Off-Label Prescribing in a Vulnerable Pediatric Marketplace

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Introduction

In 2002, a seven-year-old boy was first prescribed Risperdal, a strong antipsychotic medication, which, at the time, lacked approval for use in children for any indication.1 As a result of using Risperdal from 2002 to 2008, the young boy “claim[ed] he . . . suffered rapid weight gain, serious and permanent physical injury to his endocrine and sexual systems, gynecomastia, and other permanent physical and emotional damages.”2 He is currently suing Johnson & Johnson and its subsidiaries for criminally and recklessly promoting the use of Risperdal in a pediatric setting.3

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2. See Thomas, supra note 1 (explaining side effects the young boy experienced from using Risperdal). Gynecomastia is a medical condition in males where the development of breasts occurs. Id.

3. See Thomas, supra note 1. See also Risperdal, INJ. LAW. NEWS, injurylawyer-news.com/risperdal (last modified Sept. 17, 2014) (explaining potential side effects, FDA warnings, and lawsuits filed by patients). In 1993, FDA approved Risperdal for the treatment of schizophrenia and bipolar disorder. Id. The drug was also approved to treat irritability in autistic children in 2006. Id. In November 2008 at an FDA meeting, physicians raised concerns about side effects in children, but FDA failed to require strengthened warning labels. Id. The claimant also alleges the promotion of off-label use of the drug in children as young as three for a variety of conditions,
These allegations point to a very complicated matter that pediatric physicians face, namely, the lack of Food and Drug Administration ("FDA") approved medications for pediatric clinical use. While the lack of approved medications persists, the federal government continues to take steps in the direction of remedying the practice of "off-label" prescription usage in pediatric medicine. Issues still remain with the including Attention-Deficit-Hyperactivity Disorder ("ADHD"), Obsessive-Compulsive Disorder ("OCD"), and other conditions. Thomas, supra note 1.

4 See Henk van den Berg & Nanda Tak, Licensing and Labelling of Drugs in a Paediatric Oncology Ward, 72 BR. J. CLIN. PHARMACOL. 474 (2011) (noting pediatric drug prescriptions are known for high percentages of off-label and unregulated use); Off-Label Medications Prescribed to Nearly All Pediatric Intensive Care Patients, AM. ACAD. OF PEDIATRICS (Oct. 21, 2012), http://www.aap.org/en-us/about-the-aap/aap-press-room/pages/Off-Label-Medications-Prescribed-to-Nearly-All-Pediatric-Intensive-Care-Patients.aspx. In one hospital’s pediatric intensive care unit ("PICU") in Salt Lake City, 96% of all patients received at least one off-label drug. See Off-Label Medications Prescribed to Nearly All Pediatric Intensive Care Patients, AM. ACAD. OF PEDIATRICS (Oct. 21, 2012), http://www.aap.org/en-us/about-the-aap/aap-press-room/pages/Off-Label-Medications-Prescribed-to-Nearly-All-Pediatric-Intensive-Care-Patients.aspx. Here “[t]reatment with off-label medications is the rule rather than the exception.” Id. One physician explains that physicians attempt to find suggested doses to help the child, but admits, “it is better medicine to dose or recommend doses based on evidence.” Id. See also Jesse C. Vivian, Off-Label Use of Prescription Drugs, 28 U.S. PHARM. 50 (May 15, 2003), available at http://legacy.uspharmacist.com/index.asp?show=article&page=8_1078.htm. “The American Medical Association (AMA) has estimated that as many as 40% of all prescription drugs are issued for off-label use.” Id. See Sue Sutter, FDA Neonatology Strategic Plan Should Focus on Commonly Used NICU Drugs, PINK SHEET (March 25, 2013). About 90% of drugs used in neonatal care are off-label and have little "neonatal-specific information in drug labeling.” Id. See Aaron S. Kesselheim, Off-label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech, 37 AM. J.L. & MED. 225, 225 (2011). “Physicians can prescribe any drug for any medical condition, even outside of the parameters of the label, for a so-called 'off-label' use.” Id. See Holly Fernandez Lynch, Give Them What They Want? The Permissibility of Pediatric Placebo-Controlled Trials Under the Best Pharmaceuticals for Children Act, 16 ANNALS HEALTH L. 79, 82 (2007). Though prescribing drugs for off-label uses are legally and professionally permitted in the medical profession, it is at the very least ineffective, and at worst, dangerous. Id. at 82-83. See David M. Smolin, Nontherapeutic Research with Children: The Virtues and Vices of Legal Uncertainty, 33 CUMB. L. REV. 621, 628 (2003). Contrasting adults with children in off-label use, these drugs have at least been tested in the adult population and approved by FDA, whereas for children, there have not been clinical trials or FDA approval for the pediatric population. Id.

government's implementation of regulations and legislation. Historically, the
government has typically chosen the most lucrative targets to prosecute, instead of
pursuing those responsible for writing the off-label prescriptions—physicians. While
the government does not regulate the practice of prescribing off-label medication, 
someone, namely the prescribing physicians, must be held accountable for children's use
of medication that is not FDA approved in the pediatric marketplace.

This note analyzes physician accountability regarding inappropriate prescribing
of off-label medication to Medicaid patients and consequently, the abuse of
reimbursement that these physicians receive. Section I outlines the history of
pharmaceutical prescription regulation through FDA's approval process, specifically
pediatrics, focusing on the legislation that has been used to promote improved pediatric
drug-labeling. Section II discusses off-label prescribing as it relates to Medicaid
reimbursement. Finally, Section III offers recommendations for new remedies for False
Claims Act ("FCA") litigation, while also looking at more permanent solutions that
should be implemented with legislation and FDA approval. Section III ultimately
concludes that physicians should be held accountable for the off-label prescriptions they
write, regardless of pharmaceutical companies' involvement in persuading doctors to
prescribe certain drugs more often.

I. Regulation of Prescription Pharmaceuticals

A. History of the FDA

FDA "is the oldest comprehensive consumer protection agency in the United
States federal government." Many of FDA's regulatory functions have evolved since

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6 Michael J. Malinowski & Grant G. Gautreaux, Drug Development-Stuck in A State of Puberty?:
Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability,
56 ST. LOUIS U. L.J. 363, 393 (2012). "The drop in new drug approvals has taken place in spite
of annual governmental investments of billions of dollars in biomedical research." Id. "In
addition to the decline in new drug approvals, many of the prescription drugs the FDA has put
on the market in recent years have proven disappointing." Id. "The vast capacity to publish
research and to share knowledge is tainted by conflicts of interest which threaten the reliability
and integrity of the peer review process and, consequently, the underlying research." Id. at 399.
"Governments, professional societies, and most science journals have failed to introduce and
enforce the mechanisms necessary to manage conflicts of interest in an era of aggressive
commercialization with meaningful confidence." Id.

7 See infra notes 101-113 (discussing rise of off-label antipsychotic drug prescriptions with
pediatric patients and lawsuits stemming therefrom).

8 See Fernandez, infra note 4, at 82.

Whatwedo/History/default.htm (last updated Oct. 14, 2014). FDA dates back to around 1848,
the agency's inception, however public health continues to be its mission. After 1912, FDA's predominant focus shifted from the regulation of food to a heavier focus on drug regulation. Given that the Pure Food and Drugs Act had clearer standards for medications than it did for food, significant controversy arose in the misbranding and drug regulation.

During the 1930s, FDA voiced concerns over "legally mandated . . . prohibition

when Lewis Caleb Beck was appointed to provide chemical analyses of various agricultural products. FDA's present day regulatory functions began with the Pure Food and Drugs Act in 1906, which made misbranding food and drugs within interstate commerce illegal, a protection that was not available to consumers before the Act's passage. Id.

"FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation." What We Do, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/aboutfda/whatwedo/ (last visited Oct. 16, 2014).

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.


An amendment was later drafted to correct the language of the act, which placed the burden of proof on the bureau to show "that manufacturers of drugs labeled with false therapeutic claims intended to defraud consumers." Id.
of false therapeutic claims for drugs . . . and control of product advertising." After the passage of the Food, Drug, and Cosmetic Act ("FD&C Act"), focus shifted again, this time to pre-market approval for medical devices, cosmetics safety requirements, and veterinary medicine. In the years after FDA became part of the Public Health Service ("PHS") within the Department of Health, Education, and Welfare, but before it moved to Health and Human Services, FDA acquired several new functions and responsibilities. Over the past twenty years, changes in FDA regulations have rapidly evolved, partly based on "political pressure, consumer activism, and industry involvement." Specifically, advocacy groups have pushed for the development and approval of orphan drugs, which treat diseases affecting a small percentage of the population.

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13 See The 1938 Food, Drug, and Cosmetic Act, U.S. FOOD AND DRUG ADMINISTRATION (June 18, 2009), available at http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054826.htm (9/24/2012). FDA pointed to numerous products that exemplified the need for an updated regulatory framework that would protect consumers from the harms of mislabeling that was legal under the 1906 Act. Id. In light of a tragic "therapeutic disaster" in 1937, Congress passed a bill that would replace and be more effective than the 1906 Act. Id. See Carol Ballentine, Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident, FDA CONSUMER MAGAZINE (June 1981) (recounting the sulfanilamide incident that led to new regulatory legislation for drugs). In June, 1938, President Franklin Roosevelt signed the Food, Drug, and Cosmetic Act ("FD&C Act"), which, in part, required manufacturers to prove to FDA that new drugs were safe before the drugs were approved for marketing and could be sold. See The 1938 Food, Drug, and Cosmetic Act, supra note 13.


15 See Trends in the Last Quarter Century, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm125632.htm (last updated June 18, 2009). At that time, one of the roles FDA had within PHS was giving "pre-market licensing authority for" biological agents. Id. See also FDA Organizational Histories, supra note 5. In 1979, the Department of Health, Education and Welfare became the Department of Health and Human Services ("HHS"). Id. See also About HHS, HHS.GOV, http://www.hhs.gov/about/ (last visited Oct. 19, 2014). Now, HHS provides access to health care for millions of people and is "the government’s principal agency for protecting the health of all Americans . . . especially for those who are least able to help themselves." Id.

