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Presentation to: Ohio Academy of Medical History  
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### **Direct to Consumer Drug Advertisements: A Dangerous Game of Pitching Products to Parents**

The annual budget for drug advertising in the United States “exceeds that for all undergraduate and postgraduate medical education and comes close to the entire budget of the National Institutes of Health.”<sup>1</sup> In 2008 drug advertisers spent \$4.7 billion, down from a record \$4.8 billion in 2006, but up from \$2.6 billion in 2002.<sup>2</sup> Since the relaxation of full disclosure rules for television advertising, the amount spent on direct-to-consumer advertisements (DTCA) has soared, leading to increased sales of certain pharmaceuticals, as advertisements are placed in magazines, newspapers, internet websites and on television. These prescription-drug ads “prompt nearly one-third of Americans to ask their doctors about an advertised medicine, and 82% of those who ask say their physicians recommended a prescription.”<sup>3</sup> Opposite sides of this practice argue over whether consumers are educated and empowered by these advertisements or encouraged to seek out unnecessary drugs and treatments. Experts analyzing drug advertisements found inaccuracies, misrepresentations and other deficiencies, such as minimizing adverse reactions, misleading efficacy explanations, misusing statistics, promoting products to inappropriate populations, and using headlines and subheads not supported by the rest of the advertisement (or the drug).<sup>4</sup> Of even greater concern, for

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<sup>1</sup> Shapiro, Martin F., MD, Ph.D. “Regulating Pharmaceutical Advertising: What Will Work?” *Canadian Medical Association Journal*, 156, No.3: 359.

<sup>2</sup>Sean Gregory, “Are Direct-To Consumer Drug Ads Doomed?” *Time*, February 4, 2009, Time.com. <http://www.time.com/time/business/article>.

<sup>3</sup>Julie Appleby, “Drug Ads Push Rx Requests Higher,” *USA Today*, March 4, 2008, section A, p.1.

<sup>4</sup> Shapiro, 360.

many, is the fact that pharmaceutical companies aggressively market these products to parents and caregivers for use by their children.

My research will focus on “hidden dangers” of two specific pharmaceutical products advertised in this fashion: the side effects, contraindications, and even life-threatening risks that are not easily found in these advertisements. The two products studied will be Vyvanse, a medication to control Attention-Deficit/Hyperactivity Disorder (ADHD), and Gardasil, a vaccine designed to prevent certain types of Human Papillomavirus (HPV) that can lead to cervical cancer and genital warts. Both products are controversial, in part due to the manner in which they are aggressively advertised: Vyvanse because it is a Class II drug advertised primarily in women’s magazines, and Gardasil because it is a vaccine against a sexually transmitted disease, advertised in catchy television spots, as well as in print and electronic media.

My method for analyzing the common and “hidden” dangers of these drugs will involve studying the actual product packet information included with these prescriptions. I will study the information contained in these publications not just under “risks” or “side effects” but also throughout the entire packet. By analyzing the actual product information of these products, as well as published accounts of adverse reactions to these products, I will present the hidden dangers that many parents may never know. More importantly, I will analyze the role of the United States Food and Drug Administration (FDA), as well as the roles played by the public, the government, drug companies, and doctors in a very complicated pharmaceutical web. Of particular significance are certain pieces of legislation that have been passed in an effort to regulate drug promotion and advertising. With these laws in place and with the current role of the FDA, the best

interests of the American public are not being protected with current drug approval and advertisement practices. Changes are needed in both the approval process of new drugs and the advertisement procedures related to pharmaceutical products.

## **Background**

Before analyzing specific pharmaceutical products on the market today, it is important to understand the key legislation and relevant historical background in the pharmaceutical industry. Most Americans are familiar with the Food and Drug Administration (FDA) and its responsibility to protect the consumer from food and drug dangers. Few realize the history of the FDA is rooted in Abraham Lincoln's 1862 appointment of a chemist, Charles M. Wetherhill, to lead the newly created Department of Agriculture. This department led to the Bureau of Chemistry, which was the precursor of today's FDA.<sup>5</sup> While the first "food and drug act" would eventually be implemented in 1906 under the Roosevelt administration, the actual "muscle" behind legislation did not exist until 1927 when the Food, Drug, and Insecticide Administration (FDIA) was created as a federal law enforcement agency. One of its first acts was the Caustic Poison Act of 1927 requiring labels designed to protect children from lye and other toxic poisons.<sup>6</sup> By 1930 the name was changed to simply the FDA, and in 1938, the Federal Food, Drug, and Cosmetic Act (FDCA) was enacted by the United States Congress, requiring, among many other provisions, for medications to be proven safe prior to marketing. Post-World War II would find the FDA unable to keep up with the rapid discoveries of new medications. A 1954 reorganization of the FDA into 5 "Bureaus",

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<sup>5</sup> Suzanne Parisian, M.D., *FDA: Inside & Out* (Front Royal, VA: Fast Horse Press, 2001); 11.

