

BALANCING ON THE EDGE: THE IMPLICATIONS AND ACCEPTABILITY OF OFF-LABEL DRUG USE

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I. INTRODUCTION

Off-label drug use presents a unique paradox: it can both aid and harm the patient. Typically, the Food and Drug Administration (“FDA”) has an arduous process for pharmaceutical companies to go through to have a drug approved. The purpose of this is to certify the safety and efficacy of the drug. However, the use of off-label drugs, those that are not used for the approved indications by the FDA on the label, is prevalent. Estimates have shown that off-label drug use varies extensively from 21% to over 50% for specific medications or drug classifications.² The study further noted that some uses were a “logical extension” while others were “therapy for indications distinctly different from those for which the drug was approved.”³ Off-label drug use thus falls in the gray area between constituting human experimentation and a widely accepted practice by physicians.

Off-label drug use is rarely examined with exacting scrutiny in the law. Off-label drug use is itself legal. With a few exceptions, the law generally only prohibits manufacturers from advertising off-label drug use.⁴ Rather, off-label use is a widely accepted practice among physicians and often considered the standard of care.⁵ Typically, scientific evidence supports the use of off-label drug use; however, this is not always true.⁶

This paper argues that while off-label use does not necessarily fall under the laws of human experimentation, the discrepancies in the laws concerning off-label drug use for the manufacturers and the doctors fails to adequately protect the patient. The laws are contradictory by allowing physicians to use off-label drugs but prohibiting the manufacturer from advertising off-label drug use. Part I of the paper will explain the regulatory process of the

² David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1025 (2006); see also Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J. L. SCI. & TECH. 61, 61 (2008).

³ Radley, *supra* note 2, at 1025.

⁴ See *United States v. Caronia*, 576 F. Supp. 2d 385, 392 (E.D.N.Y. 2008). See generally 21 C.F.R. § 99.101 (2008) (listing the conditions that the manufacturer must comply with before disseminating any information concerning the off-label use).

⁵ Johnson, *supra* note 2, at 61–62.

⁶ See Radley, *supra* note 2, at 1021 (stating scientific evidence supporting off-label use is often less than what the drug manufacturer is required to produce to obtain FDA approval).

FDA, define the relevant terms, explain the benefits and harms of off-label drug use, and look to the physician's outlook on the use of off-label drugs. Part II of the paper will examine the legal restraints and the legal context in which off-label drug use arises. Part III will analyze the ethical implications of off-label drug use, balancing the competing interests at stake. Part IV analyzes the paradoxes in off-label drug use and the tenable proposition that the use of off-label drugs does not constitute human experimentation. Finally, Part V of this paper proposes a way in which the process should theoretically work—arguing that a new standard and regulations should govern the beginning stages of off-label drug use before the use is considered the standard of care.

II. SEMANTICS IN THE PROCESS

A. *The History of the FDA*

The Food and Drug Administration Act (“FDA Act”) was passed in 1906 because of public outcry for regulation of consumer products.⁷ “This law (1) required that drugs meet official standards of strength and purity, (2) defined the terms *adulterated* and *misbranded*, and (3) prohibited the shipment for sale of misbranded and adulterated foods, drinks, and drugs.”⁸ Regulation continued and in 1938, Congress passed the Federal Food, Drug, and Cosmetic Act of 1938 (“FDC Act”) in response to the accidental deaths of 107 persons in 1937 from “elixir sulfanilamide.”⁹ It is here that prescription medications became distinguished from other medications.¹⁰ Furthermore, the FDC Act passed the following provisions:

[e]xtending control to cosmetics and therapeutic devices[;]
r]equiring new drugs to be shown safe before marketing-starting a new system of drug regulation[; e]liminating the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases[; p]roviding that safe tolerances be set for unavoidable poisonous substances, authorizing standards of identity, quality, and fill-of-container for foods[; a]uthorizing

⁷ Martin S. Lipsky & Lisa K. Sharp, *From Idea to Market: The Drug Approval Process*, 14 J. AM. BOARD FAM. MED. 362, 363 (2001). Upton Sinclair's novel *THE JUNGLE* brought to light the base nature of the meatpacking industry and called for regulation.

⁸ *Id.*

⁹ *Id.*

¹⁰ *Id.*

factory inspections[;] adding the remedy of court injunctions to the previous penalties of seizures and prosecutions.¹¹

The FDC Act of 1938 marked the beginning of the change in the FDA and the future role that the FDA would play in regulating drugs and other devices.

A few years later in 1950, the U.S. Court of Appeals for the Ninth Circuit enforced the FDA regulations by requiring a drug's label to "state the purpose or condition for which the drug was intended."¹² The importance of truthful and accurate labeling was finally realized. Further regulation ensued in the passing years as the FDA began to regulate and control the abuse of barbiturates and amphetamines.¹³ In 1962, the Kefauver-Harris Amendment passed and required manufacturers to provide proof of effectiveness and safety of the drugs and known side effects.¹⁴ Again, this resulted from another terrible incident. Thalidomide was being given to pregnant women and resulted in "grossly deformed newborns."¹⁵ The FDA responded by increasing the regulation around drug trials and granted greater access to the FDA into manufacturer's records and production.¹⁶ In 1988, the Prescription Drug Marketing Act ("PDMA") was passed, banning the alteration and resale of prescription drugs and requiring them to be from licensed drug wholesalers.¹⁷ It also banned the "sale, trade or purchase of drug samples, and traffic or counterfeiting of redeemable drug coupons" and "restrict[ed] reimportation from other countries."¹⁸ After years of passing regulations focusing on the safety and efficacy of the drugs, Congress recognized the need to reevaluate the process and structure regarding drugs and passed an amendment in 1997.¹⁹ The 1997 FDA Modernization Act ("FDAMA") cut the review

¹¹ U.S. Food & Drug Admin., Milestones in U.S. Food and Drug Law History, <http://www.fda.gov/opacom/backgrounders/miles.html> (last visited Oct. 28, 2009).

¹² *Alberty Food Prods. Co. v. United States*, 185 F.2d 321, 326 (9th Cir. 1950).

¹³ U.S. Food & Drug Admin., History of the FDA: Drugs and Foods Under the 1938 Act and Its Amendments, <http://www.fda.gov/oc/history/historyoffda/section3.html> (last visited Oct. 28, 2009).

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ U.S. Food & Drug Admin., Prescription Drug Marketing Act, <http://www.fda.gov/cder/regulatory/PDMA/default.htm> (last visited Oct. 28, 2009).

¹⁸ U.S. Food & Drug Admin., *supra* note 11.