16 See Trends in the Last Quarter Century, supra note 15 (discussing increase in FDA's responsibilities).

17 See Trends in the Last Quarter Century, supra note 15. Advocacy groups pushed for laws to promote the industry for "orphan drugs," which also aided the development of accelerated drug approval techniques. Id. See J.K. Aronson, Rare Diseases and Orphan Drugs, 61 BR. J. CLIN. PHARMACOL. 3243-45 (March 2006), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1885017/. "An orphan drug can be defined as one that is used to treat an orphan disease," which can be broken into two separate but interrelated categories. Id. The first category consists of diseases physicians often neglect, while the second points to diseases affecting a small
B. FDA Approval Process

Before a drug debuts in the market, pharmaceutical manufacturing companies must demonstrate that the drug is safe and effective by performing several trials which enable FDA to determine if a drug is safe and effective in the treatment or diagnosis of disease. Drugs begin their development to treat a particular disease or condition and if deemed unnecessarily dangerous, do not make it past pre-clinical testing or subsequent phases requiring human testing, FDA approval, and marketing. However, if deemed "reasonably safe," clinical trials proceed over the course of several years, and a New Drug Application ("NDA") is submitted to FDA. The Children's Health Act governs percentage of the population. Id. See also Trends in the Last Quarter Century, supra note 15. Among the important laws that have been passed in the past twenty years are "mandated reporting of adverse reactions to medical devices... and recall authority for the FDA over medical devices." Id. In the 1990s, FDA heavily focused on evaluating therapeutic products. Id. See Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-397 (2012); What is the Approval Process for a New Prescription Drug?, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194949.htm (last updated Apr. 4, 2014) (describing approval process for new drugs). See also About FDA Product Approval, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/NewsEvents/ProductsApprovals/ucm106288.htm (last updated Feb. 26, 2009) (explaining regulation of marketing approval). No product is completely risk-free; therefore, "at the heart of all FDA's medical product evaluation decisions is a judgment about whether a new product's benefits to users will outweigh its risks." Id. FDA does not perform tests on new drugs, but instead reviews testing pharmaceutical companies perform. Id. See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm (last updated May 28, 2014) (discussing the stages of drug development and review). Pre-clinical trials are sponsored by pharmaceutical manufacturing companies, research institutions, and other organizations, which are responsible for the development of the drug and for submitting an Investigational New Drug Application ("IND") to FDA, detailing results of the testing and proposing how to move forward with human testing. Id. After FDA and a local institution review board ("IRB") determine that the drug in development is "reasonably safe" for human testing, clinical trials may begin. Id. The IRB is "a panel of scientists and non-scientists in hospitals and research institutions that oversee clinical research," approve every aspect of clinical trials, including dosages, possible participants, and objectives of the study to ensure patients are fully informed of the risks and are protected from harm. Id. Phase 1 studies, which are tested in healthy populations, test for frequent side effects and how the drug is metabolized and expelled. Id. Phase 2 studies test the drug's effectiveness in volunteers who have the certain disease or condition and compare those results to a placebo group or group receiving a different, already approved drug. See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm (last updated May 25, 2014). In Phase 3, large-scale studies are performed, and more information on effectiveness and safety is gathered, specifically in a variety of populations with different doses of the drug and in conjunction with other drugs. Id. The sponsor of the drug then submits an NDA, with information about the drug and analysis of all data collected for FDA review, prior to approval of the drug. Id. FDA's Office of Orphan Products Development ("OOPD") promotes
pediatric clinical trials, which must be in accordance with existing pediatric clinical trial regulations.\textsuperscript{21} In addition to the traditional method of FDA drug approval, an accelerated approval is an option when drugs fall within the description of orphan diseases.\textsuperscript{22}

In addition to accelerated approval options, the Office of Orphan Products Development ("OOPD"), through the Pediatric Device Consortia ("PDC") Grant Program, "stimulate[s] projects [that] will promote pediatric device development."\textsuperscript{23} FDA's Office of Pediatric Therapeutics ("OPT") focuses on ensuring safe and effective medical devices and treatment for children, similar to PDC, by providing incentives to pharmaceutical manufacturers to develop pediatric drugs.\textsuperscript{24} Pediatric product

development of products for orphan diseases by providing incentives for manufacturers and sponsors. \textit{Id.}

\textsuperscript{21} See infra Part III (discussing clinical research studies and trials involving children).

\textsuperscript{22} See \textit{FDA's Drug Review Process: Continued}, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm289601.htm (last updated Apr. 25, 2014). The accelerated approval process allows an NDA to be approved before the usual course of clinical trials for effectiveness have concluded and produced sufficient data. \textit{Id.} Instead, "surrogate endpoints... [which] are laboratory findings or signs that may not be a direct measurement of how a patient feels, functions, or survives, but are considered likely to predict benefit," are used to evaluate the effectiveness of the drug. \textit{Id.} Pharmaceutical manufacturing companies must continue effectiveness studies of the drug to confirm predicted effects, or else FDA may withdraw approval. \textit{Id.} See Aronson, supra note 17 (defining an orphan drug). "[B]arriers to the development of orphan drugs do not occur only at the premarketing stage; in some cases it may not be commercially worth mounting an efficacy trial, even of a drug whose efficacy elsewhere is well established." Aronson, supra note 17. at 244. See Developing Products for Rare Diseases & Conditions, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm (last updated July 20, 2014). FDA's OOPD promotes the development of products for orphan diseases by providing incentives for manufacturers and sponsors. \textit{Id.} The OOPD's "mission is to advance the evaluation and development of products...that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions." \textit{Id.} Since 1983, over 400 drugs and products for orphan diseases have been developed and marketed, whereas between 1973 and 1983 fewer than 10 had been developed and marketed. \textit{Id.}

\textsuperscript{23} See Pediatric Device Consortia Grant Program, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/default.htm (last updated Apr. 28, 2014) (noting PDC's promotion of pediatric device development). \textit{See also} Frequently Asked Questions Concerning the Pediatric Device Consortia (PDC) Grant Program, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/ucm233295.htm (last updated Apr. 28, 2014) (discussing pediatric consortia grant program). The program is focused on all devices in pediatric medicine, not just orphan diseases. \textit{Id.}

\textsuperscript{24} See infra notes 32-35 and accompanying text (noting incentives, such as delayed generic labeling for pharmaceutical companies); Office of Pediatric Therapeutics, U.S. FOOD AND DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/Office
development inherently poses issues as children tend to be healthier and compose a smaller percentage of the general population, resulting in fewer children who are eligible or appropriate to participate in clinical trials. While limited data and studies relating to pediatric drug interactions exist, drugs otherwise approved and available on the market are prescribed to children for off-label uses. Grave issues arise from this common off-label practice when physicians, for example, adjust dosage of medication based on body weight, giving the notion that children are simply “small adults” and react to drugs in a similar manner as adults. Children, however “have different physiology, body size and composition, growth and development, cognitive and motor function, and special organ of Science and Health Coordination/ucm2018186.htm (last updated June 3, 2014) (explaining OPT’s mission to produce safe and effective medical products for children); Pediatric Product Development, U.S. FOOD AND DRUG ADMIN., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm (last updated June 25, 2014) (noting many FDA initiatives for improved medical research in children); Frequently Asked Questions Concerning the Pediatric Device Consortia (PDC) Grant Program, U.S. FOOD AND DRUG ADMIN., http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/ucm233295.htm (last updated Apr. 28, 2014). Pediatric patients, like patients with diseases classified as orphan diseases, comprise a small percentage of the population. See Tim Mackey & Brian A. Liang, Off-label Promotion Reform, A Legislative Proposal Addressing Vulnerable Patient Drug Access and Limiting Inappropriate Pharm. Marketing, 45 U. Mich. J. Reform at 1, 16 (2011). Clinical trials can be incredibly expensive for both and may toe the line ethically. Id. See Edwards, infra note 44 at 351 (noting ethical implications in pediatric research).

25 See Pediatric Safety, U.S. FOOD AND DRUG ADMIN., http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106609.htm#ftn1 (last updated Nov. 30, 2012). The OPT Safety Team organizes Congressional mandated pediatric safety reviews, which are compiled and presented to the Pediatric Advisory Committee to “enhance further . . . understanding of the safety of a product and the risk/benefit of products used in children.” Id. The Safety Team utilizes MedSun/KidNet, which is a pediatric product safety initiative FDA implemented to enhance further study of pediatric safety. Id. “Doctors currently lack adequate dosing, safety, and efficacy data regarding pediatric use of at least sixty-five percent of drugs prescribed to children.” Fernandez, supra note 4 at 79. In addition, the information physicians have directly correlates with the age of the patient, with the least available information for the youngest patients. Id. See Rosemary Roberts et al., Pediatric Drug Labeling: Improving the Safety and Efficacy of Pediatric Therapies, 290(7) J. Am. Med. Ass’n. 905, 905 (2003).

26 See Kesselheim, supra note 4 at 225 (defining off-label use of prescribed medication).

27 See Kurt R. Karst, Pediatric Testing of Prescription Drugs: The Food and Drug Administration’s Carrot and Stick for the Pharmaceutical Industry, 49 Am. U.L. Rev. 739, 746 (2000). Pediatricians generally make educated guesses to determine the correct dosage for off-label uses of drugs, which generally have no adverse side effects in adults. Id. However, when physicians make these educated guesses for children, there could be serious consequences. Id. See Press Release, Department of Justice, Warner-Lambert to Pay $4.30 Million to Resolve Criminal and Civil Health Care Liability Relating to Off-Label Promotion (May 2004), available at http://www.justice.gov/opa/pr/2004/May/04_civ_322.htm. Potential problems that can arise from off-label use without the benefit of careful FDA oversight include the occurrence of unforeseen adverse effects because the drug was not studied in the type of patient it is being used for off-label and the appropriate dosage and course of treatment have not been established. Id.
system maturation" all of which can have substantial effects on how drugs are processed in the body and can create different outcomes from what has been previously seen in the adult population.\textsuperscript{28} Without appropriate information, pediatric physicians may be reluctant to even prescribe drugs that could ultimately be helpful to their patients for fear that their patients will react negatively to the drug; others prescribe medicine that has virtually no effect on the condition.\textsuperscript{29} With few other options available, this practice has been deemed not only appropriate within the field of pediatric medicine but medically necessary.\textsuperscript{30}

C. FDA Legislation

The lack of FDA approved medications for children is not a new issue.\textsuperscript{31} Beginning in 1974, there was a push for improved pediatric drug labeling.\textsuperscript{32} After the

\begin{itemize}
  \item \textsuperscript{28} See Fernandez, \textit{supra} note 4 at 85. Physicians also lack resources to explain how off-label prescriptions should be written for children and infants. \textit{See id.} at 82.
  \item \textsuperscript{29} See \textit{id.} at 83. Physicians frequently have to make the choice not to prescribe drugs to their pediatric patients for fear of negative side effects verses prescribing the drug, which ultimately has little to no effect on the condition. \textit{Id.} Both of these choices are utilized to preserve children's safety, which results in children being undertreated. \textit{Id.} Harmful effects, much worse than "under treatment," could easily occur if a physician were to prescribe a treatment without the appropriate treating data. \textit{Id.}
  \item \textsuperscript{30} See Mackey, \textit{supra} note 24 at 17. Instead of avoiding treatments that have not been approved for use in pediatrics, physicians reduce the dose, resulting in a trial and error experiment for the individual child. \textit{Id.} See also Fernandez, \textit{supra} note 4 at 83 (discussing experimental and non-approved process of giving milder dosages of adult medication to children). Ethical issues arise from pediatric testing, but more ethical issues arise from non-treatment of children as well as the use of untested or under-tested drugs in pediatric treatment. Mackey, \textit{supra} note 24, at 83-84. See Marc A. Rodwin, \textit{Routing Out Institutional Corruption to Manage Inappropriate Off-Label Drug Use}, 41 J. L. MED. \& ETHICS 654 (2013) (discussing how off-label prescriptions make sense as exception rather than rule in practice).
  \item \textsuperscript{31} See \textit{supra} note 22 and accompanying text (noting how few orphan drugs, as a whole, are developed and marketed). See also \textit{supra} note 27 and accompanying text (noting limited information regarding majority of drugs available, which doctors regularly prescribe children off-label).
  \item \textsuperscript{32} See Committee on Drugs, American Academy of Pediatrics, \textit{General Guidelines for the Evaluation of Drugs to be Approved for Use During Pregnancy and for Treatment of Infants and Children} (Evanston, Ill., 1974) (issuing general guidelines for drug evaluations for drugs to be used in pediatric patients). FDA later adopted these guidelines in 1977, incorporating them into FDA's own clinical guidelines. See U.S. DEP'T. OF HEW, PHS, FDA, PUB. NO. 77-3041, \textit{GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS IN INFANTS AND CHILDREN} (1977). Additionally, FDA created a "Pediatric Use" regulation, outlining requirements for drug sponsors to include pediatric uses on drug labels. See Kurt R. Karst, Comment, \textit{Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry}, 49 AM. U. L. REV. 739, 747 (2000). The regulation was amended in 1994 to give sponsors "the option to conduct pediatric research and include the data on labels" or to include a statement that explained pediatric effectiveness and safety had not been established. \textit{Id.} at 747-748.
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passage of various amendments to the FD&C Act, the next major evolution in pediatric drug law did not occur until 1997 with the Food and Drug Administration Modernization Act ("FDAMA"), when the "Pediatric List" was created.\(^3\) In 2002, the Best Pharmaceuticals for Children Act was passed to improve FDAMA, eliminating the "Pediatric List" and authorizing FDA to make specific requests regarding the approval of drugs for children.\(^4\) Specifically, FDA can authorize pediatric studies to be performed either by the holder of the approved NDA or another company or organization with experience in conducting pediatric clinical trials.\(^5\) 

