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Off-Label Use of Prescription Drugs should be Regulated by the FDA

Introduction

In an ideal world, all uses of medical drugs would be safe and effective. If a drug has passed a rigorous approval process, it has a higher likelihood of being safe and effective for its approved indication. In our real world, the government does not subject all uses of drugs to such a process. There are many justifications given for this: It would cost too much. It would prevent deployment of the latest medical treatment by needless bureaucratic delay. It would interfere with physicians' autonomy in practicing medicine.

When a practitioner prescribes a drug for a use, or in a manner, not authorized by the Food and Drug Administration (FDA), that is called off-label prescribing.¹ The indication and dosages approved by the FDA are printed in a package insert that must accompany the drug. Using the drug for a non-FDA-approved indication, varying the dosage regimen, or using a drug intended for adults in a pediatric patient are examples of off-label use. Off-label use can be experimental, standard, or even state-of-the-art. It has become a ubiquitous part of mainstream medical practice, with many off-label uses recommended by medical textbooks, research institutes, professional organizations, and standard pharmaceutical reference works.² Half the United States population currently may be taking a medication prescribed for an unapproved reason.³ The American Medical Association estimates that 40%-60% of all prescriptions in the United States are written for drugs being used in a fashion other than their approved purpose. Off-label prescribing is particularly common in obstetrics, oncology, pediatrics, and infectious disease. Although manufacturers may not promote off-label uses except in sharply delineated circumstances and with FDA approval, physicians

¹ *Veronica Henry, Off-Label Prescribing Legal Implications*, 20 J. LEGAL MED. 365 (1999).

² *Id.*

³ *Lipman, Using Approved Drugs for Unapproved Purposes*, CONSUMER REP. HEALTH, Feb. 1998, at 10.

may prescribe off-label uses with impunity.⁴ This compromise is illogical and hides a dangerous reality by permitting unregulated medical practice in the absence of full information. To resolve this problem, one writer argues that the FDA should limit its intervention into the practice of medicine.⁵ I will show that the opposite, increasing the FDA's role in medicine, is better.

First, I will describe the current system and its faults. Second, I will propose a practical system that addresses these faults, brings us closer to the ideal system, saves money, and improves health care. Third, I will critique the proposed system, and show why its disadvantages are overshadowed by its advantages. Last, I will discuss what we need to do to implement the proposed system.

The Current System

The process

Congress delegated broad powers to the FDA regarding drugs and their labels.⁶ Enabled by the Food, Drug and Cosmetics Act (FDCA),⁷ the FDA's mission includes promoting the public health by promptly and efficiently reviewing clinical research, taking appropriate action on the marketing of regulated products in a timely manner, protecting the public health by ensuring that drugs are safe and effective, and consulting with experts in science, medicine, and public health, and in cooperation with consumers, users, and manufacturers.⁸ In fulfilling its mission to control the safety and efficacy of drug use, the FDA balances two opposing risks - inappropriate approval of dangerous drugs and undue delay in making safe, effective, and

⁴FDCA § 551(a) and (b) allow manufacturers to disseminate treatment information if certain conditions are met.

⁵Robert H. Pritchard, *Off-Label Uses of Approved Drugs: A New Compromise Is Needed*, (March 25, 1999) available at leda.law.harvard.edu/leda.

⁶21 U.S.C. §§ 301-393 (1938).

⁷Codified at 21 U.S.C. § 301 et seq (1997).

⁸FDA Modernization Act of 1997, Pub. L. No. 105-115; 111 Stat. 2296 (1997).

medically useful drugs available to the public.⁹ Since drugs make up a broad category and are potentially toxic, generalizations about them should only be made with caution.¹⁰

An example of this breadth of power is the FDA's seizure of a medical textbook. It claimed the book was a misbranding, as it contained information about off-label uses of a manufacturer's drug.¹¹ However, the power is not limitless. FDCA Section 906 prohibits FDA from interfering with the practice of medicine.¹² Due to a legacy from Dr. Royal Copeland, a New York senator during the New Deal, the FDA cannot regulate choices made by individual physicians for individual patients. Remarking on the Act, Senator Copeland stated, This bill makes certain that the medical practitioner shall not be interfered with in his practice.¹³

The FDA mandates a three phase human clinical investigation. The first phase, generally in healthy volunteers, garners the drug's pharmacokinetics and pharmacodynamics. The second phase, in supervised patients, ascertains whether the drug is useful for a particular condition. The third phase examines rarer side effects, risk-benefit profiles, and provides information for labeling.¹⁴ Whenever there is a risk-benefit evaluation, we have acknowledged that some people will be harmed by the agent, but expect more to be helped.

Right now, a manufacturer may check a drug for toxicity and efficacy for one indication, and introduce it into the marketplace. The manufacturer may hope that the drug is prescribed for many other indications besides the one that the FDA's unbiased evaluators reviewed. As shown above, the manufacturer often gets its wish. This creates essentially the same situation as before the 1962 Amendment to the FDCA. Drugs go

⁹Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 96 (1999).

¹⁰Marden Dixon & Frank Woodside III, 2 DRUG PRODUCT LIABILITY: MANUFACTURERS LIABILITY § 14.01 (1997) (noting that drugs can be catastrophic even when elaborate precautions have been carefully followed).

¹¹James Bovard, *Medical Follies at the FDA*, WASH. TIMES, Dec. 20, 1994, at A17 (the manufacturer was distributing the Chemotherapy Source Book to practitioners).

¹²James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD DRUG L.J. 71 (1998).

¹³78 CONG. REC. 2728 (Feb. 19, 1934).

¹⁴Jaime A. Wilsker, *One-Half Phen in the Morning/ One Fen before Dinner: A Proposal for FDA Regulation of Off-Label Uses of Drugs*, 6 J.L. POL'Y 807 (1998).

through a safety phase pursuant to the 1938 version of the Act, and then slide through a giant loophole to circumvent the protections afforded by the 1962 Amendment. That Amendment requires a manufacturer to show that the drug is effective for a particular indication. Since the drug will be prescribed just as often for conditions or populations other than the one the manufacturer has proved its usefulness for, the only regulatory protection patients have comes from the Phase 1 trials. The drugs have not been shown to be safe in patients with diseases other than the ones that the drugs are approved for, and they have not been shown to be efficacious at all in treating other diseases.

Most drugs given to children and most chemotherapy are prescribed in an off label use. This fact, the widespread use, is often offered as a reason to allow continuation of this practice, when it should be taken as a cause for alarm. Terminal cancer patients and children are two of the most vulnerable classes of people, so the government needs to protect them the most, not the least.

Statutory authority

The term off-label comes by inference from congressional legislation and FDA regulations concerning drug labeling. The 1938 version of the FDCA required drug companies for the first time to label pharmaceutical products with various directions and warnings. Regulations currently in force and effect tell manufacturers what must be included in a drug's label, including information necessary for safe and effective use, warnings, precautions, clinical pharmacology, indications, contraindications, and adverse reactions.¹⁵ The regulations are intended to ensure that the drugs and their promotional literature contain accurate and complete in-

¹⁵*See 21 C.F.R. § 201.56(d) (1998).*

formation regarding approved use and risks.^{16,17} Once the FDA has approved a drug, it does not regulate the choice of an individual physician to use a drug for an off-label purpose once the FDA has approved the drug for any human use.¹⁸ It has stated this itself.¹⁹ Thus, the FDA is charged with regulating the labeling, marketing, and distribution of drugs without intruding upon decisions statutorily committed to the discretion of health care professionals.²⁰ The practice of medicine doctrine is inapplicable where a drug is being marketed actively or otherwise commercialized. The practice of medicine doctrine applies only to patient treatment situations. The protection afforded by the practice of medicine doctrine and the custom device exemption is destroyed by the active marketing or commercialization of the modified product.²¹

The New Drug Provisions of the FDCA prohibit introducing an article into commerce that is in violation of FDCA Section 505 (New Drugs).²² This section requires new drugs to receive FDA approval as to safety and effectiveness before entering into interstate commerce. It is unlawful to misbrand a food or drug, FDCA Section 301(k). A drug is misbranded if its labeling is false or misleading in any particular, or unless its labeling bears adequate directions for use, FDCA Section 502 (f).²³

Off-label use can occur in the privacy of a patient's home, when he takes a drug intended for another, or a dose different from the one prescribed. Policing this kind of off-label use would be impractical and entail privacy concerns.²⁴ Off-label prescription of drugs occurs when a doctor prescribes a drug in any manner that varies from labeling specifications. A doctor who prescribes a drug that has been approved by FDA

¹⁶ Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 186-7 (1999).

¹⁷ See Lars Noah, *The Imperative to Warn: Disentangling the Right to Know from the Need to Know about Consumer Product Hazards*, 11 YALE J. ON REG. 293, 326-33 (1994) (discussing the labeling requirements for prescription drugs).

¹⁸ James T. O'Reilly, *Elders, Surgeons, Regulators, Jurors: Are Medical Experimentation's Mistakes Too Easily Buried?* 31 LOY. U. CHI. L.J. 353 (2000).

¹⁹ 1982 FDA Drug Bulletin, *Use of Approved Drugs for Unlabeled Indications*, The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling.

²⁰ *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 350 (2001).

²¹ John J. Smith, *Physician Modification of Legally Marketed Medical Devices: Regulatory Implications Under the Federal Food, Drug, and Cosmetic Act*, 55 FOOD DRUG L.J. 245 (2000).

²² FDCA § 301(d) (21 U.S.C. § 331(d)).

²³ 21 U.S.C. § 352.

²⁴ Salbu, *supra* note 16 at 189.

for purpose X, in order to achieve the different purpose Y, is prescribing off-label. The term also applies to prescription of a drug to groups other than those for whom FDA approved it, for periods of use exceeding the labeled recommended use, or in combination with other FDA-approved drugs. Regulating off-label prescription of drugs is much easier than regulating off-label use. Making off-label prescribing illegal would provide physicians with a strong disincentive.²⁵

One cannot draw a definite conclusion from the off-label status of a drug-indication.²⁶ Some commentators try to infer that the FDA considers the product generally safe enough to be on the market.²⁷ That is wrong: if the targeted disease condition is serious enough, a drug can be quite dangerous but still appropriate and FDA approved for that indication. Safety, like negligence, cannot be discussed in a vacuum—it needs context.²⁸ Many chemotherapy drugs are so toxic that even the Phase 1 trials are performed on cancer patients to minimize the risks to normal volunteers.

Problems with the current system

Common sense

The current system would provide adequate protection if medical science were amenable to common sense. Unfortunately, common sense does not work when it comes to medical efficacy.²⁹ Who would have thought that bread mold will ward off bacterial infections?³⁰ Or that prescribing more and longer courses of antibiotics

²⁵ *Id.* at 181.

²⁶ *Beck*, *supra* note 12 at 84 (stating that such an omission could follow from: 1) FDA lacked sufficient information to make an affirmative finding of safety or effectiveness; 2) the manufacturer never submitted an application concerning the use to FDA; or 3) in the case of a device, FDA lacked evidence of a substantially equivalent predicate (pre-1976) device).

²⁷ *Id.* at 85.

²⁸ *Hydrogen Technology Corp. v. United States*, 656 F. Supp. 1129 (D.C. Mass. 1987).

²⁹ *Richard R. Sabo, The Challenge of Emerging Surgical Technology: The College can Help*, 87 BULL. AM. C. SURGEONS 10 (December 2002).

