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OLD LEGACIES AND NEW PARADIGMS: CONFUSING “RESEARCH” AND “TREATMENT” AND ITS CONSEQUENCES IN RESPONDING TO EMERGENT HEALTH THREATS

GAIL H. JAVITT, J.D., M.P.H.*

I. INTRODUCTION

During Operation Desert Storm, as the 1991 Gulf War campaign is known, United States military leaders feared that Saddam Hussein would unleash biological or chemical agents against United States troops.¹ Saddam was known to have used chemical agents against his own population, and available intelligence suggested he also might have biological weapons capabilities.² Two types of threats in particular were identified: (1) biological agents, including anthrax and botulinum toxin; and (2) chemical nerve agents, such as sarin, soman, tabun, and VX.³

To protect troops against these threats, the military sought to administer two agents that it believed constituted “the best preventive or therapeutic treatment” available.⁴ These were the drug pyridostigmine bromide (PB), and the botulinum toxoid (BT) vaccine.⁵ However, at the time neither of these agents was approved by the Food and Drug Administration (FDA), at least for the uses under consideration by the Department of Defense (DOD).⁶ PB is approved by FDA for treatment of myasthenia gravis (a neuromuscular transmission disorder) and for

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1. RICHARD A. RETTIG, *MILITARY USE OF DRUGS NOT YET APPROVED BY THE FDA FOR CW/BW DEFENSE: LESSONS FROM THE GULF WAR* xi, 2 (1999).

2. *See id.*

3. *Id.*

4. *Informed Consent for Human Drugs and Biologics*, 55 Fed. Reg. 52,814, 52,814 (Dec. 21, 1990).

5. *See* COMMITTEE ON HEALTH EFFECTS ASSOC. WITH EXPOSURES DURING THE GULF WAR, *INST. OF MED., GULF WAR AND HEALTH: DEPLETED URANIUM, PYRIDOSTIGMINE BROMIDE, SARIN, VACCINES* 34 (Carolyn E. Fulco et al. eds., 2000) [hereinafter *GULF WAR & HEALTH*] (noting that troops were given PB and BT when they arrived in the Persian Gulf), www.nap.edu/openbook/030907178X/html/R1.html (last visited Feb. 24, 2005).

6. Press Release, FDA, *FDA Approves Pyridostigmine Bromide as Pretreatment Against Nerve Gas* (Feb. 5, 2003), <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00870.html> (last visited Feb. 24, 2005); RETTIG, *supra* note 1.

use in reversing some effects of certain anesthetics.⁷ In this instance, however, DOD sought to use it as a pre-treatment to mitigate the effects of nerve agent exposure.⁸ DOD had filed an "investigational new drug" (IND) application with FDA for this use of PB in 1984, but the IND was still pending.⁹ Similarly, BT, which had been used for over a decade by individuals in certain agricultural occupations at risk for botulism, was, as a formal matter, the subject of an IND held by the Centers for Disease Control and Prevention (CDC).¹⁰

Perhaps foreseeing that administering products labeled investigational to troops could be controversial, DOD first sought authority from FDA to administer these products to troops.¹¹ DOD's Assistant Secretary for Health Affairs submitted a letter to FDA in which the agency requested the authority to administer IND products to troops.¹² Further, DOD requested that FDA provide a mechanism to

7. See CENTER FOR DRUG EVALUATION AND RESEARCH, FDA, MESTINON PRODUCT INFORMATION (1995), <http://www.fda.gov/cder/foi/label/2001/11665s15lbl.pdf> (last visited Feb. 24, 2005).

8. GULF WAR & HEALTH, *supra* note 5, at 207.

9. RONALD E. CLAWSON, CHEMICAL BIOLOGICAL MEDICAL SYSTEMS (CBMS), PYRIDOSTIGMINE BROMIDE: HOW WE GOT HERE AND WHAT'S NEXT AFTER LICENSURE OR AND YOU THOUGHT YOU WERE DONE WITH PB (2003), <https://mrhc.detrick.army.mil/docs/rcq/HSRRBOfSite03/Pyridostigmine%20Bromide%20Ron%20Clawson.ppt> (last visited Feb. 24, 2005).

10. *Researchers Search for Answers About Possible Adverse Effects of Vaccinations, Including Anthrax and Botulinum*, GULF WAR REV. (Veteran's Admin.) (photo. reprint) (May, 2001), available at <http://www1.va.gov/gulfwar/docs/GRiskFactor7.doc> (last visited Feb. 24, 2005).