¹⁹ *See id.* (stating that the Food and Drug Administration Act, enacted in 1997, was one of "the most wide-ranging reforms in agency practices since 1938.").

schedule time and revised the longstanding policy on off-label information.²⁰ All of these amendments demonstrate the slow progress in evaluating drugs and also demonstrates how the system ultimately fails to act proactively. This failure notes the need for a new look and further regulation for off-label drug use as the recent 1997 amendment did not go far enough to address the key issues behind off-label use.

B. The FDA Approval Process

The actual process to have a drug approved requires the manufacturer to submit an Investigational New Drug Application to the FDA for purposes of “provid[ing] . . . data showing that it is reasonable to begin tests of a new drug on humans.”²¹ To begin, the manufacturer submits information regarding pre-clinical studies that show animal pharmacology and toxicology studies, manufacturing information pertaining to the composition, manufacturer, stability and controls, and clinical protocols and investigator information.²² After this initial phase, clinical trials take place in phases 1, 2, and 3.²³ Phase 1 occurs in healthy volunteers and is “designed to determine the metabolic and pharmacological actions of the drug[s] in humans, the side effects . . . [and] to gain early evidence on effectiveness.”²⁴ Seventy-percent of the drugs pass Phase 1.²⁵ Phase 2 conducts further studies to determine effectiveness and to study “short-term side effects and risks associated with the drug.”²⁶ Typically, 33% of the drugs pass Phase 2 and continue to Phase 3.²⁷ Phase 3 then gathers more information concerning efficacy and safety, and provides the “basis for extrapolating the results to the general population and transmitting that

²⁰ Nicole Endejann, Comment, *Is the FDA's Nose Growing?: The FDA Does Not "Exaggerate Its Overall Place in the Universe" When Regulating Speech Incident to "Off-Label" Prescription Drug Labeling and Advertising*, 35 AKRON L. REV. 491, 503–04 (2002).

²¹ Ctr. for Drug Evaluation and Research, Drug Applications, <http://www.fda.gov/cder/about/smallbiz/faq.htm> (last visited Oct. 28, 2009).

²² *Id.*

²³ Lipsky & Sharp, *supra* note 7, at 364.

²⁴ Ctr. for Drug Evaluation and Research, *supra* note 21; *see also* Lipsky & Sharp, *supra* note 7, at 365.

²⁵ Lipsky & Sharp, *supra* note 7, at 365.

²⁶ Ctr. for Drug Evaluation and Research, *supra* note 21 (quoting 21 C.F.R. § 312.21 (2008)).

²⁷ Lipsky & Sharp, *supra* note 7, at 365.

information in the physician labeling.”²⁸ If the drug passes Phase 3, the manufacturer submits a new drug application to the FDA containing all the information from the clinical trials.²⁹ Once the FDA approves the drug, it goes to marketing and post-marketing surveillance is conducted.³⁰

After approval, the label is added. The label indicates approved uses and “must . . . reveal all medically relevant information regarding the appropriate use of the drug, such as dosage, directions for administration, known precautions, warnings, and contraindications.”³¹ If physicians go outside the recommendations and indications on the label, it is considered off-label use.³²

C. Definitions

Off-label drug use is the practice of prescribing drugs outside the scope of the drug’s approved label—this could be prescribing drugs beyond their intended use, duration, population or dosage. The FDA notes that

[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement [sic]. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects.³³

The FDA does not ultimately prohibit off-label use. Yet the problem is that off-label use often does not have the backing of adequate scientific data.³⁴ Rather, it becomes common practice after there have been scholarly articles by other physicians or researchers. Articles have been written based upon individual

²⁸ Ctr. for Drug Evaluation and Research, *supra* note 21.

²⁹ Lipsky & Sharp, *supra* note 7, at 366.

³⁰ *Id.*

³¹ Endejann, *supra* note 20, at 500.

³² *Id.* at 503.

³³ U.S. Food & Drug Admin., “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices, <http://www.fda.gov/oc/ohrt/irbs/offlabel.html> (last visited Oct. 28, 2009); Endejann, *supra* note 20, at 503 (“The FDA’s policy reflects the lack of power to limit a physician’s practice of medicine.”).

³⁴ Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008), available at <http://content.nejm.org/cgi/content/full/358/14/1427>.

consults, or miniature experiments, conducted by physicians as the physician tailors certain drugs to fit the needs of their individual patients without knowledge of potential risks and side-effects.³⁵ The issue lies in those first-line therapies before the use becomes standard or a commonality.

It is also important to differentiate between experimentation and therapy. The difference lies mainly in intent. If it benefits the patient the off-label usage of a drug is deemed therapy, but if the purpose is to gain general knowledge for a broader population then it is considered human experimentation.³⁶ Furthermore, “the interests of the researcher and the subject may conflict” in human experimentation.³⁷ Therapeutic misconception arises from this conflict when patients believe that the research is going to benefit them directly, even though the intent and purpose of the study is to gain general knowledge and not necessarily benefit the patient.³⁸ Thus, the ultimate purpose of research is discovery and knowledge, unlike therapy which promotes the best interest of the patient. Medical practice also recognizes “innovative therapy” that combines “research and practice”; here the “physician may wish to give a patient the best-known medication and simultaneously evaluate the medicine’s efficacy.”³⁹ However, legally defining innovative therapy comes down to the physician’s intent.⁴⁰

A further distinction often articulated by experts in the field is that “[m]edical therapy aims at relieving the suffering of people and restoring them to health[,] . . . [i]ts focus is on the individual patient,” whereas “[m]edical research, by contrast, is a scientific enterprise.”⁴¹ The other important distinction between experimentation and practice is the former’s higher degree of

³⁵ James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 *FOOD & DRUG L.J.* 71, 82–83 (1998); see Mary E. Russell et al., *Off-Label Use: An Industry Perspective on Expanding Use Beyond Approved Indications*, 19 *J. INTERVENTIONAL CARDIOLOGY* 432, 433 (2006); see also Johnson, *supra* note 2, at 69, 74–75.

³⁶ Kathryn A. Tuthill, Commentary, *Human Experimentation: Protecting Patient Autonomy Through Informed Consent*, 18 *J. LEGAL MED.* 221, 223 (1997); see also E. Haavi Morreim, *Litigation in Clinical Research: Malpractice Doctrines Versus Research Realities*, 32 *J.L. MED. & ETHICS* 474, 475 (2004).

³⁷ Tuthill, *supra* note 36, at 224.

³⁸ Paul S. Appelbaum et al., *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, 17 *HASTINGS CENTER REP.* 20 (1987).