³⁰ *Alexander Fleming's 1928 discovery of Penicillium notatum's antibacterial properties*. U.S. Department of Agriculture Agricultural Research Service available at ott.arsusda.gov/menu.htm?docid=769&page=2.

will increase, rather than decrease, the incidence of wound infections? Or that placement of a nasogastric tube to keep the stomach empty after abdominal surgery actually induces more vomiting than it prevents? Or that plugging a major chest wall artery into the heart muscle does not supply the oxygen-starved heart any more blood? There is no substitute for a well planned and executed study. In medicine, extrapolation from known facts can only be done to a small extent before running into counterintuitive findings. When a limb is at high risk for amputation due to severe trauma, but is saved, patients are no better off two years later than if they had undergone amputation.³¹ As a professor of surgery recently said, This is why we do research – what appears to be a good idea ends up being a bad idea.³²

Population screening is often touted as an effective public health tool. Logically, catching a disease early on should help patients, or at least not harm them. Screening 4 million children for neuroblastoma, the second most common childhood tumor, resulted in no saved lives, and a substantial rate of overdiagnosis in a recent study.³³ Each incorrect diagnosis of neuroblastoma subjects a child to possible needless surgery and an entire family to tremendous stress and cost.

Unexamined Traditions or Inadequate Studies

Similarly, unexamined traditional or accepted practice does not suffice.³⁴ Bloodletting was accepted practice and standard of care for a multitude of diseases (not including hemochromatosis for which it actually works) for hundreds of years. Immersion in water at various springs (Bath, Spa, Baden-Baden) has been traditionally

³¹Michael J. Bosse et al., *An Analysis of Outcomes of Reconstruction or Amputation after Leg-Threatening Injuries*, 347 NEW ENG. J. MED. 1924-1931 (2002).

³²Jonathan Link, *Rapid-Sequence Intubation Increases Mortality When Performed by Paramedics*, GEN. SURGERY NEWS, Jan. 2003 at 18 (finding that patients were dying more often after paramedics were instructed in an advanced airway securing maneuver).

³³Freimut H. Schilling, et al., *Neuroblastoma Screening at One Year of Age*, 346 N. ENG. J. MED. 1047-53 (2002).

³⁴Sabo, *supra* note 29 at 10.

regarded as good for many diverse ailments for centuries.³⁵ No matter how common the practice or how long the tradition has been in place, bathing at these springs does not cure cancer, syphilis, rheumatism, the Black Plague, skin diseases, gastrointestinal problems, or arthritis. The few medical studies that have been done had no controls and treated patients with psoriasis³⁶ and arthritic pain,³⁷ entities that have variable courses. They found no cures and questionable symptom amelioration. Diethylstilbestrol was prescribed to millions of women prophylactically to prevent miscarriage.³⁸ When its effect was studied, it was found not to affect the rate of miscarriage or premature birth.³⁹

In the 1950's, cardiac chest pain was often treated by tying off the internal mammary artery, which runs just under the sternum. When the technique was studied in a blinded fashion by having the control patients undergo sternal splitting alone, it was found to be ineffective.⁴⁰ In the 1970's, therapeutic touch became an international fad. Thirty years later, a fourth grade student performed a simple study that refuted the central tenet of the field.⁴¹ Based on a single 1992 study, Fen-Phen prescribing became epidemic.⁴² Within 4 years, 6 million people were trying it annually before its use was linked to serious pulmonary and cardiac disorders.⁴³ Because we do not gather data, we still do not have good answers to questions that should have been answered long ago. Despite a century of experience with thyroid surgery, we do not know whether we need to take out the entire thyroid gland, or only the affected lobe for thyroid cancer.⁴⁴

³⁵ *Harold Cook*, From the Scientific Revolution to the Germ Theory, in *THE OXFORD ILLUSTRATED HISTORY OF WESTERN MEDICINE* 96 (Irvine Loudon ed., 1997).

³⁶ *G Zumiani et al.*, *Bath-photo-therapy with the Thermal Water of Comano: Treatment of Psoriasis*, 146 *ACTA DERM VENEREOLOGY SUPPLEMENT* 122-3 (1989).

³⁷ 348 *N. ENG. J. MED.* (12 Feb 03).

³⁸ *RM Guiusti*, *Diethylstilbestrol Revisited: A Review of the Long-Term Health Effects*, 122 *ANNALS INTERNAL MED.* 778-788 (1995) (estimating that 5 to 10 million American women received diethylstilbestrol while pregnant).

³⁹ *WJ Dieckmann*, *Does the administration of diethylstilbestrol during pregnancy have therapeutic value?* 66 *AM. J. OBSTETRICS GYNECOLOGY* 1062-1081 (1953).

⁴⁰ *LA Cobb et al.*, *An evaluation of internal-mammary-artery ligation by a double-blind technic* 260 *N. ENG. J. MED.* 1115-8 (1959).

⁴¹ *Linda Rosa et al.*, *A Close Look at Therapeutic Touch*, 279 *J. AM. MED. ASS'N* 1005 (1998).

⁴² *Wilsker*, *supra* note 14 at 827.

⁴³ *Laura Johannes*, *Significant Heart-Valve Leaks Found in Large- Scale Study of Diet Pill Users*, *WALL ST. J. (EUROPE)*, Nov. 13, 1997, at 8.

⁴⁴ *Rosemary Frei & David Wild*, *To Remove or Not to Remove Cancerous Thyroid? That is the Question*, *GEN. SURGERY NEWS*, Jan. 2003 at 1.

Physicians are not well trained to analyze information statistically. In clinical encounters, they are often swayed by their training and recent experience more than by studies.⁴⁵ The efficacy of the Halsted radical mastectomy was accepted for 80 years, although this assumption was never subjected to scientific testing.⁴⁶ Even 14 years after widespread knowledge that lumpectomy with radiation therapy is as good in breast cancer as mastectomy, the majority of surgeons continue to perform many more mastectomies than indicated.⁴⁷ Since their training does not prepare them to accept good studies, they need encouragement by regulation. One out of every 100 hospitalized patients dies from complications of venous blood clotting.⁴⁸ There is a consensus regarding appropriate prophylaxis that would almost eliminate this risk, but only a third of high-risk patients get it.⁴⁹

Old observational studies are not adequate. Physicians have been prescribing hormone replacement therapy to women for over 50 years without rigorous data collection, believing that they were offering women cardiac protection. The rationale was sound: premenopausal women have a much lower rate of cardiac disease than men, and the rate goes up sharply after menopause, when the female hormone levels decline. Therefore, giving those hormones should keep the cardiac disease rate low. Observational studies confirmed this belief. When the therapy was finally studied in a controlled fashion (with a placebo controlled group), the researchers found that estrogen and progesterone given to women increases their risk of vascular disease and breast cancer.⁵⁰ The magnitude was enough to stop a planned 8-year study 3 years before its scheduled cessation. There were actually more strokes, heart attacks, blood clots, and invasive breast cancers, and fewer colorectal

⁴⁵ ATUL GAWANDE, *COMPLICATIONS: A SURGEON'S NOTES ON AN IMPERFECT SCIENCE* (2002).

⁴⁶ Bernard Fisher et al., *Twenty-Year Follow-up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy plus Irradiation for the Treatment of Invasive Breast Cancer*, 347 N. ENG. J. MED. 1233-1241 (2002) (noting no difference in disease-free survival or overall survival among three groups of women randomly assigned to total mastectomy, lumpectomy alone, or lumpectomy and breast irradiation).

⁴⁷ Sabo, *supra* note 29 at 10.

⁴⁸ FA Anderson Jr & A-M Audet, *Best Practices: Preventing Deep Vein Thrombosis and Pulmonary Embolism*. Center for Outcomes Research, University of Massachusetts Medical Center (1998).

⁴⁹ WH Geerts, *Prevention of Venous Thromboembolism*. Sixth ACCP Consensus Conference on Antithrombotic Therapy. 119 CHEST 132S-175S (2001).

⁵⁰ Writing Group for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 J. AM. MED. ASS'N 321-333 (2002).

cancers and hip fractures. Overall, 19 more women per 10,000 person-years suffered some serious condition attributable to the hormone replacement therapy. A later study showed that even the quality of women's lives did not improve, despite the conventional wisdom of hormone replacement's benefit on unpleasant perimenopausal symptoms.⁵¹

Even new technologies can be rapidly assimilated without proper studies. Swann-Ganz catheters, tubes that are inserted through the skin and threaded through the heart into the lung to monitor critically ill patients, became commonplace in the ICU during the 1980s and are still frequently used. One of the few randomized studies shows no benefit in a group for whom these invasive catheters have been the standard of care.⁵²

Patients with pancreatic cancer face short life expectancies. For patients wanting the best quality of life as an outcome, the best choice can be chemoradiation or no treatment whatsoever, instead of the standard pancreaticoduodenectomy.⁵³

Many unapproved uses that have not been studied in the rigorous way that the FDA demands have snuck into the standard of care. When they finally are investigated after thousands of patients have already been treated, the results are sometimes surprising. Nonsteroidal anti-inflammatory drugs cause colon polyps to regress. Physicians, logically extending this property, have been prescribing them to prevent polyp emergence as well. When such a drug was studied for its effectiveness in preventing polyps in the first place, it had no effect.⁵⁴ Clonidine, a high blood pressure drug, was prescribed more than 200,000 times to treat children with attention deficit disorders before systematic research has discovered severe side effects and a handful

⁵¹Jennifer Hays, *Effects of Estrogen plus Progestin on Health-Related Quality of Life*, available at <http://content.nejm.org/cgi/content/abstract/NEJM.0a030311v1> (to be published in the N. ENG. J. MED. on May 8, 2003).

⁵²James Dean Sandham et al., for the Canadian Critical Care Clinical Trials Group, A Randomized, Controlled Trial of the Use of Pulmonary-Artery Catheters in High-Risk Surgical Patients, 348 N. ENG. J. MED. 5-14 (2003) (reporting a 7% mortality in each group).

⁵³Gretchen P. Purcell et al., *Preferences Affect Treatment Decisions for Pancreatic Cancer*, 195 J. AM. COLLEGE SURGEONS S54 (2002).

⁵⁴Francis M. Giardiello et al., *Primary Chemoprevention of Familial Adenomatous Polyposis with Sulindac*, 346 N. ENG. J. MED. 1054-9 (2002).

of deaths.⁵⁵ Encainide, flecainide, and mexiletine were widely prescribed off-label for irregular heartbeat. Government sponsored testing later showed that these drugs caused cardiac arrest rather than preventing it, with tens of thousands of patients died prematurely.⁵⁶ Tamoxifen and Lupron, endocrine agents, were prescribed as analgesics off-label to women with painful fibrocystic breasts. Tamoxifen causes uterine cancer and blood clots while Lupron produces severe osteoporosis.⁵⁷

The time honored and intuitively appealing practice of cleansing the colon before operating on it was finally subjected to rigorous study this year. There was no difference in patient outcomes. This means that millions of patients have been subjected to discomfort, induced watery diarrhea, and abdominal cramps just before surgery for no benefit.⁵⁸

Cutting adhesions (scar tissue) in the abdomen is an accepted treatment for chronic abdominal pain. When a controlled study was finally done this year, the authors found that simply inserting a laparoscope into the abdomen and looking around without any intervention was just as effective as cutting the adhesions. Therefore, laparoscopic adhesiolysis cannot be recommended as a treatment for adhesions in patients with chronic abdominal pain.⁵⁹

Even a simple intuitive assumption like the more often you do a procedure, the better your results (practice makes perfect) is not true across the board. A study analyzing more than 30,000 patients in Ontario who had undergone major procedures showed no difference in outcome based on hospital or surgeon volume.⁶⁰

⁵⁵ *The Prescription Drug User Fee Act and Reform of the Food and Drug Administration: Hearing Before The Comm. On Commerce Subcomm. On Health And The Environment*, April 23, 1997 (statement of Jeff Bloom for the Patients' Coalition).

⁵⁶ THOMAS MOORE, *DEADLY MEDICINE* (1995) (aftermarket trial showed significantly more deaths in the treated group than in the placebo group).