11. DOD arguably could have taken the position that FDA permission was not required for the administration of unapproved products for therapeutic purposes under conditions of imminent combat. While the two agencies operated under a Memorandum of Understanding (MOU) concerning clinical testing of investigational products by the military, Memorandum of Understanding Between the Department of Defense and the Food and Drug Administration, 52 Fed. Reg. 33,472, 33,473 (Sept. 3, 1987), DOD could have argued it was not applicable in this situation. DOD could have, if challenged, asserted that distribution of drugs under these circumstances does not constitute distribution in "interstate commerce" within the meaning of the Food, Drug & Cosmetic Act. Furthermore, a court might have determined that the decision to administer products considered investigational by FDA for the purpose of force protection was within the sole discretion of the military and therefore nonjusticiable. See *Doe v. Sullivan*, 756 F. Supp. 12, 14-15 (D.D.C. 1991), *rev'd on other grounds* 938 F.2d 1370 (D.C. Cir. 1991) (rejecting service member's challenge to Interim Rule 50.23(d) on the basis that the military's decision to administer unapproved drugs to troops was "precisely the type of military decision that courts have refused to second-guess").

12. Informed Consent for Human Drugs and Biologics, 55 Fed. Reg. at 52,814. The letter stated, in part:

These are not exotic new drugs; these drugs have well-established uses (although in contexts somewhat different from our requirements) and are believed by medical personnel in both DoD and FDA to be safe. For example, one product consists of a very commonly used drug packaged in a special intramuscular injector to make it readily useable by soldiers on the battlefield. Another example involves a vaccine long recognized by the Centers for Disease Control as the primary preventive treatment available for a particular disease, but the relative infrequency of its use has slowed the accumulation of sufficient immunogenicity data to yet support full licensing of the product. Still another example involves a drug in common use at a particular dosage level, but to preserve alertness of the soldiers, we prefer a lower-dosage tablet, which is not an FDA approved

waive the requirement of informed consent “in cases in which it is established that military combat exigencies make that necessary.”¹³ DOD argued that its purpose in administering the products was to protect troops against the chemical and biological threats they could potentially encounter.¹⁴ Because of this therapeutic purpose, DOD concluded that their use did not constitute “research involving a human being as an experimental subject” within the meaning of DOD regulations governing human subjects research,¹⁵ and consent was therefore not required.

product. FDA personnel have been extremely cooperative and supportive in reviewing our proposed protocols for these products, quickly providing favorable responses to all of our submissions to date.

Id.

13. *Id.* at 52,815. The letter further articulated the rationale justifying DOD’s request:

FDA assistance is also needed on the issue of informed consent. Under the Federal Food, Drug and Cosmetic Act, the general rule is that, regardless of the character of the medical evidence, any use of an IND, whether primarily for investigational purposes or primarily for treatment purposes, must be preceded by obtaining informed consent from the patient. The statute authorizes exceptions, however, when the medical professionals administering the product “deem it not feasible” to obtain informed consent.

Our planning for Desert Shield contingencies has convinced us that another circumstance should be recognized in the FDA regulation in which it would be consistent with the statute and ethically appropriate for medical professionals to “deem it not feasible” to obtain informed consent of the patient—that circumstance being the existence of military combat exigencies, coupled with a determination that the use of the product is in the best interest of the individual. By the term “military combat exigencies”, we mean military combat (actual or threatened) circumstances in which the health of the individual, the safety of other personnel and the accomplishment of the military mission require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual’s personal preference for no treatment or for some alternative treatment.

Id. at 52,814-15.

14. *See id.* at 52,815.

15. 10 U.S.C.A. § 980 (West 1998 & Supp. 2004). At the time of the Gulf War, DOD’s governing statute, 10 U.S.C. § 980, provided that funds appropriated to the Department of Defense could not be used for research involving a human being as an experimental subject unless the informed consent of the subject was obtained in advance, or, “in the case of research intended to be beneficial to the subject,” the “informed consent of the subject or a legal representative of the subject” was obtained in advance. *Id.* When faced with the issue of administering IND drugs to military personnel, Robert Gilliat, the Assistant General Counsel of DOD, concluded in a memorandum that “the proposed uses of the drugs in question are, in fact, primarily treatment uses, not uses primarily for investigational or research purposes.” RETTIG, *supra* note 1, at 21 (quoting Memorandum from Robert L. Gilliat, Memorandum for the Assistant Secretary of Defense (Health Affairs), “Applicability of Human Subject Research Restrictions to Potential Medical Treatments in Connection with Operation Desert Shield,” (Sept. 14, 1990). Additionally, the memorandum stated:

In connection with the potential need in Operation Desert Shield for certain treatment uses of the several drugs classified as INDs, it is clear that very unusual circumstances are present. The drugs have all progressed through FDA’s IND process sufficiently to establish a high level of confidence on the part of the DOD medical community; the potential effects of the chemical and biological weapons widely reported as available to the Iraqi military are deadly; and the proposed uses, if approved by the FDA, will reflect the best scientific and medical judgment of the U.S. Government.

Id. In 2001, Congress amended 10 U.S.C. § 980 to include a new subsection (b), which provides:

Unlike the case with civilians, the consent of military personnel is not required to administer standard medical treatments.¹⁶

While FDA had in other circumstances authorized the administration of IND products for treatment purposes,¹⁷ DOD's request that FDA waive the requirement of informed consent in this context was without regulatory precedent. FDA's informed consent regulations contain exceptions in circumstances where consent is not "feasible," but this exception had previously been narrowly limited to cases of clear incapacity under emergent conditions.¹⁸ DOD's interpretation of infeasibility, by contrast, included competent military personnel whose refusal of what DOD considered to be the best available treatment would constitute an unacceptable threat to other personnel and to combat objectives.¹⁹

The Secretary of Defense may waive the prohibition in this section with respect to a specific research project to advance the development of a medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws.