³⁹ Tuthill, *supra* note 36, at 223.

⁴⁰ *Id.* at 224.

⁴¹ Beck & Azari, *supra* note 35, at 81.

risk.⁴² This is often exemplified in the FDA's drug approval process with the stringent requirements set forth by Institutional Review Boards and illustrates why there are such rigorous standards for researchers to go through.⁴³ Finally, the breach between experimentation and standard of care in practice occurs after publications in the medical community and research demonstrates other aspects of the drug or medical device. Once several journal articles have been published, and the practice becomes wide-spread, the new use is often considered to be the standard of care.⁴⁴

D. The Converse: Benefits & Harms

The legislature and the FDA acknowledge that there should not be interference with a physician's practice.⁴⁵ Even though this is recognized, acknowledgment of the harms and benefits of off-label drug use is required. Off-label use can be beneficial to patients especially in light of the fact that "manufacturers do not choose to obtain approval for all possible uses of a drug. Thus, the label for any particular drug will not list all medical indications for its use, even some for which there is good clinical trial or other evidence of efficacy."⁴⁶ Off-label drug use allows physicians to treat patients when approved drugs are not working or are not optimal for the patient.⁴⁷ Physicians can engage in their art and be creative in their solutions; otherwise known as "innovation in clinical practice."⁴⁸ The well-known "pathfinders" in interventional cardiology, Dotter & Gruntzig, improved their techniques and did so off-label.⁴⁹ Off-label use also allows patients to have earlier access to valuable medications, especially when others are not working.⁵⁰ Or it allows for treatments of "orphan" conditions.⁵¹ Orphan

⁴² Tuthill, *supra* note 36, at 222.

⁴³ Lipsky & Sharp, *supra* note 7, at 362, 364.

⁴⁴ See Proctor v. Davis, 682 N.E.2d 1203, 1209 (Ill. App. Ct. 1997) (discussing the practice of publishing unapproved uses of drugs as an unsanctioned form of advertising by manufacturers in an effort to create their own literature on the use of a drug).

⁴⁵ Beck & Azari, *supra* note 35, at 76–78.

⁴⁶ Elizabeth W. Loder & David M. Biondi, *Off-Label Prescribing of Drugs in Specialty Headache Practice*, 44 HEADACHE 636, 638 (2004).

⁴⁷ *Id.* at 638–40.

⁴⁸ Stafford, *supra* note 34, at 1427.

⁴⁹ Russell et al., *supra* note 35, at 433.

⁵⁰ Stafford, *supra* note 34, at 1427.

⁵¹ *Id.*

conditions are those drugs developed for rare diseases conditions, including diseases “such as Huntington’s disease, myoclonus, ALS (Lou Gehrig’s disease), Tourette syndrome, and muscular dystrophy”.⁵² Off-label drug use also allows pharmaceutical companies to invest more money into research and development, which is extremely valuable when the cost to develop a new drug is more than \$500 million.⁵³ This figure does not include post-marketing trials that can cost the pharmaceutical company anywhere from \$8 to \$12 billion.⁵⁴

However, there are also harms that result from off-label drug use. Off-label use first undermines the knowledge of the safety and efficacy of the drug because the drug has not been through the arduous clinical trials for that purpose.⁵⁵ Warner-Lambert produced the drug Neurontin, which was approved “solely for adjunctive or supplemental anti-seizure use by epilepsy patients.”⁵⁶ However, the company promoted the effectiveness of Neurontin “for treating bipolar disease, even when a scientific study demonstrated that a placebo worked as well or better than the drug.”⁵⁷ It also hampers the “quantity and timeliness . . . [of] clinical knowledge” and causes a “reduc[tion in] the effectiveness of practice guidelines, which lack clear and specific recommendations.”⁵⁸ The need for further regulation is demonstrated by the fact that researchers recently identified fourteen drugs that need more study before standard off-label drug use continues.⁵⁹ Included in this list are Seroquel, “approved for the treatment of schizophrenia and mania-associated bipolar disorder”, commonly used for depression and anxiety; Singulair, an asthma drug, used off-label for chronic obstructive pulmonary disorder (“COPD”); Celebrex, a drug approved for treatment of arthritis, used off-label for fibromatosis; Prinivil or Zestril, approved as an Angiotensin-

⁵² U.S. Food & Drug Admin., The Orphan Drug Act, <http://www.fda.gov/orphan/oda.htm> (last visited Oct. 28, 2009).

⁵³ Lipsky & Sharp, *supra* note 7, at 364.

⁵⁴ Johnson, *supra* note 2, at 84.

⁵⁵ Stafford, *supra* note 34, at 1427.

⁵⁶ Dep’t of Justice, Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion, USDOJ.GOV (May 13, 2004), *available at* http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm.

⁵⁷ *Id.*

⁵⁸ Johnson, *supra* note 2, at 100.

⁵⁹ Salynn Boyles, ‘Off-Label’ Drug Use is Common, WEBMD, Nov. 24, 2008 <http://www.webmd.com/news/20081124/off-label-drug-use-common>.

converting enzyme (“ACE”) inhibitor, used to treat for coronary artery disease; or Procrit or Epogen (epoetin alfa), designated to treat anemia in patients with kidney failure, but used off-label for some other chronic diseases in patients.⁶⁰

Off-label drug use also can increase healthcare costs when newer drugs are used off-label or when one’s insurance company refuses to cover the cost.⁶¹ Gabapentin, is an example of a drug that is incredibly expensive and is not always the most effective as used off-label.⁶² Gabapentin was approved in 1993 by the FDA for the treatment of partial seizures.⁶³ However, Gabapentin is now in the top twenty of most expensive drugs and has approximately fifty off-label uses including bipolar disorder, which has not been approved by the FDA and effectiveness has not been approved by any randomized control trial.⁶⁴ Harm to the patient can also result when off-label use requires physicians to rely on journal articles that sometimes do not provide adequate, neutral studies.⁶⁵ Off-label drug use also can create tension between the role of treating the patient as a physician or treating the patient in the role of the researcher.⁶⁶ It only perpetuates the risk of therapeutic misconception.⁶⁷ The tension between furthering generalized knowledge and treating the patient in the best way become fundamentally juxtaposed. It thus walks the line of being human experimentation that requires heightened protection of the patient. Finally, off-label use results in manufacturers not performing rigorous studies by undermining their incentive to do so.⁶⁸ Testimony by William B. Schultz, before the Senate Committee on Labor and Human Resources, argued that manufacturers would have decreased incentive to perform required rigorous studies; for example,

interferon alpha 2b was approved for use in hairy cell leukemia, of which there are approximately 300-400 cases per year. It

⁶⁰ *Id.*

⁶¹ Stafford, *supra* note 34, at 1427.

