FDA Accelerated Approval Program: Why Brake When You Can Get a Mandate?

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I. Introduction

Patients fear little else more than that dreaded six-letter word: Cancer. In some cases, its causes are known; in others, it is more unclear. In some cases, it is easily caught and treated; in others, it is not caught until it is too late, and treatment is experimental at best. There are different ways to discover, diagnose, track, treat, and control the different forms of cancer, and the market is filled with potentially life-saving treatments. However, cancer patients who have exhausted the treatments available to them, or who have had no success finding a viable treatment on the market must seek alternative means of relief.

The Food and Drug Administration ("FDA") is responsible for approving or rejecting a drug before it is released to the public.\(^1\) While the protocols in place are meant to help ensure that the drugs available for public consumption are safe and effective, patients with life-threatening illnesses have little to gain from lengthy approval processes, where they do not know how much time they have left to live. In addition, the more time a drug spends in the approval stage, the worse the condition of a seriously ill patient becomes. In order to expedite the drug approval process in such cases, the FDA developed the Accelerated Approval program. However, the questionable post-approval safety procedures practiced by drug manufacturers, coupled with the lax FDA enforcement of its required follow-up protocols have

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\(^1\) *How Drugs Are Developed and Approved*, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default.htm (last updated Apr. 23, 2010).
raised doubts as to the true value of expedited approval procedures, as well as an influx of drug recalls and lawsuits.

It is of further concern that Gardasil® was the first vaccine approved via these expedited procedures. Created to prevent certain types of cervical cancer by immunizing children from ages as young as nine through the age of twenty-six, Gardasil has suffered a backlash at the hands of parents who fear the effect of the vaccine on their daughters and sons at the time of injection, and the unknown implications of the vaccine on their children going forward. Since the adverse events associated with vaccination are not always accurately and completely disclosed, contrary to FDA protocol, it is unclear whether parents can truly be said to give their informed consent to the administration of the vaccine to their children. This is especially alarming in light of the fact that a few states now mandate that children entering school get the vaccine.

In this note, I will elaborate on the elements of the FDA Accelerated Approval program and the standards of Informed Consent. Particularly in cases where certain conditions can be prevented by alternative means and promptly treated, such as safe sexual practices or regular Pap smears in the case of HPV infection, the benefits of such vaccinations is questionable. Certain drugs and vaccines such as Gardasil® are of limited value to the public, and instead, may potentially be availing growing children and the public in general to new potential harm. Bearing in mind the alternative courses of treatment and currently available preventative measures, I will argue that Accelerated Approval should be limited to authorizing life-
threatening medications and should not be applied to preventative vaccines or drugs.

II. FDA Drug Approval Process and the Rise of Accelerated Approval

Prior to releasing a new drug to the public, a pharmaceutical company must obtain the approval of the FDA.\textsuperscript{2} The FDA has rules and regulations in place to ensure that, in between creating its product and being granted approval to place it on the market for patient consumption, a pharmaceutical company can show that its product is safe and effective.\textsuperscript{3} However, the FDA’s implementation of the Accelerated Approval program, which allows certain new drugs to be released after an abbreviated trial period, has raised doubts as to the degree of the safety and efficacy of new drugs, due to the limitation on the data collected at the time of review prior to FDA approval and the failure of manufacturers to complete the required post-marketing procedures, testing, and data collection.\textsuperscript{4}

A. FDA Drug Approval Process

Initially, after a company creates a new drug, upon which it has performed some preliminary testing, it submits an application to the

\textsuperscript{2} Id.


FDA, in anticipation of approval to conduct clinical studies on human subjects. Then, the company completes four phases of clinical trials, with the intent to show that its product is effective and safe to use at certain doses, for a specific purpose, on a specific population (i.e., sex, age group, clinical indication). The company’s research is conducted according to 45 C.F.R § 46, which sets the standards that must be met by these tests in order to be safe for use on human subjects. In addition, an institutional review board (“IRB”) is used to evaluate the company’s research and to ensure its compliance with the federal regulation code. IRBs also ensure that research subjects

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5 See How Drugs Are Developed, supra note 1.


7 See Thaul, supra note 3. Three of the four clinical trial phases precede FDA approval, while the last phase involves a collection and submission of post-marketing data and results. See infra Part II.A.1.

8 Specifically, 45 C.F.R. §46.111 indicates that an institutional review board (“IRB”) must ascertain that the risks posed by a new drug to subjects are minimal, that these risks are reasonable in light of anticipated benefits, and that subjects give informed consent before the trial, among other things. 45 C.F.R. §46.111. It bears mention here that the IRB evaluation standards for preclinical testing are high, and that it “scrutinizes everything about the drug--from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured.” FDA Drug Review Process, supra note 6. Most drugs do not pass this strict review, and never even reach the first clinical phase where they can be tried on human subjects. Id.

9 45 C.F.R. § 46.101 (“Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in § 46.102(e) must be reviewed and approved, in compliance with § 46.101, § 46.102, and § 46.107 through § 46.117 of this policy, by an institutional
are properly informed about the benefits and risks associated with the study. These review boards are composed of scientists and non-scientists who oversee the clinical research, with the goal of protecting the rights and safety of the human subjects on whom the clinical testing of new pharmaceuticals is performed.

IRBs approve the clinical trial protocols, which describe the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study's objectives, and other details. IRBs make sure the study is acceptable, that participants have given consent and are fully informed of their risks, and that researchers take appropriate steps to protect patients from harm.

In addition, the FDA guides the procedure used by IRBs, sets specific standards for the IRBs to follow while evaluating their clinical research, and may disregard research findings that are not evaluated by IRBs, or are otherwise not IRB-approved. IRB activities are closely monitored by the FDA, which has the authority and discretion

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11 Id.


13 FDA Drug Review Process, supra note 6. The IRB will also review the informed consent documentation to ensure that participants understand what they are reading and to make sure that the document encompasses all of the elements that are required by law. FDA 101, supra note 6. For further discussion of informed consent, see infra Part IV.A.

14 See Orlando, supra note 12, at 561.
to disqualify or sanction the IRBs that do not abide by FDA procedures.\textsuperscript{15} Furthermore, the FDA obtains the advice of outside experts in order to analyze the findings of IRBs.\textsuperscript{16} While IRBs are concerned with the safety of the human subjects of these tests, the FDA is concerned with the overall safety and efficacy of the new drug before it is released to the public.\textsuperscript{17}

1. Clinical Trials

Clinical trials are carried out in four phases. The trials performed by scientists at each phase have a different purpose and are meant to help scientists obtain a more comprehensive understanding of the drug and its capabilities.\textsuperscript{18} The IRB, after initially reviewing the protocol for the clinical trial and approving it, will periodically review the study at each phase.\textsuperscript{19} The FDA further protects the rights and safety of volunteers by reviewing the data.

\textsuperscript{15} Id. See also FDA Imposes Restrictions on Coast IRB due to Violations, U.S. Food and Drug Administration (Apr. 14, 2009), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149565.htm (where, pursuant to an FDA warning letter, an IRB shut down its clinical trial investigative operations after concerns were raised as to its ability to protect the safety of trial participants).

\textsuperscript{16} Orlando, supra note 12, at 561.

\textsuperscript{17} FDA Drug Review Process, supra note 6. However, it must be noted that the FDA also requires that the participants taking part in these clinical trials be given enough information about the study so that they can be said to give informed consent to the trial. FDA 101, supra note 6.

\textsuperscript{18} Understanding Clinical Trials, CLINICALTRIALS.GOV (Sept. 20, 2007), http://clinicaltrials.gov/ct2/info/understand#Q19.

submitted by the scientists and inspecting the site of the clinical trial as well as those involved in the research.\textsuperscript{20}

In the first trial phase, researchers collect a small group of healthy volunteers\textsuperscript{21} (approximately twenty to eighty people, but sometimes as low as twelve) on whom to test the new drug or treatment in order to evaluate the safety of the drug, to determine safe dosage levels and frequencies, and to identify the drug’s side effects.\textsuperscript{22} In the second phase of trials, the group of people on whom the drug is tried is increased to roughly one-hundred to three-hundred people in order to test the effectiveness of the new drug and to perform further evaluations of its safety.\textsuperscript{23} Toward Phase II’s end, the FDA and sponsors of the new drug attempt to agree as to how to carry out the next, larger-scale trials.\textsuperscript{24} The objectives of Phase III trials, in which the new drug or treatment is administered to approximately one-thousand to three-thousand people, are to confirm the drug’s effectiveness, to further monitor its side effects, and to compile more information on the drug in order to assure that it will be used

\textsuperscript{20} FDA 101, supra note 6. Furthermore, “FDA often provides extensive technical input to researchers conducting clinical trials, which may help them design better trials that can characterize effects of a new product more efficiently, while reducing risks to those participating in the trials.” Id.

\textsuperscript{21} FDA Drug Review Process, supra note 6.