<sup>6</sup> *Ibid.*, 15.

including a “Bureau of Medicine” was designed to meet the rising demands of a rapidly expanding consumer market.<sup>7</sup>

The FDCA was amended in 1962, with the Kefauver-Harris Drug Amendment, which required medications to be both safe and efficacious prior to being advertised to the public. “Efficacy” was also mandated retroactively on previously “safe” drugs approved by the FDA. The subsequent years would find “literally thousands of prescription drug items” removed from market because they were not efficacious.<sup>8</sup> Pharmaceutical advertisements, as required by the FDCA, needed to include a “brief summary” of risks that was a misnomer – many of these products required a long and detailed list of contraindications and possible adverse effects.<sup>9</sup> Prior to 1992, the FDA independently analyzed the safety and efficacy of new drugs prior to approving their use. With the rapid introduction of new products, this burden stretched the agency’s resources, both financially and in regards to available personnel. In 1992, the Prescription Drug User Fee Act (PDUFA) was enacted, requiring drug companies to pay an approximately \$300,000 fee for each new drug application, roughly half the cost of processing a new application. While this fee expedited the process by improving the FDA’s funding pipeline, it also created an obvious conflict of interest: drug companies were paying nearly half the cost of an “objective” review of their new product.<sup>10</sup>

1997 brought two more dramatic changes to federal legislation: The FDA Modernization Act provided incentives to sponsors to conduct pediatric studies and the

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<sup>7</sup> Parisian, 16 – 18.

<sup>8</sup> Ibid., 19.

<sup>9</sup> Ziad F. Gellad and Kenneth W. Lyles, “Direct-to-Consumer Advertising of Pharmaceuticals,” *The American Journal of Medicine* 120 (2007): 475 – 476.

<sup>10</sup> John Abramson, *Overdosed America: The Broken Promise of American Medicine*, (New York: Harper Collins, 2004), 85.

FDA began to allow advertisements in broadcast and electronic media to replace the “brief summary” with an “adequate provision.” Basically this requirement involved referring the consumer to a source of further information: a doctor, a website, a toll-free phone number, or a print advertisement.<sup>11</sup> In the industrialized world, only the United States and New Zealand allow direct-to-consumer advertising (DTCA) of prescription drugs.<sup>12</sup> Illustrating a growing concern for young consumers of prescription medications, congress passed the 2002 Best Pharmaceuticals for Children Act, mandating that “during a one year period beginning on the date a drug receives pediatric exclusivity, all adverse event reports associated with the use of the drug will be reviewed by the FDA and reported to a Pediatric Advisory Committee in a public forum.”<sup>13</sup> In 2007 this act was reauthorized, with additional stipulations related to marketing, tracking of studies, and reporting of adverse effects.

Reflective of regulatory relaxation, and the inherent conflict of the “new,” pharmaceutical-company-subsidized drug approval process, was the decline of traditionally “unbiased” or “objective” drug studies conducted at university research centers. In the 1990s the “drug industry turned increasingly to new, independent, for profit medical research companies that emerged in response to commercial funding opportunities.”<sup>14</sup> By 2000 the shift was nearly complete, with a mere one-third of clinical trials completed in university settings and the remaining two-thirds done in for-profit research company settings paid directly by the drug companies.<sup>15</sup> Most of the public is unaware of the strong hand of pharmaceutical companies in the FDA approval

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<sup>11</sup>Gellad and Lyles, 476.

<sup>12</sup>Ibid.

<sup>13</sup>Murphy and Roberts, 37.

<sup>14</sup>Abramson,95.

<sup>15</sup>Ibid.

process as well as in the advertising realm. A 1998 survey in California found 50 percent of the public thought DTCA are submitted to the FDA for approval and 43 percent thought only “completely safe drugs” could be advertised.<sup>16</sup> Neither of these beliefs are based in truth: the FDA does not pre-approve advertisements, but rather reviews them after they have appeared in print or on air, and often only if complaints have been filed by consumers. And many unsafe drugs, most notably Vioxx, have been promoted by pharmaceutical companies eager to boost sales by arousing consumer interest: the Government Accountability Office (GAO) estimated that about 8.5 million Americans received prescription drugs in 2000 after viewing advertisements and asking for specific products.<sup>17</sup>

In the realm of print advertising, most advertisements are directed at a “target” market based on the product involved. For instance, nearly any newspaper sports page or sports magazine for men contain advertisements for erectile dysfunction (ED) pharmaceuticals. Likewise, women’s magazines, or newspaper entertainment or living sections will often feature advertisements for contraceptives or anti-depressants. For either gender, these advertisements are aimed at a population capable of inquiring about a drug for a specific personal condition or need. But what about pharmaceuticals designed for children? In the case of Vyvanse, one of the newest ADHD drugs on the market, a deliberate choice was made to target mothers, with advertisements prominently placed in women’s magazines such as *Family Circle*, *Woman’s Day*, and *Redbook*.<sup>18</sup> And for good

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<sup>16</sup> Gellad and Lyles, 477.