10 U.S.C.A. § 980(b) (West 1998 & Supp. 2004).

16. See DEP'T OF THE ARMY, ARMY COMMAND POL'Y: ARMY REGULATION 600-20, § 5-4 (May 13, 2002), http://www.army.mil/usapa/epubs/pdf/r600_20.pdf (last visited Feb. 24, 2005). The Regulation also states that "a soldier on active duty or active duty for training will usually be required to submit to medical care considered necessary to preserve his or her life, alleviate undue suffering, or protect or maintain the health of others." *Id.*

17. See *infra* notes 84-99 and accompanying text; Treatment Use of an Investigational New Drug, 21 C.F.R. § 312.34 (2004).

18. General Requirements for Informed Consent, 21 C.F.R. § 50.20 (2004) provides that "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative." *Id.* Prior to the Interim Rule, section 50.23(a) provided that consent "shall be deemed feasible" unless both the investigator and a non-participating physician certify in writing that:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article. (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject. (3) Time is not sufficient to obtain consent from the subject's legal representative. (4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

21 C.F.R. § 50.23(a).

19. See Informed Consent for Human Drugs and Biologics, 55 Fed. Reg. at 52,815. The Assistant Secretary's request stated:

In all peacetime applications, we believe strongly in informed consent and its ethical foundations. In peacetime applications, we readily agree to tell military personnel, as provided in FDA's regulations, that research is involved, that there may be risks or discomforts, that participation is voluntary and that refusal to participate will involve no penalty. But military combat is different. If a soldier's life will be endangered by nerve gas, for example, it is not acceptable from a military standpoint to defer to whatever might be the soldier's personal preference concerning a preventive or therapeutic treatment that might save his life, avoid endangerment of the other personnel in his unit and accomplish the combat mission. Based on unalterable requirements of the military field commander, it is not an option to excuse a non-consenting soldier from the military mission, nor would it be defensible militarily – or ethically – to send the soldier unprotected into danger.

Id.

FDA granted the Assistant Secretary's request while imposing several conditions. FDA's Interim Rule 50.23(d), issued in 1990, included time-limits on the period of waiver, the requirement that requests for waiver be made in writing, IRB review of the proposed administration of an IND product to troops, and the maintenance of records regarding product administration.²⁰ Following the issuance of the Interim Rule, DOD submitted, and FDA granted, specific waiver requests for PB and BT.²¹

Although a federal appellate court upheld FDA's decision as a proper exercise of the agency's authority,²² critics argued at the time, and continue to

20. *Id.* at 52,817. Under the Interim Rule, any waiver request was "limited to a specific military operation involving combat or the immediate threat of combat," and time-limited to twelve months, and any determination that obtaining consent was NOT feasible was similarly limited. *Id.* Requests were required to include written justification supporting the conclusions of the military physician and investigator identified in the IND that:

[A] military combat emergency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate the accomplishment of the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or some alternative treatment.

Id. The requests were required to include a statement that an institutional review board (IRB) had reviewed and approved the use of the investigational product without consent. *Id.* FDA Commissioner could grant the request "only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy." *Id.* In making the determination, the Commissioner would consider:

(i) the extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use; (ii) the context in which the drug will be administered, e.g., whether it is intended for use in a battlefield or hospital setting or whether it will be self-administered or will be administered by a health professional; (iii) the nature of the disease or condition for which the preventive or therapeutic treatment is intended; and (iv) the nature of the information to be provided to the recipients of the drug concerning the potential benefits and risks of taking or not taking the drug.

Id. FDA also exempted DOD from many of the record-keeping requirements usually mandated for administration of IND products. RETTIG, *supra* note 1, at 19. DOD contended that detailed record-keeping regarding what products were administered, when, and to whom, were not possible under conditions of battle. *Id.* FDA agreed to waive or reduce some of the record-keeping requirements, and DOD appears to have agreed, before the fact, to conduct some degree of record-keeping. *Id.* Notwithstanding prior agreements, however, DOD was later faulted for its inadequate record-keeping, which impeded the ability to study the possible health-effects experienced by veterans. DOD also requested a waiver from the labeling requirements for IND products. *Id.* at 17. Such products ordinarily must contain language stating "Caution: New Drug - Limited by Federal (or United States) law to investigational use." Labeling of an Investigational New Drug, 21 C.F.R. § 312.6(a) (2004). DOD argued that this language would undermine soldiers' confidence in the product and even encourage non-use. RETTIG, *supra* note 1, at 17. FDA therefore permitted different labeling that stated "FOR MILITARY USE AND EVALUATION." Human Drugs and Biologics; Determination That Informed Consent Is NOT Feasible or Is Contrary to the Best Interests of Recipients, 64 Fed. Reg. 54180, 54,184 (Oct. 5, 1999) (to be codified at 21 C.F.R. pts. 50 and 312).