\textsuperscript{22} See Understanding Clinical Trials, supra note 18; see also What is a Clinical Trial?, NATIONAL CANCER INSTITUTE, http://www.cancer.gov/clinicaltrials/education/what-is-a-clinical-trial (last updated Apr. 8, 2008).

\textsuperscript{23} Understanding Clinical Trials, supra note 18.

\textsuperscript{24} FDA Drug Review Process, supra note 6.
safely.\textsuperscript{25} In this phase, the drug is also compared to present, commonly-used treatments, in order to determine the drug’s additional value over current drugs that are on the market.\textsuperscript{26} After these trials, the manufacturer applies to the FDA.\textsuperscript{27} Phase IV trials cover post-marketing studies, which provide additional information about the drug, including its potential risks, benefits, and ideal use,\textsuperscript{28} so they are performed after the drug has been released to the public, for consumption on a wider scale.

2. Applying for FDA Approval

After three phases of its clinical trials, the manufacturer submits a New Drug Application or a Biologics Licensing Application to the FDA, to obtain permission to market its product.\textsuperscript{29} At this point, the FDA reviews these applications,\textsuperscript{30} seeking evidence of the drug’s safety and effectiveness. If there is not enough information, the FDA may request additional data from the manufacturer, as well as the performance of additional trials.\textsuperscript{31} The FDA is primarily responsible

\textsuperscript{25} Understanding Clinical Trials, supra note 18.

\textsuperscript{26} Id.

\textsuperscript{27} See FDA Drug Review Process, supra note 6.

\textsuperscript{28} Understanding Clinical Trials, supra note 18.

\textsuperscript{29} Thaul, supra note 3.

\textsuperscript{30} The FDA team that reviews these applications is composed of doctors, pharmacologists, chemists, and various other experts. FDA Drug Review Process, supra note 6.

\textsuperscript{31} Thaul, supra note 3. It is a little disconcerting, however, that in 2011, the FDA approved over half of the innovative drugs that came to it for review “on the ‘first cycle’ of review, i.e., without requests for additional information that would lead to another cycle of review.” U.S. FOOD AND DRUG ADMINISTRATION, FY 2011 INNOVATIVE DRUG APPROVALS 4 (November 2011), available at
for establishing the efficacy and ensuring the safety of new drugs.\textsuperscript{32} This responsibility imposes on the FDA a need to balance patients' desires to gain access to new medications that may treat serious or life-threatening illnesses against the government's desire to ensure that patients are protected from abuses by manufacturers taking advantage of the approval process.\textsuperscript{33} "The structure of the FDA's regulatory procedures is, therefore, essential to providing safe, effective medical treatments to patients."\textsuperscript{34} The regulations and guidelines the FDA has set forth create standards and practices to be followed by pharmaceutical companies in order for their new drugs to be released to the public.\textsuperscript{35} Furthermore, the standard of safety used by the FDA accounts for possible side effects posed by the drug, and the FDA "evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use."\textsuperscript{36} Therefore, in


\textsuperscript{32} However, concerns have been raised regarding the FDA’s approval of new drugs in spite of the safety questions voiced by members of the advisory panel of experts. See Laurence Landow, FDA Approves Drugs Even When Experts on its Advisory Panels Raise Safety Questions, 318 BRIT. MED. J. 944 (1999), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1115361/pdf/944a.pdf ("Rather than regulating the drug industry to protect the health of consumers of prescription drugs, the administration has become the industry’s partner, rapidly approving drugs for marketing even when medical experts on its own advisory panels raise serious safety questions.").

\textsuperscript{33} See Orlando, supra note 12, at 543-544. Such actions, in turn, exploit disadvantaged and often desperate patients as well.

\textsuperscript{34} Id. (quoting 21 U.S.C. 393(b) (codifying the FDA's function and mission, including its duties to review clinical research and marketing of regulated products, as well as to monitor the safety and efficacy of drugs)).

\textsuperscript{35} See 21 C.F.R. 314.500-.560 (delineating the guidelines for the Accelerated Approval Program).

\textsuperscript{36} FDA Drug Review Process, supra note 6.
its evaluation of safety, the FDA seeks evidence that the new drug’s benefits outweigh the risks that it poses and its side effects at a therapeutic dose.\textsuperscript{37}

At the very end of this evaluation process, the FDA decides whether or not to approve the application, without which, the drug cannot be marketed and sold to the public.\textsuperscript{38} Under the regular approval process, this procedure usually takes approximately fifteen years (and hundreds of millions of dollars)\textsuperscript{39} from the idea development stage to the final FDA approval.\textsuperscript{40} However, “in 1992 [the] FDA instituted the Accelerated Approval regulation, allowing earlier approval of drugs to treat serious diseases, and that fill an unmet medical need based on a surrogate endpoint.”\textsuperscript{41} In the case of the Accelerated Approval process,\textsuperscript{42} the aforementioned FDA-set standards and procedures are vital in ensuring that drug companies do not take advantage of the shortened trial period in order to expedite placing

\textsuperscript{37} Id.

\textsuperscript{38} See Thaul, supra note 3.


\textsuperscript{40} See Thaul, supra note 3.


\textsuperscript{42} See infra Part II.B.
their product on the market for patient consumption, in order to expedite their profits from sales of this drug.  

B. The Accelerated Approval Process

Accelerated Approval shortens the amount of time a company has to spend researching its drug prior to submitting a New Drug Application, but not the actual review time of the marketing application,\(^\text{44}\) in order to expedite the approval “of a drug or biologic product that provides a ‘meaningful therapeutic benefit . . . over existing treatments.’”\(^\text{45}\) In consideration of the appropriateness of a drug’s approval through Accelerated Approval, three criteria must be satisfied: “(1) the disease studied must be serious or life-threatening, (2) there must be an available surrogate that is reasonably likely to predict clinical benefit, (3) there must be demonstration of improved activity over approved drugs or activity in a population in need of additional therapeutic options.”\(^\text{46}\) This not only means that approval is “‘based on clinical trials . . . rather than using standard outcome measures such as survival or disease progression,’”\(^\text{47}\) but that, where the use of

\(^{43}\) See Orlando, supra note 12, at 543-544.

\(^{44}\) Shoemaker, supra note 4.

\(^{45}\) Thaul, supra note 3 (citation omitted).


\(^{47}\) Thaul, supra note 3 (quoting The Animal Efficacy Rule (21 CFR 314.610 and 21 CFR 601.91), which allows data collected from animal studies to be submitted as evidence supporting the applications of new products where the effectiveness of a drug has been demonstrated, and “when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field
these drugs could only be considered safe and effective under a set of
restrictions, a limitation may be imposed on prescribing or dispensing
them.\textsuperscript{48} The result here is that Accelerated Approval New Drug
Applications are approved before the effectiveness otherwise required
for approval in other, regular approval studies is demonstrated.\textsuperscript{49}
Furthermore, the surrogate endpoint is considered a likely predictor
of the benefit offered by the new drug, but it is acknowledged that it
may be limited in predicting how a patient will feel, function, or
survive after administration of the drug.\textsuperscript{50} Consequently, the FDA
requires that companies seeking Accelerated Approval perform the
necessary Phase IV post-marketing studies on their products.\textsuperscript{51} The FDA
can revoke its approval for the drug (thereby removing it from the
market) if the product company fails to perform the necessary post-
marketing studies, or where post-marketing trials prove that the drug
is dangerous or fails to show efficacy in actual clinical results.\textsuperscript{52}

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\item \textsuperscript{48} See Thaul, supra note 3. It is interesting to note that in certain cases,
the approval of drugs has been advocated even if their use will be limited to
treat a specific strand of a disease. See Emily P. Walker, \textit{FDA Mulls Fastest
Track for 'Limited-Use' Drugs, MEDPAGE TODAY} (Mar. 8, 2012),
http://www.medpagetoday.com/PublicHealthPolicy/PublicHealth/31577 (indicating
the need for new antibiotics to treat hospital-acquired infections, especially a drug to combat a particular type of pneumonia).
\item \textsuperscript{49} \textit{FDA Drug Review Process, supra note 6.}
\item \textsuperscript{50} \textit{Id.}
\item \textsuperscript{51} See \textit{Understanding Clinical Trials, supra note 18.}
\item \textsuperscript{52} See Shoemaker, \textit{supra note 4.}
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The FDA maintains that expedited methods of approval are not intended to jeopardize the safety and effectiveness of the newly-approved drugs.\(^{53}\) The FDA also asserts that its approval methods have progressed and changed since they were first developed, and that it "has been vigilant in assuring that reducing the time necessary for drug development has not compromised the safety and effectiveness of drugs for patients with serious diseases."\(^{54}\) This defense was raised in response to reports that over half of the drugs granted Accelerated Approval only present data from a single-arm trial,\(^ {55}\) indicating that drug companies are not abiding by FDA and industry standards, and are relying upon a limited set of test results.\(^ {56}\) Heeding these reports, "the FDA panel was concerned that drugmakers are failing to conduct required post-marketing studies to verify surrogate endpoints on a timely basis, undermining the veracity of the Accelerated Approval

\(^{53}\) See Fast Track, supra note 41.