⁵⁷ *The Prescription Drug User Fee Act and Reform of the Food and Drug Administration: Hearing Before The Comm. On Commerce Subcomm. On Health And The Environment*, April 23, 1997 (statement of Jeff Bloom for the Patients' Coalition).

⁵⁸ Oded Zmora et al., *Colon and Rectal Surgery without Mechanical Bowel Preparation: A Randomized Prospective Trial*, 237 *ANNALS SURGERY* 363-367 (2003).

⁵⁹ DJ Swank, *Laparoscopic Adhesiolysis in Patients with Chronic Abdominal Pain: a Blinded Randomised Controlled Multicentre Trial*, 361 *LANCET* 1247-1251 (2003) (of 100 patients randomly allocated to either laparoscopic adhesiolysis (52) or laparoscopy alone (48), both groups reported substantial pain relief and significantly improved quality of life, with no difference between the groups).

⁶⁰ David R. Urbach & Peter C. Austin, *Conventional or Multilevel Analysis of Volume-Outcomes Associations for Surgical Procedures?* 195 *J. AM. COLLEGE SURGEONS* S59 (2002).

Special Populations

Oncology

Cancer patients pose a special problem. Faced with a terminal illness, the downsides of a particular drug regimen, however unproven, appear tolerable.⁶¹ These patients will take huge risks and are very gullible. Terminal patients will grasp for anything that offers some hope.⁶² A recent international joint law enforcement effort shut down a scheme by a Canadian firm providing sham cancer therapy to U.S. patients in Mexico using magnetic fields as strong as those from refrigerator magnets. Thousands of patients spent \$15,000 each, and, what is worse, precious time away from their loved ones, on these bogus treatments. Mark McClellan, the FDA Commissioner, stated that patients need to be careful about cancer treatments. Howard Beales, the director of the Federal Trade Commission's Bureau of Consumer Protection, called the scheme one of the most reprehensible seen by the FTC.

ClinicalTrials.gov, run by the National Institutes of Health, can connect cancer patients with legitimate innovative treatments.⁶³ Chemotherapy often causes significant side effects and oncologists spend considerable time managing these effects as well as the effects of the disease itself.⁶⁴

Doctors may be solely motivated by what their patients want — a chance, no matter how slim, of living longer or suffering less.⁶⁵ The same thought pattern and clinical pattern multiplied throughout the country means thousands of cancer patients across the US are getting questionably efficacious and definitely toxic treatment. Government regulations need to protect credulous patients from ineffective, but well-wishing,

⁶¹ Reed Abelson, *Drug Sales Bring Huge Profits, and Scrutiny, to Cancer Doctors*, N.Y.TIMES, Jan. 26, 2003.

⁶² Mary Papenfuss, *The Patient Or The Portfolio?* Salon.com Dec. 9, 2002 available at www.salon.com/mwt/feature/2002/12/09/clinictrials/index_np.html.

⁶³ Susan J. Landers, *Cancer center called sham, closed down*, AMNEWS STAFF March 10, 2003.

⁶⁴ *Because of this toxicity, phase I studies of new anticancer agents almost always are conducted in patients with refractory cancers, instead of healthy volunteers in specially dedicated clinical pharmacology units, which is typical of most drugs. Statement of the American Society of Clinical Oncology: Critical Role of Phase I Clinical Trials in Cancer Treatment*, (November 8, 1996) available at <http://www.asco.org>

⁶⁵ Abelson, *supra* note 61.

oncologists.⁶⁶ Terminal cancer patients are very vulnerable, and many would take questionable drugs with severe unpleasant side effects. It would be a serious disservice to cause nausea, hair loss, skin sensitivity, and recurrent infections leading to hospitalization and time away from their families in isolation wards for patients in the last few weeks of life without a corresponding benefit.⁶⁷ In a recent colon cancer study where chemotherapy was stopped after 3 months for some patients and continued indefinitely for the rest, there was no benefit in continuing therapy. Patients on intermittent chemotherapy had significantly fewer toxic effects and serious adverse events than those in the continuous group. If this data is not collected, future patients will continue to be subjected to toxic, dangerous drugs.⁶⁸

One of the few things medicine can offer is some prognostic information. Physicians may have a duty to tell patients about their prognosis.⁶⁹ In a recent survey, surgeons reported that the most common ethical dilemmas in palliative surgery involved providing patients with honest information while preserving patient choice and without destroying hope.⁷⁰

Chemotherapy drugs are very expensive and are often quite profitable for oncologists, who can make as much from selling drugs as from their medical professional services.⁷¹ This leads to a great incentive to

⁶⁶ *Recently, I met an oncologist by chance. I mentioned this paper and asked for her comments about the ubiquity of off-label use of chemotherapeutic drugs in clinical oncology. The response was "Thousands of patients will die if you banned off label drug use. What would YOU do if you had cancer and only had a month or two to live, and there is no approved drug? Of course you would try the off-label drug." I responded that in that dire circumstance, I would acquiesce to trying the off-label drug, but only in the context of a clinical study, or at least a data-gathering system, so future cancer patients could know whether to take that drug. The oncologist stated that "Most patients do not care about future patients and won't get involved in studies. They just want what's best for them." Pressing on, I asked how we know what's best for them without studying the drugs in that disease context. The reply was "We have to give them hope and try something. The drugs have gone through Phase I (toxicity) trials so they are safe." I was left with a strong impression that some oncologists may pressure patients into taking chemotherapy or feel pressure to offer chemotherapy because "Something must be done."*

⁶⁷ *Abelson, supra note 61* (in a 2001 study of cancer patients in Massachusetts, conducted by a team of researchers led by Dr. Ezekiel J. Emanuel of the National Institutes of Health, the authors found that a third of those patients received chemotherapy in the last six months of their lives, even when their cancers were considered unresponsive to chemotherapy.)

⁶⁸ *T S Maughan et al., Comparison of Intermittent and Continuous Palliative Chemotherapy for Advanced Colorectal Cancer: A Multicentre Randomised Trial*, 361 LANCET 457 (2003).

⁶⁹ *Arato v. Avedon*, 858 P.2d 598 (Cal. 1993) (Appellate court held that physicians had duty to tell pancreas cancer patient about his high chance of death; the California Supreme Court reversed, holding that physicians have no duty regarding patients' nonmedical interests).

⁷⁰ *Laurence E. McCahill et al., Decision Making in Palliative Surgery*, 195 J. AM COLL SURGEONS 411 (2002).

⁷¹ *Standard treatment for woman with HER-2 positive metastatic breast cancer (six courses of paclitaxel and trastuzumab) has a Medicare allowed amount of \$24,000. By contrast, the 2002 Medicare fee to surgeon for breast removing procedure and 3 month post-operative care is capped at \$ 653.22 to \$1168.66, depending on locale and type of procedure. Standard treatment for advanced non-small cell lung cancer is gemcitabine and cisplatin, Medicare allowed amount \$15,000. White paper, American*

recommend drugs. The AMA Ethics Guidelines recommend that no more than 25% of physician salaries should be linked to a formula, to prevent conflicts of interest. A GAO report on off label drugs noted that reimbursement policies played a role in physicians' choice of cancer therapy.⁷² Even the American Society of Clinical Oncology supports reducing the chemotherapy drug markup.⁷³

Children

Much of pediatric practice, particularly in hospitals and by specialists, has involved the off-label use of medications and educated guesses about doses, safety, and effectiveness.⁷⁴ Pediatric treatments often rely completely on off label use as clinical studies cost \$30,000 per child and pose special informed consent hurdles. Federal regulations require institutional review boards to hold pediatric studies to a higher standard; as a result, they reject some studies that might have been approved in adults.⁷⁵ This leads to the current situation, where although no drug can be approved without first undergoing extensive tests in adults, drugs taken by children are approved frequently without any pediatric testing.⁷⁶ Over 80% of all drugs prescribed for children carry orphaning clauses (disclaimers with respect to pediatric use that FDA requires because of the paucity of clinical studies involving children) in their package labels.⁷⁷

Society of Clinical Oncology, Reform Of The Medicare Payment: Methods For Cancer Chemotherapy, May 2001.

⁷² *Beck, supra* note 12 at 79.

⁷³ *White paper, American Society of Clinical Oncology, Reform of the Medicare Payment: Methods for Cancer Chemotherapy, May 2001* (and to increase the payment amounts for the related services).

⁷⁴ *Robert Steinbrook, Testing Medications in Children*, 347 N. ENG. J. MED. 1462 (2002).

⁷⁵ *Id.* at 1463.

⁷⁶ *Althea Gregory, Denying Protection to Those Most in Need: FDA's Unconstitutional Treatment of Children*, 8 ALB. L.J. SCI. & TECH. 122 (1997).

⁷⁷ *Robert Levine, ETHICS AND REGULATION OF CLINICAL RESEARCH* 241 (2d ed. 1986).

Other special populations

Some pharmacologists think minority groups need a separate standard dose, including L. DiAnne Bradford at Morehouse.⁷⁸ Gender differences may be crucial as well. Although digoxin has been used to treat heart failure for a hundred years, its effect in women was just recently studied. At first, the investigating group found no difference in death rates between heart patients who received digoxin and those who received placebo. Digging further, they found that women taking digoxin actually died more often than those on placebo did.⁷⁹ Because the study was not set up to study gender differences, digoxin for heart failure in women needs to be studied further, not just discontinued.

Off-label drugs have already been approved, so safety has already passed, but only in the context of that disease and healthy people. For example, metronidazole is tolerated by most people but not by alcoholics.⁸⁰ The FDA has been said to protect the ignorant, the unthinking, and the credulous or those who are most vulnerable and least able to fend for themselves.⁸¹ Cancer patients, children, and people with rare diseases are over represented in off-label drug treatment. These are some of the most vulnerable classes of individuals in our society, and need the highest level of protection by the government.

⁷⁸ Emily Liber, *Designer Drugs: Tailoring Medicine to Fit the Patient*, THE SCIENCES 9 (Jul/Aug 2000).

⁷⁹ Saif S. Rathore et al., *Sex-Based Differences in the Effect of Digoxin for the Treatment of Heart Failure; Trends in the Incidence of and Survival with Heart Failure; Increased Mortality among Women with Heart Failure Treated with Digoxin*, 347 N. ENG. J. MED. 1403-1411 (2002) (33% in the digoxin group vs. 28.9% in the placebo group).

⁸⁰ CS Williams & KR Woodcock, *Do Ethanol and Metronidazole Interact to Produce a Disulfiram-Like Reaction?* 34 ANN PHARMACOTHERAPY 255-257 (2000).

⁸¹ *U.S. v. Strauss*, 999 F.2d 692 (2d Cir. 1993).

Illogical interpretation of the FDCA and the FDA's mission

A drug may be regarded as new if it is offered in a new dosage form.⁸² A new indication is a much greater change than a simple dosage form. If a new dosage form requires FDA approval, it makes no sense for a new indication not to require similar approval. A drug is new if there is no general recognition of safety and efficacy or absence as to such recognition regarding a particular proposed use.⁸³ Courts give the FDA broad discretion in determining whether a new drug exists.⁸⁴ Given the judicial deference and the language, the FDA may be able to assert that a new indication for a drug classifies it as a new drug.