⁶² IDAHO DRUG UTILIZATION REVIEW, OFF-LABEL USE OF GABAPENTIN (2004), <http://idahodur.isu.edu/leaflets/2004/GABAPENTIN%20EDU%20LEAFLET%202004.pdf>.

⁶³ *Id.*

⁶⁴ *Id.*

⁶⁵ See, e.g., Proctor v. Davis, 682 N.E.2d 1203, 1208–10 (Ill. App. Ct. 1997).

⁶⁶ Ken Gatter, *Fixing Cracks: A Discourse Norm to Repair the Crumbling Regulatory Structure Supporting Clinical Research and Protecting Human Subjects*, 73 UMKC L. REV 581, 582–83 (2005).

⁶⁷ Appelbaum, *supra* note 38, at 20.

⁶⁸ Stafford, *supra* note 34, at 1427–28.

subsequently was approved to treat chronic hepatitis B and C, of which there are tens of thousands of cases per year. If S. 1477 had been in effect, the manufacturer of interferon alpha 2b could have sought approval for hairy cell leukemia and then just promoted for chronic hepatitis B and C—the much broader use—based on preliminary data.⁶⁹

From decreased incentives to undermining efficacy and safety, serious concerns arise from off-label drug use.

E. A Look From the Physician's Viewpoint

The FDA and legislature recognize the need to let physicians practice their art. Physicians appreciate the ability to treat their patients in the best way possible and are typically in support of off-label use. Physicians often urge that off-label use could satisfy unmet needs.⁷⁰ Furthermore, off-label use “is a widely-accepted practice, and can even constitute the standard of care.”⁷¹ Physicians also see off-label prescribing as within the appropriate benefits and harm analysis, because the “safety and efficacy have been amply demonstrated.”⁷² This conclusion, however, rests on the premises that scholarly articles have been published and that the use has become a commonality. As we have seen, this belief is not always true.⁷³

The tension between standard of care and human experimentation for off-label drug use is best demonstrated in the case of *Proctor v. Davis*. In *Proctor v. Davis*, the court found that the use of a periocular injection of Depo-Medrol was experimentation.⁷⁴ This drug was only approved for intramuscular, intra-articular, and intralesional injections.⁷⁵ Upjohn, the manufacturer, provided an ophthalmologist with vials of the drug and wrote a letter emphasizing that the manufacturers were interested in the result as to the use of

⁶⁹ *Testimony on Unapproved Uses of Prescription Drugs, Before the S. Comm. on Labor and Human Resources*, 103rd Cong. 5 (1996) (statement of William B. Schultz, Deputy Commissioner for Policy, Food & Drug Admin.).

⁷⁰ Russell, *supra* note 35, at 433.

⁷¹ George S. Craft Jr., *Promoting Off-Label in Pursuit of Profit: An Examination of a Fraudulent Business Model*, 8 HOUS. J. HEALTH L. & POL'Y 103, 108 (2007).

⁷² Loder & Biondi, *supra* note 46, at 638.

⁷³ See *Proctor v. Davis*, 682 N.E.2d 1203, 1213 (Ill. App. Ct. 1997) (showing Upjohn knew of the potential adverse reactions and failed to warn doctors, yet encouraged off-label use of the drug which induced treating physicians to do so).

⁷⁴ *Id.* at 1212.

⁷⁵ *Id.* at 1206.

Depo-Medrol in ophthalmology, injected near the eye as no tests had yet been performed.⁷⁶ The ophthalmologists began using Depo-Medrol to treat ophthalmology problems and injecting it near the eye, where it was insoluble, and then helped to spread the unapproved off-label use throughout the medical community.⁷⁷ When harmful side-effects became apparent, the medical community was not warned about the unsafe uses of Depo-Medrol; therefore, the court found that the manufacturer had a duty to warn the medical community.⁷⁸

While this is a clear case in which physicians used a drug for an off-label use that deviated from the standard of care, and did not realize they breached their fiduciary duty to their patient, some physicians do recognize that off-label use has inherent risks and has an implicit aspect of experimentation. “Off-label drug use ‘should be undertaken with care and caution due to the uncontrolled experiment to which a patient is being subjected.’”⁷⁹ Ultimately, physicians wish to be able to treat their patients effectively and in doing so must be able to tailor to the specific patient. The experimentation aspect is thus only a corollary acknowledgement to the supposed greater need for physicians to treat their patients. Physicians’ practice is thus arguably seen as “state-of-the-art treatment.”⁸⁰

III. THE LEGAL RESTRAINTS

The art of physicians is not completely unregulated. A plethora of laws exist governing common uses of drugs and devices in order to ensure safety and efficacy of the product. As seen from the history of the FDA, consumers are wary of adulterated or misbranded drugs. Congress acted numerous times in the past in response to public outcry, regulating drugs and devices traveling through interstate commerce. Parallel to the history of the FDA, several codes and principles have been developed to govern and guide researchers in the aspect of human experimentation.

⁷⁶ *Id.* at 1206.

⁷⁷ *Id.* at 1206–07.

⁷⁸ *Id.* at 1213.

⁷⁹ *Doctors Describe Off-Label Drug Use*, UPI, Oct. 28, 2008, http://www.upi.com/Health_News/2008/10/28/Doctors_describe_off-label_drug_use/UPI-65781225251766/.

⁸⁰ William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 *FOOD & DRUG L.J.* 247, 249 (1993).

A. The Nuremberg Code

The Nuremberg Code was one of the first codes published to govern standards for human subject research.⁸¹ In response to the medical horrors that occurred during the Holocaust, the Nuremberg Code was published to give legal and moral principles for research of human subjects.⁸² Ten rules have been promulgated to regulate experimentation: (1) “voluntary consent . . . is absolutely essential”; (2) the study should produce useful results within the proper means for the greater good of society; (3) the study should be based on animal experimentation and natural knowledge; (4) the study should “avoid all unnecessary physical and mental suffering and injury”; (5) if death or severe injury occurs the study should not be conducted; (6) risk should be balanced against the benefit of the problem to be solved; (7) the study should have adequate facilities and preparations; (8) the study should “be conducted only by scientifically-qualified persons”; (9) the volunteer should be able to leave the study at any time; and (10) the researcher should be prepared to end the study at any point when the harms outweigh the risks.⁸³ While these rules often received little attention when first issued—“[i]t was a good code for barbarians but an unnecessary code for ordinary physicians”—the principles have come to be essential guidelines for human research.⁸⁴

B. The Declaration of Helsinki

Following the rules of the Nuremberg Code, the international medical community attempted to enunciate standards in line with medical research with a therapeutic intent on an international scale.⁸⁵ In 1964, the World Medical Association

⁸¹ U.S. DEP’T OF HEALTH AND HUMAN SERVS., GUIDELINES FOR THE CONDUCT OF RESEARCH INVOLVING HUMAN SUBJECTS AT THE NAT’L INSTS. OF HEALTH 15 (2004), available at <http://ohsr.od.nih.gov/guidelines/GrayBooklet82404.pdf>.