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\(^3\) See Karst, supra 32 at 749; Fernandez, supra note 4, at 93-94. Michael S. Labson, Pediatric Priorities: Legislative and Regulatory Initiatives to Expand Research on the Use of Medicines in Pediatric Patients, 6 J. HEALTH CARE L. & POL’Y 34, 62-63 (2002). The “Pediatric List” is a list of previously approved drugs, but additional pediatric research information may be helpful. Labson, supra. Food and Drug Administration (FDA) Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified at 21 U.S.C. §§ 301-392 (Supp. 1997)). “With the passage of FDAMA, Congress enhanced [the] FDA’s mission in ways that recognized the Agency would be operating in the 21st century characterized by increasing technological, trade and public health complexities.” Food and Drug Administration Modernization Act (FDAMA) of 1997, U.S. FOOD AND DRUG ADMINISTRATION, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ (last updated 6/18/2009). See also Fernandez, supra 4 at 92-93. In 1962, an amendment to the FD&C Act added a regulatory requirement for effectiveness of new drugs, but there was no requirement for pediatric research and testing. Id. FDA intended this amendment to encourage sponsors to research pediatric effectiveness and safety, but instead, sponsors disclaimed the lack of testing in pediatric fields, as was mandated, to reduce the cost of drug studies. Id. This sparked the danger of total lack of data for usage of drugs in pediatrics. Id. See Food and Drug Administration Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (codified at 21 U.S.C. §§ 351 et seq.). FDAMA, unlike the 1962 amendment, included pediatrics. Incentives were created that delayed generic competition by creating economic incentive to perform needed pediatric research. Id.

\(^4\) See Labson, supra note 33, at 71; Fernandez, supra note 4 at 94-95 (outlining FDA’s ability to make request for new two tiered system to incentivize pediatric studies).


(b) Contracts for Pediatric Studies.-- The Secretary shall award contracts to entities that have the expertise to conduct pediatric clinical trials (including qualified universities, hospitals, laboratories, contract research organizations, federally funded programs such as pediatric pharmacology research units, other public or private institutions, or individuals) to enable the entities to conduct pediatric studies concerning one or more drugs identified in the list described in subsection (a).

(c) Process for Contracts and Labeling Changes.-- (1) Written request to holders of approved applications for drugs lacking exclusivity.-- The Commissioner of Food and Drugs, in consultation with the Director of the National Institutes of Health, may issue a written request (which shall include a timeframe for negotiations for an agreement) for pediatric studies concerning a drug identified in the list described in subsection (a)(1)(A) (except clause (iv))
Taking FDA’s power a step further, Congress enacted the Pediatric Research Equity Act ("PREA"), in response to the "Pediatric Rule’s" invalidation, allowing FDA to require pediatric testing of drugs already marketed.\(^3\) However, PREA allows sponsors to defer the requirement for pediatric studies for a number of reasons.\(^3\) Sponsors may defer studies where evidence strongly suggests that the drug would be ineffective or dangerous in pediatric settings, where the drug will not offer a meaningful benefit over already approved therapeutic drugs in the market, or until additional data is available for adult patients.\(^3\) Additionally, if a drug is frequently utilized in pediatric

to all holders of an approved application for the drug under section 505 of the Federal Food, Drug, and Cosmetic Act. Such a written request shall be made in a manner equivalent to the manner in which a written request is made under subsection (a) or (b) of section 505A of the Federal Food, Drug, and Cosmetic Act, including with respect to information provided on the pediatric studies to be conducted pursuant to the request.

\(^{36}\) See 21 C.F.R. §§ 201, 312, 314, 601 (2001); 63 Fed. Reg. 6632 (1998). Ass’n of Am. Physicians and Surgeons, Inc. v. United States Food and Drug Admin. challenged the “Pediatric Rule” in federal court, where the plaintiffs claimed that the rule exceeded FDA’s authority. 226 F. Supp. 2d 204 (D.D.C. 2002). The court held that FDA lacked any statutory authority to create and enact such a rule, and that while the policy may be sound behind the rule, it would be better enacted by Congress. Id. See Lauren Hammer Breslow, Note, The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing, 40 HARV. J. ON LEGIS. 133, 160 (2003). Testing and labeling for new pediatric drugs was favored and the PREA allowed FDA to punish manufacturers for noncompliance. Id.

\(^{37}\) See Pediatric Research Equity Act, Pub. L. No. 108-155, 117 Stat. 1936 (2003). In relevant part, the act states “[a] person that submits an application (or supplement to an application) [for a drug] . . . shall submit . . . [an] assessment . . . [of] . . . the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations . . .” Id.

\(^{38}\) Id.

(3) Deferral.— On the initiative of the Secretary or at the request of the applicant, the Secretary may defer submission of some or all assessments required. until a specific date after approval of the drug or issuance of the license for a biological product if—(A) The Secretary Finds that—(i) the drug or biological product is ready for approval for use in adults before the pediatric studies are complete; (ii) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or (iii) there is another appropriate reason for deferral.

\(^{3}\) Id.

(A) Full waiver.— On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to the submit assessments for a drug or biological product under
medicine, consistent with its labeled use, but is not approved or indicated for pediatric use, FDA can require further studies to be performed. If research has been conducted in adult populations or in pediatrics but not necessarily in all age groups, the data from these studies may be sufficient if such data can be extrapolated and no further pediatric studies may be required.

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this subsection if the applicant certifies and the Secretary finds that—(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed); (ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or (iii) the drug or biological product— (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (II) is not likely to be used in a substantial number of pediatric patients.

Id.

(B) Partial waiver.—On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments for a drug or biological product under this subsection with respect to a specific pediatric age group if the applicant certifies and the Secretary finds that—(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that group are geographically dispersed); (ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group; (iii) the drug or biological product— (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group; or (iv) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

Id. "If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product." Pediatric Research Equity Act, 117 Stat. 1936 (2003).

39 See id.

(1) In general.—After providing notice in the form of a letter... the Secretary...may require the holder of an approved application for a drug... or the holder of a license for a biological product... to submit by a specified date the assessments... if the Secretary finds that— (A) (i) the drug or biological product is used for a substantial number of pediatric patients for the labeled indication.

Id.

40 See id.
D. Pediatric Research Studies and Clinical Trials

Clinical studies are an essential element of FDA’s approval process to ensure the safety and efficacy of new drugs or older drugs with added on-label uses. However, clinical trials have a long history and in pediatric research specifically, there has been an enormous abuse of power.\(^1\) Clinical researchers, in their desire to further understand diseases, have used children as human subjects, frequently without informed consent by both the child and parent or guardian, or when consent was obtained, it was not informed consent and parents or guardians often did not fully understand the ramifications of their decisions.\(^2\) The vulnerability of the pediatric population,

(i) In general.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients... (ii) Extrapolation between age groups.—A study may not be needed in each pediatric age group in data from one age group can be extrapolated to another age group.


\(^{2}\) See Leonard H. Glantz, Research with Children, 24 AM. J.L. & MED. 213, 215 (1998). In the 1800s while he was studying smallpox, Edward Jenner exposed about fifty children to smallpox, including his own son, without any regulatory oversight. Id. Jenner initially injected his one-year-old son with cowpox to determine if he would be immune to smallpox. Id. He also injected an eight-year-old boy with the smallpox virus as a vaccine to determine if the boy would be immune. Id. In 1802, he tested the vaccine on forty-eight children to test their immunity to the smallpox virus. Id. Later, in the 1900s, Alfred Hess began conducting research at the Hebrew Infant Asylum in New York by modifying children’s diets in order to cause the children to fall ill with various diseases, including rickets and scurvy. Id. See Glantz, supra at 215-16. Hess worked at the asylum as the medical director, and noted that it offered perfect conditions because they were similar to the “conditions which are insisted on in considering the course of experimental infection among laboratory animals, but which can rarely be controlled in a study of infection in man.” Id. See BARUCH A. BRODY, THE ETHICS OF BIOMEDICAL RESEARCH: AN INTERNATIONAL PERSPECTIVE 120 (1998). This abuse of children continued and culminated during World War II with the Nazis experimenting on human subjects, including children. Id. In 1941, William Black subjected a one-year-old baby to the herpes simplex virus and proceeded to write an article, which he attempted to submit to the Journal of Experimental Medicine. Id. at 119. See Glantz, supra at 216. The article was rejected with the note that “the inoculation of a twelve month old infant with herpes . . . was an abuse of power, an infringement of the rights of an individual, and not excusable because the illness which followed had implications for science.” Id. See also Ann E. Ryan, Protecting the Rights of Pediatric Research Subjects in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 23 FORDHAM INT’L L.J. 848, 854 (2000) (noting violations of ethics within pediatric research). From 1955 to 1970, another violation of pediatric research ethics occurred when mentally challenged
especially within the context of clinical research studies gives cause of alarm about children's safety.43

Though potential abuse is a valid concern, it is important for children to participate in clinical research to ensure that appropriate treatment and drugs are available for future pediatric treatments.44 In 2000, Congress enacted the Children's Health Act, mandating that research involving children must be in compliance with existing pediatric rules.45 Generally, there are three applicable federal risk categories: minimal risk, therapeutic research, and non-therapeutic research.46 The first category only allows investigations that provide "no greater than minimal risks to children" and parents' consent is required.47 The next category applies to therapeutic research, when

students in a state institution were exposed to the hepatitis virus so that researchers could study the disease. Id. While parental consent was given to allow these children to participate in the study, there is evidence that parents were not fully informed and were sometimes coerced into giving consent. Id.

43 See Cohen, supra 41 at 674. Among the host of reasons that children are vulnerable, ethically, within clinical research studies, they specifically are unable to consent to their participation in the research study and must rely on parents or guardians to make that determination for them. Id. The individual who ultimately gives consent for a child to participate in a research study may have interests that conflict with the interests of the child or that individual may be coerced into providing consent. Id.

44 See S.D. Edwards & M.J. McNamee, Ethical Concerns Regarding Guidelines for the Conduct of Clinical Research on Children, 31 J. MED. ETHICS 351, 351 (2005) (noting need for pediatric research). There are three major reasons why pediatric clinical research is important. Id.