21. *Id.* at 54,183-84.

22. *Doe v. Sullivan*, 756 F. Supp. 12 (D.D.C. 1991). In *Sullivan*, the district court rejected a service member's challenge to Interim Rule 50.23(d) on the basis that the military's decision to administer unapproved drugs to troops was "precisely the type of military decision that courts have repeatedly refused to second-guess." *Id.* at 15. While the appellate court reversed the lower court's

maintain, that FDA was complicit in serious ethical violations perpetrated by DOD against its personnel.²³ While criticism may have been fueled in part by concerns that unapproved treatments could have been a causal factor in Gulf War Syndrome,²⁴ critics also insist that the use of investigational products constitutes human experimentation and is categorically prohibited, both ethically and legally, unless all the requirements for human subjects protection, including the requirements for informed consent, are met.²⁵ They consider the unconsented-to administration of an investigational product to be a per se violation of human rights, and ground this position in the first principle of the Nuremberg Code.²⁶

This paper takes issue with that claim. It argues that horrific atrocities of the past are a poor paradigm when considering the therapeutic use of investigational products in emergent circumstances. While there should be, in 2004, no dispute that using another human being solely as a means in the service of gaining scientific knowledge is ethically abhorrent, this principle does not shed light on how to resolve the vexing problem of ensuring the timely availability of safe and effective therapeutic agents to protect both military personnel and civilians from emergent health threats – both those that are the result of bioterrorism and those that are of natural origin. In addition, as a purely definitional matter, the administration of a product for the purpose of treatment cannot constitute “research” as it is currently defined in federal regulations.

This paper posits instead a new regulatory paradigm, one that draws clear lines between research and treatment activities, and that recognizes that a product’s

finding on review because it construed the petitioners’ case as a challenge to the authority of FDA, not DOD, it did not refute the lower court’s assertion that the underlying decision whether or not to administer the drugs was within the sole discretion of the military. *Doe v. Sullivan*, 938 F.2d 1370 (D.C. Cir. 1991).

23. See, e.g., George J. Annas, *Blinded By Bioterrorism: Public Health and Liberty in the 21st Century*, 13 HEALTH MATRIX 33 (2003) [hereinafter Annas, *Blinded by Bioterrorism*]; George J. Annas, *Protecting Soldiers from Friendly Fire: The Consent Requirement for Using Investigational Drugs and Vaccines in Combat*, 24 AM. J.L. & MED. 245 (1998) [hereinafter Annas, *Protecting Soldiers from Friendly Fire*]. See also Michael J. O’Connor, Note, *Bearing True Faith and Allegiance? Allowing Recovery for Soldiers Under Fire in Military Experiments that Violate the Nuremberg Code*, 25 SUFFOLK TRANSNAT’L L. REV. 649 (2002); Claire A. Milner, Comment, *Gulf War Guinea Pigs: Is Informed Consent Optional During War?*, 13 J. CONTEMP. HEALTH. L. & POL’Y 199 (1996); Robyn Pfort Ryan, *Should Combat Troops Be Given the Option of Refusing Investigational Drug Treatment?*, 52 FOOD & DRUG L. J. 377 (1997); Suzanne B. Seftel, *Waiving for the Flag: Should Informed Consent Rules Apply in the Context of Military Emergencies?*, 60 GEO. WASH. L. REV. 1387 (1992).

24. While no single definitive cause of Gulf War Syndrome has been identified, PB has been identified as a possible contributor to the development of at least some of the illnesses reported by Gulf War veterans. See, e.g., BEATRICE ALEXANDRA GOLOMB, NATIONAL DEFENSE RESEARCH INSTITUTE, A REVIEW OF THE SCIENTIFIC LITERATURE AS IT PERTAINS TO GULF WAR ILLNESSES: PYRIDOSTIGMINE BROMIDE 3-4, n. 1 (1999), <http://www.rand.org/publications/MR/MR1018.2/MR1018.2.pdf/> (last visited Feb. 24, 2005).

25. E.g., O’Connor, *supra* note 23, at 676-77.

26. See, e.g., Annas, *Blinded by Bioterrorism*, *supra* note 23, at 37; Annas, *Protecting Soldiers from Friendly Fire*, *supra* note 23, at 246-47.

safety and effectiveness can be under investigation while it is simultaneously administered with a therapeutic or prophylactic intent. Moreover, it argues that recipients of investigational products for therapeutic purposes do not fall into the category of “research subjects” merely because of the product’s investigational status. Rather, they are research subjects only if the product is administered for the purposes and in the context of research. While recipients of investigational products administered for therapeutic purposes must, legally and ethically, receive full information about the risks and benefits of the investigational product, such disclosure would not be different in kind (though possibly in degree) from the disclosures that are required to be made to all patients undergoing medical treatment.