⁸² *Id.*

⁸³ The Nuremberg Code, Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No.10. Vol. 2, 18182 (1949), available at <http://www.copernicugroup.com/irbForms/NurembergCode.pdf>.

⁸⁴ Ruth R. Faden et al., *U.S. Medical Researchers, the Nuremberg Doctors Trial, and the Nuremberg Code*, in *ETHICAL AND REGULATORY ASPECTS OF CLINICAL RESEARCH* 7-9 (Ezekiel J. Emmanuel et al. eds., 2003) (noting that in 1959 at the National Conference on the Legal Environment of Medicine, the Nuremberg Code’s ten principles became solidified as the main guidelines for human research).

⁸⁵ *Part II Introduction, Ethical and Regulatory Guidance for Research with*

disseminated the Declaration of Helsinki.⁸⁶ This became the basis for the Institutional Review Board process.⁸⁷ The Declaration departed from the Nuremberg Code and also addressed the issue of informed consent—it allowed for a surrogate decision-maker or legal guardian to provide informed consent such as in cases of children or mentally ill participants.⁸⁸ The original 1964 Declaration also distinguished between non-therapeutic and therapeutic research, although this distinction was removed in the 2000 revision.⁸⁹

C. The Belmont Report

A decade later in 1974, the National Research Act was enacted and charged the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the commission) with identifying the ethical principles that should govern research for protection of human subjects.⁹⁰ The commission subsequently issued the Belmont Report in 1978 addressing these issues.⁹¹ It laid out three basic principles: respect for persons, beneficence, and justice.⁹² The report outlined applications of these principles to informed consent, assessment of risks and benefits, and selection of subjects.⁹³ The Belmont Report argued that the difference between practice and research is that the former is for the benefit of the individual, whereas the latter tests hypotheses and furthers general

Humans, in ETHICAL AND REGULATORY ASPECTS OF CLINICAL RESEARCH 26 (Ezekiel J. Emmanuel et al. eds., 2003).

⁸⁶ WORLD MEDICAL ASSOCIATION, World Med. Ass'n, Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects ¶ 32, at 5 (adopted 1964) (2008) *reprinted in* ETHICAL AND REGULATORY ASPECTS OF CLINICAL RESEARCH 30 (Ezekiel J. Emmanuel et al. eds., 2003).

⁸⁷ Elizabeth Banker, Dartmouth College, & Jeffrey A. Cooper, AAHRPP, Inc., Lecture for Collaborative Institutional Training Initiative: History and Ethical Principles (Dec. 4, 2004); *see* ADIL E. SHAMOO & DAVID B. RESNIK, RESPONSIBLE CONDUCT OF RESEARCH 196–98 (explaining how the basic principles in the Nuremberg Code and Declaration of Helsinki are in many ethic codes and that the U.S. enacted the NRA creating policies for IRBs the same year that the World Medical Association promulgated the Declaration of Helsinki).

⁸⁸ Emmanuel, *supra* note 84, at 25–26.

⁸⁹ *Id.*

⁹⁰ Nat'l Insts. of Health, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (Apr. 18, 1979), *available at* <http://ohsr.od.nih.gov/guidelines/belmont.html> [hereinafter Belmont Report].

⁹¹ *Id.*

⁹² *Id.*

⁹³ *Id.*

knowledge.⁹⁴ The commission noted that

[w]hen a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is “experimental,” in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective.⁹⁵

The commission also articulated three basic ethical principles. The first is respect for persons. Here, researchers must remember to treat individuals “as autonomous agents” and “persons with diminished autonomy are entitled to protection.”⁹⁶ Thus, researchers must respect the patient’s wishes and opinions. This principle also requires volunteers to “enter into the research voluntarily and with adequate information.”⁹⁷ The second principle is beneficence. Beneficence argues that one has a duty to do what is best for others thereby helping them. Thus, here it is an obligation, binding researchers to “(1) do not harm and (2) maximize possible benefits and minimize possible harms.”⁹⁸ This has short-term and long-term consequences, requiring researchers to look at the individual study and in the long-term for general scientific research to evaluate the benefits and risks that can occur in society.⁹⁹ Finally, we have to keep in mind a sense of justice. “[E]quals ought to be treated equally.”¹⁰⁰ Specific examples include “the selection of research subjects needs to be scrutinized in order to determine whether some classes . . . are being systematically selected simply because of their easy availability, their compromised position, or their manipulability” and that the results of the research should be available to all and not based on one’s wealth.¹⁰¹ The Belmont Report then applies these principles and argues for informed consent, a careful selection of subjects, and emphasizing the importance of weighing the risks and benefits of the

⁹⁴ *Id.*

⁹⁵ *Id.*

⁹⁶ Belmont Report, *supra* note 90.

⁹⁷ *Id.*

⁹⁸ *Id.*

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

experiment.¹⁰²

D. The FDA Modernization Act

After these precursors, the Food and Drug Administration Modernization Act (FDAMA) was passed in 1997.¹⁰³ As discussed earlier, the FDAMA revised the policies relating to off-label use.¹⁰⁴ The act allows a manufacturer to “disseminate to (1) a health care practitioner; (2) a pharmacy benefit manager; (3) a health insurance issuer; (4) a group health plan; or (5) a Federal or State governmental agency; written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling of a drug”¹⁰⁵ if the manufacturer (1) files a new drug application, (2) the information is “unabridged [] reprint or copy of an article . . . reference publication . . . [and would] not pose a significant risk to the public health [or be false or misleading]”¹⁰⁶, (3) the clinical research is not conducted by another manufacturer, (4) the manufacture submits a copy of the information to the FDA, (5) submits a supplemental application if needed¹⁰⁷, and (6) “prominently display[s]” disclosures of the disseminated information.¹⁰⁸ While the FDAMA offered much needed advice and guidance, the act is not perfect because it requires the manufacturer to submit a supplemental application for other uses not initially approved, which manufacturers are often hesitant to do.¹⁰⁹

E. Further Regulations

There are also regulations for when physicians become investigators in any investigational new drug (“IND”) or investigational device exemption (“IDE”) clinical trial. A physician may participate as an Investigator for an IND, whereby she conducts and initiates the clinical trials that are often used for a new indication of an approved product.¹¹⁰ The

¹⁰² Belmont Report, *supra* note 90.