Drugs and their prescribing should fall under general commercial law or a higher standard, and should meet the U.C.C. merchantability guidelines to protect society from the unknown.⁸⁵ Moreover, if a physician prescribes a drug for a particular purpose, and there is reliance on his judgment, there is an implied warranty that the drug shall be fit for that purpose.⁸⁶ As an ordinary seller's judgment can be held accountable when the buyer relies on it in accepting goods which later proved ineffective for the specific purpose they were purchased for, so should the physician be held liable for his indiscriminate dispensing of medications while reassuring patients of their effectiveness.⁸⁷ Prescribing drugs in combination when they are approved singly may also be dangerous. Drinking and driving are both legal if you are of a certain age and pass state-mandated tests. In combination, they can be lethal.⁸⁸ Prescribing certain drugs or combinations for some conditions without adequate study is essentially experimentation without the usual checks.⁸⁹

If a drug's label bears inadequate directions for use, it is misbranded and therefore illegal, FDCA Section

⁸² *Wilsker*, *supra* note 14 at 844.

⁸³ *Act of June 25, 1938, ch. 675, 52 Stat. 1040, 75th Cong. (1938)*.

⁸⁴ *Farquhar v. FDA*, 616 F. Supp. 190, 193 (D.D.C. 1985).

⁸⁵ *U.C.C.* § 2-314.

⁸⁶ *U.C.C.* § 2-315.

⁸⁷ *Wilsker*, *supra* note 14 at 845.

⁸⁸ *Wilsker*, *supra* note 14 at 845.

⁸⁹ *R. Alta Charo, Human Subjects Have it Worse Than Guinea Pigs*, 46 CHRON. OF HIGHER EDUC., June 25, 1999, at A64.

502(f).⁹⁰ This provision has not been successfully applied to prevent physicians from prescribing drugs in ways other than specified on the label. The FDCA was not intended to regulate the practice of medicine but was obviously intended to control the availability of drugs for prescribing by physicians.⁹¹ This distinction is illusory. The purpose of the FD&C Act is to protect U.S. lives and control drug use. It is not to increase the freedom of physicians to practice as they see fit. The practice of medicine doctrine does not have a reasonable rationale. Protecting physicians' autonomy is not a legitimate goal of health care or drug regulation. We want physicians to treat patients with the best known drugs. This implies taking away their freedom to prescribe other, inferior, therapy. We should not be concerned that limiting physician autonomy will chill the pool of bright students who want to enter medicine.⁹² Today's HMO environment already constrains physicians. My proposal only requires adhering to excellent care, not the least expensive professionally ethical alternative treatment.⁹³ Just as physicians are not allowed to prescribe any drugs they want, they should not be authorized to prescribe a particular drug for any indication they want. The Act limits the selection of drugs available for prescription; that regulates the practice of medicine. The FDCA limits the FDA's power to regulate a physician's off-label activity but makes no distinction between safe and unsafe activity. The FDA has never abdicated the position that more direct regulation of off-label prescribing is within its power.⁹⁴ The FAA regulates pilots' behavior, and yet there is no claim that the FAA is trying to fly airplanes.⁹⁵ The 1962 amendment requires new drugs to be effective.⁹⁶ The current practice of off label drug use essentially negates the amendment.

A combination of two drugs, both of which are FDA approved for a particular indication, is considered a new

⁹⁰ 21 U.S.C. § 352.

⁹¹ *United States v. Evers*, 643 F.2d 1048 (5th Cir. 1981).

⁹² *Barbara Barzansky & Sylvia I. Etzel, Educational Programs in US Medical Schools, 2001-2002*, 288 J. AM. MED. ASS'N 1067-1072 (2002) (noting that there were 2 applicants for every acceptance, and the academic qualifications of medical students entering in 2001 were unchanged from 1999).

⁹³ *Simon Margolis, Most Cost-Effective Professional and Ethical Treatment*, HomeCare, May 1, 2002 available at homecaremag.com/ar/medical_costeffective_professional_ethical/index.htm

⁹⁴ *William L. Christopher, Off-Label Drug Prescription: Filling The Regulatory Vacuum*, 48 FOOD DRUG L.J. 251 (1993).

⁹⁵ *FAA General Operating and Flight Rules, 14 CFR § 91 (2003)*.

⁹⁶ *P.L. 87 - 781, 76 Stat 780, amending 21 U.S.C. 321(p), 355 (1962)*.

drug by the FDA.⁹⁷ If that is so, why is a drug when used for a different indication not similarly considered a new drug? In the former, at least there been study showing the both drugs are safe and effective for that indication. Physicians can prescribe both together to patients while maintaining and on label use policy only, and yet the FDA bars the combination even as an off label drug. In the latter, there is no such evidence. If a physician promotes a drug for an off-label use to other physicians, he may be misbranding it. If he authors a published study describing his new indication, there is an implied promotion. If we take the argument for the current system to heart, it would make sense for the FDA to approve drugs based solely on safety, and not effectiveness at all. The first phase of the current system should be sufficient. After all, off-label indications never pass the other phases. Even the current regimen requires effectiveness because we recognize that all drugs are dangerous; they are useful only to the extent that their benefits outweigh their risks.⁹⁸

Missed Opportunities for Furthering Medical Knowledge

Some side effects take a very long time to manifest. For example, diethylstilbestrol causes clear cell adenocarcinoma of the vagina, not in the woman taking it, but in her daughters twenty years later. An unusual disease can be traced to an unusual activity. Clear cell adenocarcinoma is rare, and its link with diethylstilbestrol ingestion was therefore noted. Similarly, *Pneumocystis* pneumonia and Kaposi's sarcoma, two rare conditions, were initially traced to homosexual behavior, and then to HIV within a few years of their emergence. Hundreds of patients have contracted infections from the receipt of neurografts or from contaminated surgical instruments.⁹⁹ It is much harder to figure out the causes of a common disease because there are so

⁹⁷ 21 U.S.C. 355 (b)1; S. Res. 194, 74th Congress, second session (1937).

⁹⁸ Beck, *supra* note 12 at 75.

⁹⁹ Donald E. Fry, *Governors' Committee deals with range of risks*, 87(2) BULL. AM. C. SURGEONS 26 (Feb. 2002) (discussing prion infections, caused by proteins, not bacteria, viruses, or other organisms).

many confounding variables. Peptic ulcer disease is now thought to be caused by a bacterium, *Helicobacter pylori*, not stress or too much red pepper.¹⁰⁰ Coronary artery disease may be caused by a Chlamydia infection.¹⁰¹ Common diseases and their causes can be teased out with data mining by health-care actuaries and statisticians. Daily use of aspirin is associated with a significant reduction in the incidence of colorectal adenomas in patients with previous colorectal cancer.¹⁰² This type of association can be noticed much earlier by large aggregated databases.

The Proposed System

Categories

We can divide FDA approval of drugs into four categories regarding a particular indication:

Category 1: FDA approved for that indication.

Physicians may prescribe drugs freely.

Manufacturers may advertise Category 1 indications.

Category 2: Not FDA approved, but there is good evidence that a drug is useful for a particular indication.

Physicians may prescribe drugs freely.

At least two suitable controlled trials must be published in peer reviewed medical journals.

Manufacturers may not advertise Category 2 indications.

Category 3: Insufficient data regarding that drug for a particular indication.

¹⁰⁰L Laïne et al., *Bismuth-Based Quadruple Therapy Using A Single Capsule Of Bismuth Biscalcitrate, Metronidazole, And Tetracycline Given With Omeprazole Versus Omeprazole, Amoxicillin, And Clarithromycin For Eradication Of Helicobacter Pylori In Duodenal Ulcer Patients: A Prospective, Randomized, Multicenter, North American Trial*, 98 AM. J. GASTROENTEROLOGY 562-567 (2003).

¹⁰¹JP Higgins, *Chlamydia Pneumoniae and Coronary Artery Disease: The Antibiotic Trials*, 78 MAYO CLINIC PROCEEDINGS 321-332 (2003).

¹⁰²Robert S. Sandler et al., *A Randomized Trial of Aspirin to Prevent Colorectal Adenomas in Patients with Previous Colorectal Cancer*, 348 N. ENG. J. MED. 883 (2003).

Physicians may prescribe drugs, but must report the use and results.

Category 4: Good evidence that a drug is not useful for that indication.

Such use is prohibited.

Evidence based medicine is gaining wide support. Restricting clinical drug use to those indications that have been shown to be effective is a part of this philosophy. Category 1 is the familiar on-label FDA approved use. Category 2 should encompass all current off-label uses. Two studies are required because medical studies usually use a $p < 0.05$ to signify a positive result. With the hundreds of journals publishing thousands of articles monthly, one out of 20 will be falsely positive. Requiring two studies reduces the risk of a false positive to one in 400. We can reduce even this level of error by the FDA's review process. Once a drug-indication set has passed the FDA process, it will rise to Category 1. For clinical physicians, there will be no practical effect. Patients will get the benefit of cutting edge treatment with a minimal delay and minimal risk (0.25%) of inappropriate therapy. Studies will still be done on Category 2 sets, as manufacturers will want to be able to promote the new indications.

Many current off-label uses fall into Category 3. That Category will lead to all new indications. In order to prevent society from pouring resources into treatments that do not work, all Category 3 uses must be reported in a de-identified manner. The data can be collated by the drug manufacturer, a governmental agency, or a researcher. These uses will then fall into either the evidence based Category 2 (if it works) or Category 4 (if it does not). Physicians should be prohibited from prescribing drugs in Category 4 without superior informed consent and a reason to repeat or further the prior studies.

Stream Of Information from Practitioners to Manufacturers to FDA

Drug manufacturers must already report adverse side effects to the FDA, which can only decrease a drug's popularity.¹⁰³ These adverse reactions are added to the drug label. The manufacturer has an ongoing duty to warn physicians of dangers newly brought to their attention.¹⁰⁴ The duty to warn of drug dangers is essential because they are not open or obvious.¹⁰⁵ Logistically it will be no harder to add indications as well, when warranted. Drug companies should be very happy to supply funds for this change in labeling.¹⁰⁶ Drug manufacturers must submit all new studies to the FDA (as is done now).¹⁰⁷ The FDA would be charged with evaluating these studies in an ongoing fashion and approve or deny new indications based on these studies, or keep them in the need further study Category 3. The FDA should take the initiative in Category 2 uses where manufacturers have little incentive (due to free riding, see below) to pursue FDA approval. That daily aspirin results in a decreased risk for a first heart attack is both well known and supported by overwhelming evidence, but this use of aspirin is off-label.¹⁰⁸

As mentioned above, the FDA once seized a textbook about chemotherapy for violating the misbranding rules.¹⁰⁹ The correct course of action should have been to analyze the recommendations in the text, work with the drug manufacturers, and approve (or disallow) the drug-indication sets or ask for more studies. Instead, most chemotherapy, even now, 10 years later, is off-label.

¹⁰³ *FDA MedWatch Program, 21 C.F.R. § 314.80(c)1 (2002)* (manufacturer must maintain a record of all adverse drug experiences for 10 years).

¹⁰⁴ *Braniff Airways, Inc. v. Curtiss-Wright Corp.*, 411 F.2d 451 (2d Cir 1969).

¹⁰⁵ *Tampa Drug Co. v. Wait*, 103 So. 2d 603, 607 (Fla. 1958).

¹⁰⁶ *Beck*, *supra* note 12 at 83.

¹⁰⁷ *21 C.F.R. § 314.81(b)2(vi) (2002)*.

¹⁰⁸ *Marvin M. Lipman, Office Visit: Using Approved Drugs for Unapproved Purposes*, CONSUMER REP. ON HEALTH at 10 (Feb. 1998).

¹⁰⁹ *James Bovard, Medical Follies at the FDA*, WASHINGTON TIMES, Dec. 20. 1994 at A17.

Fast track for New Indications of previously approved drugs

The FDA can minimize Category 2 above by scrutinizing data in a timely fashion. If the evidence is sufficient, the drug-indication combination becomes a Category 1. The FDA, with a history of careful, scientific, unbiased, authoritative analysis of available data, is well poised to aggrandize its current jurisdiction. It acknowledges that unlabeled uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature.¹¹⁰ If a use has been studied and reported extensively, the FDA should simply analyze the studies and move the use into Category 1.