This paper further proposes that this paradigm receive concrete expression through a new category of FDA regulatory approval, tentatively termed “interim approval” or “limited use approval.” Such a paradigm shift would create a clearer distinction between activities that are correctly considered research and those more appropriately viewed as treatment. This distinction could help restore public confidence in human subjects research and eliminate specious claims that recipients of IND products are “guinea pigs” simply by virtue of the product’s investigational status. In addition, this new paradigm could foster availability of less-than-fully-approved products with adequate disclosure and safeguards in cases where the product is reasonably believed to constitute the best available therapy to combat an emergent health threat.

II. NUREMBERG: HISTORY AND CODE

During World War II, Nazis used concentration camp prisoners in a variety of experiments aimed at gaining scientific knowledge beneficial to their own soldiers and citizens, while also causing severe pain, serious injury, and death to the research subjects.²⁷ Such experiments included infecting healthy prisoners with malaria, typhus, and other infectious agents to test antidotes or vaccines.²⁸ Many prisoners died either from the disease or the treatments being tested.²⁹ In other experiments, prisoners were put in low-pressure tanks to see how long they could survive without oxygen, were forced to remain outdoors without clothing in freezing weather so that rewarming could be attempted, were subjected to chemical or x-ray sterilization, or were fed poisons through their food.³⁰ There was

27. ETHICAL AND REGULATORY ASPECTS OF CLINICAL RESEARCH 2 (Ezekiel J. Emanuel et al. eds., 2003)[hereinafter ETHICAL AND REGULATORY ASPECTS].

28. *Id.*

29. *Id.*

30. *Id.*

absolutely no therapeutic intent in any of these experiments; to the contrary their aim was to inflict harm as well as to gain knowledge.

After the war, these medical experiments came to light during the Nuremberg Doctors Trials, at which twenty-three Nazi doctors were tried, and seven hanged, for their participation in wartime atrocities.³¹ The judges of the Nuremberg Military Tribunal also articulated what became known as the Nuremberg Code, ten principles defining acceptable research involving humans.³² The first principle of the Code states that the "voluntary consent of the human subject is absolutely essential."³³ It goes on to explain:

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.³⁴

31. Annas, *Protecting Soldiers from Friendly Fire*, *supra* note 23, at 245-46; Alexander Mitscherlich & Fred Mielke, *Epilogue: Seven Were Hanged*, in *THE NAZI DOCTORS AND THE NUREMBURG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* 105 (George J. Annas & Michael A. Grodin eds., 1992) [hereinafter *THE NAZI DOCTORS AND THE NUREMBURG CODE*].

32. Annas, *Protecting Soldiers from Friendly Fire*, *supra* note 23, at 246.

33. NUERNBURG MILITARY TRIBUNALS, TRIALS OF WAR CRIMINALS 181 (1949).

34. *Id.* at 181-82. The Nuremberg Code continues:

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature. 3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment. 4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury. 5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects. 6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment. 7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death. 8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment. 9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible. 10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has

The Nuremberg Code has been termed “the most widely known document on the ethics of research.”³⁵ Certainly it was an important declaration of human rights, setting boundaries on wartime treatment of prisoners and categorically renouncing certain modes of behavior toward other human beings. At the same time, the document, perhaps not surprisingly, did not generate much reaction from United States physicians. Many physicians and researchers viewed it as a “good code for barbarians but an unnecessary code for ordinary physicians.”³⁶ United States researchers felt it “had its origins in extraordinary circumstances” and therefore was “not necessarily pertinent” to the United States research context.³⁷ While United States history does contain incidents in which patients or healthy “volunteers” were the unwitting subjects of experiments with no therapeutic intent,³⁸ this was not the context in which most United States researchers viewed themselves.³⁹ Given its origins, the Nuremberg Code did not seem applicable to sick patients for whom participation in research might be beneficial.

The leaders of the international medical community therefore tried to mesh the standards enunciated in the Nuremberg Code with the realities of medical research. The 1964 statement by the World Medical Association, commonly known as the Declaration of Helsinki,⁴⁰ created two separate categories laying out rules for human experimentation: “Clinical Research Combined with Professional Care,” and “Nontherapeutic Clinical Research.”⁴¹ In the former category, physicians were required to obtain consent from patient-subjects only when “consistent with patient psychology.” In nontherapeutic clinical research, the consent requirements were more absolute: “Clinical research on a human being

probably [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Id.

35. ETHICAL AND REGULATORY ASPECTS, *supra* note 27, at 2.

36. Ruth R. Faden et al., *U.S. Medical Researchers, the Nuremberg Doctors Trial, and the Nuremberg Code*, in ETHICAL AND REGULATORY ASPECTS, *supra* note 27, at 8. (quoting Jay Katz, *The Consent Principle of the Nuremberg Code: Its Significance Then and Now*, in THE NAZI DOCTORS AND THE NUREMBERG CODE, *supra* note 31, at 228).