\(^{54}\) Id.

\(^{55}\) Single-arm trials, although conveniently short and not resource-intensive, offer limited information on the clinical safety of a drug and its benefit to patients. The use of single-arm trials has been acceptable for diseases which have no available therapy. However, "[a]s a greater number of drugs are [sic] approved, identification and documentation of a refractory population is increasingly problematic. In addition, marginal response rates observed in single arm trials in a refractory setting make it difficult to determine whether the findings are 'reasonably likely' to predict clinical benefit." Oncologic Drugs Advisory Committee, Accelerated Approval & Oncology Experience, U.S. Food and Drug Administration (Feb. 8, 2011), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM242009.pdf. For these reasons, the FDA recommends randomized trials as an alternative, which "provide the opportunity to look at a wider variety of endpoints and allow for an improved characterization of safety." Id.

\(^{56}\) See Silverman, supra note 4.
There have been previous cases where "(1) lax FDA policy enforcement; (2) the pharmaceutical company's negligence; and (3) potentially unavoidable dangers associated with clinical trials," such as those in which no apparent toxicity was exhibited, have led to abuse of the FDA Accelerated Approval program. Such cases have been construed to indicate the need for adequate funding of the Accelerated Approval process with regard to new drugs in order to ensure that the FDA has sufficient resources to properly monitor the behavior of pharmaceutical companies, and for advancement in the FDA's enforcement capabilities. Especially because the program involves a higher risk that potential problems with the drug were not caught in pre-marketing trials (due to the shortened course during which these trials took place), Phase IV trials are of added significance in Accelerated

57 Id.

58 Orlando, supra note 12, at 554. However, some argue that, despite drug withdrawals due to the identification and reporting of adverse drug reactions after a new drug’s marketing, the FDA has not become lax in its approval standards. “The occurrence of rare, but recall prompting clinical events may be the inevitable result of market progress, making the drug manufacturers victims of their own success. . . . Wider use of more drugs, which provides pharmaceutical companies with record profits, also exposes them to greater risks of jeopardising [sic] that business. More people taking more new drugs will result in larger numbers of adverse reactions. This too is a statistical inevitability that will continue into the foreseeable future and one more bittersweet fact of medical progress.” J. D. Kleinke & Scott Gottlieb, Is the FDA Approving Drugs too Fast? Probably Not—but Drug Recalls Have Sparked Debate, 317 BRR. MED. J. 899, 899 (1998) (footnotes omitted), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1113977/pdf/899.pdf.

59 See Orlando, supra note 12, at 554. Congress created the Prescription Drug User Free Act ("PDUFA") “to ensure that the FDA had the necessary resources for the safe and timely review of new drugs.” U.S. FOOD AND DRUG ADMINISTRATION, supra note 31, at 3. Among its objectives, PDUFA is said to have advanced the speed and quality of the FDA’s drug reviews. Funding by PDUFA has provided the FDA “with additional resources for hiring and training scientific reviewers, keeping FDA scientists abreast of innovative technologies, and improving the scientific basis for regulatory decisions.” Id.
Approval drugs, and lax enforcement of this post-marketing surveillance program cannot be overlooked.\textsuperscript{60} Despite the FDA’s progress toward working directly with pharmaceutical companies so that safety information is quickly relayed to physicians and dangerous drugs are pulled from the market, consumers are still at risk for the dangers posed by marketed unsafe drugs.\textsuperscript{61}

Pharmaceutical companies are said to have an incentive to develop safe drugs and not to abuse the Accelerated Approval process inasmuch as Section 402A of the Restatement (Second) of Torts (comment k) indicates that special liability applies to any "[s]eller of [a] [p]roduct for [p]hysical [h]arm to [a] [u]ser or [c]onsumer."\textsuperscript{62} Essentially, this entails that pharmaceutical companies risk strict liability for any drugs that are later rendered to be harmful.\textsuperscript{63} “This

\textsuperscript{60} See FDA Drug Review Process, supra note 6. It is of added concern that the FDA generally does not properly monitor Phase IV trials, and that the FDA does not prioritize oversight of post-marketing study commitments. See Amanda Brower, Phase 4 Research Grows Despite Lack of FDA Oversight, BIOTECHNOLOGY HEALTHCARE 16 (2007) available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2651713/pdf/bh0405016.pdf (“only 25 percent of postmarketing studies are either in progress or have been submitted”). This is especially disconcerting in light of the short trial span of Accelerated Approval drugs, and the emphasis on Phase IV trials as proving the safety and efficacy of these drugs, the failure of which will lead to rescission of FDA approval and the withdrawal of the drug from the market. See FDA Drug Review Process, supra note 6.

\textsuperscript{61} See Orlando, supra note 12, at 554 (“the FDA has . . . begun working with pharmaceutical companies to rapidly get safety information to physicians and to pull drugs from the market that pose safety risks to consumers or otherwise sanction pharmaceutical companies for false advertising.”).

\textsuperscript{62} Id. at 548 (quoting Restatement (Second) of Torts § 402A cmt. k (1965)).

\textsuperscript{63} Oddly enough, this risk has not caused drug manufacturers to be more responsible with regard to withdrawing drugs that they have discovered are dangerous from the market, regardless of the process by which these drugs were approved. Alastair J. J. Wood, The Safety of New Medicines: The Importance of Asking the Right Questions, 281 JAMA 1753, 1753 (2009), available at http://healthandpharma.awardspace.com/Week%208%20Rec/Wood%20The%20Safety%20of
strict liability exemption reduces the risk posed to companies that provide adequate warnings and labeling of their drugs, yet allows liability if the companies have acted negligently." However, despite this incentive, the limited amount of research and safety data collected by the manufacturer under Accelerated Approval procedures makes it difficult for companies to ascertain that their drug is indeed safe, and patients may only learn that a drug is not safe when it is too late and they are harmed as a result. In most cases, this harm will be irreversible and difficult to compensate.

1. From Life-Threatening Diseases to Non-Life-Threatening Diseases

Originally intended only to expedite the approval of (sometimes experimental) treatments for patients suffering from life-threatening diseases, the FDA Accelerated Approval process has expanded to include the review of treatments for non-life-threatening diseases and conditions as well. Although the focus of this note is on the latter group, the Accelerated Approval process has resulted in adding to the

%20New%20Medicine.pdf ("It is surprising that terfenadine was removed from the market, not when the adverse effects were identified, but after the manufacturer had developed a new product to substitute for it.")

64 Orlando, supra note 12, at 548.


66 See Mylotarg, supra note 65 (where patients experienced a serious liver condition and, in the worst case, death as a result of a drug that was later proven unsafe and ineffective).

67 See Orlando, supra note 12, at 555.
woes of patients even within the former group, who were originally intended to benefit from the program.

One example of such a drug is Mylotarg, which received Accelerated Approval to treat Acute Myeloid Leukemia (“AML”), a bone marrow cancer, and was later found to raise concerns regarding its safety and benefit to patients.\textsuperscript{68} Initially, the drug was meant for patients ages sixty and up with recurrent AML, who were not candidates for other forms of chemotherapy.\textsuperscript{69} Later, post-approval trials proved that the drug offered no additional survival benefit, actually increased the number of patient deaths, and that the risk for a fatal liver condition initially observed to be associated with the drug before approval increased after taking the drug.\textsuperscript{70} Mylotarg has since been withdrawn from the market by Pfizer.\textsuperscript{71}

Similarly, Avastin, which was developed to treat many different types of cancers,\textsuperscript{72} was found to be no more effective for treating breast cancer when coupled with chemotherapy than the chemotherapy alone, and imposed serious side effects on patients.\textsuperscript{73} Although this

\textsuperscript{68} Mylotarg, supra note 65.

\textsuperscript{69} Id.

\textsuperscript{70} Id.

\textsuperscript{71} E.g., Id.; Pfizer to Withdraw Cancer Therapy Mylotarg\textregistered from the U.S. Market, Medco (Jun. 22, 2010), https://www.afspa.org/home/pdfs/Mylotarg_flash.pdf; Silverman, supra note 4 (explaining that there was an unexpected number of deaths on account of the drug, and that it lacked a clinical benefit).


\textsuperscript{73} Silverman, supra note 4.
did not affect its use for other types of cancers, the FDA found that Avastin did not prolong the survival rate in breast cancer patients treated with the drug, nor did it sufficiently slow the disease progression to outweigh the substantial health risks to patients.\(^74\)

Concerns surrounding consumer safety as a result of extending the scope of the Accelerated Approval process to non-life-threatening illnesses stem from the failure of pharmaceutical companies to comply with FDA-set follow-up procedures involving clinical result reports as well as the reporting of adverse events.\(^75\) This suggests that the FDA is at least partially responsible for abuses by pharmaceutical companies and should be held accountable for them due to its failure to enforce the procedures it was meant to safeguard. Likewise, because Congress is responsible for providing and ensuring adequate FDA funding, Congress can not only control the FDA's behavior, but it also bears the authority to allot greater enforcement powers to the

\(^{74}\) “These risks include severe high blood pressure; bleeding and hemorrhage; the development of perforations (or 'holes') in the body, including in the nose, stomach, and intestines; and heart attack or heart failure.” \textit{Bevacizumab Injection}, supra note 72.