First, certain diseases are characteristically childhood diseases and so meaningful research on them needs to be conducted on children. Secondly, there are well known problems in extrapolating pharmacological data from adults to children owing to metabolic differences between children and adults. . . Thirdly, research on children is necessary to determine what is normal development in order to ensure that treatments given are appropriate . . . [meaning, some] conditions can be identified as abnormal only when they are seen in relation to what is normal.

Id.

45 See Children's Health Act of 2000, Pub. L. No. 106-310, 114 Stat. 1167 (noting pediatric research must comply with Federal Regulations). "Notwithstanding any other provision of law . . . all research involving children that is conducted, supported, or regulated by the Department of Health and Human Services be in compliance with subpart D of part 46 of title 45, Code of Federal Regulations." Id. See also 45 C.F.R. § 46.401-409 (discussing when research is appropriate in pediatric populations).

46 See Fernandez, supra 4, at 102-114.

47 See 21 C.F.R. § 50.51 (2013) (noting pediatric research must be compliant with existing pediatric rules). See also Fernandez, supra 4, at 101. An objective definition of 'minimal risk' has been implemented, referring to "the daily life of the average healthy child, as opposed to those risks facing the particular subject in his or her particular life." Id. Types of procedures used
there are "more than minimal risk[s] to children but that presents the prospect of direct benefit to individual subjects." 48 Finally, non-therapeutic research must be likely to advance knowledge and treatment concerning a disease or condition, but the research does not necessarily benefit the individual participants. 49

Generally, there are ethical concerns involving children in clinical research studies because children are unable to give informed consent to participate in clinical studies. 50 However, there is a competing concern to study potential treatments for children to ensure equal access to FDA approved drugs. 51 Additionally, FDA works to ensure that parents, who ultimately decide whether or not their child should participate in a trial, are fully informed and understand the risks and implications that come with participation in a clinical trial. 52 While it is possible for parental abuse of power to occur in deciding whether or not a child should participate in a clinical trial, FDA has imposed safeguards in attempts to minimize those risks. 53

Though regulations have been enacted to ensure access to FDA approved medications for children, issues arise when the burden shifts from the pharmaceutical

would be “clean-catch urinalysis, obtaining stool samples, administering electroencephalograms, requiring minimal changes in diet or daily routine, the use of standard psychological tests.” Id. 48 See 21 C.F.R. § 50.52 (2013) (noting that pediatric research must be compliant with existing pediatric rules). See also Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20589 (April 24, 2001). In addition, the statute requires documentation showing that the risks are justified by the benefits, the benefits are equal to that which is already available, and parents or guardians must be able to give their informed consent. Id. Researchers generally perform studies on children with the disease or condition that the drug is intended to treat. Id. 49 See 21 C.F.R. § 50.53 (2013) (detailing pediatric research must be compliant with existing pediatric rules); Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. at 20589 (noting FDA can require pediatric studies when studies provide meaningful therapeutic benefit over existing treatments).

50 See Edwards, supra note 44, at 351-52 (noting ethical considerations in pediatric research).

51 See Committee on Drugs, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, 90 PEDIATRICS 286 (1995) (detailing need for pediatric drug research).


53 See Cohen, supra 41, at 686-87 (noting who must consent and when it is required). When research involves “no greater than minimal risk,” not only is the child’s assent required but also the permission of at least one parent. Id. When research involves “greater than minimal risk” but there is a significant possibility of direct benefit to those involved in the trial, both the child’s assent and both parents’ permission are required, if both parents are available. Id. When research involves “greater than minimal risk” and there may not be a direct benefit, but a general increase in knowledge of a disorder that can be gleaned from the study, the child’s assent and both parents’ permission are required, if both parents are available. Id.
companies manufacturing approved pediatric drugs, to parents deciding if participating in a clinical trial will benefit or harm their child. Parents consider a host of factors when determining whether or not to enroll their child in a clinical research study which include: their child's safety, access to other medications to treat their child, and the role their child could play in research for the benefit of society. There is a significant amount of misunderstanding by parents, however, when they begin to consider whether or not to allow their child to participate in a study. With increased and more effective communication between parents and clinical researchers, parents may feel more empowered to provide consent for their child to participate in studies that are important to ensuring appropriate treatment and drug options for various diseases.

54 See Pediatric Clinical Trials are on the Rise as New Law Goes into Effect, PR NEWSWIRE (Aug. 4, 2000), available at http://www.prnewswire.com/news-releases/pediatric-clinical-trials-are-on-the-rise-as-new-law-goes-into-effect-expect-from-the-childrens-hospital-of-Philadelphia-provides-guidelines-for-parents-72708522.html. Usually, drugs are tested in adults before they are tested in children, unless the drug or condition only affects children. Id. Additionally, parents often must make decisions for their children because children may be unable to make that decision on their own, due to age, development, or understanding. Id. See also Committee on Drugs, supra note 51, at 859 (concluding that appropriate access to important medications for children is needed).


56 See id. at 1. In one study involving ninety-five families, parents informed researchers that the parents were often confused or could not remember specific details about the trial that their child was involved in, attributing the confusion or limited memory to heightened emotions, stress, and overload of information given to them. Id. at 3-5. Frequently parents also had misunderstandings regarding access to availability of medication outside of the study. Id. at 4-5. Additionally, parents did not understand how children were selected and placed into the placebo controlled, or the active medication, arms of the study. Id. at 4.

57 See id. at 6. “Researchers have a social responsibility and awareness of the fact that young patients and their families are often not able to calculate the risks of participation or understand the conceptual framework of medical research including randomization.” Justin D. Rothmier et al., Factors Influencing Parental Consent In Pediatric Clinical Research, 111 PEDIATRICS 1037-1041 (2003). Additionally, clinical researchers need to ensure that parents, and children if possible, comprehend the information and literature available to them before participating in the trial. See Falk Wulf et al., Determinants of Decision-Making And Patient Participation In Paediatric Clinical Trials: A Literature Review, 2 OPEN JOURNAL OF PEDIATRICS 1, 3-4 (2012) available at http://www.scirp.org/journal/PaperDownload.aspx?paperID=17983. For example, researchers “should be aware of the level of cognitive and reading comprehension of potential . . . participants.” Id. at 6. If the family cannot understand the information and literature available to them, then clinical researchers must adjust the way they communicate with the family. Id.
II. Medicaid and the False Claims Act

A. Billing Medicaid

Medicaid, governed by the Medicaid Act, provides health insurance coverage to nearly sixty million Americans, primarily based on income eligibility.\(^\text{58}\) Under Medicaid regulations, there are limitations regarding coverage of prescription medications prescribed for off-label uses.\(^\text{59}\) Specifically, the Medicaid Act provides that coverage for

\(^\text{58}\) See 42 U.S.C. § 1396 (describing Medicaid and Children’s Health Insurance Program payment and access commission). See also Eligibility, MEDICAID.GOV, http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Eligibility/Eligibility.html (last visited Oct. 17, 2014). States may expand eligibility for coverage above what federal standards require. Id. Medicaid is administered by states but funded by state and federal government. Id. See also Children’s Health Insurance Program (CHIP), MEDICAID.GOV, http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Childrens-Health-Insurance-Program-CHIP/Childrens-Health-Insurance-Program-CHIP.html (last visited Oct. 17, 2014). The Children’s Health Insurance Program (“CHIP”) is an insurance program for children whose families do not qualify for Medicaid because of their income level. Id. CHIP, like Medicaid, is also administered by the states but funded through state and federal government contributions. Id. Federal guidelines require certain mandatory benefits and provide for optional benefits that states may choose to provide through their expansion of the Medicaid program. See Medicaid Benefits, MEDICAID.GOV, http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Medicaid-Benefits.html (last visited Oct. 17, 2014). According to the federal guidelines, outpatient prescription drug coverage is not mandatory, unless the state has expanded their Medicaid program for such coverage. See Prescription Drugs, MEDICAID.GOV, http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Prescription-Drugs.html (last visited Oct. 17, 2014). Currently, all states cover prescription drugs in their Medicaid plans. Id. However, once a state decides to adopt outpatient prescription drugs into its own Medicaid program, the state becomes subject to federal requirements. See Edmonds v. Levine, 417 F. Supp. 2d 1323, 1326 (S.D. Fla. 2006). In 2009, the Children’s Health Insurance Program Reauthorization Act (“CHIPRA”) was signed, not only reauthorizing the CHIP program, but also improving it by granting more funding for states to be able to reach out to children who are not enrolled, but would otherwise be covered by CHIP. See CHIP, MEDICAID.GOV, http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Childrens-Health-Insurance-Program-CHIP/Childrens-Health-Insurance-Program-CHIP.html (last visited Oct. 17, 2014).

\(^\text{59}\) See Philip Hickey, PhD, Submitting Claims for Off-label Prescriptions to Medicaid May Constitute Fraud, BEHAVIORISM AND MENTAL HEALTH (Sept. 12, 2013), http://www.behaviorismandmentalhealth.com/2013/09/12/submitting-claims-for-off-label-prescriptions-to-medicaid-may-constitute-fraud (noting off-label and unapproved by compendia may constitute fraud). Physicians are allowed to bill Medicaid when, in specific circumstances, the compendia has endorsed the drug, which is then approved by Congress. Id. See also Loreen Brown, Gain a Solid Understanding of Compendia and its Impact on Patient Access, FORMULARY (July 1, 2012), http://formularyjournal.modernmedicine.com/formulary-journal/news/clinical/clinical-pharmacology/gain-solid-understanding-compendia-and-its-impact. Therefore, when a physician bills Medicaid for a drug prescribed off-label which is not endorsed by any of the compendia, the physician may face the possibility of a charge of Medicaid fraud. Id. “Drug compendia are defined as summaries of drug information that are compiled by experts who have reviewed
a drug must be prescribed when there is a “medically accepted indication” for the prescription.60 However, when the prescription drug is not specifically approved for the purpose the physician intends to treat, individual states, through authorization under the Medicaid Act, may deny prescription reimbursement coverage.61

The Medicaid Act gives states the authority to limit coverage of off-label prescriptions under certain circumstances, such as when a state has excluded a drug from its formulary for off-label indications or requires prior authorization.62 States create a drug formulary, developed by a committee of physicians, pharmacists, and other medical professionals, which indicates the states' list of accepted prescription drugs and their associated uses to be covered.63 Further, states are allowed to remove Medicaid eligible drugs from the formulary if there is some indication that another drug in the formulary would be better suited for treatment.64 If the formulary excludes a drug for coverage, and the prescribing physician still wishes to prescribe the excluded drug, the physician may seek an exception.65 The Medicaid Act provides for two requirements for prior approval.66 First, the state must respond to the prescribing physician within twenty-four hours of the request and second, a seventy-two hour supply of the drug must be made available in emergency situations.67 With the statutory requirement for clinical data on drugs.” Id. According to the Centers for Medicare and Medicaid Services, the compendia, unlike disease treatment guidelines which are indexed by disease, should be indexed by drug and should include pharmacologic characteristics for each drug that may include dosage and recommended uses. Id. Experts may consider certain off-label uses as “acceptable,” and positive and negative classifications may have a significant impact on whether the product is covered. Id. One negative endorsement may impact the likelihood of a product receiving coverage. Id. See 42 U.S.C. § 1396r-8 (2012) (outlining payment for covered outpatient drugs). Compendia used by state Medicaid include American Hospital Formulary Service Drug Information, United States Pharmacopeia- Drug Information and DRUGDEX Information Systems. Id.