<sup>17</sup> Ibid. , 478.

<sup>18</sup> Karen Klein, “Pencils, Pens, Meds: As Kids Head to Class, Pharmaceutical Companies Ramp Up Their Drug Marketing – And It Works.” *The Los Angeles Times*, August 20, 2007. [www.latimes.com](http://www.latimes.com)

reason: analysts from Merrill-Lynch “expect the United States ADHD market (including adult patients) to exceed US\$4 billion by 2010 on the back of new products.”<sup>19</sup>

### **ADHD and Vyvanse**

According to a 2005 survey by the Center for Disease Control (CDC), approximately 4 million United States children between the ages of 3 and 17 have received a diagnosis of ADHD. And while accurate diagnosis of ADHD is considered a “clinical imperative,” the reality is that “there is no gold standard for diagnosis of ADHD, (with) data from multiple sources and procedures...usually aggregated in clinical practice.”<sup>20</sup> Doctor Sandra DeJong, of the Harvard Medical School, has published an overview of pediatric psychopharmacology designed to provide a general understanding of the variety of treatments available for this complicated condition, emphasizing “medications alone are rarely the optimal treatment for a psychiatric problem. Other treatment modalities such as individual psychotherapy, family therapy...etc., are often warranted.”<sup>21</sup> DeJong acknowledges and explains the myriad choices of medications for children diagnosed with ADHD while offering the caution that “until recently, the FDA did not require that psychiatric medications under development be studied in children...many medications that are increasingly used in children and adolescents have not been FDA approved.”<sup>22</sup>

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<sup>19</sup>Michael Schlander, “Impact of Attention Deficit/Hyperactivity Disorder (ADHD) On Prescription Drug Spending for Children and Adolescents: Increasing Relevance Of Health Economic Evidence,” *Child Adolescent Psychiatry and Mental Health*, 1, No. 13 (2007): 1.

<sup>20</sup>Michael J. Manos, “Pharmacologic Treatment of ADHD: Road Conditions in Driving Patients to Successful Outcomes,” *The Medscape Journal of Medicine*, 10, No. 1 (2008): 1-2.

<sup>21</sup>Sandra DeJong, “An Introduction to Pediatric Psychopharmacology.” Cambridge Hospital, Harvard Medical School. (October 2007):1.

<sup>22</sup> Ibid.



Vyvanse, however, did receive approval from the FDA, specifically for treatment of ADHD in children and adolescents aged 6 to 12.<sup>23</sup> Yet even with approval as a treatment, critics argue that advertising this drug, and similar drugs, considered Schedule II controlled substances (C-II)<sup>24</sup>, violates the 1971 Convention on Psychotropic Substances. This act, approved by 159 countries, including the United States, involved an agreement to ban consumer-targeted marketing of psychotropic medications – which all ADHD drugs are – that carry the potential for addiction or dependency.<sup>25</sup> Generally speaking, the pharmaceutical companies complied with this restriction through the end of the twentieth century. But in 2001, “one company began buying ads in the September issue of women’s magazines in the US to draw attention to Metadate CD, a long-acting form of methylphenidate. Other companies quickly followed suit.”<sup>26</sup> Vyvanse, manufactured by New River Pharmaceuticals, is simply following several other products, produced by a variety of companies, into the advertising realm. Trying to keep up with this trend, the FDA has issued a public health advisory for drugs approved for ADHD “to provide more information for patients about potential risks of ADHD medications.”<sup>27</sup>

The risks associated with these drugs deserve close attention, particularly the so-called “hidden dangers” that are often not advertised prominently. In the case of

Vyvanse, the manufacturers tout its novelty as a

prodrug composed of the amino acid L-lysine bound to the amino group of the therapeutically active ingredient d-amphetamine. When taken orally, the therapeutic effects characteristic of amphetamine are blocked by the conjugated amino acid. However, when the prodrug is absorbed from the gastrointestinal tract, it must go through

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<sup>23</sup>Jim. Rosack, “Novel Drug for ADHD Wins FDA Approval,” *Psychiatric News*, 42, No. 7, (April 6, 2007): 1.