37. *Id.* at 10 (quoting Memorandum from Joseph W. Gardella, Assistant Dean, Harvard Med. School, to George P. Berry, Dean, Harvard Medical School (1961)).

38. For a discussion of some of these historical abuses see ETHICAL AND REGULATORY ASPECTS, *supra* note 27, at 1-23.

39. See generally Jonathan D. Moreno, *Reassessing the Influence of the Nuremberg Code on American Medical Ethics*, 13 J. CONTEMP. HEALTH L. & POL'Y 347 (1997) (arguing that “recent revelations about Cold War era deliberations among high ranking officials enable a . . . deeper understanding of the Code’s role during the years following the war . . .”).

40. THE WORLD MEDICAL ASSOCIATION, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (1964), <http://www.wma.net/e/policy/pdf/17c.pdf> (last visited Feb. 24, 2005).

41. *Id.*

cannot be undertaken without his free consent, after he has been fully informed."⁴² Unlike the Nuremberg Code, the Declaration of Helsinki allowed for third-party permission from a legal guardian.⁴³ The Declaration was widely approved by United States medical researchers who viewed it as more practical and more tailored to their circumstances.

III. THE DEVELOPMENT OF UNITED STATES REGULATIONS TO PROTECT RESEARCH SUBJECTS

One particularly egregious United States example of medical experimentation on patients with no potential for therapeutic benefit was the Tuskegee Syphilis Study, sponsored by the United States Public Health Service from 1932 to 1972. The study's purpose was to determine the natural course of untreated, latent syphilis, and the subjects were black males.⁴⁴ No treatment was offered to the study participants, nor were they informed of its availability, even after penicillin became available in the 1950s.⁴⁵

This episode, as well as several others, led to the passage of the National Research Act⁴⁶ in 1974, which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.⁴⁷ The Commission, in turn, issued the seminal Belmont Report, which proposed ethical principles and guidelines for the protection of human subjects of research.⁴⁸ In

42. *Id.*

43. *Id.*

44. See NATIONAL CENTER FOR HIV, STD, AND TB PREVENTION, CDC, TIMELINE – THE TUSKEGEE SYPHILIS STUDY: A HARD LESSON LEARNED (2004) [hereinafter CDC, TUSKEGEE SYPHILIS STUDY], <http://www.cdc.gov/nchstp/od/tuskegee/time.htm> (last visited Feb. 24, 2005); see also Allan M. Brandt, *Racism and Research: The Case of the Tuskegee Syphilis Study*, in ETHICAL AND REGULATORY ASPECTS, *supra* note 27, at 20-23.

45. See CDC, TUSKEGEE SYPHILIS STUDY, *supra* note 44; see also Brandt, *supra* note 44.

46. National Research Service Award Act of 1974, Pub. L. No. 93-348, 88 Stat. 342 (1974) (codified in scattered sections of 42 U.S.C.).

47. *Id.* at 348. Title II of the Act, Protection of Human Subjects of Biomedical and Behavioral Research, enumerated the duties of the Commission, which included:

identifying[ing] the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects, develop[ing] guidelines [for] such research . . . , and mak[ing] recommendations to the Secretary (I) for . . . administrative action . . . to apply such guidelines . . . , and (II) concerning any other matter pertaining to the protection of human subjects of biomedical and behavioral research.

Id. at 349.

48. NAT'L COMM. FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, FDA, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979) [hereinafter BELMONT REPORT], http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4066b1_22_Belmont%20Report.pdf (last visited Feb. 24, 2005).

particular, the Belmont Report articulated three principles – respect for persons, beneficence, and justice – that should undergird all human subjects research.⁴⁹ This report became the basis for the implementation of regulations to protect human subjects, now known as the “Common Rule.”⁵⁰ These regulations apply to research conducted at all federal institutions and to all federally funded research with human subjects.⁵¹ The regulations define “research” as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”⁵² These regulations also apply to any research for which a federal agency has oversight responsibility – including investigational new drug requirements overseen by FDA.⁵³

The Common Rule requires institutional review boards (IRB) to review research protocols in accordance with specified requirements. The IRB is required to review all research protocols and has the authority to approve, require modification of, or disapprove of all research activities covered by the Rule.⁵⁴ In order to approve a protocol, the IRB must determine that risks to subjects are minimized; that risks are reasonable in relation to anticipated benefits; that selection of subjects is equitable; that the research plan makes adequate provision for data monitoring, if needed, to protect subject safety; that privacy and confidentiality of data are maintained; that vulnerable subjects are adequately protected; and that informed consent is sought from all subjects or their legal representatives and is appropriately documented.⁵⁵

The Common Rule also outlines the required elements of informed consent. At its essence, informed consent requires the researcher to provide necessary information to the research subject so that the subject can make a reasoned judgment about whether to participate in the research.⁵⁶ To that end, the subject must be provided a “statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental.”⁵⁷ Other information that must be provided includes: (1) any reasonably foreseeable risks and discomforts

49. *Id.* at 2, 4-6.