60 See also 42 U.S.C.S. § 1396r-8(k)(6) (2012). “Medically accepted indication [is defined as] any use for a covered outpatient drug which is approved under the Federal Food, Drug, and Cosmetic Act . . . or the use of which is supported by one or more citations included or approved for . . . in any of the compendia . . .” Id.
64 See id. at 1328. Drugs are generally excluded from the formulary, with the result that the drugs future coverage and reimbursement will be denied, when there are issues of clinical safety and effectiveness. Id. When the formulary is created, the Medicaid Act also provides that states must establish procedures for prior authorization. Id.
65 See id. Prior authorization from Medicaid must be acquired before the drug is dispensed. Id.
66 See 42 U.S.C. § 1396r-8(d)(5)(A)-(B) (stating both requirements necessary for prior approval).
67 See 42 U.S.C. § 1396r-8(d)(5)(A)-(B) (describing two specific prongs required for prior authorization); Edmonds, 417 F. Supp. 2d at 1328 (outlining process of prior authorization).
both formularies and prior authorizations, courts have determined that, at the very least, states must consider coverage of excluded drugs on a case-by-case basis.\textsuperscript{68} Yet the final decision regarding coverage rests with the state.\textsuperscript{69} Additionally, there is a second type of prior approval program when states have not developed a formulary but still require prior approval for prescription drugs.\textsuperscript{70} In this second scheme, the ultimate prescribing decision rests with the prescribing physician.\textsuperscript{71}

Regardless of Medicaid's formulary restrictions, off-label drug prescriptions are still legal and prescribing off-label is common practice in the medical field.\textsuperscript{72} An increase in off-label prescriptions has been observed, most notably in atypical antipsychotics.\textsuperscript{73} Between 1995 and 2008, off-label prescriptions of antipsychotics doubled and between 2001 and 2010, the prevalence of these drugs increased by more than one hundred sixty-nine percent.\textsuperscript{74} This class of drugs is controversial and is the

\textsuperscript{68}See Pharm. Research & Mfrs. of Am. v. Meadows, 304 F.3d 1197, 1207-08 (11th Cir. 2002) (discussing drugs that require prior authorization and exclusion from drug formularies).

\textsuperscript{69}See id. at 1208.

\textsuperscript{70}See Edmonds, 417 F. Supp. 2d at 1329 (detailing second type of prior approval program). The Medicaid Act does not authorize states to deny coverage this way, but only precondition coverage and reimbursement on a phone call from the prescribing physician. \textit{Id}. In addition, when there is no formulary in place, physicians are not required to heed the recommendation from the state to choose a different drug. \textit{Id}.

\textsuperscript{71}See id.

\textsuperscript{72}See Kesselheim, supra note 4, at 225. See also Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 351 (2001) (recognizing that physicians may prescribe medication and devices off-label); Nightingale Home Healthcare, Inc. v. Anodyne Therapy, LLC, 589 F.3d 881, 884 (7th Cir. 2009) (noting off-label prescribing is a "professional judgment"); Plyott v. La. Mun. Police Emps.' Ret. Sys., 74 A.3d 612, 614 (Del. 2013) (noting off-label use "is well known, and not illegal"); Philip Hickey, Ph.D., \textit{Submitting Claims for Off-label Prescriptions to Medicaid May Constitute Fraud, Behaviorism and Mental Health} (Sept. 12, 2013), http://www.behaviorismandmentalhealth.com/2013/09/12/submitting-claims-for-off-label-prescriptions-to-medicaid-may-constitute-fraud (discussing how off-label drug prescriptions are legal).

\textsuperscript{73}See Sandra G. Boodman, \textit{Off-Label Use of Risky Antipsychotic Drugs Raises Concerns, Kaiser Health News}, (March 12, 2012), http://www.kaiserhealthnews.org/stories/2012/march/13/off-label-use-of-risky-antipsychotic-drugs.aspx (noting the drastic increase in prescribing atypical antipsychotics). Antipsychotic drugs, notably Seroquel, Zyprexa, and Abilify, are prescribed off label for conditions not approved for by FDA, including behavioral problems in toddlers, anxiety, and attention-deficit disorder. \textit{Id}. In addition, "children ... in foster care, some less than a year old, are taking more psychotropic drugs than other children, including those with the severest forms of mental illness." \textit{Id}.

\textsuperscript{74}See Rosanne Spector, \textit{Evidence Lacking for Widespread Use of Costly Antipsychotic Drugs, Says Researcher, Stanford School of Medicine} (Jan. 6, 2011), http://med.stanford.edu/isrn/2011/january/antipsychotics.html (last visited Oct. 18, 2014). Many of these top-selling medications lack strong evidence that would indicate effectiveness off-label, and many safety issues arise with the off-label use of these drugs. \textit{Id}.
target of the most litigation under the federal False Claims Act.\textsuperscript{75}

**B. False Claims Act**

In regards to prescription drugs, pharmacies pay pharmaceutical companies via wholesalers and then pharmacies submit claims to Medicaid for reimbursement for the purchased drugs.\textsuperscript{76} When false claims are alleged, pharmacists are not held liable but physicians and pharmaceutical companies are held liable.\textsuperscript{77} Under the False Claims Act ("FCA"), liabilities are imposed against any person who:

- (A) knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval;
- (B) knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim; 
- (C) conspires to commit a violation [of any section A-G]. . .\textsuperscript{78}

In addition, the statute allows for \textit{qui tam} claims, where a private party brings an action on behalf of the government, naming a defendant for alleged violations of the

\textsuperscript{75} See \textit{id}. Many manufacturing companies have settled cases regarding these antipsychotic and psychotropic drugs or are under investigation regarding their reporting and marketing schemes. \textit{Id.} See, e.g., \textit{Johnson & Johnson to Pay More Than $2.2 Billion to Resolve Criminal and Civil Investigations, DEPARTMENT OF JUSTICE (Nov. 4, 2013), available at http://www.justice.gov/opa/pt/2013/November/13-ag-1170.html} (discussing Johnson & Johnson resolving criminal and civil liability from allegations of off-label promotion).

\textsuperscript{76} See 42 U.S.C. §§ 1396a(a)(23)(A), (32) (2012). States can also elect to administer the program and pay the upfront costs for which the federal government then reimburses. \textit{Id.}


FCA. Suits brought under the FCA focus on “three essential elements: (1) the defendant made a statement in order to receive money from the government, (2) the statement was false, and (3) the defendant knew it was false.”

While the FCA intends to hold physicians as well as pharmaceutical companies liable for their actions, the majority of prosecutions for false claims submitted to Medicaid for off-label prescriptions have been against pharmaceutical companies. FDA regulations bar pharmaceutical companies from promoting drugs for off-label purposes. FDA’s Office of Prescription Drug Promotion (“OPDP”) bears the responsibility of policing the information that pharmaceutical companies disseminate and identifying where violations occurred, especially misbranding of off-label drugs.

79 See United States ex rel. Lu v. Ou, 368 F.3d 773, 774 (7th Cir. 2004). The private party who brings the suit on behalf of the government is called a relator. See 31 U.S.C. § 3730 (2012). The United States may choose to intervene but it is not required to in order for the suit to move forward. Id. If the prosecution is successful, the private citizen, or relator is given a portion of the court award for bringing attention to the false claim. Id.

80 See United States ex rel. Crews v. NCS Healthcare of Ill., Inc. 460 F.3d 853, 856 (7th Cir. 2006) (citing United States ex rel. Gross v. AIDS Research Alliance-Chicago, 415 F.3d 601, 604 (7th Cir. 2005)).


82 See 21 U.S.C. §§ 301-397 (2012). See also Thompson v. W. States Med. Ctr., 535 U.S. 357, 368 (2002). FDA claims that three important governmental interests are achieved from prohibiting pharmaceutical companies from promoting drugs for off-label purposes. Id.

The first is an interest in "preserv[ing] the effectiveness and integrity of the... [FD&C Act's] new drug approval process and the protection of the public health that it provides." Brief for Petitioners 19. The second is an interest in "preserv[ing] the availability of compounded drugs for those individual patients who, for particularized medical reasons, cannot use commercially available products that have been approved by the FDA." Id. at 19-20. Finally, the Government argues that "achieving the proper balance between those two independently compelling but competing interests is itself a substantial governmental interest." Id. at 20.

Id. at 368 (quoting Brief for Petitioners).

83 See GOVT ACCOUNTABILITY OFFICE, GAO-08-835, PRESCRIPTION DRUGS: FDA'S
When violations are uncovered, FDA may pursue regulatory or criminal and civil enforcement actions against violating pharmaceutical companies through the Department of Justice ("DOJ"). Additionally, qui tam lawsuits are another avenue for pursuing actions against pharmaceutical companies who promote their drugs off-label.

United States ex rel. Franklin v. Parke-Davis is one of the major qui tam suits pursued against a pharmaceutical manufacturer for its off-label marketing tactics, in which a former employee of Parke-Davis was instructed to make false claims about off-label uses for the drug Neurontin. The case eventually settled when Warner-Lambert, Parke-Davis' parent company, agreed to pay $430 million in fines and pled guilty to promoting the drug off-label. United States ex rel. Garriy v. Novartis Pharm. Corp. serves as an example of the oversight of the promotion of drugs for off-label uses. This oversight process is limited, and "[the] FDA reports it is unable to review all submissions because of the volume of materials it receives..." Instead of a systematic manner to triage these submissions, FDA utilizes its staff to review submissions and make determinations of which violations to review. See generally The Office of Prescription Drug Promotion (OPDP), U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm (last visited Oct. 15, 2014) (discussing the mission of OPDP and how to submit requests for advisory).

See Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses, supra note 83. FDA issued forty-two warning letters to various pharmaceutical companies "in response to off-label promotions." Between 2003 and 2007, the DOJ has pursued both criminal and civil actions, none of which were identified by FDA, which have led to eleven major settlements.