\(^{75}\) Orlando, supra note 12, at 555. See also Guidance for Industry, supra note 46, at 2 (explaining that some trial protocols prevent manufacturers from discovering this data: “[s]afety data from uncontrolled or expanded access protocols may be useful, but often lack the degree of detailed reporting obtained in controlled clinical trials. In addition, the assessment of causal relationships between a drug and an adverse event is more difficult when relying on uncontrolled safety data.”). Furthermore, “[w]hile the IRB assumes responsibility for oversight and continuing review [of a recently approved drug], the clinical investigator and the research site retain the responsibility for the conduct of the study.” \textit{Cooperative Research - Information Sheet}, U.S. Food and Drug Administration http://www.fda.gov/RegulatoryInformation/Guidances/ucm126422.htm (last updated Aug. 10, 2011).
Thus, critics argue that the degree of control that Congress maintains over the FDA can provide the administration with the necessary incentives to effectively review and approve New Drug Applications more rapidly, while simultaneously ensuring public safety.\textsuperscript{77}

With regard to non-life-threatening diseases and preventative measures such as vaccinations, companies are required to comply with the Vaccine Adverse Event Reporting System ("VAERS"), which allows the FDA and Centers for Disease Control ("CDC") to "closely monitor the safety of all vaccines... VAERS receives unconfirmed reports of possible side effects following the use of Gardasil and all vaccines licensed in the U.S. VAERS reports are regularly reviewed for safety concerns or trends of adverse events (possible side effects)."\textsuperscript{78} These reports track adverse drug reactions ("ADRs"), but it is important to note that "[t]he ADRs listed in these combined databases are voluntary, spontaneous reports filed primarily by health care professionals such as clinicians, physicians, and pharmacists," which entails that filing these events is at the filer's discretion.\textsuperscript{79}


\textsuperscript{77} See Orlando, supra note 12, at 555.


\textsuperscript{79} See Grabowski & Wang, supra note 76, at 386-387. In 1986, Congress passed the National Childhood Vaccine Injury Act ("NCVIA"), which "requires health professionals and vaccine manufacturers to report to the U.S. Department of Health and Human Services (HHS) specific adverse events that occur after the administration of routinely recommended vaccines." About the VAERS Program,
Notwithstanding this drawback, some acknowledged strengths of these databases are their ability to cover a broad spectrum of patient populations “and all therapeutic uses, including approved indications and possible off-label use[;] . . . detecting rare ADRs that are not captured in clinical trials[,] and for detecting drug-drug interactions.” Based on the severity of the reported ADRs within the first few years that a drug is on the market, revisions may be made to a drug's label, new warnings may be issued, and products may be withdrawn from the market. However, this, again, assumes honest, straightforward, and complete reporting of ADRs. In many cases, ADRs are underreported, causation issues may be unclear, and “there is no risk adjustment for utilization and other factors.” It has been found that the adverse events are most likely to be reported, and

VAERS, http://vaers.hhs.gov/about/index (last visited Feb. 27, 2012). Four years later, the FDA and CDC established VAERS. Id. However, anyone can report to VAERS by submitting an online report through the system’s website. Frequently Asked Questions, VAERS, http://vaers.hhs.gov/about/faqs#how (last visited Feb. 27, 2012).

80 Grabowski & Wang, supra note 76, at 386-387.

81 Id. In many cases, drug withdrawal is not perceived to be enough to ensure public safety. Some argue that “[a]fter a marketed drug is withdrawn or development of a new drug is terminated because of adverse toxic effects, an open public attempt to define what happened and why is an important element in improving the drug development and safety monitoring process.” Wood, supra note 63, at 1754.

82 Grabowski & Wang, supra note 76, at 386-387. ADRs have been found to be underreported for numerous reasons. Among them, investigators have reported that the process required too much effort, in some cases this has been a result of a deliberate attempt to defraud, and then in others, investigators have been unaware of what constitutes an ADR. JOHN TALBOT & PATRICK WALLER, STEPHENS’ DETECTION OF NEW ADVERSE DRUG REACTIONS 10 (5th ed., 2004).
indeed the rate of reporting is highest, within the first two years subsequent to a drug’s approval.\textsuperscript{83}

As applied to the vaccine approval process, “vaccine lots [(batches in which vaccines are manufactured)] are routinely tested and must pass all tests before they can be used, and vaccine manufacturers must comply with strict manufacturing standards. [The] FDA also analyzes adverse events (possible side effects) associated with individual lots to look for any unusual patterns.”\textsuperscript{84} It turns out that, “[a]djusted for sales volume, [A]ccelerated [A]pproval [drugs] have the highest number of ADRs per thousands of [standard units];”\textsuperscript{85} in addition “more novel drugs, including priority products, those with accelerated approvals, and biological products, have more associated serious adverse events.”\textsuperscript{86} Bearing this in mind, it is clear that Accelerated Approval should be limited to the approval of serious and life-threatening diseases. It is unlikely that the original objectives of the program were to impose the kind of risks that the ADRs presented above entail upon patients with alternate means of treatment.

2. \textit{Fast Track and Priority Review}

The FDA’s endeavor to release drugs more quickly to the public includes the Fast Track and Priority Review programs in addition to the Accelerated Approval program. Although new drugs can be eligible

\begin{itemize}
\item \textsuperscript{83} Grabowski & Wang, supra note 76, at 386-387.
\item \textsuperscript{84} Gardasil Vaccine Safety, supra note 78.
\item \textsuperscript{85} Grabowski & Wang, supra note 76, at 391.
\item \textsuperscript{86} Id. at 394.
\end{itemize}
for all three designations, the three programs serve different purposes.\textsuperscript{87}

Fast Track generally refers to the process created to expedite the development and FDA review of drugs that not only fit a medical need that is currently unmet, but are also used to treat serious diseases.\textsuperscript{88} Although Fast Track drugs are more likely to be eligible for Accelerated Approval and Priority Review, the Fast Track designation is not dispositive in and of itself; other elements must be shown for eligibility in the former groups.\textsuperscript{89} Accelerated Approval allows drug manufacturers to test whether a drug fits a medical need that is currently unmet based on a surrogate endpoint.\textsuperscript{90} In order for a Fast Track drug to be considered for Accelerated Approval as well, the drug manufacturer must prove to the FDA that the surrogate endpoint that it plans to use in its study is “reasonably likely to predict” the clinical benefit intended for the drug on human subjects.\textsuperscript{91} Then, Priority Review is offered to drugs that present remarkable advances to available treatments, or provide treatment where there is currently no sufficient therapy.\textsuperscript{92} Unlike Standard

\textsuperscript{87} Fast Track, supra note 41.

\textsuperscript{88} Id.

\textsuperscript{89} Id.

\textsuperscript{90} Id. A surrogate endpoint is a “short-term, intermediate endpoint[] in a clinical study that [is] thought to be representative or predictive of longer-term outcomes.” Glossary, NCBI (2005), http://www.ncbi.nlm.nih.gov/books/NBK22321/.

\textsuperscript{91} Fast Track, supra note 41.

\textsuperscript{92} Id.
Review, under which a drug that provides no more than only minimal improvement over presently available treatments is granted a time frame of ten months for the completion of a New Drug Application, Priority Review cuts down this completion time to six months.\(^93\) Priority Review status is available not only to drugs meant to treat serious illnesses, but also to drugs meant to treat less serious diseases.\(^94\) The “Priority” designation does not affect the clinical trial period, nor does it affect the evidence necessary or scientific standard for approval.\(^95\) Gardasil\(^\circledR\) was approved under all three expedited processes.\(^96\)

III. The HPV Vaccine: Gardasil\(^\circledR\)

On June 8, 2006,\(^97\) the first vaccine approved by the FDA under the provisions of the Fast Track process,\(^98\) Accelerated Approval

\(^{93}\) \textit{Id.}\n
\(^{94}\) \textit{Id.} For instance, crofelemer, created to treat diarrhea in AIDS patients, was granted Priority Review in February 2012 and may potentially expand to cover the treatment of irritable bowel syndrome and other digestive conditions. Frank Vinluan, \textit{Priority Review for SLXP Diarrhea Drug, But Shouldn’t Patients Have It By Now?}, \textit{MEDCITY NEWS} (Feb. 7, 2012), http://www.medcitynews.com/2012/02/priority-review-for-slxp-diarrhea-drug-but-should-patients-have-it-by-now/?utm_source=rss&utm_medium=rss&utm_campaign=priority-review-for-slxp-diarrhea-drug-but-should-patients-have-it-by-now.