50. Protection of Human Subjects, 45 C.F.R. § 46 (2003). For references to the “Common Rule,” see OFFICE OF HUMAN RESEARCH PROTECTIONS, U.S. DEP’T OF HEALTH AND HUMAN SERVICES, CODE OF FEDERAL REGULATIONS TITLE 45: PUBLIC WELFARE, at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm> (last visited Feb. 24, 2005).

51. 45 C.F.R. § 46.101(a).

52. *Id.* § 46.102(d).

53. *Id.* § 46.102(e).

54. *Id.* § 46.109(a).

55. *Id.* § 46.111.

56. See Protection of Human Subjects, 45 C.F.R. § 46.116(a) (2003).

57. *Id.* § 46.116(a)(1).

from the research, (2) any benefits to the subject or to others that may reasonably be expected to arise from the research, (3) any alternatives to the research that might be beneficial to the subject, (4) information on compensation or treatment, if any, that will be provided in case of injury, and (5) a statement that participation is voluntary and may be discontinued by the subject at any time without penalty.⁵⁸ Informed consent must, in most cases, be documented in writing.⁵⁹

IV. THE DICHOTOMY BETWEEN RESEARCH AND TREATMENT

Nuremberg and United States research abuses led to the development of a defined, formalized, and rigorous process for activities falling within the definition of "research." While some have argued the process is too rigid⁶⁰ and others have claimed that its protections are inadequate,⁶¹ there is today a distinct and identifiable enterprise known as clinical research.

Traveling a different path, another legal tradition evolved within the rubric of tort law, that of informed consent to medical treatment. Informed consent in this context has its origins in the tort of battery.⁶² In the 1914 case *Schloendorff v. Society of New York Hospital*,⁶³ Justice Cardozo opined that "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages."⁶⁴ Several other cases during the same time period demonstrated that courts would find physicians (typically surgeons) liable for battery if they performed an operation without first securing the patient's consent or deviated during the course of surgery from the procedure that had been agreed to by the patient.⁶⁵ The patient's consent to the treatment thus distinguished the tort of battery from legally permissible treatment.

While the tort of battery served to ensure that the patient consented, it did not necessarily follow that the doctor had a duty to provide information to the patient

58. *Id.* § 46.116(a)(2)-(8).

59. *Id.* § 46.117.

60. *E.g.*, Richard S. Saver, *Critical Care Research and Informed Consent*, 75 N.C. L. REV. 205, 208-11 (1996) (discussing the doctrine of informed consent as applied to critical care research and its various deficiencies).

61. *E.g.*, Sharona Hoffman, *Regulating Clinical Research: Informed Consent, Privacy, and IRBs*, 31 CAP. U. L. REV. 71 (2003) (arguing for the enhancement of protections for human subjects of clinical research).

62. See RUTH R. FADEN & TOM L. BEAUCHAMP, A HISTORY AND THEORY OF INFORMED CONSENT 119-20 (1986).

63. 105 N.E. 92 (N.Y. 1914).

64. *Id.* at 93.

65. For a discussion of these cases, see FADEN & BEAUCHAMP, *supra* note 62, at 120-23.

to ensure that such consent was informed. The 1957 case *Salgo v. Leland Stanford Jr. University Board of Trustees*⁶⁶ made the requirement of informed consent explicit for the first time, holding that physicians must disclose “any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment.”⁶⁷ While *Salgo* relied on battery theory to justify this requirement, later cases began to shift the legal analysis, and to rely on negligence theory in evaluating whether a patient had been injured by the doctor’s failure to obtain informed consent.⁶⁸ Through these cases, the failure to secure informed consent itself became a tort, i.e., the basis for a lawsuit against a doctor separate from whether the doctor’s actual treatment deviated from acceptable practice.⁶⁹

A physician cannot, of course, disclose every foreseeable circumstance. To determine whether the physician has discharged the informed consent obligation, courts apply a “materiality” standard, meaning information that will be material to the patient’s decision-making process.⁷⁰ Material information includes the nature, consequences, risks, and alternatives to, a particular course of treatment.⁷¹ Some courts view materiality from the physician’s perspective, asking what a reasonable physician would have disclosed under the circumstances, while others apply a patient-centered view of materiality, asking whether the information would be material to the reasonable patient under the particular circumstances.⁷²

One issue that courts have had to consider in determining materiality is whether the fact that a treatment is “innovative” or “experimental” is always material.⁷³ While the case law does not evidence a coherent principle, it clearly demonstrates that such information is not *presumptively* material.⁷⁴ For example,

66. 317 P.2d 170 (Cal. Dist. Ct. App. 1957).

67. *Id.* at 181.