Franklin was awarded approximately $24.64 million for his involvement as a whistleblower in the suit. Most importantly to the government's case, the "scheme deprived federally-funded Medicaid programs across the country of the informed, impartial judgment of medical professionals – judgment on which the program relies to allocate scarce financial resources to provide necessary and appropriate care to the poor." As a result of the settlement, Pfizer,
as another example of a *qui tam* suit in which Doctor Jeremy Garrity, the relator and a sales consultant for Novartis, alleged that the company failed to acknowledge an FDA warning letter cautioning Novartis of their improper off-label marketing techniques.88

Only one month after Garrity filed suit, Novartis settled and agreed to pay $422.5 million in civil and criminal fines, arguably because “[Novartis does not] have a legal leg to stand on.”89

These two companies are not the only ones to face litigation regarding misbranding off-label drugs.90 Unlike the previous examples of off-label marketing

Warner-Lambert’s parent company, agreed to institute a compliance program. *Id.*


89 *See Duff Wilson, *Novartis Settles Off-Label Marketing Case Over 6 Drugs for $422.5 Million, N.Y. TIMES, Oct. 1, 2010, at B5, available at http://www.nytimes.com/2010/10/01/health/policy/01novartis.html?_r=0* (noting Novartis guilty plea for off-label marketing). In addition to paying civil and criminal fines in the settlement, Novartis “also signed a five-year corporate integrity agreement with [HHS], which requires the company to monitor its sales practices and report any irregularities.” *Id.*

90 *See Gardiner Harris, *Pfizer Pays $2.3 Billion to Settle Marketing Case, N.Y. TIMES, Sept. 2, 2009, at B4, available at http://www.nytimes.com/2009/09/03/business/03health.html (discussing illegal marketing of Pfizer’s Bextra, a painkiller). The case involving Bextra has been Pfizer’s fourth settlement over illegal marketing activities since 2002 and was the largest settlement to date of this kind of case. Id.*

litigation, the most recent litigation has moved from pharmaceutical companies quickly settling to the introduction of arguments that these FDA regulations “cannot restrict truthful, non-misleading commercial speech promoting the use of a pharmaceutical product, even if off-label.” The Supreme Court in *Sorrell v. IMS Health Inc.* specifically noted that “[t]he First Amendment requires heightened scrutiny whenever the government creates a regulation of speech because of a disagreement with the message it conveys . . . Commercial speech is no exception.” Pharmaceutical companies continue to be prosecuted for false claims on the basis that they are marketing off-label to physicians and also providing kickbacks. Regardless of whether a company pursues an argument that they are practicing their First Amendment rights of free speech or settles the off-label marketing claim to avoid a costly and risky trial, patients are deprived of a process where physicians make impartial treatment decisions.

which it was not approved. *Id.* The suit eventually settled for $491 million in civil and criminal fines. *Id.*

91 See Marcia M. Boumil, *Off-Label Marketing and the First Amendment*, 368 NEW ENG. J. MED. 103, 104 (2013). Laws that have been discriminatory on the basis of the content of the message do not pass constitutional muster. *Id.* at 103. See also Boumil & Dunn, *supra* 88 (noting courts’ allowing pharmaceutical companies to use non-misleading commercial speech to promote drugs).

92 *Sorrell*, 131 S. Ct. 2664 (2011) (discussing regulation of First Amendment free speech). In *Sorrell*, the Supreme Court ultimately held that a Vermont statute prohibiting data mining of physicians’ prescribing habits violated the First Amendment. *Id.* Following in the wake of *Sorrell*, two further cases were decided. See *United States v. Harkonen*, 510 F. Appx. 633 (9th Cir. 2013) (discussing commercial speech under the First Amendment); *United States v. Caronia*, 703 F.3d 149 (2nd Cir. 2012) (noting use of commercial speech in promoting drugs off-label). The *Caronia* court specifically upheld the constitutionality of FDA’s misbranding provisions, stating, “any right Caronia had as Xyrem’s sales representative to express as commercial speech the truthful promotion of Xyrem’s off-label uses is not unconstitutionally restricted.” *United States v. Caronia*, 576 F. Supp. 2d 385, 402 (E.D.N.Y. 2008). The Second Circuit overturned Caronia’s conviction and held that “the government cannot prosecute pharmaceutical manufacturers and their representatives under the . . . [FD&C Act] . . . for speech promoting the lawful, off-label use of an FDA approved drug.” *Caronia*, 703 F.3d at 169. In *Harkonen*, the court upheld the conviction of wire fraud. *Harkonen*, 510 F. Appx. at 635-36. The chief executive officer at InterMune, a pharmaceutical manufacturer, issued a press release inaccurately representing conclusions of a medical study for the drug Actimmune, suggesting that the drug would be appropriate for an off-label use. *Id.* See also Press Release, FDA, Interferon gamma-lb (marketed as Actimmune) – Full Version (Mar. 5, 2007) available at http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm076951.htm (last visited Oct. 16, 2014). “Actimmune is a synthetic version of interferon gamma-lb, a naturally occurring biologic response modifier… approved… to decrease the number and severity of infections in patients with chronic granulomatous disease and to delay the progression of severe, malignant osteoporosis.” *Id.*

have not been held accountable for prescribing off-label drugs after a false claim has been submitted to Medicaid for reimbursement. In a system where physicians, not pharmaceutical companies and pharmaceutical sales representatives, make the final decision of which drug to prescribe their patients, the physician prescribing a drug off-label is not typically bearing some of the burden when an FCA claim is filed.

C. Litigation of Physicians Under the False Claims Act

Antipsychotics are often considered controversial not only because of their severe side effects but because the drugs are generally not FDA approved when used in pediatrics. Arguably, the most controversial use of antipsychotics occurs within pediatric settings. In 2006, Rebecca Riley, a four-year-old girl from Boston, was found dead as a result of an overdose of antipsychotic drugs she was taking as treatment for bipolar disorder and manic depression that were prescribed off-label. Due to lack of clinical testing and trials, it is often unclear how a child will react and metabolize a drug tested and approved for adults. Antipsychotics continue to be the source of rising concerns surrounding the practice of off-label prescribing in pediatrics.

95 See Law Project ex rel/ United States v. Matsutani, 454 F. App’x 644 (9th Cir. 2011) (noting suit against physician after pharmaceutical manufacturer was prosecuted was redundant and unnecessary).
96 See infra note 101-106 and accompanying text (discussing physicians facing responsibility for inappropriate prescribing practice)
97 See infra notes 98-100 and accompanying text (discussing use of antipsychotics in pediatric medicine).
98 See Sandra G. Boodman, Off-Label Use of Risky Antipsychotic Drugs Raises Concerns, KAISER HEALTH NEWS (March 12, 2012), http://www.kaiserhealthnews.org/stories/2012/march/13/off-label-use-of-risky-antipsychotic-drugs.aspx (discussing use of antipsychotics in pediatric medicine). “Antipsychotics . . . were typically prescribed to children to control disruptive behavior, which often stemmed from their impoverished, chaotic or dysfunctional families... Sedation is the key reasons these meds get used.” Id. (internal quotation marks omitted).
99 See Kyra Darnton, What Killed Rebecca Riley?, 60 MINUTES (last visited Oct. 16, 2014), http://www.cbsnews.com/stories/2007/09/28/60minutes/main3308525_page2.shtml. Doctors prescribed Rebecca three different drugs for bipolar disorder, Seroquel, Depakote, and Clonidine, after a number of sessions over eight months with a doctor at Tufts-New England Medical Center. Id. Rebecca was prescribed more than ten pills a day. Id. These sessions were prompted when Rebecca, at the age two, was “[c]onstantly getting into things, running around, [and] not being able to settle down.” Id. (internal quotation marks omitted). Riley’s parents were charged with first-degree murder. Id. Additionally, Rebecca’s brother, 10 years old, and her sister, four years old, were being treated for bipolar disorder. Id. The prosecutor in this case alleged that Rebecca’s parents were overmedicating her in order to make her and her siblings sleep. Darnton, supra.
100 See id. One physician notes that physicians “don’t really know how these drugs interact or effect [sic] developing brains because most are being used off-label, which means they haven’t been approved by the FDA for use in children.” Id.
101 See Ed Silverman, False Claims, Off-Label Prescribing and Doctors, Part Two, PHARMALOT, (Sept. 4,
In *United States ex rel. Law Project for Psychiatric Rights v. Matsutani*, the Law Project for Psychiatric Rights ("PsychRights") filed a suit under the False Claims Act naming state officials, psychiatrists, pharmacies, hospitals, and mental health agencies as defendants for filing claims for off-label prescriptions.102 In *United States v. King Vassel*, Dr. Toby T. Watson, a *qui tam* relator, sued Dr. Jennifer King-Vassel for filing false claims for off-label prescriptions under the False Claims Act.103 The commonality between these two cases is the fact that the suits were not filed against pharmaceutical companies, but instead and most importantly, against physicians.104 These are both rare cases in the history of Medicaid fraud lawsuits, since suits are generally not filed against physicians under the False Claims Act for off-label prescribing.105

While *United States ex-rel Law Project for Psychiatric Rights v. Matsutani* was decided

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103 See United States v. King-Vassel, 728 F.3d 707, 710 (7th Cir. 2013). Dr. Toby T. Watson, who initiated the *qui tam* suit, identified forty-nine prescriptions that fall within the category of false claims. *Id.* at 709. Watson filed this suit after reaching out to N.B., a juvenile who had been seen and prescribed off-label drugs by King-Vassel. *Id.* at 709-10. The district court granted summary judgment for King-Vassel on the basis that Watson needed an expert witness regarding the Medicaid claim process, and to determine the alleged false claims were “false” under the FCA definition. *Id.* at 710. However, the Seventh Circuit disagreed, finding an expert witness would not be necessary in this case. *Id.* The court further noted expert witnesses “may be required for matters that are beyond the common understanding of a lay juror.” *Id.* at 712.

104 See King-Vassel, 728 F.3d at 708 (describing background information of case, initiated against a psychiatrist); Law Project ex. Rel. United States v. Matsutani, 454 Fed. Appx. 644 (9th Cir. 2011).

105 See Silverman, supra note 101. Generally, the government finds suing physicians futile because the damages are not as great as when pursuing suits against pharmaceutical companies. *Id.*
and ultimately dismissed, *United States v. King Vassel* is currently good law, though on appeal the law was found to establish a responsibility for physicians in the prescriptions they write.\(^{106}\) The district court initially granted the motion for summary judgment but the Seventh Circuit subsequently reversed the decision.\(^{107}\) Unlike the district court, the Seventh Circuit stated, "Watson [the relator] need only show that King-Vassel [the physician] had reason to know of facts that would lead a reasonable person to realize that she was causing the submission of a false claim . . . or that King-Vassel failed to make a reasonable and prudent inquiry into that possibility."\(^{108}\) The Seventh Circuit believed Watson could show that a "rational jury [could] find that King-Vassel showed reckless disregard to the existence of a potentially false claim."\(^{109}\) The court first looked to King-Vassel's state of mind, noting that the 'knowingly' aspect of the statute is not simple.\(^{110}\) After significant discussion, the Seventh Circuit stated that relator Watson did

\(^{106}\) *Compare* United States ex-rel Law Project for Psychiatric Rights v. Matsutani, 454 Fed. Appx. 644 (9th Cir. 2011) *with* United States v. King-Vassel, 728 F.3d 707, 713 (7th Cir. 2013) (discussing *King-Vassel* as a viable suit, unlike *Matsutani*). See also Silverman *supra* note 101 and accompanying text (discussing role of medical professionals involved in illegal practice of prescribing off-label drugs). Attorney Jim Gottstein filed *Matsutani's qui tam* claim, arguing that federal agencies should be applying the False Claims Act in a way to "make it possible to crack down on inappropriate prescribing by doctors . . ." which he believes will make it much more difficult for pharmaceutical companies to persuade physicians to write off-label prescriptions. Silverman, *supra* note 101.

\(^{107}\) See United States v. King-Vassel, 2012 U.S. Dist. Lexis 152496, at *15 (E.D. Wis. Oct. 23, 2012) (describing procedural posture of the case). The District Court for the Eastern District of Wisconsin granted Dr. King-Vassel's motion for summary judgment on the grounds that the relator, Dr. Toby Watson, failed to submit the name of an expert witness to testify as to how Medicaid reimbursements are processed and whether Dr. King-Vassel received these reimbursements, as well as "the off-label nature of the prescriptions made." *Id.* The court noted that "[t]his is a confusing way of arguing that Dr. Watson has not made the requisite showing to establish an actual Medicaid fraud." *Id.*

\(^{108}\) See *King-Vassel*, 728 F.3d at 713. *See also supra* note 80 and accompanying text (explaining three essential elements to prove violation FCA).