\(^{95}\) \textit{Fast Track, supra} note 41.

\(^{96}\) See infra Part III.


regulations,\textsuperscript{99} and Priority Review standards\textsuperscript{100} was Gardasil\textsuperscript{®}, the Human Papillomavirus ("HPV") vaccine.\textsuperscript{101} On its way to gaining Accelerated Approval, an open session meeting of the Vaccines and Related Biological Products Advisory Committee was held, during which a conflict of interest was to be resolved as to whether efficacy trial endpoints were suitable for vaccines targeted at preventing HPV.\textsuperscript{102} Presenting her position as to the viability of the vaccine, Dr. Elizabeth Unger, of the CDC, presented that "there has been a consistent epidemiologic association of HPV with cervical cancer, and cervical cancer pre-cursor lesions. There are plausible biologic mechanisms for HPV oncogenesis, and it should be kept in mind that this oncogenesis is a rare event, with a long interval between

\textsuperscript{99} U.S. DEP’T OF HEALTH AND HUMAN SERV. FOOD AND DRUG ADMIN. CTR. FOR BIOLOGICS EVALUATION AND RESEARCH, VACCINES AND RELATED BIOLOGICAL PROD. ADVISORY COMM., OPEN SESSION 85 (Nov. 26, 2001) [hereinafter Transcript], available at http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3805t1_01.pdf (statement of Dr. Karen Goldenthal, FDA) ("The original and current purpose of [A]ccelerated [A]pproval is to serve the best interests of the public, and I did want to note that presented vaccines have not been previously approved using [A]ccelerated [A]pproval regulations.").


\textsuperscript{102} Transcript, supra note 99, at 8.
infection and cancer."

Dr. Unger went further to say that infection by HPV alone is not sufficient to cause cancer, and that additional factors are necessary to create a tumor or a formation of cancerous tissue. Moreover, she highlighted that there are a lot of aspects regarding HPV infection that are still poorly understood, the most common involving HPV elimination from a host. Essentially, not only does HPV affect every host differently, but not all HPV leads to cancer, and most of the time, HPV disappears on its own.

It is especially odd that Gardasil® obtained Accelerated Approval, knowing that cervical cancer is so rarely caused by HPV alone, and particularly because the virus often disappears by itself. It is unclear how a program which was initially meant to help treat people who had been unable to obtain other treatment for serious or

103 Id. at 21 (statement of Dr. Elizabeth Unger, CDC). Still, some urge that the limitation of epidemiological studies should be emphasized. Gary Taubes, Do We Really Know What Makes Us Healthy?, N.Y. TIMES (Sept. 16, 2007), available at http://www.nytimes.com/2007/09/16/magazine/16epidemiology-t.html?page=$=d$=do%20we%20really%20know%20what%20makes%20us%20healthy&st=cse&scp=1 (‘‘Epidemiologic studies, like diagnostic tests, are probabilistic statements. They don’t tell us what the truth is . . . , but they allow both physicians and patients to ‘estimate the truth’ so they can make informed decisions.’ (citation omitted)). However, one must evaluate such a study to ascertain whether the uncertainties are so great as to prevent the drawing of a useful conclusion. Id.

104 Transcript, supra note 99, at 21 (statement of Dr. Elizabeth Unger, CDC).

105 Id. This means that in most cases, the body heals itself of HPV with no adverse effects, without any outside treatment. See id. It is still unknown why HPV only leads to cancer in some individuals. Julie E. Gendel, Playing Games With Girls’ Health: Why It Is Too Soon to Mandate the HPV Vaccine For Pre-Teen Girls As a Prerequisite to School Entry, 39 SEETON HALL L. REV. 265, 268 (2009) (citation omitted).

106 See Genital HPV Infection – Fact Sheet, CENTERS FOR DISEASE CONTROL AND PREVENTION, http://www.cdc.gov/std/hpv/stdfact-hpv.htm (last updated Feb. 15, 2012) (indicating that 90% of cases of HPV infection are naturally cleared by a person’s own immune system).

107 Drug Report, supra note 101.
life-threatening diseases was extended to cover a vaccine meant to eliminate a virus that resolves itself in the majority of cases.\footnote{\textit{Guidance for Industry, supra note 46, at 2.}} Furthermore, despite the high number of deaths caused by cervical cancer in the 1930s, Dr. Goldenthal indicated in this open session that deaths had since decreased dramatically due to Pap smears, which help to identify HPV and tissue abnormalities early enough to treat them.\footnote{\textit{Transcript, supra note 99, at 69 (statement of Dr. Karen Goldenthal, FDA). Merck also underscores that Gardasil does not replace routine Pap screenings. \textit{What You Should Know About HPV, Cervical Cancer, and Genital Warts, GARDASIL (Oct. 2009), http://www.gardasil.com/downloads/grd_yaf_tear_pad.pdf [hereinafter What You Should Know].}}}

Regular Pap smears have been found to have decreased “\textit{[a] woman’s lifetime risk of developing cervical cancer in the U.S. [to] . . . 0.85 percent; and the risk of dying from this disease [to] . . . 0.3 percent.\textit{}}”\footnote{\textit{Transcript, supra note 99, at 75 (statement of Dr. Karen Goldenthal, FDA).} In her elaboration of reservations about accelerating the approval of the HPV vaccine, or generally creating and releasing such a vaccine to the public, Dr. Goldenthal expressed among her list of disadvantages: “\textit{[m]ost HPV infection resolves, [echoing Dr. Unger’s assertion earlier,] and [that] there would be important questions about the durability of protection, especially if one had . . . a trial, for several years with virology,\textit{}}”\footnote{\textit{Transcript, supra note 99, at 69-70 (statement of Dr. Karen Goldenthal, FDA). But see U.S. \textit{Dep’t of Health and Human Serv. Food and Drug Admin. Ctr. for Biologics Evaluation and Research, Vaccines and Related Biological Prod. Advisory Comm., Open Session 108-109 (Nov. 28, 2001), http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3805t1_02.pdf [hereinafter Transcript 2] (statement of Ms. Cindy Pearson, National Women’s Health Network) (indicating that perhaps the best use of the vaccine is in low income areas, where women do not pursue or otherwise do not have access to regular Pap smears).}} and what that would
indicate about the change in one’s lifetime risk for lesions, tissue deformation, or cancer.\textsuperscript{112} Also, she expressed concerns about the fact that “[v]irology is not as approximal to cancer as other endpoints, and it is possible that one may want definitive high grade clinical endpoint data prior to extensive deployment of a new HPV vaccine,”\textsuperscript{113} thus rendering Accelerated Approval inappropriate.\textsuperscript{114} It is unclear what kind of surrogate endpoint could sufficiently predict the likelihood of success on a virus that is so fleeting in nature. It is additionally unclear how such an endpoint could show anything about the longevity of the vaccine.\textsuperscript{115} Such testing would require a long span of time in order to truly demonstrate efficacy going forward, the very facet of traditional approval that Accelerated Approval was created to circumvent.

The last of Dr. Goldenthal’s doubts involved the quality of future trials, namely their feasibility, size, duration, and the ability and resources necessary to track subjects and their

\textsuperscript{112} Id.

\textsuperscript{113} Id.

\textsuperscript{114} See id. “And the purpose of the [A]ccelerated [A]pproval regulations is that they are intended to make available promising therapies while definitive, confirmatory efficacy trials . . . [are] being completed.” Id. at 85. See also, e.g., 21 CFR 314.500 – 314.510; Guidance for Industry, supra note 46, at 2.

\textsuperscript{115} Some vaccines require booster doses to maintain protection, and while Gardasil requires three shots within a six month period, these three doses are necessary for protection, and are not meant to serve the booster purpose of maintaining coverage over an extended period of time. See Tetanus Vaccine: Questions and Answers, IMMUNIZATION ACTION COALITION, http://www.vaccineinformation.org/tetanus/gandavax.asp (last updated Nov. 2010); What You Should Know, supra note 109.
Her preoccupation with trial subjects reiterates the Accelerated Approval program’s emphasis on “the confirmatory post-marketing study[,] [which] is usually well underway at the time of accelerated approval,” and is no less important than the surrogate trials.\(^{117}\) Finally, “[t]he trial for the confirmatory endpoint must be adequate and well controlled, and it must be carried out with due diligence.”\(^{118}\) This emphasis on post-marketing trials highlights the importance of consistently filing VAERS reports, something that is set forth by FDA protocols, but which has not been strictly enforced in practice.