¹⁰³ 21 U.S.C. § 301 et seq. (2009).

¹⁰⁴ *See supra* Part I.A.

¹⁰⁵ 21 U.S.C. § 360aaa (2009).

¹⁰⁶ § 360aaa-1; *see also* 21 C.F.R § 99.101 (2009).

¹⁰⁷ 21 U.S.C. § 360aaa-3 (2009); § 360aaa.

¹⁰⁸ § 360aaa.

¹⁰⁹ *Id.*

¹¹⁰ Ctr. for Drug Evaluation and Research, U.S. Food and Drug Admin., Investigational New Drug (IND) Application Process, http://www.fda.gov/cder/Regulatory/applications/ind_page_1.htm (last visited Oct. 28, 2009). The

FDA must approve any plan through the process discussed earlier in this paper.¹¹¹ Physicians cannot promote or commercially distribute an IND.¹¹² Physicians must agree to informed consent standards promulgated by the FDA and accept the extra obligations.¹¹³ For these trials, an Institutional Review Board must still approve the investigational plan.¹¹⁴ Thus, there is still regulatory approval and FDA guidance for these trials, thereby separating these from the current issue being discussed.

IV. THE ETHICAL DEBATE

Much of the conversation concerning off-label drug use does not delve into the ethical debate surrounding it. The ethics behind human research was brought to light the most, however, by Dr. Henry Beecher in his famous article, "Ethics and Clinical Research," published in the *New England Journal of Medicine* on June 16, 1966.¹¹⁵ Dr. Beecher identified twenty-two examples of research studies that had questionable ethics although performed and published by reputable researchers and journals.¹¹⁶ His article identified problems in the following areas: (1) lack of informed consent; (2) coercion or undue pressure on volunteers (or on a parent to volunteer their child); (3) use of a vulnerable population; (4) exploitation of a vulnerable population; (5) withholding information; (6) withholding available treatment; (7) withholding information about risks; (8) putting subjects at risk; (9) risks to subjects outweigh benefits; (10) deception; and (11) violation of rights.¹¹⁷ One of the most well-known studies that Beecher identified was the Public Health Service Syphilis Study, also known as the Tuskegee Institute experiment, conducted between 1932-1971.¹¹⁸ Here,

specific content and format for submission of the investigation is codified at 21 C.F.R. § 312.23 (2009).

¹¹¹ 21 C.F.R. § 312.20 (2009); *see also supra* Part I.A.

¹¹² § 312.7.

¹¹³ § 312.60; *see also* Beck & Azari, *supra* note 35, at 85–86 (citing *in re* Orthopedic Bone Screw Products Liability Litigation, 1996 WL 107556, at *4 (E.D. Pa. Mar. 8, 1996)).

¹¹⁴ 21 C.F.R. §§ 56.109(a), 312.66, 812.42 (2009).

¹¹⁵ Henry Beecher, *Ethics and Clinical Research*, 274 *New Eng. J. Med.* 1354, 1354–60 (1966), *reprinted in* ETHICAL AND REGULATORY ASPECTS OF CLINICAL RESEARCH 16-20 (Ezekiel J. Emanuel et al. eds., 2003).

¹¹⁶ *Id.*

¹¹⁷ *See id.*

¹¹⁸ Allan M. Brandt, *Racism and Research: The Case of the Tuskegee Syphilis Study*, in ETHICAL AND REGULATORY ASPECTS OF CLINICAL RESEARCH 20, 20

close to 400 Southern African-American men were studied, without their knowledge, by physicians refusing to give the first effective medicine, penicillin, to treat their syphilis.¹¹⁹ Many of the men were also actively discouraged from seeking treatment and went untreated for years.¹²⁰

The Belmont Report attempted to address many of these areas by elucidating the three primary ethical principles for researchers to follow.¹²¹ However, the Belmont Report has a strong utilitarian influence that fails to address adequately all angles of the ethical issues at stake.

Patient autonomy is one of the fundamental principles that form the basis of ethical debate especially in the realm of healthcare. Patient autonomy enables the patient to be able to choose for himself, without undue interference. In the United States, this principle is highly valued. Most often, this principle plays out in the area of informed consent.¹²² Allowing a patient to fully understand and know the risks, benefits, and side-effects of a medication is important. Informing the patient allows the patient to make an informed choice, and exercise her autonomy and what she feels is best for her. The act of informed consent allows for a conversation between the physician and the patient to elicit the best plan of treatment and respect the patient's wishes.

However, the importance of this theory is often undermined in off-label drug use, at least at the beginning stages, because physicians cannot adequately tell patients the necessary information.¹²³ The unknown risks and side-effects inherently hamper the process and disrespects the sacred principle of autonomy. However, this issue is usually considered resolved by experts once scholarly articles have been published and studies done on numerous patients. It remains unresolved in respect to

(Ezekiel J. Emanuel et al. eds., 2003).

¹¹⁹ *Id.* at 20, 22.

¹²⁰ BARRY R. FURROW ET AL., *BIOETHICS: HEALTH CARE LAW* 411 (6th ed. 2008).

¹²¹ Belmont Report, *supra* note 90.

¹²² *See id.* at 35–36 (showing how informed consent is necessary to show respect for the person and that this consent must be voluntary).

¹²³ *See* Russell, *supra* note 35, at 433 (explaining that patient well-being is at risk where physicians are not aware of safety or efficacy concerns regarding the off-label use of the drug). *See generally* Johnson, *supra* note 2, at 72–73 (explaining that while practicing doctors *could* wait to prescribe drugs until they have been approved for a particular use, they often do not wait because these physicians do not “exert a high demand for convincing scientific proof of effectiveness for off-label uses”).

the incidence where a physician fails to tell the patient that the drug is used off-label or adequately explain the risks and side-effects. In this instance, the physician is violating her fiduciary responsibility to the patient to respect the autonomy of the patient. The main issue, however, that clearly arises in off-label drug use lies in the beginning: after market-approval but before the off-label use becomes standard of care with numerous articles and studies providing scientific evidence.