Perhaps the best way would be to add a new Center for the Evaluation of Unapproved Drug Indications. This new Center should not be part of the New Drug Application section. Drug manufacturers and the FDA itself associate the NDA section with a slow costly process, and the new Center should be fast and able to evolve. It can work closely with the section that monitors currently approved drugs. That section can order new labels or even recall drugs on the basis of negative new studies.¹¹¹ It would be logical to allow that section to upgrade a drug-indication set to Category 1 based on positive studies. The FDA already reviews promotional material disseminated about drugs for off label use by the manufacturer, FDAMA Section 551c. The FDA is already evolving to become a more responsive organization. In January 2003, it launched an initiative to hasten the availability of innovative medical technologies and to reduce their development costs. The initiative will take the form of avoiding multiple cycles of FDA review, adopting a quality systems approach to reviews, and providing clearer guidance for particular diseases and emerging technologies.¹¹²

One example of an initiative that worked, but was recently struck down is the Pediatric Exclusivity Rule

¹¹⁰ 12 FDA DRUG BULLETIN 4-5 (1982) (cited in 59 FED. REG. 59,820, 59,821 (Nov. 18, 1994)).

¹¹¹ Beck, *supra* note 12 at 76.

¹¹² Press release PO3-05 January 31, 2003 available at www.fda.gov/bbs/topics/NEWS/2003/NEW00867.html.

(Rule).¹¹³ Once a manufacturer had submitted studies showing that a drug important to children was safe and effective in the pediatric population, the manufacturer gained exclusive rights not only to the studied product, but also to other formulations and dosage forms that contain the same active moiety.¹¹⁴ A 2001 FDA status report stated the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date.¹¹⁵ As of August 2002, the FDA had plans for 595 studies, mostly of efficacy, safety, or pharmacokinetics, involving more than 34,000 children.¹¹⁶ The FDA had already granted exclusivity for 63 cases in response to 71 studies.¹¹⁷ These drugs include six of the 10 most frequently dispensed prescription drugs in the United States during 2000 — atorvastatin, omeprazole, amlodipine, metformin, loratadine, and sertraline.¹¹⁸ The list also includes medications for human immunodeficiency virus infection and hepatitis. As of 2001, 10 had made substantial changes to their labeling regarding doses, safety, or use. Studies spurred by the Rule found that betamethasone, a topical corticosteroid, and propofol, a sedative, were more dangerous for children than similar agents.¹¹⁹

Pediatric exclusivity was financially rewarding to drug companies. The Wall Street Journal calculated that the studies required to gain exclusivity would likely cost hundreds of thousands to millions of dollars, but that a drug company could make hundreds of millions of dollars in sales for a top-selling medication.¹²⁰ The calculations showed that most of the patients who pay the higher prices might be adults. Kessler, the former FDA commissioner, said: There are those who think the industry is gaining too much. I would love

¹¹³ 63 FR 66632 (Dec. 2, 1998).

¹¹⁴ Robert Steinbrook, *Testing Medications in Children*, 347 N. ENG. J. MED. 1465 (2002).

¹¹⁵ Food and Drug Administration, *The Pediatric Exclusivity Provision: January 2001 Status Report to Congress*. WASHINGTON, D.C.: DEPARTMENT OF HEALTH AND HUMAN SERVICES, 2001.

¹¹⁶ Center for Drug Evaluation and Research, *Frequently Asked Questions on Pediatric Exclusivity (505a), The Pediatric Rule, and Their Interaction*. WASHINGTON, D.C.: FOOD AND DRUG ADMINISTRATION, 2001.

¹¹⁷ *Approved Active Moieties to Which FDA has Granted Pediatric Exclusivity for Pediatric Studies under Section 505a of the Federal Food, Drug, and Cosmetic Act*, WASHINGTON, D.C.: FOOD AND DRUG ADMINISTRATION, 2002.

¹¹⁸ *US Top 10 Products By Prescriptions*, Fairfield, Conn.: IMS HEALTH, 2002.

¹¹⁹ *Letter from AstraZeneca Pharmaceuticals to health care providers*. Wilmington, Del.: ASTRAZENECA PHARMACEUTICALS, March 26, 2001.

¹²⁰ R. Zimmerman, *Child play: pharmaceutical firms win big on plan to test adult drugs on kids*, WALL STREET JOURNAL, February 5, 2001 at A1.

to titrate [the financial incentives] a little more closely. In the end, getting the data is so important.... If it costs us a little more, my sense is we are willing to do it.

Unfortunately, the Rule was struck down as beyond the regulatory authority of the FDA.¹²¹ The Association of American Physicians and Surgeons, Competitive Enterprise Institute, and Consumer Alert, not any patient groups or drug manufacturers, brought the lawsuit.

Regulating MDs

We should not require submission of an IND for off label use.¹²² The current regime has too few safeguards. We need a middle road: physicians can prescribe drugs that they feel is in the best interest of their patients, but if it is in a manner that has not already been studied, then they must tell the patients of this lack of good medical science, and submit the treatment and results to an appropriate agency. Off-label applications subject the public to drug treatment as part of an uncontrolled experiment where no one is keeping track of... who's helped and who's hurt.¹²³

Category 3 drug use must be accompanied by data gathering (either in a formal study, or informally). Since most clinicians do not gather data systematically, they are not able to give their personal statistics truthfully. The 80% rate of continence and erectile function often given to prostate cancer patients for prostate surgery is probably falsely optimistic.¹²⁴ In prostate cancer, this is especially poignant, as radical prostatectomy

¹²¹ *Ass'n of Am. Physicians & Surgeons, Inc. v. United States*, 226 F. Supp. 2d 204 at 209 (DC Cir 2002) (granting plaintiffs' motion for summary judgment for lack of statutory authority to promulgate the Rule; to hold otherwise would open the door to FDA's regulation of all off-label-uses, based solely on the manufacturer's knowledge that those uses are common-place. The court also found that the Rule was inconsistent with the pediatric testing incentives reauthorized by Congress in the Best Pharmaceuticals for Children Act. Congress adopted an incentive scheme while the FDA adopted a command and control approach).

¹²² *Beck*, *supra* note 12 at 82.

¹²³ *FDA to Ease Off-Label Use Restrictions*, HEALTH LINE, June 8, 1998, available in LEXIS, News Library, ALLNWS File.

¹²⁴ *Anne Barnard, Men Seek The Truth on Prostate Treatments*, BOSTON GLOBE, Jan. 18, 2003, at A1.

may not even be helpful.¹²⁵ The public, and most patients, are not aware of the natural history of prostate cancer. A randomized study noted that the slow progression and low cancer-specific mortality rate among patients with prostate cancer require a control arm; otherwise, excellent results may be imputed to a therapy when those results may be due just to the indolence of the disease.¹²⁶

Straight financial incentives may not have an effect on physician behavior. Financial productivity incentives to physicians did not affect the performance of preventive care.¹²⁷ Neither did showing physicians how much tests or treatments cost.¹²⁸

Enhancing the information physicians rely on to make their decisions at the point of use has been shown to work for years.¹²⁹ In today's computerized society and electronic hospital information system, the latest relevant studies can be made available to physicians at the bedside.¹³⁰

Physicians usually have individual patients' narrow interests in mind. In some cases, these interests may run counter to those of society. Physicians must then be regulated so they are not placed in a position of having to place any interests over the patient's. For an individual physician facing an individual patient, it may be hard to withhold antibiotics if the symptoms could be due to a bacterial infection.¹³¹ Physicians perceive little harm in prescribing an antibiotic for a nonindicated use.¹³² Overprescription of antibiotics, as well as patient failure to comply with treatment regimens, has led to the development of drug resistant

¹²⁵ *TJ Wilt & MK Brawer, The Prostate Cancer Intervention Versus Observation Trial (PIVOT)*, 11 ONCOLOGY 1133-9 (1999, describing an ongoing study to determine whether radical prostatectomy or expectant management provides superior length and quality of life for men with clinically localized prostate cancer).

¹²⁶ *JE Johansson, Expectant management of early stage prostatic cancer: Swedish experience*, 152 J. UROLOGY 1753-6 (1994).

¹²⁷ *Wee CC et al., Influence of financial productivity incentives on the use of preventive care*, 110 AM J MED 181-7 (2001)

¹²⁸ *Bates DW et al., Does the computerized display of charges affect inpatient ancillary test utilization?* 157 ARCH. INTERNAL MED. 2501-8 (1997). *But see* Abelson, *supra* note 61 (All the evidence suggests that doctors do respond to money, said Dr. Susan D. Goold, at the University of Michigan Medical School – direct financial incentives probably do increase physician health care supply).

¹²⁹ *Bates DW et al., Potential identifiability and preventability of adverse events using information systems*, 1 J. AM. MED. INFO. ASS'N. 404-411 (1994).

¹³⁰ *JH Kim, A web-based rapid prototyping and clinical conversational system that complements electronic patient record system*, 10 MEDINFO 628-632 (2001).

¹³¹ *S. B. Markow, Penetrating the Walls of Drug-Resistant Bacteria: A Statutory Prescription to Combat Antibiotic Misuse*, 87 GEORGETOWN LAW JOURNAL 535 (1998).

¹³² *U.S. Congress, Office of Technology Assessment, Impacts of Antibiotic-Resistant Bacteria*, OTA-H-629 at 51-52 (Sept. 1995).

bacteria.¹³³ Voluntary and educational programs have met with limited success. At one hospital, restricting access to some antibiotics by requiring consultation and approval from an infectious disease specialist reduced antibiotic cost, decreased mortality due to bacterial infections, and slowed the emergence of drug resistant bacteria.¹³⁴

Tort: Admit Device or Drug Status into Evidence

As the FDA regulatory status does not affect the nature, risks, benefits, and alternatives of medical procedures or drugs, there may be no need to tell patients of the FDA status. However, the regulatory status is relevant, as it indicates that there have been at least some baseline testing and studies regarding that particular indication. It is a proxy for the direct information, but with excellent credentials.

In a medical malpractice case, showing that a physician used a drug in a Category 1 or 2 manner would be an absolute defense. This is analogous to following a practice guideline. Guidelines are generally developed by expert groups of medical scientists and practitioners after exhaustive literature searches and review of the available studies. If the drug were used in a Category 3 or 4 manner without appropriate informed consent and the safeguards of a data gathering study, the physician would be liable for resulting harm. A recent case shows that a court can hold a health care provider responsible for failing to follow such a guideline.¹³⁵

If a manufacturer could foresee that a drug would be used in an off-label fashion to a patient's detriment, it might be liable under an analogy to attractive nuisance, which creates an obligation to protect immature victims from foreseeable injuries.¹³⁶ Given the effects of severe illness, individuals facing a choice of death or

¹³³ H. C. Neu, *The Crisis in Antibiotic Resistance*, 257 SCIENCE 1065 (1992).

¹³⁴ Salom Z. Hirschman et al., *Use of Antimicrobial Agents in a University Teaching Hospital*, 148 ARCHIVES OF INTERNAL MED. 2001, 2001-07 (1988).

¹³⁵ Noble A et al., *Snyder v. American Association of Blood Banks: a re-examination of liability for medical practice guideline promulgators*, J EVAL CLIN PRACT, Feb 1998, at 49-62.

¹³⁶ J.D. Lee & Barry Lindahl. 3 MODEM TORT LAW 59 (1994).

an unapproved use of a drug may not be capable of making a mature decision with respect to untested uses of approved drugs, thereby establishing a duty for the manufacturer to take steps to prevent off-label uses.