It is noteworthy that during this same open session, Karen Vanderhoof-Forschner, a co-founder of the Lyme Disease Foundation, voiced her objections to the OspA-vaccine, intended to prevent Lyme Disease.\(^{119}\) Almost immediately after the vaccine gained FDA approval in 1998 and was administered to patients, concerns arose about its side effects, principally the development of arthritis.\(^{120}\) Ms. Forschner called attention to the flaws in the vaccine approval process, highlighting that information was being withheld from the FDA and the Vaccine Advisory Committee (“VAC”) regarding the dangers of

\(^{116}\) See Transcript, supra note 99, at 80, 83 (statement of Dr. Karen Goldenthal, FDA).

\(^{117}\) Id. at 85.

\(^{118}\) Id.

\(^{119}\) Transcript 2, supra note 110, at 115.

the OspA-vaccine by the manufacturer’s investigators, who were holding very limited trials. She further implored the FDA and the VAC “to demand that the manufacturers fully complete all safety and efficacy studies and [to] never again let [manufacturers] promise [the FDA and VAC] a study tomorrow for [the FDA’s] approval today.” In 2002, about a year later, GlaxoSmithKline withdrew the vaccine from the market, citing poor sales due to lack of demand. Sadly, Ms. Forschner’s concerns still hold true today and are equally applicable to Gardasil.

A. Gardasil® Clinical Trial Phases and Results

Over the course of seven years, beginning in 1997 and ending in 2004, Merck conducted a total of six Phase I and Phase II trials. Approximately three-thousand participants were involved in these trials altogether, and the results of the studies suggested that the vaccine was safe for use on a larger number of subjects as well as the appropriate dosage to use in the Phase III trials. The open session took place during the course of these clinical trials, but before the commencement of Phase III trials.

121 Transcript 2, supra note 110, at 115 (statement of Karen Vanderhoof-Forschner, Co-Founder, Lyme Disease Foundation) (she called specific attention to the absence of experts from these trials).

122 Id. This is especially remarkable as OspA was granted approval through the regular approval process, and manifests the same concerns presented by the Accelerated Approval program.

123 Nardelli, supra note 120, at 27.

124 VRBPAC Background Document, supra note 98, at 3.

125 Id.

126 Transcript, supra note 99, at 1.
The Phase III clinical trials began in 2002, and consisted of two randomized, double-blinded tests that involved a controlled placebo to evaluate the safety and efficacy of Gardasil. Approximately eighteen-thousand participants were enrolled in the studies altogether, after preliminary screenings eliminated potential subjects with a history of four or more sexual partners, or with a condition that could have possibly interfered with participation in the study. These Phase III trials found that the most effective way to use the vaccine was to immunize patients before exposure to HPV. Most of the side effects experienced by participants in the trials were mild to moderate reactions at the injection site. Of the serious effects suffered by girls who had participated in the trial, all were attributed to other causes, and review of the reported serious adverse events in randomized subjects of the trial were not perceived to raise any serious concerns as to the vaccine’s safety.

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127 A placebo is a medically ineffectual drug used in a controlled experiment in order to track the difference between the test group, which is administered the actual drug being tested, and the control group, which is not exposed to the new drug and is given the placebo instead. Placebo, MERRIAM-WEBSTER, http://www.merriam-webster.com/dictionary/placebo (last visited Feb. 26, 2012).


129 Id. at 4, 8.

130 Id. Subjects with a higher number of sexual partners would compromise study participation due to the risk of HPV exposure prior to vaccination. See id. at 15.

131 See id. (indicating that the vaccine lacks efficacy for those who were previously exposed to the virus and have not cleared the infection).

132 Id. at 22.

133 Id. at 21.
Reports of the studies also indicate that the same rate of serious adverse events and deaths were echoed in the placebo groups.  

B. Approval and Approbation

Originally, Gardasil was approved and licensed for use in girls, ages nine through twenty-six, “for prevention of HPV 6, 11, 16, and 18-related outcomes (i.e., vaginal, vulvar, and cervical precancers and cancers and genital warts).” In October 2009, three years later, it was licensed for use in males of this age group as well, in order to reduce their chances of contracting genital warts. “The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of females at age 11 or 12 years and catch-up vaccination for females aged 13 through 26 years.” However, “ACIP does not recommend [Gardasil] for routine use among males,” despite findings that “HPV-associated cancers in males include certain anal, penile, and oropharyngeal and oral cavity cancers caused primarily by HPV.

134 Id. at 21. Some serious adverse events that were reported were Guillain-Barré Syndrome (muscle weakness caused by a neurological disorder) and blood clots. Reports of Health Concerns Following HPV Vaccination, CENTERS FOR DISEASE CONTROL AND PREVENTION, http://www.cdc.gov/vaccinesafety/vaccines/hpv/gardasil.html [Hereinafter HPV Health Concerns] (last updated Oct. 24, 2011)

135 Centers for Disease Control, FDA Licensure of Quadrivalent Human Papillomavirus Vaccine (HPV4, Gardasil) for Use in Males and Guidance from the Advisory Committee on Immunization Practices (ACIP), 59 MORBIDITY AND MORTALITY WKLY. REP. 630, 630 (May 28, 2010) [hereinafter CDC, Gardasil Licensure], available at http://www.cdc.gov/mmwr/pdf/wk/mm5920.pdf. Note that Gardasil does not protect against all strands of HPV, of which there are over forty, and that even vaccinated women may still develop cervical cancer. See Genital HPV Infection – Fact Sheet, supra note 106 (“Vaccines can protect males and females against some of the most common types of HPV that can lead to disease and cancer.”) (emphasis added)).

136 CDC, Gardasil Licensure, supra note 135, at 630.

137 Id.
Among its concerns, the ACIP lists vaccine efficacy, safety for use in males, and the cost-effectiveness of vaccinating males. On the other hand, girls are encouraged to be immunized with Gardasil before sexual activity, as exposure to the strands of HPV targeted by Gardasil before vaccination eliminates its effectiveness. Since Gardasil was approved through the Accelerated Approval program, Merck must comply with the post-marketing clinical commitments outlined in its original submission to the FDA.

Although “[n]o [unusual adverse event] patterns have been observed in [the] FDA's review of HPV vaccine lots since the vaccine was licensed,” “Gardasil contains extremely high levels of aluminum and polysorbate 80, a known cause of sterility in lab tests on mice, and also known to cause sterility in humans.” Regardless of

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138 Id.

139 Id. And yet, males are encouraged to be immunized in order to prevent spreading these strands of HPV to females. Panel: Boys Should Get Vaccine for HPV, Too, MSNBC.com (Oct. 25, 2011, 11:42 AM), http://www.msnbc.msn.com/id/45031684/ns/health-mens_health/t/panel-boys-should-get-vaccine-hpv-too/#.T2_Z9TE7WAg.

140 E.g., Gendel, supra note 105, at 268; CDC, Gardasil Licensure, supra note 135, at 631.

141 Drug Report, supra note 101; 21 CFR 601.12 (which requires post-application changes to be reported to the FDA).

142 Gardasil Vaccine Safety, supra note 78.

disputable concerns about the contents of the vaccine, it is unsettling to observe the increase of side effects associated with the vaccine as years have passed.

Since marketing Gardasil in 2006, Merck changed its patient information sheet to reflect the emergence of new information regarding side effects. The 2006 patient information sheet listed pain, swelling, itching, redness at the injection site, fever, and occasional difficulty breathing as the only side effects. By contrast, the December 2007 patient information sheet includes nausea, dizziness, vomiting, fainting, difficulty breathing, wheezing, hives, rash, swollen glands, GBS [(Guillain-Barré Syndrome)], headache, joint pain, aching muscles, “unusual tiredness or weakness, and generally feeling unwell.”

In addition, some patients have experienced paralysis and, in the worst scenario, death. Shockingly enough, the National Cancer Institute website informs visitors that “no serious side effects have been shown to be caused by [Gardasil]. The most common problems have been brief soreness and other local symptoms at the injection site. These problems are similar to ones commonly experienced with other vaccines.”

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146 Human Papillomavirus (HPV) Vaccines, NATIONAL CANCER INSTITUTE, http://www.cancer.gov/cancertopics/factsheet/prevention/HPV-vaccine (last visited Nov. 19, 2011). However, the institute does warn that HPV vaccines have not sufficiently been tested during pregnancy, indicating that the vaccine should not be administered to pregnant women. Id.
It is also too soon to discover what kind of latent side effects might arise in the future.\textsuperscript{147} After the conclusion of clinical trials, it has been found that the chances that these future side effects will be discovered are higher with Gardasil than any other vaccine, "[b]ecause few women were followed for more than three years in compiling safety data on Gardasil . . . ."\textsuperscript{148} Since it is unclear how effective Gardasil will be after a number of years, it is of added importance that post-marketing studies be conducted past the three-year mark.\textsuperscript{149} Additionally, because "Gardasil has not been on the market long enough to gather post-approval safety information[,] [t]he consequence is that medical uncertainties which might otherwise be discovered hang over users of Gardasil . . . ."\textsuperscript{150} This is especially disconcerting where the administration of Gardasil has been and currently still is mandatory.\textsuperscript{151}

\textsuperscript{147} See Gendel, \textit{supra} note 105, at 273 (citing Taubes, \textit{supra} note 103) (as a worst-case-scenario example, drug manufacturers have encouraged women to undergo hormone replacement therapy in the past, only to discover that this seemingly beneficial practice had fatal side effects).