The principle of patient autonomy is often contrasted with paternalism. The State often has a paternalistic attitude, especially when trying to protect the health and safety of its citizens.¹²⁴ Thus, the FDA extensively regulates drugs, medical devices, and clinical trials. After a history of public outcry and devastating events from the Elixir Sulfanilamide incident in 1937 to the Tuskegee Institute experiment, the FDA strictly monitors the safety and efficacy of products.¹²⁵ Off-label use at the initial stage thus often escapes this paternalistic attitude by the government and courts that are wary to interfere with physicians. The absence of the paternalistic attitude occurs in the face of the contrasting fear of regulating physicians and the physicians' attempt to provide the best treatment and protection for patients.

Finally, as noted earlier, experimentation versus practice can set up a conflict between the physician and the patient's interest. When a patient goes to a physician, the patient desires the best treatment from the physician individually. When a physician is acting also in the capacity of the researcher, the physician has a dual goal of not only aiding the patient, but also furthering generalized knowledge about the procedure or drug. Therapeutic misconception becomes widespread in this instance. As seen in *Proctor v. Davis*, the ophthalmologists' use of the off-label drug muddied the interests at stake and ultimately harmed the patient.¹²⁶ The ophthalmologist did not have the sole goal of

¹²⁴ For example, the paternalistic attitude is shown by the establishment of the FDA to protect the public by ensuring that the products that reach the markets are safe. U.S. Food & Drug Admin., FDA's Mission Statement, <http://www.fda.gov/opacom/morechoices/mission.html> (last visited Oct. 28, 2009).

¹²⁵ See *supra* note 9 and accompanying text (discussing the Elixir Sulfanilamide incident); FURROW, *supra* note 120, at 411–12; U.S. Food & Drug Admin., *supra* note 124.

¹²⁶ See generally *Proctor v. Davis*, 682 N.E.2d 1203, 268–69, 275–76 (Ill. App. Ct. 1997) (explaining that off-label use of Depo-Medrol for the treatment of

benefiting the patient; rather it was also to see the effects of the new innovative treatment.¹²⁷ Neither the manufacturer nor the physician took the care to warn or desist once the possibility of harmful side-effects became apparent.¹²⁸ Again, the tension and murkiness of off-label drug use befuddles and sets up a potential conflict of interest between the physician and the patient.

V. OFF-LABEL USE AND HUMAN EXPERIMENTATION

Medicine is both an art and a science. Thus, courts and Congress are wary of infringing upon the physicians' ability to treat their patients effectively. Currently, there is a failure by Congress in drafting the laws to adequately acknowledge the entire implications of off-label use; on the one side, there is hesitancy to interfere with a physician's diagnostic and treatment procedures, and on the other is a desire to ensure the safety and efficacy of drugs on the market. The FDA explicitly notes that

once a drug or device is on the market, a 'physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his [or her] patient or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.'¹²⁹

While off-label use does not necessarily fall under the laws of human experimentation *per se*, the dichotomy in the laws concerning off-label drug use for the manufacturers and the doctors fails to sufficiently protect the patient.

A. Advertising Versus Use

The law prohibits manufacturers from promoting off-label drug use, *but* also overtly allows physicians to prescribe off-label drugs.¹³⁰ Even more, physicians often consider the use of off-label drugs to be the standard of care. However, pharmaceutical companies cannot provide guidance to physicians for appropriate

ophthalmic conditions through periocular injection ultimately resulted in a patient having to surgically remove an eye).

¹²⁷ *Id.* at 1207–09.

¹²⁸ *Id.* at 1213.

¹²⁹ Richardson v. Miller, 44 S.W.3d 1, 13 (Tenn. Ct. App. 2000) (citing Proposed Rules, 37 Fed. Reg. 16503 (proposed Aug. 15, 1972) (to be codified at 21 C.F.R. pt. 130)).

¹³⁰ See United States v. Caronia, 576 F. Supp. 2d 385, 392 (E.D.N.Y. 2008); see also Washington Legal Found. v. Henney, 202 F.3d 331, 332–33 (D.C. Cir. 2000).

off-label use, nor is the Physician's Desk Reference any aid to physicians as it must comply with FDA labeling requirements. In fact, if pharmaceutical companies provide off-label information the company is guilty of misbranding.¹³¹ An exemplary case is that of *United States v. Caronia* where the Court noted that "[i]t is well established that under the FDA's 'intended use' regulations, the promotion of a drug for an off-label use by the manufacturer or its representative is prohibited regardless of what directions the manufacturer or representative may give for that use."¹³² *United States v. Caronia* demonstrates the fundamental disjoint of allowing physicians to use off-label drugs but also prohibiting manufacturers from advertising or providing information in regard to off-label drug use.¹³³ In this case, a sales representative promoted Xyrem (a drug approved by the FDA "to [only] treat excessive daytime sleepiness [] in patients with narcolepsy" and "to treat cataplexy" that has a "black box" warning) to a doctor for other uses including "fibromyalgia, EDS, muscle disorders, chronic pain and fatigue."¹³⁴ Xyrem had serious side effects including the potential for abuse, dependence, seizures, coma, or death.¹³⁵ The Court denied the defendant's motion to dismiss the two counts and charged him with violation of the misbranding provisions of the Food and Drug Cosmetic Act.¹³⁶

B. Insurance Laws

There is a disjoint in the insurance laws. Insurers and Medicare alike often "deny payment for 'experimental' or 'investigational' therapy."¹³⁷ The logic behind this is that the Health Care Financing Administration ("HCFA") has defined "an experimental drug use as one that is not 'safe or effective'" and

¹³¹ 21 U.S.C. § 352(f) (2006).

¹³² See *Caronia*, 576 F. Supp. 2d at 392 ("FDCA 'generally prohibits the manufacturer of a new drug or medical device from distributing a product in interstate commerce for any intended use that the FDA has not approved as safe and effective The intended use or uses of a drug or device may also be determined from advertisements, promotional material, oral statements by the product's manufacturer or its representatives, and any other relevant source.'" (quoting *Decision in Wash. Legal Found. v. Henney*, 65 F.R. 14286 (Mar. 16, 2000))).

¹³³ *Id.* at 393.

¹³⁴ *Id.* at 388–89.

¹³⁵ *Id.* at 389.

¹³⁶ *Id.* at 385, 403.

¹³⁷ Christopher, *supra* note 80, at 256.

therefore it has “expressly limit[ed] mandated coverage to labeled uses.”¹³⁸ NY law also posits the dichotomy in that it allows insurers to exclude off-label use that is not indicated on the label by the FDA but requires insurers to cover off-label drug use of cancer drugs providing that it is “recognized for treatment of the specific type of cancer for which the drug has been prescribed” by either the AMA Drug Evaluations, the American Hospital Formulary Service Drug Information, or the U.S. Pharmacopeia Drug Information.¹³⁹ Yet, again, the laws are in conflict allowing for the exclusion of off-label drug use but at the same time requiring it. The benefit of the NY law is that it recognizes the importance of documentation, requiring it to be in one of three compendia or other journal article. It thus excludes the initial stage, which is at issue here.