Criticisms of the Proposed System

Enlarging the FDA will be too Complex

The FDA will need to expand to take on these additional duties. It should be done by enlarging the MedWatch section, as mentioned above. The FDA continues to monitor cleared drugs, and can order new labels or even recall a drug.¹³⁷ Despite the changing world of medicine, requiring complete labeling would not be too complex. Adverse side effects are already reported and drug labels adjusted accordingly. New indications will be far less numerous, and drug manufacturers will be eager to promote them and supply funds for this change in labeling.¹³⁸

The Proposal will Cost too Much

Any system has to be economically feasible. The proposed system will save overall health care dollars. Requiring physicians to gather data is costly, but the resulting data will be very valuable. The fact that data will be gathered will decrease questionable uses, analogous to the Hawthorne effect. Many treatments will be found to be useless, or even harmful. The overall result may well be a decrease in health care cost. We can see this in action with a single study: Osteoarthritis of the knee is a common condition in the elderly.¹³⁹ When

¹³⁷ *Beck, supra* note 12 at 76.

¹³⁸ *Id.* at 76.

¹³⁹ *Felson DT, Zhang Y, An update on the epidemiology of knee and hip osteoarthritis with a view to prevention*, 41 *ARTHRITIS RHEUMATOLOGY* 1343-55 (1998) (about 12% of adults over 65 have painful knee osteoarthritis).

medication is ineffective, arthroscopic lavage or débridement is often recommended. More than 650,000 such procedures are performed each year at a cost of roughly \$5,000 each, or more than \$3 billion annually.¹⁴⁰ Much of this is paid by Medicare. When a controlled trial was finally performed, the outcomes (pain) after arthroscopic lavage or arthroscopic débridement were no better than those after a placebo procedure.¹⁴¹ Eliminating this one procedure from Medicare reimbursement would more than double the FDA's annual budget.

Evidence based medicine is very cost-effective. In an attempt to reduce pneumonia in ventilator-dependent patients, a hospital promulgated a 10-page self-study module (from evidence-based data gleaned from the literature) that dealt with: epidemiology, risk factors, etiology, definition, methods to reduce risk, procedures for collecting sputum, and clinical and economic outcomes. The cost of the program was about \$29,000, but with the reduction in pneumonia, this actually resulted in a cost savings to the hospital of at least \$425,000.¹⁴² With the current system, we are still learning that washing your hands decreases infection rates.¹⁴³ The program costs are offset within the first two weeks by the cost savings of avoiding hospital-acquired infection. The pressure may come from private sources, perhaps even physician groups themselves, as they see that guidelines and scientific practice saves money.¹⁴⁴

We actually save even more. Finding out about and stopping ineffective treatment will save billions of dollars in direct costs as well as treatment of complications. Adverse events occur in 3% of hospitalizations,

¹⁴⁰MF Owings, LJ Kozak, *AMBULATORY AND INPATIENT PROCEDURES IN THE UNITED STATES, 1996*. VITAL AND HEALTH STATISTICS. Series 13. No. 139. Hyattsville, Md.: National Center for Health Statistics, November 1998. (DHHS publication no. (PHS) 99-1710.

¹⁴¹J. Bruce Moseley et al., *A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee*, 347 N. ENG. J. MED. 81 (2002).

¹⁴²JE Zack, et al., *Effect of an Education Program Aimed at Reducing the Occurrence of Ventilator-Associated Pneumonia*, 30 CRITICAL CARE MED. 2407-2412 (2002).

¹⁴³Lawrence Prescott, *Hospital Infections Decline Sharply with use of Alcohol-Based Hand Rub*, GEN. SURGERY NEWS, Jan. 2003 at 1.

¹⁴⁴Marc Leib, *Physician Joint Negotiations: New Possibilities/Old Prohibitions*, 15 HEALTH LAWYER 5 (Sep 2002) (describing MedSouth, a Denver Independent Physician Association whose member physicians face expulsion if they do not follow the practice guidelines).

complicating 4-19% of surgical procedures.¹⁴⁵ Adverse medical events in Utah and Colorado alone accounted for \$300 million, or 5% of their outlay, in 1996.¹⁴⁶ If we stop those procedures that have no definite benefit, we save not just the cost of the procedures, but also the cost of caring for the resulting complications.

Implementing the proposed system will be expensive, but it will be worthwhile. Medical care is expensive, taking up 14% of the gross national product. Medicare outlays totaled \$225 billion in fiscal year 2002, dwarfing the amount spent by the FDA (\$1 billion), CDC (\$4 billion), and even the NIH (\$23 billion). A 3% savings in providing health care (perhaps achieved by eliminating ineffective treatments or adverse hospital events related to questionable procedures, for example) would increase the FDA's budget five-fold with no net governmental increase.

Most new drug candidates fail to reach the market because they are too toxic, carcinogenic, ineffective, or economically nonviable. Typically, less than 1 percent of the compounds examined in the pre-clinical period make it into human testing. Only 20 percent of the compounds entering clinical trials survive the development process and gain FDA approval.¹⁴⁷ Furthermore, the full R&D process from synthesis to FDA approval involves undertaking successive trials of increasing size and complexity. The pre-clinical and clinical testing phases generally take more than a decade to complete.¹⁴⁸

Drug manufacturers spend \$403 million in research and trials for each drug that comes to market. Given the length of time to get to market, the capitalized total cost estimate is \$802 million, with time costs accounting for half of the total cost.¹⁴⁹

From the drug manufacturer's point of view, the current system provides little incentive to pursue further

¹⁴⁵ Atul Gawande et al., *The Incidence And Nature Of Surgical Adverse Events In Colorado And Utah In 1992*, SURGERY, Jul 1999, at 66-75.

¹⁴⁶ Thomas EJ et al., *Costs of medical injuries in Utah and Colorado*, 36 INQUIRY 255-64 (1999).

¹⁴⁷ Joseph A. DiMasi, *Success Rates for New Drugs Entering Clinical Testing in the United States*, 58 CLINICAL PHARMACOLOGY AND THERAPEUTICS 1-14 (1995).

¹⁴⁸ Joseph A. DiMasi, *Trends in Drug Development Costs, Times and Risks*, 29 DRUG INFORMATION JOURNAL 375-384 (1995); Kenneth I Kaitin & Joseph A. DiMasi, *Measuring the Pace of New Drug Development in the User Fee Era*, 34 DRUG INFORMATION JOURNAL 673-680 (2000).

¹⁴⁹ Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price Of Innovation: New Estimates Of Drug Development Costs*, 22 J. HEALTH ECONOMICS 151-185, (2003).

indications once it has gained approval on one and thereby has entered the market. If a manufacturer wishes to add an indication, it must apply to FDA for approval as it would for a new drug. The manufacturer of a drug with multiple uses must gain FDA approval several times before it can fully exploit its market potential. If off-label prescribing is allowed, and is rampant, adding that indication may not increase sales.¹⁵⁰

The proposed system erects barriers to the off-label market. This creates an incentive for manufacturers to continue to get approval for more indications. Many physicians will stop prescribing Category 3 drugs. They will escape the data gathering and reporting requirement and avoid the tricky informed consent talk with their patients, trying to explain that they are prescribing drugs that have not been shown to be effective. Drug manufacturers will want their Category 3 indications to move to Category 2, so physicians can prescribe them without having to gather data. They will want to then move the drugs up again to Category 1, so they can promote the new indications.

If the FDA raises its standards, a drug manufacturer may be leery of applying for a new indication if it thinks that the FDA will re-open the original Phase 1 data. However, since the FDA's mission is to protect the public, the manufacturer is at risk of stricter scrutiny regardless of any new applications.

The manufacturer that gets a new indication approved should have a period of exclusivity modeled after the Pediatric Exclusivity Rule to recoup its costs and provide incentives for further indications. After this period, other manufacturers may market the new indication as well.

The Center for the Evaluation of New Indications has to be fast and inexpensive. Given its limited jurisdiction, it can be. This prevents litigation and sanctions such as those imposed on Johns Hopkins Hospital for using unproven cardiac devices from 1985-1996.¹⁵¹

¹⁵⁰Salbu, *supra* note 16 at 181.

¹⁵¹*Justice Dept. joins suit on Medicare charges Boston Globe, Jan. 16, 2003, at A2.*

Physician Autonomy

Creating the Categories and requiring physicians to do certain additional functions for Category 3, and prohibiting prescription of Category 4 drugs outright infringes on physician autonomy. If such autonomy conflicts with the best care of the patient, it should always be abrogated. Medicine's goal is to serve patients, not to provide a vehicle for physicians' power.

Copeland's principle of the practice of medicine, off label drug use is permitted by the FDA. However, as stated above, the FAA's regulation of pilots does not elicit a similar response that the agency is trying to fly airplanes. Even though the proposed system has the practical effect of dictating medical care, it is not the practice of medicine. Medicare's coverage decisions often dictate medical treatment, but are not considered the practice of medicine.

We should trust physicians. The medical training process is long, difficult, and deters most people without the best of intentions. Intentions, training, and dedication are simply not enough. After all, we put our lives into their hands when we are ill. King Charles II of England, when he came down with the fits, was treated by a group of the most highly respected and prestigious physicians available. They used cupping, scarification, purgatives, enemas, and opened both of his jugular veins.¹⁵² Edward Gibbon, author of *The Decline and Fall of the Roman Empire*, decided to have his slowly enlarging hydrocele treated. The surgeons drained it, which is ineffective as the fluid simply reaccumulates. Shortly thereafter, the surgical site became infected, and he died very painfully thereafter.¹⁵³

Some critics are concerned that too much regulation will squelch the art of medicine. They feel that government should not constrain physicians in their clinical endeavors. The art of medicine is not to treat identical patients differently; it is the human aspect, the comforting tone of voice, and the assurance that the patient

¹⁵²RICHARD GORDON, GREAT MEDICAL DISASTERS 41-5 (1983).

¹⁵³*Id.* at 47-8.

will not go through the disease process or difficult treatment alone. It should not be treating different patients with the same preferences and diseases differently due to a physician's intuition.¹⁵⁴ Patient preference, age, and functional status are common reasons for such distinctions. George Lundberg, editor of the Journal of the American Medical Association testified before Congress that there are too many clinical variations and too much regulatory delay to allow the government to impede the physician's ability to practice in these regards when it is medically appropriate.¹⁵⁵ The last phrase is crucial. How do we know that a treatment is medically appropriate in the absence of good studies? If good science backs up the indication, it is a Category 2 use: physicians may prescribe it and the FDA needs to review the studies or commission more to place the drug into Category 1. Many uses have insufficient or poorly done anecdotal studies backing them up. Those uses are not medically appropriate if we consider medicine to be scientific. Modern medicine has a veneer of being science based. We exalt the double blind cross-over placebo-controlled randomized study, and yet the majority of medical practice has not been subjected to this type of careful analysis. Evidence based medicine is a growing phenomenon, having started in 1990 in Canada. The frightening implication is that the majority of our practice is not evidence based.¹⁵⁶

While there are occasional incompetent physicians, most errors in most disciplines are committed by well-trained, well-motivated individuals.¹⁵⁷ To minimize adverse events, health care needs to be addressed from a systems perspective. Blaming individuals is not helpful. Institutions that have a history of high reliability (nuclear aircraft carriers, air traffic control systems, and nuclear power plants) are preoccupied by failure and its prevention.¹⁵⁸ They continuously train their people to recognize and correct problems. In the off-label prescription setting, physicians are placed in a system wherein they feel that the best treatments are

¹⁵⁴ Sabo, *supra* note 29 at 10.

¹⁵⁵ *Promotion of Drugs and Medical Devices for Unapproved Uses: Hearing Before the Human Resources and Intergovernmental Relations Subcomm. of the House Comm. on Gov't Operations*, 102d CONG., 1ST SESS. 103 (1991).

¹⁵⁶ Sabo, *supra* note 29 at 12.