<sup>24</sup> Ibid.

<sup>25</sup> Klein.

<sup>26</sup> Ibid.

<sup>27</sup> Manos, 1.

the patient's liver to undergo first-pass metabolism...(where) the conjugated L-lysine is removed, and the d-amphetamine regains its therapeutic potential.<sup>28</sup>

The idea of a prodrug is to reduce potential abuse as well as provide a full day's worth of symptom control. As psychotropic drugs, ADHD medications have long been attractive for drug-abusers, yet theoretically, Vyvanse "should carry less liability for diversion and abuse because of the necessity to metabolize the drug before it can become active."<sup>29</sup>

This emerges as a strong selling point of the drug, but does not address the actual risks and potential complications inherent to the medication.

Vyvanse, according to the prescription information packaged with the drug, presents these common side effects: upper belly pain, dizziness, irritability, nausea, weight loss, decreased appetite, dry mouth, trouble sleeping, and vomiting. Other serious side effects include: slowing of growth (height and weight) in children; seizures, mainly in patients with a history of seizures; and eyesight changes or blurred vision.<sup>30</sup> In the advertisements featured in print, the most common side effects are noted in small print at the bottom of the page, as well as a warning about the possibility of abuse with amphetamine use, noting abuse can lead to dependence or "may cause sudden death or serious cardiovascular adverse events." Other concerns, as listed in the advertisement, are "aggression, new abnormal thoughts/behaviors, mania, growth suppression, worsening of motion or verbal tics, and Tourette's syndrome... with use of drugs of this type."<sup>31</sup> In the magazine advertisements, on the reverse side of the page containing the

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<sup>28</sup>Rosack, I.

<sup>29</sup>Ibid.

<sup>30</sup>Vyvanse (lisdexamfetamine dimesylate) package information leaflet, 2007. New River Pharmaceuticals, Inc., Blacksburg, Virginia, 24060, USA. Distributed by Shire US Inc, Wayne, PA, 19087: 4.

<sup>31</sup>Vyvanse print advertisement, *Ladies Home Journal*. April, 2008. Copyright 2007 Shire US Inc., Wayne, PA 19087.

ad, complete information from the package insert is also included. Acknowledging that Vyvanse is a stimulant medicine, the manufacturers report two main areas to watch: heart-related and mental (psychiatric). Under heart related problems, “sudden death in patients who have heart problems or heart defects; stroke and heart attacks in adults; and increased blood pressure and heart rate” problems are noted, warning that if you have a family history of any heart problems, your doctor should be made aware of them before prescribing Vyvanse.<sup>32</sup> While troublesome, generally the 6 – 12 year old targeted cohort for Vyvanse will not have heart problems or hypertension precluding the use of this medication.

Of more concern, and what seems most dangerous as a “hidden” risk, are the psychiatric problems that have occurred. All patients, youth and adults, are at risk for “new or worse behavior and thought problems; new or worse bipolar illness; and new or worse aggressive behavior or hostility.” Additionally, children and teenagers may face “new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms.”<sup>33</sup> The potential for these adverse reactions, while admittedly small (though no percentages or numbers are offered), would seem indicative of extreme caution in prescribing. Yet the biggest hidden danger, in this research, is not found in the warnings or contraindications sections, but in the “indications and usage” section that many patients and parents probably do not read, assuming it to be for the prescribing physician. Vyvanse is an ADHD medication designed to be taken to keep children with ADHD “consistent” through the day, every day, as long as necessary. Nonetheless,

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<sup>32</sup> Ibid.

<sup>33</sup> Ibid.

the effectiveness of Vyvanse for long-term use, i.e., for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Vyvanse for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.<sup>34</sup>

It is precisely this type of unknown risk, in products yet to be clinically evaluated over time, that frequently bring calls from medical professionals as well as governmental officials to consider implementing a new drug assessment period where new products could not be advertised to the general public until the product has been used as prescribed for one or more years.

### **HPV and Gardasil**

In fact, the other featured product, Gardasil, is similar in this respect. Not only did Merck, the manufacturer, advertise the product as soon as it achieved FDA approval, they also promoted it indirectly through public service announcements about HPV and its potential link to cervical cancer *prior* to approval. These television advertisements, run concurrently with print advertisements, emphasized the “Tell Someone” theme; that is, tell someone you know and love that a virus causes cervical cancer. Merck ran these advertisements primarily during programs appealing to women, and especially mothers and daughters. While no specific number of viewings can be assessed for Gardasil advertisements, industry experts have estimated, based on average television viewing patterns, that an “adult is exposed to 100 minutes of DTCA for each minute spent with their doctor.”<sup>35</sup> Another study found that everyday, the average American was exposed to nine prescription drug advertisements on television.<sup>36</sup> An estimated sixteen hours of

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<sup>34</sup>Vyvanse Package Information, 1.