C. Understanding the Disjoint

Off-label drug use is not inherently bad—it can have benefits. The problem is that it is constantly overlooked in the time between the beginning stages where the FDA approved drug enters the market and when off-label use becomes the standard of care. This results in the contrasting laws and views on the subject. Furthermore, it is in this initial stage when off-label drug use should be considered experimentation.¹⁴⁰ Experimentation exists when the outcome cannot be predicted because the safety and efficacy of the particular use of the drug has yet to be proven.¹⁴¹ Furthermore, it constitutes the beginning of research where “[r]esearch means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under

¹³⁸ *Id.* (citing Criteria and Procedures for Making Medical Services Coverage Decisions That Relate to Health Care Technology, 54 F. R. 4302, 4306, 4316 (Jan. 30, 1989) (to be codified at 42 C.F.R. pts. 400 & 405)).

¹³⁹ N.Y. INS. LAW § 3216(h)(12)(A) (McKinney 2008).

¹⁴⁰ Experimentation is done for the purpose to gain general knowledge to treat future conditions. It does not necessarily provide any benefit to the patient. *See supra* Part I.C.

¹⁴¹ Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 362–3 (2002) (stating that federal regulation requires “proof of safety and effectiveness” in order to be an approved treatment option).

a program which is considered research for other purposes.”¹⁴² It is recognized that “[a] treatment found to be in accordance with generally accepted standards of medical practice would hardly be experimental.”¹⁴³ Many of the arguments asserting that off-label drug use is not human experimentation rely on the fact that it is customary practice by physicians to use the drug in that way, even if off-label.¹⁴⁴ Furthermore, those expressing these views argue that the FDA has given regulatory review of many of the off-label uses.¹⁴⁵ While this may be true for stages further on, the stage where scholarly articles have been published or more post-marketing studies have been undertaken, this again ignores the beginning stage of using a drug for an off-label use before it has become standard of care.

I have previously defined human experimentation and practice—and the turning point is that much of it comes down to the intent of the physician. Even when we have “innovative therapy,” the intent of the physician is controlling.¹⁴⁶ While “innovative therapy” is a useful definition of describing the beginning stages of off-label use,¹⁴⁷ we note that the “physician may wish to give a patient the best-known medication and simultaneously evaluate the medicine’s efficacy.”¹⁴⁸ The physician is essentially conducting a miniature experiment. Here, the physician wants to treat the patient for the various reasons previously discussed, but also to see if the off-label use is practical and can be used for others. We thus put the patient and physician in a difficult position, wanting the best for the situation but also allowing the physician to have an ulterior motive, possibly with or without the knowledge of the patient. Regulatory status of the drug does not always have to be disclosed to the patient, although the physician must still inform the patient of all the risks and benefits of the drug. This is troubling especially as patients assume that the physician is

¹⁴² 45 C.F.R. § 46.102 (2007).

¹⁴³ Beck & Azari, *supra* note 35, at 82 (quoting *Pirozzi v. Blue Cross-Blue Shield*, 741 F. Supp. 586, 590 (E.D. Va. 1990)).

¹⁴⁴ *Id.* at 83–84 (arguing that status of the drug “can change over time” and that these customary off-label uses are safe and effective, and thus do not constitute human experimentation).

¹⁴⁵ *Id.* at 84.

¹⁴⁶ Tuthill, *supra* note 36, at 223–24 (citing Elliott J. Schuchardt, Comment, *Walking a Thin Line: Distinguishing Between Research and Medical Practice During Operation Desert Storm*, 26 COLUM. J.L. & SOC. PROBS. 77, 95–96 (1992)).

¹⁴⁷ *Id.*

¹⁴⁸ *Id.* at 223.

acting in their best interest—it is the same problem that lies at the root of therapeutic misconception. Yet, again we have the issue that the risks and benefits are not fully known for this off-label use so that patient’s autonomy is diminished. Thus, informed consent is in some ways not truly informed; while the physician abided by the legal requirements for informing the patient, it is not necessarily true that the patient was informed in the sense which underlies the concept of informed consent. Currently we have failed to address this situation—walking the line between human experimentation and practice in the first uses of off-label drug use.

VI. HOW SHOULD IT WORK?

Walking on the edge, off-label drug use presents complex situations. On the one hand, physicians should have the ability to prescribe drugs that will benefit their patients. In cases where indicated uses of drugs are not adequate for the patient, other drugs should be available to treat the patient. It takes a certain amount of individual tailoring and creativity for the physician to treat the patient in the best possible way. However, there must be acknowledgement that off-label use that has become the standard of care is drastically different from the beginning stages where the drug is being used off-label without evidence of the efficacy and safety. It is these beginning stages that need to be regulated.

Historically, the FDA has increased regulation after public outcry or acknowledgement that the safety of the public is at issue. Recent cases demonstrate that there is an issue with off-label use in some circumstances.¹⁴⁹ Physicians that choose to be innovative and treat their patients with off-label uses of drugs before the off-label use has become customary or standard of care should have to enroll in some kind of trial or system and be regulated. A less stringent standard than that of an investigational new drug (“IND”) application should be upheld. The purpose is not to burden the physicians but to balance the

¹⁴⁹ See generally *Proctor v. Davis*, 682 N.E.2d 1203, 1212 (Ill. App. Ct. 1997) (discussing how manufacturer of drug knew of danger involved in off-label use of drug, but never made those dangers known to physicians who were prescribing the drug for that off-label use.); see also *United States v. Caronia*, 576 F. Supp. 2d 385, 391–92 (E.D.N.Y. 2008) (discussing violations of the Federal Food Drug and Cosmetic Act by pharmaceutical sales representatives providing physicians with information that promoted drugs for off-label uses).

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hands-off approach of medicine with the need to protect patients. Physicians should be required to inform their patients of the regulatory status of the drug, with physicians noting the off-label use, and obtain consent, explaining the possible risks and the fact that most of the side-effects will be potentially unknown. Additionally, physicians then will have to publish their findings. This is not too far off the process that occurs today in which physicians are innovative and share their findings; the part that differentiates is the requirement of informed consent for regulatory status and regulation of the physicians. It is a fine line between allowing physicians to practice their “art” and also protecting the best interests of their patients.