¹⁵⁷ David Carter, *The surgeon as a risk factor*, 326 BRIT MED J. 832 (2003).

¹⁵⁸ James Reason, *Human error: models and management*, 320 BRITISH MED. J. 768-770 (2000).

sometimes drugs that have not been approved for that indication. We need to change the system, so that best treatments are always in Category 1 or 2.

The FDA tried to get manufacturers and then professional physician associations to supply it with information, but this initiative failed. Therefore, we need this mandatory system.

Physicians are Practitioners, not Scientists

Many assertions attempt to separate medical science from clinical medicine. I will address them here.

*A physician's use of drugs off-label does not convert them into experimental or investigational products.*¹⁵⁹ Generally accepted medical treatment should not be considered experimental.¹⁶⁰ A medical ethicist claims that many drugs are prescribed for uses that are not listed on the FDA-approved package label. This does not mean that all such uses must be made the object of a formal study designed to establish safety and efficacy.¹⁶¹ Without adequate study, the drugs may turn out to be ineffective for those uses. In fact, classifying the uses as experimental would be better, as that classification implies that the practitioner must gather data and report the results. Currently, as the uses are not experimental, there is little medical progress.

*The primary purpose is to benefit the individual patient in clinical off label use.*¹⁶² This sounds good, but what we want is not purpose, it is effect. Despite this laudable purpose, if the effect of off label drug use is to harm the individual patient, who would still argue for it? If we do not mandate gathering data, how do we know what we are not harming patients more than we are helping them? Individual feelings

¹⁵⁹ 21 C.F.R. 312.3(b) and § 50.3(c).

¹⁶⁰ *Pirozzi v. Blue Cross-Blue Shield*, 741 F. Supp. 586, 590 (E.D. Va. 1990).

¹⁶¹ *Robert Levine*, ETHICS AND REGULATION OF CLINICAL RESEARCH 241 (2d ed. 1986).

¹⁶² *Beck*, *supra* note 12 at 81.

or personal experience is just not reliable enough.¹⁶³ See the above discussions about bloodletting. The history of medicine is littered with examples of clinical practices that have turned out to do more harm than good.

Practice is designed solely to help individual patients and with a reasonable expectation of success.¹⁶⁴ How can an expectation of success be reasonable, if it is not because of studies? Common sense, extrapolation (more is better, for example in antibiotics, screening, surgical margins), and personal beliefs have been shown not to work, so relying on them is unreasonable.¹⁶⁵

*Treatment in accordance with generally accepted standards is not experimental.*¹⁶⁶ But how did the treatment become generally accepted? If by any method other than rigorous studies, it is faulty. It can be termed not experimental, but it is not in the best interest of the individual patient or society at large.

*Maybe the practice of medicine is too difficult and complex to be amenable to guidelines or regulations.*¹⁶⁷ This is belied by the hundreds of guidelines, algorithms, and critical pathways that are in use today.

Passage of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) shows the public's concern with privacy regarding medical data.¹⁶⁸ The Act as implemented by the DHHS has good safeguards to prevent identifiable data from falling into inappropriate hands and severe penalties. As all health care providers must comply with HIPAA, they will be used to removing personally identifiable data. The pertinent clinical data will be available to the manufacturer, governmental agency, or researcher conducting the study without violating patient confidentiality or privacy.

¹⁶³ *Sabo, supra* note 29 at 10.

¹⁶⁴ *Beck, supra* note 12 at 81.

¹⁶⁵ *Sabo, supra* note 29 at 10.

¹⁶⁶ *Beck, supra* note 12 at 82.

¹⁶⁷ *Garnick DW et al., Can practice guidelines reduce the number and costs of malpractice claims?*, 267 J. AM. MED. ASS'N. 2602-3 (1992).

¹⁶⁸ *Public Law 104-191, Aug. 21, 1996 amending 42 U.S.C. § 1301 et seq. (providing for up to \$250,000 and 10 years in prison for obtaining or disclosing protected health information with the intent to sell, transfer or use it for commercial advantage, personal gain or malicious harm).*

Overkill: the current system works well enough

All regulations have direct and indirect costs. If the current system works, why spend more to fix what is not broken? As the many examples recited above can attest, the current system does not work.

FDA labeling changes do not make the drug any more or less able to treat a particular condition.¹⁶⁹ That is true of the initial approval process as well. We require initial approval to prove to us that the drug is effective, not to make the drug effective.

Drug safety is not an attribute that can stand alone; it always requires a backdrop of a condition or disease for which a drug, if given, is effective and does more good than harm. Therefore allowing that drug to be given for other conditions for which efficacy has not been proven, essentially negates the safety finding by the FDA. Aspirin and other nonsteroidal anti-inflammatory drugs are responsible for 7600 deaths annually,¹⁷⁰ and Tylenol 94.¹⁷¹ Even pure water can kill in at least three ways: asphyxia (drowning), intravenous administration (creating hyposmolar hemolysis and resulting kidney failure), and water intoxication by over ingestion (causing cerebral edema).¹⁷² Nitroglycerin is effective in relieving both angina and anal fissures.¹⁷³ However, it may be clinically useful only for angina, if its morbidity rate precludes it from being used for the less serious condition.

Besides oncology and pediatrics, medical conditions whose standard treatments involve extensive off-label

¹⁶⁹ *Beck, supra* note 12 at 83.

¹⁷⁰ *Robyn Tamblyn et al., Unnecessary Prescribing of NSAIDs and the Management of NSAID-Related Gastropathy in Medical Practice*, 127 *ANNALS INTERNAL MED.* 429-438 (1997).

¹⁷¹ *American Academy Of Pediatrics Committee on Drugs, Policy Statement: Acetaminophen Toxicity in Children*, 108 *PEDIATRICS* 1020-1024 (2001).

¹⁷² *JW Gardner & FD Gutmann, Fatal water intoxication of an Army trainee during urine drug testing*, 167 *MILITARY MEDICINE* 435-437 (2002).

¹⁷³ *JH Scholefield, A dose finding study with 0.1%, 0.2%, and 0.4% glyceryl trinitrate ointment in patients with chronic anal fissures*, 52 *GUT* 264-269 (2003).

use include cardiac disease,¹⁷⁴ AIDS,¹⁷⁵ dialysis,¹⁷⁶ osteoporosis,¹⁷⁷ spinal fusion surgery,¹⁷⁸ and various uncommon diseases.¹⁷⁹ Many common treatments are off label.¹⁸⁰

Much of current medical practice has not been well studied.¹⁸¹ Modern health care includes many unproven practices. Patients would be better served by proven treatment than by unproven treatment. Historically, medicine grew out of spiritual and superstitious beliefs without any rigorous evidence. Only in the nineteenth century did scientists start conducting proper medical experiments.¹⁸² As it evolved, it appears to have helped overall health. However, much of the current good health we enjoy is due more to public sanitation and infrastructure developments than individual medical treatment.

¹⁷⁴Gregory Mundy et al., *Current Medical Practice & The Food & Drug Administration*, 229 J. AM. MED. ASS'N 1744, 1746 (1974) (describing prevalence of off-label use in treating angina and hypertension). *FDA Seeking Prioritized List of Off-Label Uses Deemed Most Important by 10 Professional Societies*, 5 HEALTH NEWS DAILY 4 (May 6, 1993) (quoting letter from FDA that off-label use of beta-blockers following heart attacks has proved of immense value).

¹⁷⁵Carol Brosgart et al., *Off-Label Use in Human Immunodeficiency Virus Disease*, 12 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES & HUMAN RETROVIROLOGY 56, 57-58 (1996) (stating that more than 80% of AIDS patients are treated off-label, and more than 40% of all AIDS drugs are prescribed off-label).

¹⁷⁶*FDA and Dialyzer Makers Spar Over Device Reuse*, FOOD & DRUG LETTER, Apr. 8, 1994 (stating that 70% of dialysis patients use their equipment in an off-label manner).

¹⁷⁷*F-D-C REP* (The Pink Sheet), Dec. 20, 1993, at T&G-4 (describing osteoporosis treatments as the most commonly reported off-label use by manufacturers to FDA).

¹⁷⁸*Pedicle Screws*, 21 FDA MED. BULL. 10 (1994) (stating that off-label use of bone screws occurs in a large portion of the 30,000 to 70,000 spinal stabilization procedures performed annually). See, e.g., *American Academy Of Orthopedic Surgeons, Position Paper* (Oct. 27, 1993) (surgery utilizing pedicle screws represents the best available treatment for patients).

¹⁷⁹Abbey S. Meyers, Pres., *National Org. for Rare Diseases, Inc., Prepared Testimony Before Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. on Gov't Reform and Oversight* (Sept. 12, 1996) (stating that most diseases afflicting fewer than 200,000 Americans have no FDA-labeled treatment and 90% of patients must rely on off-label uses to have any treatment at all).

¹⁸⁰See, e.g., Katie Rodgers, *Dealing with Incontinence*, 140 DRUG TOPICS 114 (1996) (six of seven treatments for urinary incontinence in guidelines of Agency for Health Care Policy & Research are off-label uses); Doug Podolsky, *Doing Double Duty*, U.S. NEWS & WORLD REP., June 26, 1995, at 62-63 (listing six common off-label uses of drugs); Richard Palmer & Shanthi Gaur, *Off-Label Use of Prescription Drugs & Devices*, RX FOR DEF., Spring 1995, at 4, 5 (listing five common off-label uses of drugs and three common off-label uses of medical devices); Ricahrd Samp & Alan Slobodin, *FDA Censorship Threatens Patient Medical Care*, 77 CONSUMER'S RES. MAG. 16 (1994) (listing medically accepted off-label uses for 28 common drugs); *Some Drugs' Unapproved Uses Bring Results*, CHARLESTON GAZETTE, Oct. 31, 1994, at 3B (listing 10 double-duty drugs with common off-label uses); S. Carrell, *Unapproved Uses for Drugs Decrease with Time on Market*, 137 DRUG TOPICS 44 (1993) (looking at the 22 most-prescribed drugs in 1989, off-label prescriptions totaled more than 50% for 6 drugs and more than 20% for 11 drugs); Cosprophar, 32 F.3d at 692 (45% of sales of Retin-A, a drug approved for acne, are for off-label treatment of aged skin).

¹⁸¹*Sabo, supra* note 29 at 12 (describing that 14 of the first 16 surgical procedures critically examined have insufficient data on safety and efficacy).

¹⁸²Harold Cook, *From the Scientific Revolution to the Germ Theory*, in THE OXFORD ILLUSTRATED HISTORY OF WESTERN MEDICINE 97 (Irvine Loudon ed., 1997) (describing Claude Bernard and François Magendie's experiments of vegetable extracts on animals).

Slow Down Medical Research

New uses are often discovered after the FDA approves a package insert. Valid new uses are often discovered serendipitously.¹⁸³ We want to encourage this, but even more uses will be found if data is collected systematically. Proponents of the current system worry that medical discovery will be slowed if it has to heed the FDA's regulatory machinery.¹⁸⁴ They assert that forcing physicians to obtain FDA approval before prescribing drugs may create havoc with the practice of medicine.¹⁸⁵ But if we think about this closely, new uses in clinical practice can only be discovered when either (1) a doctor notices an unexpected beneficial side effect to a patient who is being given a drug for a labeled use, or (2) a doctor decides to try a drug on a patient for that purpose without any prior studies supporting it and without conducting a study. The only rational conclusion from the first scenario is to undertake a proper study and see if the serendipitous effects hold up in the long run. Spreading the word informally without requiring follow-up is very dangerous. The latter scenario is human experimentation done poorly, as the clinician will not follow the patients as closely and report his findings as well as if he were doing a formal study.