<sup>35</sup>Gellad and Lyles, 477.

<sup>36</sup>Abramson, 151.

prescription drug advertisements are seen by an average American television viewer each year.<sup>37</sup> And these exposures are measured in profits for the pharmaceutical companies: in 1998 the “largest drug companies generated \$22.50 in sales for every dollar spent advertising to consumers and primary care doctors.”<sup>38</sup> Clearly it is not just public awareness that motivates pharmaceutical advertising.

While Gardasil is also advertised in print and electronic media, its television presence is the focus here. While Vyvanse has targeted women’s magazines, Gardasil has targeted women’s television, as girls and women between the ages of 9 – 26 are the target market for this vaccine. Gardasil is a “non-infectious recombinant, quadrivalent vaccine prepared from the highly purified virus-like particles of the major capsid protein of HPV types 6,11, 16, and 18.” In girls and women previously unexposed to these four types of HPV, the vaccine protects them from contracting or developing possible disease effects of these strains.<sup>39</sup> Of the four HPV strains, two (16 and 18) are responsible for nearly 70% of all cervical cancer cases, and the other two (6 and 11) cause the majority of genital warts infections.<sup>40</sup> Over one hundred strains of HPV exist, but this vaccine is designed to help prevent the development of both cervical cancer and genital warts. Originally advertised as the “first vaccine against cancer,” that description is not accurate. Cervical cancer develops from various strains of HPV, and not exclusively those prevented by Gardasil. Once the most deadly form of cancer for United States’ women,

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<sup>37</sup>Dominick I., Frosch and others, “Creating Demand for Prescription Drugs: A Content Analysis of Television Direct-to-Consumer Advertising,” *Annals of Family Medicine*, 5, No. 1, (2007): 6.

<sup>38</sup> *Ibid.*, 159.

<sup>39</sup> Gardasil (Human Papillomavirus Quadrivalent (types 6,11,16, and 18) vaccine, Recombinant) Product Packet Information, (2006), Merck and Company, Inc., Whitehouse Station, New Jersey, 08889, USA: 1.

<sup>40</sup>Alisa B Ames and Patti Gravitt, “Human Papillomavirus Vaccine Update,” *Current Infectious Disease Reports*, 9 (2007): 151.

the rates have dropped by over 75% since Pap test screening has become commonplace.<sup>41</sup> HPV is the most common sexually transmitted infection in the United States, but the high-risk types (16 and 18) have a relatively low prevalence, representing 3.4% of all HPV infections. And in that group, not everyone will develop cervical cancer.<sup>42</sup> Many question the efficacy of the vaccine in young girls, the cohort most strongly targeted for vaccination, since that particular group has not been thoroughly tested in clinical trials. “The longer-term effectiveness and safety of the vaccine still need to be evaluated among a large population, and particularly among younger girls.”<sup>43</sup> Seemingly contradictory is the position of the Center for Disease Control’s (CDC’s) Advisory Committee on Immunization Practices who voted unanimously, in July of 2006 when Gardasil was approved, to recommend that all girls ages 11 and 12 receive the vaccine.<sup>44</sup> Gardasil, in part due to the sense of urgency created by Merck’s pre-release public relations work, received “expedited consideration” from the FDA, taking “six months from application to approval” as opposed to the normal 3-year vaccine-waiting period. Furthermore, the “5 to 10 year” wait for “universal acceptance” was greatly accelerated with Merck’s marketing, lobbying, and advertising.<sup>45</sup> Yet the question remains, is Gardasil a breakthrough vaccine or a potentially dangerous, largely unnecessary product?

Gardasil, like Vyvanse, has prominently displayed side effects and less well known and displayed risks. Since the television commercials are able to rely on the

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<sup>41</sup> Juliet V. Spencer, *Deadly Diseases and Epidemics: Cervical Cancer*. (New York: Chelsea House Publishers, 2007), 10.

<sup>42</sup> Lawrence O. Gostin, JD, LLD and Catherine D. De Angelis, “Mandatory HPV Vaccination: Public Health vs. Private Wealth,” *The Journal of American Medical Association*, 297. No.17 (2007): 1921.

<sup>43</sup> Ibid.

<sup>44</sup> Ibid.

<sup>45</sup> Elisabeth Rosenthal, “Shots are Popular, but Fail to Cure Doubt,” *International Herald Tribune*, August 19 2008. [www.iht.com/bin/printfriendly.php?id=15437772](http://www.iht.com/bin/printfriendly.php?id=15437772).

