unprecedented control over the evaluation of its own products. As noted by the former Editor-in-Chief of the *New England Journal of Medicine* Dr. Marcia Angell, "Drug companies now finance most clinical research on prescription drugs, and there is mounting evidence that they often skew the research they sponsor to make their drugs look better and safer."[52] With regard to Gardasil, we noted that often in trials sponsored by the vaccine manufacturer, the assessment of the frequency of ADRs was limited to those trial cohorts which comprised of participants who did not receive the full three doses of the HPV vaccine.[53] The result of such population sample bias is a lesser sensitivity for detecting serious ADRs, as such events may be expected to occur less frequently if fewer doses of the vaccine are administered.

In a lengthy report of potential conflicts of interests of the Gardasil pre-licensure FUTURE II trial study, the majority of authors declared "receiving lecture fees from Merck, Sanofi Pasteur, and Merck Sharp & Dohme." In addition, it was declared that "Indiana University and Merck have a confidential agreement that pays the university on the basis of certain landmarks regarding the HPV vaccine."[54] Commenting on conflicts of interests in HPV vaccine trials in the 2009 *JAMA* editorial, Haug noted that, "When weighing evidence about risks and benefits, it is also appropriate to ask who takes the risk, and who gets the benefit. Patients and the public logically expect that only medical and scientific evidence is put on the balance. If other matters weigh in, such as profit for a company or financial

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or professional gains for physicians or groups of physicians, the balance is easily skewed. The balance will also tilt if the adverse events are not calculated correctly."[55]

Clear evaluation of risks is important for vaccines, which, contrary to other drugs, are administered predominantly to healthy individuals and often to prevent a disease to which an individual may never be exposed. Because of this, according to the FDA, "there is low tolerance for significant adverse events associated with vaccines-that is, caused by vaccines."[56] Thus, it may be worth re-considering whether it is prudent to put preadolescent girls at risk of death or a life-long neurodegenerative/autoimmune condition for a vaccine that has not thus far prevented a single case of cervical cancer, when the same can be prevented with regular Pap screening and LEEP, neither of which carry such risks.

FDA and Merck: What Have We Learned from Vioxx?

The U.S. FDA is not infallible. The Agency's approval of rofecoxib (Vioxx) in 1999 resulted in the "single greatest drug safety catastrophe in the history of this country or the history of the world."[57] This charge was laid by Dr. David Graham, the FDA associate director in the Office of Drug Safety, at the U.S. senate hearings on the FDA, Vioxx and its manufacturer, Merck. Senator Grassley added that the FDA "has lost its way when it comes to making sure drugs are safe" and that its relationship with drug companies was "too cosy." Dr. Graham concurred, stating that the FDA "as currently configured is incapable of protecting America against another Vioxx."[58] It took an estimated 88,000 to 139,000 Americans to suffer heart attacks and strokes as a result of taking Vioxx[59] before the drug was withdrawn from the market in 2004.[60]

In 2006 when Gardasil gained FDA approval, the acting FDA Commissioner Andrew von Eschenbach requested that the Science Board, which is the Advisory Board to the Commissioner, form a Subcommittee to assess whether science and technology at the FDA can support current and future regulatory needs. The findings of the Subcommittee as outlined in the Science and Mission at Risk Report were as follows.[61]

- The Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities
- The FDA's inability to keep up with scientific advances means that American lives are at risk
- The world looks to the FDA as a leader in medicine and science. Not only can the agency not lead, it can't even keep up with the advances in science

The Subcommittee concluded that "in contrast to previous reports that have issued many of the same warnings, there are now sufficient data proving that failure to act in the past has jeopardized the public's health." In light of these and other admissions by the Subcommittee (Table 3), as well as what appear to be legitimate concerns regarding both vaccine safety and effectiveness,[62] perhaps it is warranted for the FDA to re-evaluate its *Fast Track* approval of Gardasil.

Currently, however, "Based on the review of available information by FDA and CDC, Gardasil continues to be safe and effective, and its benefits continue to outweigh its risks."[63] In regard to what constitutes

Table 3

Major Findings from the FDA Science and Mission at Risk Report[68]

Mission Statement and Overview
• The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs
• The benefits of a robust, progressive Agency are enormous; the risks of a debilitated, under-performing organization are incalculable
Major Findings
• The FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak
• The development of medical products based on "new science" cannot be adequately regulated by the FDA
• There is insufficient capacity in modeling, risk assessment and analysis
• The FDA science agenda lacks a coherent structure and vision, as well as effective coordination and prioritization
• Due to constrained resources and lack of adequate staff, the FDA cannot adequately monitor development of food and medical products because it is unable to keep up with scientific advances
• The FDA cannot fulfill its mission because its IT infrastructure is obsolete, unstable, and lacks sufficient controls to ensure continuity of operations or to provide effective disaster recovery services
• Reports of product dangers are not rapidly compared and analyzed, as inspectors' reports are still handwritten and slow to work their way through the system.
• There are inadequate emergency backup systems in place, which has resulted in the loss of FDA data in the past
• Recommendations of excellent FDA reviews are seldom followed*

*The Subcommittee's final conclusions and recommendations: "There is a long history of excellent reviews of the FDA that have been followed by little to no action taken to achieve the recommendations. Our final recommendation is based in our belief that effective resolution of the issues outlined in this report is urgent. In contrast to previous reports that have issued many of the same warnings, there are now sufficient data proving that failure to act in the past has jeopardized the public's health."

as "available information" according to the U.S. FDA, "FDA routinely reviews manufacturing information and has not identified any issues affecting the safety, purity, and potency of Gardasil."[64]

Any federal agency responsible for assuring drug safety should not exclusively rely on data provided by the drug manufacturer, as unreliable research (i.e., use of an reactive and potentially toxic placebo) cannot be used to reliably evaluate the safety of any drug.

Conclusion

Merck's HPV vaccine Gardasil failed (and continues to fail) to meet a single one of the four criteria required by the FDA for *Fast Track* approval. Gardasil is demonstrably neither safer nor more effective than Pap screening combined with LEEP, nor can it improve the diagnosis of serious cervical cancer outcomes. In spite of this, Gardasil continues to be promoted as if it already had post-phase 4 confirmatory trial approval and proven efficacy against cervical cancer. Given the demonstrable success of regular Pap smear screens in reducing the incidence of mortality from cervical cancer in the developed world, which is currently very low (i.e., 1.4-2.3/100,000 women), it is further unlikely that HPV vaccination (even if proven effective against cervical cancer) would reduce mortality rates beyond those already accomplished with routine Pap screening.[65] Thus, further reduction of cervical cancer burden may be best achieved by targeting other risk factors of the disease (i.e., smoking, use of oral contraceptives, multiple sexual partners, or suboptimal hygiene and nutritional status, etc.) in conjunction with regular Pap screens.

Coercive measures such as vaccine mandates supported solely by vaccine manufacturer's data do little to instill public confidence in vaccination programs. Physicians and other medical authorities need to adopt a more rigorous evidence-based medicine approach in order to give a balanced and objective evaluation of vaccine risks and benefits to their patients. The public equally needs life-saving drugs as it needs protection from potentially hazardous ones.

Note

LT and CAS conducted a histological analyses of autopsy brain samples from two Gardasil-suspected death cases. CAS is a founder and shareholder of Neurodyn Corporation, Inc. The company investigates early state neurological disease mechanisms and biomarkers. This work and any views expressed within this manuscript are solely those of the authors and not of any affiliated bodies or organizations.

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