\textsuperscript{148} \textit{Id.} at 274. \textit{See also} Sigrid Fry-Revere, The Rush to Vaccinate, N.Y. TIMES (Mar. 25, 2007), available at http://www.nytimes.com/2007/03/25/opinion/25CIfry-revere.html?scp=1&sq=the%20rush%20to%20vaccinate&st=cse (indicating that this short period cannot predict how long the immunity will last or what long-term risks Gardasil may entail).

\textsuperscript{149} See supra text accompanying notes 110-111.

\textsuperscript{150} Gendel, \textit{supra} note 105, at 274.

\textsuperscript{151} \textit{See generally} id. \textit{See also} Fry-Revere, \textit{supra} note 148. "In 1976, swine influenza caused only one documented death in the United States, but the vaccine administered by government mandate seriously injured or killed hundreds. It turned out that the vaccine caused Guillain–Barré syndrome, a rare paralytic disease similar to polio, with a 5 percent fatality rate and a 10 percent rate of permanent paralysis." \textit{Id.} Guillaine-Barré syndrome has been observed after Gardasil vaccinations as well. E.g., \textit{HPV Health Concerns, supra} note 134; Kochuba, \textit{supra} note 144, at 773.
However, not all of the concerns are due to uncertainty with regard to long term effects. Several movements have been generated by groups who are aware of injuries that patients have already suffered at the hands of the vaccine, but are either not reported by Merck, or are unheeded by the FDA. Due to the incomplete reports released to the public regarding the safety of Gardasil, and the incomplete VAERS reports filed by the manufacturer, parents of children who have been injured by vaccines have organized to form the National Vaccine Information Center (“NVIC”), and have appealed to federal health agencies in order to demand that more research be done with regard to dangerous vaccines. The organization’s website also offers a link by which those harmed by the vaccine may file their own VAERS report in order to increase the accuracy of information available to the public.

152 See, e.g., Judicial Watch Investigates Side-Effects of HPV Vaccine, JUDICIAL WATCH, http://www.judicialwatch.org/story/2008/may/judicial-watch-investigates-side-effects-hpv-vaccine (last visited Nov. 21, 2011) ("’The FDA adverse event reports on the HPV vaccine read like a catalog of horrors. Any state or local government now beset by Merck’s lobbying campaigns to mandate this HPV vaccine for young girls ought to take a look at these adverse health reports.'" (quoting Tom Fitton)); Merck’s Gardasil Vaccine not Proven Safe for Little Girls, CHILDREN OF G-D FOR LIFE, http://www.coqforlife.org/gardasilNVIC.htm (last visited Nov. 21, 2011) ("[The National Vaccine Information Center] maintains that Merck's clinical trials did not prove the human papillomavirus (HPV) vaccine designed to prevent cervical cancer and genital warts is safe to give to young girls."); Say "NO" To Mandatory HPV Vaccine!, CARE 2 PETITION SITE (Feb. 2, 2007), http://www.thepetitionsite.com/1/say-no-to-mandatory-hpv-vaccine/ (intended to collect signatures on a petition to stop Texas Gov. Rick Perry from mandating the HPV vaccine).

Still, others argue that the media should do more to communicate the limitation of the available studies.\textsuperscript{155} In the end, patients are often unprepared for the vaccine’s side effects where those effects are largely unknown and are only partially disclosed.

IV. Health Law’s Concern for the Patient: Informed Consent

A relatively new concept for courts and doctors, the doctrine of informed consent was adopted in the 1950s.\textsuperscript{156} Essentially, a patient can only be said to give informed consent when he or she knows both the benefits and the risks of a certain procedure or treatment, enough to make a voluntary decision as to his or her course of action.\textsuperscript{157}

A. Informed Consent as a Necessary Requirement for Treatment

A patient is required by law to give informed consent before being treated; this has been codified as law both by the legislature and by the judiciary.\textsuperscript{158} Further, although informed consent statutes may differ from state to state, they are substantially similar across

\textsuperscript{154} See Transcript 2, \textit{supra} note 110, at 131.

\textsuperscript{155} See Taubes, \textit{supra} note 103.

\textsuperscript{156} \textsc{Institute of Medicine}, \textit{Risk Communication and Vaccination: Summary of a Workshop} 13 (Geoffrey Evans et al. eds., 1997).

\textsuperscript{157} \textit{Id.}

\textsuperscript{158} See 21 C.F.R. § 50.20; see also Moore v. Regents of Univ. of Cal., 51 Cal. 3d 120, 129 (1990) ("The scope of the physician's communication to the patient . . . must be measured by the patient's need, and that need is whatever information is material to the decision." (quoting Cobbs v. Grant, 8 Cal.3d 229, 245 (1972)))); Cobbs, 8 Cal. 3d at 242-43 (doctor must provide a patient with all material information that a reasonable patient would want in consenting, but every possible detail related to the procedure in question is not necessary); Crain v. Allison, 443 A.2d 558, 562 (D.C. Ct. App. 1982) (a physician must at least inform the patient of "the nature of the proposed treatment, any alternative treatment procedures, and the nature and degree of risks and benefits inherent in undergoing and in abstaining from the proposed treatment.").
the United States. The only real differences among these statutes is a current trend toward requiring a higher degree of disclosure as well as requiring doctors to tell their patients what they need to know in order to make an independent decision, as opposed to the bare minimum regarding the treatment or procedure.\textsuperscript{159} The application of informed consent is guided by 21 C.F.R. § 50.25, which also applies to human subjects of medical research.\textsuperscript{160} In the 1970s, courts took the view that the relationship between a patient and his or her doctor is a partnership in decision making, and not a doctors' monopoly.\textsuperscript{161} In keeping with this perception, "[o]n the issue of informed consent, the courts took the view that doctors had an affirmative duty to present all material facts, including risks of treatment, to the patient."\textsuperscript{162} Where a doctor fails to comply with this standard, and neglects to

\textsuperscript{159} See \textsc{George J. Annas, The Rights of Patients: The Basic ACLU Guide to Patient Rights} 84 (1991) [hereinafter \textsc{Annas, The Rights of Patients}]. In fact, courts have found that doctors owe a fiduciary duty to patients as a result of the doctor-patient relationship. \textsc{George J. Annas, Some Choice: Law, Medicine, and the Market} 66 (1998).

\textsuperscript{160} 21 C.F.R. §§ 50.25(a)(2), (a)(4), (a)(6), (a)(7), (b)(1) (requiring the "description of any reasonably foreseeable risks or discomforts to the subject," the "disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject," an explanation of medical treatments available to treat injury incurred as a result of research involving more than minimal risk, an explanation as to whom to contact if an injury is suffered by the subject as a result of the research, and a "statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.")

\textsuperscript{161} \textsc{Paul Starr, The Social Transformation of American Medicine} 389 (1982).

\textsuperscript{162} \textit{Id.}
disclose such risks, a patient may sue the doctor for malpractice if he or she suffers an injury as a result of the treatment.\textsuperscript{163}

Generally, a patient’s “consent must be competent, voluntary, informed, and understanding.”\textsuperscript{164} With regard to medical procedures, case law has guided that the physician must communicate to the patient any information that is material for that patient to make a decision.\textsuperscript{165} Currently, courts limit these communications to the degree necessary to disclose to the patient known or foreseeable medical risks. However, where it has been held that informed consent does not require the disclosure of unforeseeable risks, it has normally involved unique or highly individualized risks.\textsuperscript{166}

Interestingly enough, health care providers and other health officials believe that they are acting in the best interest of the public when they encourage the masses to seek immunization, while minimizing the communication of potential risks of these immunizations.\textsuperscript{167} Yet, it must be noted here that informed consent

\begin{footnotesize}
\textsuperscript{163} Id. See N.Y. Pub. Health Law § 2805-d(4) (McKinney) for an example set of exclusions for informed consent.

\textsuperscript{164} ANNAS, THE RIGHTS OF PATIENTS, supra note 159, at 89.

\textsuperscript{165} See Moore v. Regents of Univ. of Cal., 51 Cal. 3d 120, 129 (1990); Cobbs v. Grant, 8 Cal.3d 229, 245 (1972).

\textsuperscript{166} Kochuba, supra note 144, at 773. The laws have developed the doctrine of informed consent into the primary protection of the patient’s right of self-determination, which includes both knowledge and volition. Matter of Jobes, 529 A.2d 434, 454 (N.J. 1987). “The doctrine of informed consent presupposes that the patient has the information necessary to evaluate the risks and benefits of all the available options and is competent to do so.” Matter of Conroy, 486 A.2d 1209, 1222 (N.J. 1985).