“adequate provision” rule that merely requires touching on the main benefits and risks, while referring the consumer to a web site for more information, the ads are upbeat and catchy. The young women featured talk about being “one less” victim of cancer, while the moms calmly list the potential side effects. Claire Dederer, writing for *The New York Times* online, February 18, 2007, interprets the advertisement this way:

The cool girls want to be “one less”; the moms are the ones putting on the brakes. Having mothers voice the downside of Gardasil reinforces the message that if you get this vaccination, you’re a rebellious, independent thinker. “Forget the side effects. Forget Mom. I’m getting vaccinated.”

For those who might be interested, the package information with the product, or on the website mentions that the common side effects are pain, swelling, itching, and redness at the injection site; fever; nausea; and dizziness.<sup>46</sup> Reading the brochure more closely, there are also side effects such as syncope (fainting), myalgia, and nasopharyngitis. Listed under “post-marketing reports” are experiences involving hypersensitivity reactions with the immune system as well as Guillain-Barre syndrome (a disorder in which the body's immune system attacks part of the peripheral nervous system).<sup>47</sup> In work done by Judicial Watch and the National Vaccine Information Center (NVIC), the possible link to Guillain-Barre syndrome occurred as a “statistically significant risk” when Gardasil was co-administered with other vaccines, in particular with the meningococcal vaccine (Menactral).<sup>48</sup> It is likely this “hidden danger” has emerged as young women, preparing for college, often “catch up” on their vaccinations: the catch-up combination of Gardasil and Menactral could leave them at risk. Even the CDC has said

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<sup>46</sup> Gardasil packet information, 13.

<sup>47</sup> Ibid., 11-14.

<sup>48</sup> Alliance for Human Research Protection. 2008. “Gardasil Update: The Damage and The Death Count Rise,” <http://ahrp.blogspot.com/2007/08/Gardasil.html>

that there is not enough evidence to “prove Gardasil could be used safely with other vaccines.”<sup>49</sup>

Perhaps the most alarming potential danger from Gardasil is found in the manufacturer’s own product information pamphlet. Gardasil is not recommended for pregnant women. That is clearly stated. In reading through the information contained under “Pregnancy,” it states, “it is not known whether Gardasil can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity.”<sup>50</sup> Describing the clinical trials conducted where Gardasil was inadvertently given to pregnant women, there does not appear to be an elevated risk for pregnancies in general; however, “for pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received Gardasil compared to 0 cases of congenital anomaly in the group that received the placebo.”<sup>51</sup> It would appear that the manufacturer should expand the scope of the warning to include currently pregnant women as well as women who might be pregnant and not know it, or women who are engaging in sexual relations without contraception around the time of the vaccine’s administration. Furthermore, the unknown nature of Gardasil’s impact on “reproductive capacity” seems alarming, particularly in light of the target cohort: adolescent girls who are still developing physically. How many years will need to pass before the impact on this group can be determined, as most of them will not reproduce for a decade or more?

One final concern about the Gardasil vaccine is that consumers will confuse protection against four strains of HPV with total protection against all strains of HPV and

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<sup>49</sup> Ibid.

<sup>50</sup> Gardasil packet information, 9.

<sup>51</sup> Ibid.



cervical cancer, itself. Gardasil does not prevent cervical cancer. Nor is it intended to replace one of the most effective screening tools for cancer ever discovered – the Pap test. Merck’s product information does carry this warning: “vaccination does not substitute for routine cervical cancer screening.”<sup>52</sup> In the United States, with nearly 80% of women utilizing the Pap test, the American Cancer Society believes that they have successfully fought cervical cancer, even without a vaccine. “When the disease is detected early through Pap testing, the survival rate is more than 90 percent.” The article further points out that with drug trials averaging only three years, Merck and the public knows little about long-term risks or how long immunity might last.<sup>53</sup>

Clearly both Gardasil and Vyvanse have risk factors that may not be fully realized until time has passed, and long-term studies have been conducted. In the meantime, both products are being heavily promoted to parents and caregivers through advertisements. Drew Altman, president of the Kaiser Foundation, said, “Our survey shows why the drug companies run all these ads: They work. Many people get drugs they otherwise wouldn’t.”<sup>54</sup> The focus of this paper is not to debate whether people asking for and receiving specific medications indicates a public service, an improved relationship between patient and doctor, or a dangerous path towards self-diagnosis and hypochondria. The question is: are parents and caregivers aware of what they are “buying into” when they give their children drugs like Gardasil and Vyvanse? And is the FDA doing enough to regulate pharmaceutical advertising and promote safe and efficacious drug use?