\(^{109}\) See *King-Vassel*, 728 F.3d at 713. Specifically, Watson filed "an affidavit from Christine Maxwell Meyer, N.B.'s mother . . . that, if believed, could lead a rational jury to find that King-Vassel showed reckless disregard to the existence of a potentially false claim." *Id.* In the affidavit, Meyer explained that she gave King-Vassel N.B.'s Medicaid information. *Id.* Additionally, she "never paid out of pocket" for any of N.B.'s appointments and King-Vassel never suggested that Medicaid had not been billed for those appointments. *Id.* When filling prescriptions, Meyer "always used [her] medical assistance card to pay for N.B.'s medication," which was verified by records from the Wal-Mart where the prescriptions had been filled. *Id.* Watson failed to produce records indicating King-Vassel had been paid by Medicaid. *Id.*

\(^{110}\) See *King-Vassel*, 728 F.3d at 712. Under the FCA, King-Vassel must have acted with actual knowledge, deliberate ignorance, or reckless disregard when submitting these potentially false claims, but not necessarily with the specific intent to defraud Medicaid or the applicable state agency. *Id.* When determining whether to further define the phrase, "reckless disregard," the court has found no need to further define the phrase, other than saying "innocent mistakes or negligence" are not included. *Id.*
not need an expert to establish King-Vassel's state of mind in the submission of the alleged claims, but instead to show King-Vassel "had reason to know of facts that would lead to a reasonable person to realize that she was causing the submission of a false claim. . . or that [she] failed to make a reasonable and prudent inquiry into that possibility." The court, focused on the fact that it is a "prerequisite that the defendant have actually caused the submission of the false claim." The court reversed and remanded the district court's grant of summary judgment, leaving a viable claim for the district court to decide.

III. Analysis

While physicians are legally permitted to prescribe medication off-label, it is increasingly clear that unregulated use of these medically unsupported prescriptions undermines FDA's mission to protect patients. The continued unregulated use of off-label drugs, which are medically unsupported, will continue to harm children.

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111 See id. at 713. The court noted that Watson had an affidavit and supporting records that if believed, would show King-Vassel's reckless disregard. Id. The facts in the affidavit are within the scope of the declarant's personal knowledge. Id. at 713 n.1. Additionally, the court stated that while "including expert testimony would no doubt make many cases stronger," here they did not believe that "King-Vassel's state of mind [was] beyond the common understanding of the common juror." King-Vassel, 728 F.3d at 713.

112 Id. at 712. This prerequisite is a proximate cause issue, therefore, if there were an event that broke the "chain of causation," King-Vassel should not be found liable. See id. at 714; Restatement (Second) of Torts § 443 (1965) (discussing superseding events breaking chain in proximate causation). However, a "reasonably foreseeable intervening force" will not supersede the defendant's liability. See King Vassel, 728 F.3d at 714. In this case, the Seventh Circuit believed the potential intervening superseding factors were "reasonably foreseeable," and thus may not break the "chain of causation." Id. In addition, the court did not find that the Medicaid reimbursement process caused a "proximate cause problem" itself. Id. at 714-15. The court concluded that the jury did not need expert testimony to understand the process of getting a prescription through Medicaid and the likelihood that the prescription will be reimbursed by Medicaid. Id. at 715.

113 See King-Vassel, 728 F.3d 707.

114 See supra note 9 and accompanying text (explaining FDA as "oldest comprehensive consumer protection agency in the U.S. federal government"). See also supra note 27 and accompanying text (noting doctors' limitations in their ability to make educated guesses when prescribing off-label drugs to children); Rodwin, supra note 30, at 655. Specifically, FDA exists to "protect patients from dangerous and ineffective drug therapies." Rodwin, supra note 30, at 655. In addition, "[u]nmanaged off-label drug use... compromises the medical ideal that physicians should prescribe medications based on careful evaluation of the risks and benefits." Id. See supra note 44 and accompanying text (noting the importance of clinical research in pediatric medicine). This harm may not be immediate and it may not be to the individual child who is being prescribed a drug; rather the harm may be society-wide, as clinical research studies are not performed in order to have drugs produced on label for pediatric medicine. See supra note 44 and accompanying text.

115 See supra note 114 and accompanying text (noting possible dangers off-label drugs pose for
complication arising for physicians is the lack of on-label drugs available for pediatric prescribing. The major issue that patients and FDA face is that drugs are prescribed inappropriately to children, specifically off-label, without the appropriate indications indicating that the drug can be beneficial, rather than innocuous or harmful.

FDA, from the point of its inception to the present, has maintained its mission to protect patients from mislabeled and potentially dangerous drugs through regulatory measures and has made significant recent efforts in pediatrics. Thus far, the steps taken have been less than successful, indicating a need for change. Specifically, physicians must be held accountable for prescribing off-label drugs when there is little or no information supporting the efficacy of the drug. Pharmaceutical companies must research and test drugs for the pediatric market, as well as expand labels to include pediatrics, which would enable physicians to prescribe drugs with more confidence that the drugs will be safe and effective for the indicated purpose.

A. Deterring Physicians From Prescribing Unsupported Off-Label Drugs

Thus far, the government has not been entirely successful in deterring...
pharmaceutical companies from using aggressive marketing methods to enhance the off-label sales of their drugs. With each concluded litigation or settlement, another suit is brought against another pharmaceutical manufacturer alleging similar FCA issues and the company's off-label marketing scheme to produce greater sales based on off-label use. In United States ex rel. Franklin v. Parke-Davis, the relator filed the action as a result of Parke-Davis's campaign using false statements to promote physicians prescribing certain drugs for off-label uses for which there was no indication of the drug's effectiveness. Since Parke-Davis, over twenty actions for off-label drug promotion have been filed and subsequently settled. Naturally pharmaceutical companies bear a significant amount of responsibility for promoting off-label drugs, when these companies are actively reaching out to physicians and knowingly causing violations of the FCA. However, allowing the physician to escape unscathed from litigation without consequence contradicts the purpose of the FCA. Litigation would not have occurred had the physician not prescribed an off-label drug, unsupported by FDA approved indications.

By prescribing a drug off-label without support of accepted indications in the relevant compendia, physicians behave in a similar manner to pharmaceutical companies and should be held accountable. When a physician prescribes an off-label drug,}

122 See supra note 82, 88, 100 and accompanying text (showing sheer number of FCA actions against pharmaceutical companies that have been decided or settled). See also supra note 90 (noting Pfizer's involvement in bulk of off-label marketing suits, four suits from 2002-2009).

123 See supra note 82, 88, 100 and accompanying text (noting various FCA claims filed against different pharmaceutical companies without deterring other companies).


125 See supra notes 82, 88, 100 and accompanying text (noting FCA claims that have been filed and subsequently settled).

126 See supra notes 82, 88, 100 and accompanying text (discussing various FCA claims against pharmaceutical companies).

127 Supra notes 104, 105 and accompanying text (discussing new approach to FCA claims by holding physicians accountable when they prescribe drugs off-label).

128 Supra notes 104, 105 and accompanying text (discussing new approach to FCA claims by holding physicians accountable when they prescribe drugs off-label). See supra note 78 and accompanying text (noting harm cannot be hypothetical and false claim must be submitted for litigation).

129 See Thompson v. W. States Med. Ctr., 535 U.S. 357, 368 (2002) (noting most important government interests achieved by prohibiting pharmaceutical companies from promoting off-label drugs). Arguably, these interests can also be achieved if the government were to prohibit physicians from prescribing off-label drugs that are not indicated in any of the compendia for the purpose they are being used for. Id. See also Philip Hickey, Submitting Claims for Off-label Prescriptions to Medicaid May Constitute Fraud, (Sept. 12, 2013), http://www.behaviorismandmental
specifically when the drug is unsupported by clinical trial data or approved indications, the physician is aware that the prescription is not being used for its contemplated purpose. In situations in which the patient's medical bills are covered by Medicaid and physicians choose to prescribe off-label drugs that are not supported by medically accepted indications, physicians know that the claim will eventually be processed and paid for by the government, and thus might violate the FCA.

In United States ex-rel Law Project for Psychiatric Rigbts v. Matsutani, the court incorrectly dismissed the case on the basis that the pharmaceutical manufacturer had already been prosecuted for FCA violations and the government had already recovered a significant amount of money. In Matsutani, the physician's off-label actions were of no importance to the court because the amount of damages paled to those of the pharmaceutical manufacturer. Additionally, by only prosecuting pharmaceutical companies, physicians can justify the practice of prescribing improper off-label drugs to children knowing there will be no ramifications to them. By allowing physicians to escape liability for their own actions, the cycle of pharmaceutical companies marketing drugs for off-label purposes and giving kickbacks to physicians for prescribing those drugs will continue. When physicians escape repercussions for off-label prescribing when unsupported by any studies or evidence, there is nothing to deter physicians from continuing to prescribe such drugs to children.

health.com/2013/09/12/submitting-claims-for-off-label-prescriptions-to-medicaid-may-constitute-fraud. See also Slade, supra note 77 (noting physicians and pharmaceutical manufacturers liable for false claims involving events causing false claims).

See Sutter, supra note 4 (noting "[p]hysicians can prescribe any drug for any . . . condition, even . . . for so-called "off-label" use").

See supra note 58 and accompanying text (describing Medicaid implemented through states but funded through both state and federal government); See Hickey, supra note 59 (explaining when physician may be held liable under FCA).

See United States ex rel. Law Project for Psychiatric Rights v. Matsutani, 454 Fed. Appx. 644 (9th Cir. 2011); supra note 106 (arguing physicians should be held accountable for inappropriately prescribing off-label drugs).

See supra note 102 and accompanying text (noting government negotiated large pharmaceutical manufacturer settlement, court did pursue FCA claims further).

See supra note 102 and accompanying text (describing claim against physician was dismissed because claim against pharmaceutical manufacturer already pursued and settled). Compare supra notes 86-90 and accompanying text (detailing various cases that have been filed against pharmaceutical companies) with supra note 105, 106, and accompanying text (highlighting only two off-label prescribing cases filed against physicians, demonstrating government belief suing physicians not worth time).

See supra note 105 and accompanying text (noting claim rarity against physicians due to government's incentive of pursuing pharmaceutical manufactures' deeper pockets).

See supra notes 99-101, 105 and accompanying text (noting government continues to neglect freedom for prescribing off-label drugs, collectively endangering targeted patients).
The court in United States v. King-Vassel has given potential to these new types of claims against physicians, compared to the court in United States ex rel. Law Project for Psychiatric Rights v. Matsutani, where the claim against the prescribing doctor was dismissed because a different relator had sued the pharmaceutical manufacturer. While off-label claims submitted to Medicaid for reimbursement are not per se false claims, the new possibility for these types of claims will be fact based to decide whether or not a claim is false. By analyzing all the facts surrounding off-label prescriptions seeking Medicaid reimbursement, courts will now be able to address the increasing concern that doctors prescribe inappropriate drugs for children. Courts will have the ability to decrease false claims for off-label prescriptions, while holding physicians accountable for their actions. Additionally, it is still appropriate to charge pharmaceutical companies in false claims litigation if these companies contributed to persuading the physician to write a prescription through inappropriate marketing techniques.