Unclear studies

Even high quality research does not always point to a specific answer. Clinical practice guidelines are important to facilitate evidence-based practice. These guidelines are statements generated to assist in decisions about appropriate health care for specific clinical circumstances. High-quality evidence based on research data is essential to the development of clinical practice guidelines. Oncologists are fortunate that therapy

¹⁸³ *Beck, supra* note 12 at 77.

¹⁸⁴ *General Accounting Office, Report To The Chairman, Comm. On Labor And Human Resources, U.S. Senate, Off-Label Drugs: Reimbursement Policies Constrain Physicians In Their Choice Of Cancer Therapies* 11 (1991).

¹⁸⁵ *Beck, supra* note 12 at 79.

of breast cancer has benefited from randomized clinical trials, the highest level of evidence.¹⁸⁶ Two well respected bodies, the National Institutes of Health Consensus Development Conference and the 2001 Seventh International Conference on Adjuvant Therapy of Primary Breast Cancer reviewed the excellent randomized clinical trials, the highest level of evidence, for early stage breast cancer. Despite reviewing identical data, they arrived at slightly different practice guidelines.¹⁸⁷

As long as the guideline development process subscribes to some basic tenets, practitioners can deal with slight discrepancies.¹⁸⁸ In the proposed system, as long as there are good studies to support a treatment, the fact that there may not be universal consensus should not keep us from acting. In ambiguous situations, clinicians use their judgment; choosing either option is acceptable. It is unacceptable for clinicians to recommend treatment that has been shown not to be effective, or uncertain treatment without gathering data. Financial conflicts of interest are common in biomedical research; studies from researchers that have a significant industry association are three fold more likely to be in favor of the industry than those without.¹⁸⁹ Several cancer researchers, including clinical investigators enrolling patients, invested heavily in the companies making the investigational drugs.¹⁹⁰ Physicians can collect up to \$10,000 for each patient they enroll in a clinical study.¹⁹¹

What about ambiguous results that do not show whether a particular adverse reaction is actually due to a drug, or a definite answer to the risk/benefit profile? In these situations, the drug-indication set remains in

¹⁸⁶ Nancy E. Davidson & Mark Levine, *Breast Cancer Consensus Meetings: Vive la Difference?* 20 J. CLINICAL ONCOLOGY 1719-1920 (2002).

¹⁸⁷ *Id.* (noting that the NIH guidelines recommended no endocrine treatment for premenopausal women with receptor-positive breast cancer, while the panelists at St Gallen emphasized the role of endocrine therapy, especially ovarian ablation/suppression).

¹⁸⁸ *Id.* The authors must describe the sources of their research evidence. They must explicate the reasoning behind all recommendations. They must provide level 1 evidence (at least one large randomized trial with a clear difference in outcomes or a well-conducted meta-analysis of many randomized trials).

¹⁸⁹ Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 J. AM. MED. ASS'N. 454-465 (2003)

¹⁹⁰ Papenfuss, *supra* note 62 (describing how M.D. Anderson Cancer Center president John Mendelsohn used his ImClone holdings to make \$6.3 million and University of Pennsylvania's Institute for Human Gene Therapy's James Wilson made \$13.5 million in stock from Genovo, which markets the gene technique used on 18-year-old Jesse Gelsinger, who died at the Institute from viral gene therapy in 1999).

¹⁹¹ *Id.* (noting that the fees can become a major source of income for doctors).

Category 3 awaiting further testing.

Tort system is not a good policing device

Courts sometimes offer tort law and medical ethics as a remedy to ensure appropriate treatment. That argument proves too much: if tort law is truly sufficient, why regulate physicians and drug manufacturers at all? Negligence is very poorly correlated with bringing malpractice claims.¹⁹² It is also poorly correlated with claims outcomes.¹⁹³ Outcomes correlate much more with patient disability, suggesting that the tort system is being used as insurance, rather than deterrence.¹⁹⁴ As an insurance mechanism, it is inefficient and costly, with patients getting less than half of the money expended. A deeper issue is how the tort system can work in the absence of data, and especially in the presence of a system that does not even gather the necessary data. At trial, juries are faced with a decision when there has been a bad outcome, with dueling expert witnesses. They decide the standard of care by siding with one party or the other. How can a set of laypeople figure out whether a particular drug should or should not have been prescribed in the express absence of this knowledge among the learned? This does not seem to be a logical constraint upon physician prescribing.

¹⁹²DM Studdert, *Negligent care and malpractice claiming behavior in Utah and Colorado*, 38 MED CARE 250-60 (2000) (97% of patients who suffered negligent injury did not sue, while 78% of suits were brought without any negligent behavior).

¹⁹³Localio AR et al., *Relation between malpractice claims and adverse events due to negligence. Results of the Harvard Medical Practice Study III*, 326 N. ENG. J. MED. 245-251 (1991).

¹⁹⁴Brennan TA et al., *Relation between negligent adverse events and the outcomes of medical-malpractice litigation*, 335 N. ENG. J. MED. 1963-7 (1996).

Implementing the Proposed System

Repeal FDAMA § 214

The FDAMA Section 214 states that a statute cannot limit the authority of the physician to prescribe anything to a patient. There is little legitimate justification for this statute. We do not want to stifle new uses of approved drugs. The FDA wrote valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations.¹⁹⁵ Having only well-meaning, bright, dedicated individuals in the medical field is just not enough of a safeguard. Witness the bloodletting, done by premier physicians who were trying their best to cure George Washington of his pneumonia. They all probably saw a few people improve with their methods. The nature of medicine and health is such that 80% of all ailments improve spontaneously. Humans, with a strong drive to link temporal events with causation, will infer that their intervention caused the improvement. To overcome the placebo effect and the natural history of symptoms, we must require well-conducted studies as a basis for medicine. Anything less is experimentation. This by itself is not bad; it just must include mandatory data gathering and reporting for real medical progress.¹⁹⁶ Congress has partially addressed the off label problems, at least for devices, in mandating disclosure of harms arising from off label uses reasonably likely to arise, but only for five years, and not for drugs at all.¹⁹⁷ There is no plausible reason for treating devices and drugs differently here. Many more drugs than devices are used off label, so a similar requirement would be a greater burden on drug manufacturers than device manufacturers. Exactly because off label drug use is so prevalent, it puts many more patients at risk. Therefore, it needs to be at least as regulated as devices.

¹⁹⁵ 12 FDA DRUG BULLETIN 4-5 (1982) (cited in 59 FED. REG. 59,820, 59,821 (Nov. 18, 1994)).

¹⁹⁶ *Beck*, *supra* note 12 at 72.

¹⁹⁷ 21 U.S.C. 360C(i)(1)E(i)

Partial transition system

So many chemotherapy drugs are used off-label that for an interim period we can implement an automatic system whereby if two trials in peer reviewed journals support that indication, the drug will be presumed to be in Category 1. If there is not even this minimal level of evidence, then the drug cannot be considered the standard of care, and must be used in a clinical trial setting or with informed consent including a message conveying that “This use of this drug has not been shown to work and may do more harm than good. FDA currently recommends using it only in a controlled study.”

For pediatric off-label use, the FDA, Congress, and the White House administration agree that more drugs needs to be tested and placed into Category 1 (or 4). The Best Pharmaceuticals for Children Act (BPCA) endorses the goal of increasing the number of drugs studied in pediatric populations.¹⁹⁸ The BPCA creates a six-month marketing exclusivity for a manufacturer that tests appropriate drugs on a pediatric population.¹⁹⁹ It does not authorize the FDA to require manufacturers to conduct pediatric testing, and the FDA lost a recent case when it tried to do so.²⁰⁰ In compliance with the BPCA, the Department of Health and Human Services (DHHS) will begin testing a dozen drugs commonly prescribed for pediatric use.²⁰¹ So far, these drugs have only been studied in adults despite their frequent use in the pediatric population.

In the mature system, unapproved uses would not be allowed at all. They would be per se malpractice. In a transitional period, physicians can prescribe off label, but if there is harm leading to a claim, the status of the drug can be admissible in court as evidence that it has not been studied well enough for that indication to be a standard treatment. Physicians would have to disclose drug status to patients, and report results to the drug manufacturer. Any adverse results would be reported to the government (as is already required by

¹⁹⁸ *Public Law No. 107-109, 115 Stat. 1408 (2002).*

¹⁹⁹ *citing 21 U.S.C. § 355a(a), (c).*

²⁰⁰ *Ass’n Of Am. Physicians & Surgeons, Inc. v. United States*, 226 F. Supp. 2d 204 at 209 (DC Cir 2000).

²⁰¹ *Press Release available at <http://www.hhs.gov/news/press/2003pres/20030121.html>*

MedWatch). In the mature system, there would be no reimbursement for off label uses. On the other side, prescribing a drug in accordance with practice guidelines and indicated uses would be a complete defense. Patients may refuse widely accepted therapies when they are told that they are off-label.²⁰² This active involvement should be welcomed, as physicians can then educate patients about the data they are relying on for those recommendations. If they have no data, they should reevaluate their recommendation. For current off label uses that are standard of care by virtue of being recommended by institutes, texts and professional organizations, the FDA needs to review the relevant studies and add those uses if appropriate. The Center for Medicare and Medicaid Services already only pays if the treatment is reasonable and necessary. We can expand this so that only Category 1 and 2 indications are covered for prescription drugs. They pay for treatment listed in major drug compendia.

In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, the United States Supreme Court cited publication in a peer-reviewed journal as one of several factors that judges can consider when asked to admit novel scientific evidence.²⁰³ Congress can repeal the Copeland doctrine and pass narrower legislation allowing a drug to be considered as Category 2, and therefore able to be freely prescribed for a particular indication, when it had been found useful in two published studies in peer reviewed medical journals.²⁰⁴ The Food and Drug Administration Modernization Act of 1997 allows drug manufacturers to disseminate such studies even regarding off-label use.²⁰⁵ Under the FDAMA, manufacturers have three years to perform safety studies on off-label drug uses and acquire FDA approval.²⁰⁶ The FDA would still be charged with shepherding the drug-indication coupling into Category 1 (or down to Category 4), as being published is not proof of

²⁰² *Beck, supra* note 12 at 85.

²⁰³ 509 U.S. 593-4 (1993).

²⁰⁴ Lars Noah, *Sanctifying Scientific Peer Review: Publication As A Proxy For Regulatory Decisionmaking*, 59 U. PITT. L. REV. 677 (1998).

²⁰⁵ *Pub. L. No. 105-115, § 401(a), 111 Stat. 2296, 2356-65 (codified at 21 U.S.C. § 360aaa)*.

²⁰⁶ Bruce Ingersoll, *Congress Clears Bipartisan Bill to Speed FDA Review of New Drugs and Devices*, WALL ST. J., Nov. 10, 1997, at B12.

impeccable quality.²⁰⁷ The FDA should also conduct studies, and mandate post-marketing surveillance.²⁰⁸

Conclusion

The current system allows drugs that are safe and effective for one indication to be used for any other indications without adequate safeguards. The system I describe has safeguards, and advances medical science, decreases overall societal costs, and improves health care delivery, at the cost of physician autonomy and perhaps an additional burden on drug manufacturers.

²⁰⁷ *Marilyn Chase, FDA Reform May Open a Door to Abuses in Drug Promotions*, WALL ST. J., Sept. 29, 1997, at B1 (quoting Arthur Relman, former editor of the N. ENG. J. MED. as saying, All this pious reference to peer-reviewed literature is nonsense.... A lot that passes for peer-reviewed literature isn't very good).

²⁰⁸ *Apryl A. Ference, Rushing to Judgment on Fen-Phen and Redux: Were the FDA, Drug Manufacturers, and Doctors too Quick to Respond to Americans' Infatuation with a Cure-All Diet Pill for Weight Loss?* 9 ALB. L.J. SCI. & TECH. 109 (1998).