### **Role of FDA**

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<sup>52</sup> Ibid.

<sup>53</sup> Sigrid Fry-Revere, “The Rush to Vaccinate,” *The New York Times*, March 25, 2007, Section 14WC, Column 1.

<sup>54</sup> Appleby, A1.

I believe my discussion of the hidden dangers of each of these products successfully illustrates the potentially “hidden” risks, side effects, and serious adverse reactions that are linked to these drugs. Studies need to be conducted to more thoroughly gauge the degree of information an average parent reads and understands in specific drug usage. In particular, both pharmaceutical products, with their “quick to market” approach, have not had adequate time in widespread usage to determine long-term or cumulative effects, and only the most interrogative approach would uncover this fact for a consumer. Parents and caregivers need to be made aware of these dangers clearly and succinctly before they can balance whether the potential benefit of their child taking Vyvanse, or receiving the Gardasil vaccine, outweighs the known risks and possible rare or unknown dangers of each. The impetus for education lies, at this point, with the doctor or health care provider. In one respect, this is the proper venue for medications to be discussed and debated. A doctor knows his or her patient more fully than any pharmaceutical company, pharmacist, or FDA official can. Yet with the proliferation of advertisements, and the ensuing pressure placed on physicians by patients who ask for certain treatments by name, more of the responsibility needs to rest with drug companies as enforced by the FDA.

Unfortunately, the current condition of the FDA is inadequate:

The FDA is understaffed, under funded, and under pressure, according to its own employees. Even worse, the FDA has fallen under the influence of the drug and medical-device industries, so much so that it was labeled “a servant of industry” by Dr. Richard Horton, the editor of the British journal *The Lancet*.<sup>55</sup>

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<sup>55</sup>Abramson,85.

A 2007 article in *The New England Journal of Medicine* found several signs that the “FDA’s capacity to enforce regulations has weakened in recent years.” Reasons cited included a more legalistic environment which creates long delays in violation letters being sent to pharmaceutical companies, a decline in staff members relative to the ever-increasing number of advertisements that need reviewed, and the number of broadcast advertisements receiving pre-airing review declining. In 1999, 64% of advertisements were reviewed before airing; in 2004, the percentage was a mere 32%.<sup>56</sup> The FDA, at the very least, needs to be retooled to complete their oversight role with the resources and manpower necessary to cover the information explosion of the twenty-first century. Funding and staffing standards set long before the rapid increase of print, media, and electronic advertisements must be adjusted in line with the overwhelming task of not just reviewing new medications, but controlling the dissemination of information about them.

On one extreme of the proposals for change is that of Peter Mansfield, a lecturer in general practice at the University of Adelaide in Australia:

Governments have a responsibility to act in the best interests of their citizens by banning DTCA. All of the claimed benefits of DTCA can be gained more effectively and more cheaply with less adverse consequences in other ways, including publicly funded drug information services and health promotion campaigns.<sup>57</sup>

New Zealand, the only other industrialized country that allows DTCA, has considered an outright ban on the practice. A full ban would alleviate the burden on the FDA in the United States, as well, since currently most of their regulatory action “typically occurs

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<sup>56</sup>J.M Donohue, M. Cevasco and M.B. Rosenthal, “A Decade of Direct-to-Consumer Advertising of Prescription Drugs,” *The New England Journal of Medicine*, 357, No. 7, (2007): 675.

<sup>57</sup>Roxanne. Nelson, “When Ads Trump Evidence: Is Direct-to-Consumer Advertising Leading Practice?” *American Journal of Nursing*, 107, No. 10, (2007): 25.

long after an ad has begun airing on television (or in print).”<sup>58</sup> In fact, more than their drug approval process, which is vulnerable to criticism due to the aforementioned conflict of interest with drug company subsidies, is the FDA’s enforcement of regulations governing DTCA, which has been criticized by the Government Accountability Office (GAO) and others. Specifically challenged? “The adequacy of the FDA’s review of pharmaceutical advertisements, as well as the level and speed of enforcement actions taken subsequent to review.”<sup>59</sup> As pointed out by Abramson, and echoed by Gellad and Lyles, simple lack of manpower is partly to blame: the FDA’s Division of Drug Marketing, Advertising, and Communications has only 40 employees to review all DTCA, print, television, and electronic.<sup>60</sup> Even without a full understanding of the job itself, the pressures upon 40 staffers entrusted with overseeing more than \$4 billion worth of advertising cannot be overstated.