B. Challenges With FDA

While both physicians and pharmaceutical companies may bear blame for prescribing and promoting drugs off-label, FDA is not entirely absolved from responsibility. Specifically, FDA has been informed of numerous occasions where pharmaceutical manufacturing companies are in violation of the FCA because of the companies' marketing and promotion for unapproved uses for off-label drugs. Additionally, FDA has been informed of drugs' warning labels that are not worded

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137 Compare United States ex-rel. Law Project for Psychiatric Rights v. Matsutani, 454 Fed. Appx. 644 (9th Cir. 2011), with United States v. King-Vassel, 728 F.3d 707 (7th Cir. 2013). In King-Vassel, the Seventh Circuit disagreed with the district court, concluding that that the suit should not be decided by summary judgment. 728 F.3d at 717.


139 See generally id.

140 See supra note 106 and accompanying text (focusing litigation on prescribing doctors will hinder pharmaceutical manufacturers' influence on doctors' prescribing off-label drugs).

141 See supra note 90 and accompanying text (believing FCA claims filed were legitimate and companies needed to be prosecuted for illegal activity).

142 See supra note 126-128 and accompanying text (arguing physicians and pharmaceutical companies bear significant blame in use off-label drug prescriptions). See also supra note 83-84 and accompanying text (describing the FDA's lack of systematic review of FCA allegations).

143 See U.S. Gov't Accountability Office, Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses, GAO-08-835 (2008), available at http://www.gao.gov/assets/280/278832.pdf (describing how the FDA is unable to handle the sheer number of submissions for the promotion of off-label drugs and therefore has no systematic way to review the submissions, though suggestions have been made).
strongly enough, but has often failed to require the strengthening of warning labels.\textsuperscript{144}

While FDA predominately satisfies its mission, the specific areas that are lacking must be addressed, possibly with the suggestions that have already been given to improve oversight.\textsuperscript{145} Specifically, FDA should implement a systematic approach for its staff to review and categorize all reports of alleged promotion of off-label uses for drugs.\textsuperscript{146} Additionally, when physicians voice concerns regarding warning labels not being strong enough, FDA should follow through and take action or provide justification as to why no action was taken.\textsuperscript{147} With improved resources for reviewing submissions of alleged off-label uses and means of communicating action when reviewing warning labels’ strength, FDA may not prevent all off-label marketing and inappropriate prescribing but policing these violations will become more streamlined and systematic, enabling FDA to ensure review of these areas of concern.\textsuperscript{148}

C. Increase the Number of On-Label Drugs for Pediatric Use

Ultimately, a streamlined and systematic review process for allegations of false claims is important and FDA must focus its attention to increase the number of on-label pharmaceutical options for the pediatric market.\textsuperscript{149} The pediatric market comprises a small fraction of the population, thereby constituting a vulnerable population.\textsuperscript{150} At least 65% of drugs prescribed to children lack adequate information regarding dosage

\textsuperscript{144} See Injury Lawyers News, supra note 3 (noting physicians bringing up concerns to FDA about strength of warning labels in certain drugs).

\textsuperscript{145} See supra note 142 and accompanying text (articulating FDA’s review of FCA allegations).


\textsuperscript{148} See supra note 83-84 and accompanying text (discussing FDA lacking systematic review process for reviewing alleged false claims).

\textsuperscript{149} See supra note 83-84 and accompanying text (discussing FDA lacking systematic review process for reviewing alleged false claims); see Mackey, supra note 24, at 15-16 (highlighting FDA's failure to implement incentives to expand approved labeling for vulnerable populations, like children).

\textsuperscript{150} See Mackey, supra note 24, at 16. Children are similar to orphan disease patients because they comprise a small portion of the population, and thus are vulnerable because there is a “lack [of] access to crucial information regarding treatment options.” Id. at 3.
and safety. Instead of relying on FDA mandated labeling to ensure the proper dosage for their patients, physicians make educated guesses using various factors, including age, body weight, and height to determine the prescription dose. In such a vulnerable market, it is dangerous and inappropriate for children to be placed at risk when their medication may have undetected hazardous side effects because the necessary research and clinical trials were not conducted.

Off-label use may be the standard of care among pediatricians and arguably can be the right course of treatment in many situations. However, when physicians are prescribing off-label drugs that are unsupported by research studies or evidence, they potentially put patients at risk without knowing the ramifications of their actions, similar to how research was conducted before standards of clinical trials were put in place. While courts do not find off-label prescribing to be a false claim per se, there are situations that arise where off-label prescriptions can turn into false claims within the meaning of the FCA.

While off-label prescriptions are not defined as per se false claims, off-label drug use should not be the standard but instead the exception. Physicians should prescribe drugs to their patients with compelling evidence that a specific drug will do what the physician intends for it to do. The challenge arises when how physicians should prescribe based on approved indications conflicts with how physicians actually

151 See Fernandez Lynch, supra note 4; Sutter, supra note 4 (noting about 90% of neonatal care drugs lack “neonatal-specific [drug labeling] information”).
153 See Kesselheim, supra note 4 at 225 (describing once FDA approves drug, FDA cannot control how physicians actually prescribe); Fernandez, supra note 4 at 82-83 (believing lack of appropriate clinical research data could have toxic or harmful effect on child). See also Mackey, supra note 24 at 17 (noting physicians use trial and error to determine what they believe is correct pediatric dosage).
154 See supra note 4 and accompanying text (providing examples how physicians view and use off-label drugs).
155 See supra note 74 (noting lack of information regarding drugs used off-label and safety issues that arise); supra section III.A (describing requirements of off-label prescriptions for patients to be reimbursed by Medicaid); supra notes 41-42 and accompanying text (raising significant abuse that occurred in pediatric research from 1800s-1970s).
157 See id; Rodwin, supra note 30, at 654.
158 See AMERICAN ACADEMY OF PEDIATRICS, supra note 4 (reporting dosing based on evidence constitutes good medical practice); Fernandez, supra note 4, at 82-83 (discussing how off-label prescriptions may be ineffective or dangerous).
prescribe based on the limited number of on-label drugs that are indicated for use in pediatric medicine.159 Within the off-label market, adults have the benefit of using medications tested on other adults and in turn, physicians generally are able to hypothesize how drugs will affect individuals and have evidence for that hypothesis.160 On the other hand, the majority of all approved medications have not been tested on children and thus the pediatric population is unable to determine how the individual patient will react, except by trial and error.161

Interestingly, there has been an increasing focus on the pediatric drug market.162 There has not been a correlative jump in the number of drugs approved for the pediatric market in comparison to initiatives that have been put into place.163 These initiatives should persuade and entice pharmaceutical companies to increase studies on already approved drugs for different indications but that has not been the case.164 Instead of increasing the number of drugs approved for the pediatric market, less action has been taken than should have been expected, indicating that pharmaceutical companies are not complying with initiatives and legislation.165 Another indication that may be gleaned from the fact that a limited increase of drugs on-label has been observed is that parents and guardians are still uncomfortable and ill-informed regarding how clinical pediatric research is conducted.166 Without parents who are willing to permit their children to take part in clinical trials, medications cannot become FDA approved and labeled for use in pediatrics.167 Regardless of why there has not been an increase in pediatric indications, FDA must push for more effective legislation requiring pharmaceutical

159 See supra note 4 and accompanying text (highlighting limited number of on-label drugs are available in pediatrics).
160 See Smolin, supra note 4, at 629 (raising drugs used off-label in pediatrics generally never been tested in pediatric population); Fernandez, supra note 4, at 82 (noting prescribing off-label drugs may not have useful outcomes).
161 See Smolin, supra note 4, at 629 (explaining unreliability of applying adult research results concerning off-label use to children); Fernandez, supra note 4, at 82. Many drugs have not been tested in pediatrics and physicians lack information regarding dosage for infants and children for off-label drugs. Id.
162 See supra notes 20-25 and accompanying text (noting various programs and laws put into place specifically for pediatric market).
163 See Fernandez, supra note 4, at 92-93. The amendment to FD&C Act was intended to persuade pharmaceutical companies to research pediatric effectiveness and safety, but sponsors chose not test for pediatric effectiveness and safety in order to reduce the cost of studies. Id.
164 See id.
165 See id.
166 See supra notes 54-57 and accompanying text (describing parents making decisions for their children continue to lack full understanding of pediatric clinical trials).
167 See supra notes 54-57 and accompanying text (noting parents must make decisions regarding pediatric clinical trials for their children).
manufacturers to conduct pediatric studies. Additionally, FDA must implement standardized methods to effectively communicate with parents to ensure they understand the risks and value of participating in studies.

IV. Conclusion

Prescribing medications off-label should be the exception and not the norm when dealing with the vulnerable pediatric population, to ensure that physicians prescribe drugs that are not only appropriate for their illness or condition but are also safe and effective. Currently, on-label pediatric prescriptions are relatively rare. Physicians are fortunate when they are able to prescribe a drug that has been tested in pediatric clinical trials. In the current market, FDA is forced to deal with the difficulties in implementing standards and legislation relating to the enforcement of FDA’s mission of protecting the public’s health through drug safety standards and advancing public health through drug innovations.

Both pharmaceutical companies and physicians are able to take a significant amount of responsibility for these difficulties. Pharmaceutical companies have focused their attention on marketing drugs for unapproved and off-label purposes, though not substantially increasing their pediatric pharmaceutical research, while physicians inappropriately prescribe off-label drugs for uses that are not approved or are not supported by evidence. Pharmaceutical companies, at least have been penalized for their inappropriate marketing methods and the government has recovered a significant amount of money for these companies' behavior. Physicians, on the other hand, have escaped unscathed with little prosecution surrounding their improper practices of prescribing off-label drugs which are unsupported by medically accepted indications in the compendia. While FDA is not responsible for oversight of doctors' prescribing habits, FDA does become informed of possible FCA violations through its violations triage process. Without holding physicians accountable for their own prescribing practices, FDA’s mission of protecting public health and promoting new technologies to increase public health cannot be realized. Physicians must be held accountable, like pharmaceutical companies, as they actually prescribe the off-label drug that is medically unsupported in the compendia and are ultimately the reason pharmaceutical companies are subject to prosecution under the FCA. Instead of only prosecuting the most lucrative claims against pharmaceutical manufacturers, the DOJ should additionally seek

168 See supra note 51 and accompanying text (arguing need for equal access to on-label drugs for pediatrics).
169 See supra notes 56-57 and accompanying text (raising reasons why parents are confused or unable to remember specifics about clinical research trials).
claims that might legitimately have potential to deter the practice of writing off-label prescriptions which have no medically accepted indications, the likely candidate being the prescribing physician.

Physicians and pharmaceutical manufacturing companies are responsible for the dangerous practice of prescribing and marketing off-label drugs with no clinical trials to verify safety or efficacy. FDA is not an entirely innocent party. The current process of reviewing false claims lacks practicality and ignores the flawed review process, which is especially harmful to the pediatric market. By listening to suggested improvements, FDA will be more likely to address allegations of false claims, thus enforcing its own mission and protecting those who are most vulnerable in the market.

Until these steps are taken, vulnerable patients, especially the pediatric population, face the unnecessary risk of obtaining prescriptions for medications which may be ineffective and possibly dangerous. State Medicaid programs will continue to be defrauded and lose money with submissions for reimbursement of an off-label drug with no approved indication. Without change, there will likely continue to be only limited production of drugs that are tested and approved for the pediatric market. If on-label drugs are introduced into the pediatric market, this vulnerable class of patients will have access to healthcare that does not compromise medical ideals and will have access to drugs that can be prescribed with empirical research verifying its safety and effectiveness.