\textsuperscript{167} INSTITUTE OF MEDICINE, supra note 156, at 14.
\end{footnotesize}
operates differently for different kinds of treatments, and that vaccinations operate under a unique set of information procedures.

**B. Vaccine Information Statements and Gardasil**

Vaccine Information Statements ("VISs") are produced by the CDC and explain a vaccine’s benefits and risks. VISs are required by federal law to be distributed before each dose of a vaccination is given.\(^\text{168}\) Gardasil is one such vaccine.\(^\text{169}\) Despite the safety concerns surrounding this vaccine, Gardasil’s VIS informs patients and their parents only of the minimal side effects experienced by patients.\(^\text{170}\) It must further be noted that the acknowledged “uncertainties surrounding Gardasil's risks and benefits are of a systemic nature, attributed to the vaccine's limited clinical study,”\(^\text{171}\) meaning that a complete VIS is likely currently unfeasible. This is a matter of concern not only to patients who are being immunized, but also to parents who must choose whether or not to vaccinate their daughters, and now their sons as well. Parents are put in an especially precarious position with regard to the vaccine, encouraged by doctors and television advertisements, and in the most extreme cases mandated

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\(^{169}\) *Vaccine Information Statements*, supra note 168.


\(^{171}\) Kochuba, supra note 144, at 773.
by statute,\textsuperscript{172} to immunize their children with Gardasil, under repeated assertions that the vaccine has been proven very safe by virtue of its use around the world.\textsuperscript{173} Furthermore, the VAERS reports which are meant to inform consumers of the risk of the vaccines do not necessarily contain all of the information that parents must know.\textsuperscript{174} The limited data available to consumers, coupled with the limited degree of disclosure made to parents makes informed consent on the parent’s part that much more difficult to attain. “[P]arents are most likely to consent to HPV vaccination of their children when they believe that the vaccine will benefit their child's health, influenced by the opinions of peers and a doctor's recommendation.”\textsuperscript{175} However, on the other hand, parental consent to this vaccination decreases as a result of parental concern that the vaccine will be dangerous to the child, or that the child will suffer significant discomfort from vaccination.\textsuperscript{176} In the end, it is up to the parent to perform the risk-benefit calculation with regard to immunizing his or her child.

\textsuperscript{172} See Gendel, supra note 105, at 266.

\textsuperscript{173} See Elisabeth Rosenthal, Drug Makers’ Push Leads to Cancer Vaccine’s Rise, N.Y. TIMES (Aug. 19, 2008), http://www.nytimes.com/2008/08/20/health/policy/20vaccine.html?pagewanted=all (calling attention to the amount of money and lobbying involved in advertising the HPV vaccine, and exploring the possibility that rapid and irresponsible dissemination of the vaccine “‘could cause more deaths,’ from side effects, for example, or from giving girls false security that they are protected for life and no longer need to be screened”); see also What You Need to Know, supra note 170.

\textsuperscript{174} NVIC Report, supra note 153.

\textsuperscript{175} Kochuba, supra note 144, at 774.

\textsuperscript{176} Id.
with Gardasil, and consent to the vaccination depends on the parent’s valuation of the vaccine. 177

Inevitably, in the case of such vaccines, the element of consent is always present when the parent agrees to vaccinate his or her child, but the degree to which this consent is informed depends in some part on what the doctors say and, in most cases, what the parent has discovered as a result of independent investigation. With regard to Gardasil specifically, the pharmaceutical company presents limited information with regard to the vaccine, as

[t]he patient information sheets provided upon Gardasil vaccination do not mention the vaccine’s abbreviated clinical study, the lack of knowledge regarding duration of immunity, or the limited availability of current safety data . . . . The transient nature of information provided in the patient information sheets reflects an overall lack of complete safety and efficacy data, and does not adequately convey the uncertainties surrounding Gardasil’s risks and benefits. 178

Patients and parents of patients are left to do their own research into the quality of the vaccine, as they are not given enough facts by their doctors or even the drug manufacturers. The effects not disclosed by the pharmaceutical companies, in addition to the effects of which they are currently unaware, added to doctors’ limited disclosure leave patients and parents of patients unable to truly give informed consent to these vaccines. 179

177 Id.

178 Id. at 778-779. This can also be seen in the VIS, whose distribution is required by law before the vaccine is administered. Vaccine Information Statements, supra note 168.

179 See Kochuba, supra note 144, at 778-779.
Furthermore, those in opposition to state-mandated vaccinations argue that compulsion by authorities violates patient autonomy, let alone parental authority over their children, and the laws requiring informed consent. “Without more candid acknowledgment from both Merck and healthcare providers of the limited knowledge of Gardasil's overall safety and efficacy, mandatory HPV vaccination violates the core principle of informed consent, which recognizes a patient's right to make a reasonably informed and intelligent treatment decision.”

Historically, where policymakers and health officials have encouraged the public to obtain immunizations without adequately communicating the risks involved, these actions have weakened public trust of these officials. It has been established that health care providers are responsible for providing their patients with information that is both accurate and unbiased, and the same standard applies to vaccinations and the extent and the nature of their risk. Further, “failure to communicate what medical science does and does not know about vaccine risks . . . [has been] perceived as a

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180 This applies both to adults and minors, as even “[a]n ‘immature’ minor has no less right to make decisions regarding her own body than a mature adult.” Hodgson v. Minnesota, 497 U.S. 417, 473 (1990).

181 See Wisconsin v. Yoder, 406 U.S. 205, 213-14 (1972) (reinforcing the rights of parents to hold the primary position in making decisions for their children)


183 Kochuba, supra note 144, at 779.

184 INSTITUTE OF MEDICINE, supra note 156, at 14.

185 Id.
fundamental betrayal of trust by those who [are] being asked to take the risks[.]

Somewhere in its “concern” for the public health, health care officials and the government have jeopardized their legitimacy in the public’s eye by forfeiting the necessary communication to the masses and opting instead for blind orders. This is especially disconcerting when compared to statutes that compel doctors not only to disclose to patients the reasonably foreseeable benefits and risks of a certain course of treatment, but also the alternatives to that treatment. Since courts aim to protect the person’s right to bodily integrity, doctors may be liable for negligence where they obtain consent that is not sufficiently

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186 Id.

187 This is especially odd as, within the court’s endeavor to protect one’s bodily integrity, there is a reluctance to compel an individual to permit such an intrusion in order to benefit another person’s health. In re A.C., 573 A.2d 1235, 1243-44 (D.C. 1990) (holding that a patient must give informed consent, unless that patient is incompetent or otherwise unable to give informed consent to the proposed course of medical treatment).

188 See INSTITUTE OF MEDICINE, supra note 156, at 14. The state mandates requiring children entering school to be immunized against HPV without communicating the potential risks of the vaccine are examples of such blind orders.

189 N.Y. Pub. Health Law § 2805-d (McKinney) (the statute holds the information that the doctor discloses to a standard that a “reasonable medical, dental or podiatric practitioner under similar circumstances would have disclosed, in a manner permitting the patient to make a knowledgeable evaluation reasonable”). In the case of vaccination with Gardasil, pap screenings and, to a degree, safe sexual practices are ways to diagnose and treat HPV infection earlier, or prevent contracting the virus altogether. See Genital HPV Infection – Fact Sheet, supra note 106.

Moreover, courts have gone as far as holding that the patient’s right to informed consent “also encompasses a right to informed refusal.” Especially where states mandate that the vaccine be administered to children, the violation is twofold, as parents are not only deprived of the right to give informed consent, but they are also denied the right to decline to inoculate their children with a vaccine whose effects are not completely known.

V. Conclusion

It is difficult to reconcile the data present with regard to some of the Accelerated Approval drugs, especially Gardasil, with the information required for patients to give informed consent. Although a lesser degree of information is required for patients to give consent to be immunized, as VISs are sufficient to meet this standard, it does not seem that the Gardasil VISs satisfactorily fulfill this requirement. There is still substantial controversy regarding the HPV vaccine generally, resulting from its short testing time, limited subject pool, its short time on the market, and the question of what its true side effects are, as opposed to what is presented to patients.

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191 Crain, 443 A.2d at 561-562. See also N.Y. Pub. Health Law § 2805-d (McKinney) (indicating that the doctor’s failure to disclose sufficient information for the patient to give informed consent must be a proximate cause of the patient’s injury).


It is undeniable that the Accelerated Approval program has the potential to offer seriously ill patients life-saving treatments, but it is unclear just how necessary or helpful its expansion to non-life-threatening conditions has really been. Although Phase IV trials have been neglected in the past, this practice is all the more unacceptable where, despite a brief trial period, drugs are approved and heavily advertised and even mandated to a young generation as a prerequisite for school enrollment. Particularly in light of the law’s concern for the patient, the Accelerated Approval program should be limited to the approval of treatments for serious, life-threatening diseases, lest a healthy and growing population be put at risk for present and future risks that have not been discovered, reported, and which could have been avoided by other means.