### **Suggestions for Change: Advertisements and Approvals**

One relatively simple adjustment to the overwhelming task of advertisement oversight would be to delay a new product from being advertised for a certain time period after its introduction. The American Medical Association backed this position for new drugs in June of 2006. They proposed a moratorium on DTCA of new prescription drugs.<sup>61</sup> PhRMA, the pharmaceutical trade group, has suggested that manufacturers voluntarily delay advertisement campaigns for new drugs “until after health professionals have been sufficiently educated.”<sup>62</sup> A ban on new-to-market pharmaceutical product advertisements within the first year or two of usage would allow the drugs to be

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<sup>58</sup>Frosch, 12.

<sup>59</sup> Donohue and others, 673.

<sup>60</sup> Gellad and Lyles, 479.

<sup>61</sup>Ibid.

<sup>62</sup> Donohue and others, 675.

consumer tested in larger numbers without doctors being pressured to prescribe to every patient who saw an advertisement. This ban would allow drugs found harmful to be withdrawn from the market. The number of drugs being withdrawn has risen sharply since the onset of pharmaceutical company subsidies for the application and approval process and the rise of DTCA advertisements. Between 1993 and 1996, 1.6% of drugs brought to market were withdrawn for safety reasons: this percentage increased to 5.3% between 1997 and 2000. The mistake of “quick-to-market” should not be compounded with the potential harm of “quick-to-advertise.”

Alongside the implementation of a total or partial ban on advertising is the need for FDA improvements. Americans, often quick to complain about “big brother” or too much government, are often the first to point an accusing finger at an institution like the FDA for failing to protect us. In 2008, the “enforcement of current and future laws rests with the FDA, which may require more staff to fulfill this mandate. At present, FDA regulatory action typically occurs long after an ad has begun airing on television.”<sup>63</sup> The FDA’s Division of Drug Marketing, Advertising, and Communications (DDMAC), which oversees promotional labeling and advertising of prescription drugs, does not require prior approval of DTCA; however, they are “happy to review proposed ads if a drug company makes a request.” Many take advantage of this service already. According to Kathryn J. Aiken, a social scientist in DDMAC, “Manufacturers typically want to make sure they’re getting started on the right foot.”<sup>64</sup> Voluntary compliance by many manufacturers seems to indicate a willingness to be guided and even corrected by

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<sup>63</sup> Frosch and others, 12.

<sup>64</sup> Carol Rados, “Truth in Advertising: Rx Drug Ads Come of Age,” *FDA Consumer Magazine*, (July-August 2004), [http://www.fda.gov/fdac/features/2004/404\\_ads.html](http://www.fda.gov/fdac/features/2004/404_ads.html).

the FDA. If many companies are already seeking this guidance pre-advertisement, by extension requiring pre-approval of drug advertisements seems a natural step. The issue of how the FDA would increase funding to hire the additional staff needed is a topic for further research; however, increased fines for DTCA violators would be a simple first step.

Changes in the approval process of new drugs must also be considered. The conflict of interest that exists under the current pharmaceutical approval subsidization by drug companies would be eliminated if a pool of funding were created. Based on factors such as the number of new products brought to market, the sale figures for those products, the size of the company and other quantifiers, pharmaceutical companies would annually or semi-annually contribute funds to the pool that would then be used to approve new applications, or disapprove, as the case may be. Without the direct financial link to the specific pharmaceutical company seeking approval, the FDA would gain credibility with more latitude to refuse drugs deemed unsafe or in need of further testing. Furthermore, streamlined approvals of drugs, such as Gardasil, should be limited to products that have been scientifically proven to provide technological or medical innovation. Merely claiming a drug is a “breakthrough” product should not fast track the application. Finally, the 2002 Best Pharmaceuticals for Children Act should be expanded beyond drugs exclusively formulated for children to include all drugs potentially prescribed to children. A higher standard must be maintained for products given to children by parents and caregivers. Children are more vulnerable to side effects and many risks due to the still developing and hormonally changing nature of their bodies.

## **Conclusion**

It seems disconcerting to contemplate that Gardasil's "unknown" effect on reproductive capacity of 11 and 12 year old girls might be sterility or fetal defects – effects that will not be known for a decade or more. The possibility that Vyvanse could trigger psychotic episodes in adults who received it for many years as adolescents to stay "consistent" should be a concern for all. I am not advocating the removal of these products from the market, simply suggesting that more research over a longer time period is needed before these "wonder" drugs are safe to promote across the board, and to advertise widely to consumers. Pharmaceutical products can greatly enhance lives by improving both their quality and quantity; however, dangers inherent to drug products should be more clearly displayed, particularly when children are targeted. Conflicts of interest must be eliminated from the drug approval process and advertisements need tighter restrictions and regulation. The FDA needs to be reevaluated and potentially retooled to enable it to better serve the needs of twenty-first century American consumers.

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