68. FADEN & BEAUCHAMP, *supra* note 62, at 129-32. See also *Natanson v. Kline*, 350 P.2d 1093, 1106 (Kan. 1960) (limiting a physician’s duty to disclose to “those disclosures which a reasonable medical practitioner would make under the same or similar circumstances” and reasoning that “where the patient fully appreciates the danger involved, the failure of a physician in his duty to make a reasonable disclosure to the patient would have no causal relation to the injury”), *reh’g denied*, 354 P.2d 670, 673 (clarifying that “[n]egligence is an essential element of malpractice, and... a causal relation must be established by the patient, between the negligent act of the physician and the injury of the patient, to sustain the burden of proof where damages are sought in a malpractice action for injury”).

69. FADEN AND BEAUCHAMP, *supra* note 62, at 132-34. See also Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361 (2002).

70. *Id.* at 367-68.

71. *Id.* at 365-67.

72. *Id.* at 367-68.

73. *Id.* at 371.

74. See *id.* at 371-72 (citing *Salgo v. Leland Stanford Jr. Univ. Bd. of Trustees*, 317 P.2d 170, 175, 180 (Cal. Ct. App. 1957); *Natanson v. Kline*, 350 P.2d 1093, 1101 (Kan. 1960); *Fortner v. Koch*, 261 N.W. 762, 765 (Mich. 1935); *Alvarez v. Smith*, 714 So. 2d 652, 655 (Fla. Ct. App. 1998); *Klein v. Biscup*, 673 N.E.2d 225, 231 (Ohio Ct. App. 1996); *Southard v. Temple Univ. Hosp.*, 781 A.2d 101, 107-08 (Pa. 2001); *Ramon v. Farr*, 770 P.2d 131, 135-37 (Utah 1989); James M. Beck & Elizabeth D.

courts have rejected the argument that a physician must always disclose the off-label use of an FDA approved product.⁷⁵ On the other hand, when the particular treatment or product use deviates too much from the "norm," courts have found disclosure of such deviation by the physician to be material.⁷⁶

Thus, the law recognizes that the physician, acting in what he or she perceives is the best interest of the patient, may need to rely on "innovation" or "experimentation," and that such behavior does not necessarily constitute malpractice.⁷⁷ The law has also recognized that such innovative practice need not always be disclosed to the patient.⁷⁸ The law realizes that every therapeutic decision is individualized, and therefore not exactly like the previous one, but the type and degree of disclosure depends on individual circumstances.⁷⁹

Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 100-01 (1998).

75. The term "off-label use" refers to a product that has been approved for one indication by FDA and is subsequently administered by a health care provider for a use not indicated in its labeling may constitute an off-label use. See FDA, GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS: 1998 UPDATE, <http://www.fda.gov/oc/ohrt/irbs/offlabel.html> (last visited Feb. 24, 2005). FDA has long taken the position that the decision to administer a product for indications not included in labeling is within the scope of medical practice and constitutes a clinical judgment, and is therefore not appropriately within the purview of FDA regulations. See *id.* For many diseases, off-label prescribing is a necessary and even indispensable part of appropriate medical treatment. *E.g.*, Beck & Azari, *supra* note 74 (arguing that physicians should not be required to explain FDA regulatory status of drugs and medical devices in informed consent discussions with patients).

76. Noah, *supra* note 69, at 372 (citing *Corrigan v. Methodist Hosp.*, 869 F. Supp. 1202, 1207 (E.D. Pa. 1994); *Retkwa v. Orentreich*, 584 N.Y.S.2d 710, 712-13 (Sup. Ct. 1992); *Shadrick v. Coker*, 963 S.W.2d 726, 729-30, 734-35, 736-37 (Tenn. 1998); PA. STAT. ANN. tit. 40, § 1301.811-A(a)(5) (1999)).

77. See, *e.g.*, *Fortner v. Koch*, 261 N.W. 762, 765 (Mich. 1935) ("We recognize the fact that, if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on; but such experiments must be done with the knowledge and consent of the patient or those responsible for him, and must not vary too radically from the accepted method of procedure."); *Salgo*, 317 P.2d at 180 (concluding that a drug manufacturer's written instructions for using a drug "cannot establish as a matter of law the standard of care required of a physician in the use of the drug."); *Costa v. Regents of Univ. of Cal.*, 254 P.2d 85, 93 (Cal. Dist. Ct. App. 1953) (finding that "[i]n fighting so dangerous a condition as [the cancer] here involved, physicians may take serious risks and in doing so must rely on their judgment in deciding how far to go" and that "[t]o hold [physicians] responsible in the cases where the bad chance unfortunately materializes would be evidently unjust and most dangerous if physicians were deterred from going to the extent which gives their patient the best chance of survival."); *Karp v. Cooley*, 493 F.2d 408, 423-24 (5th Cir. 1974) (explaining that an action for non-therapeutic experimentation must be measured by "traditional malpractice evidentiary standards" and that therefore "[w]hether there was informed consent is necessarily linked to the charge of experimentation..." (footnote omitted)); *Heinrich v. Sweet*, 308 F.3d 48, 65 (1st Cir. 2002) (reasoning that defendant physician's reporting of negative results of an experimental treatment conducted on patients represented by plaintiffs was not an admission of negligence and that although "medical research at times produces results less than hoped for...[t]his does not logically lead to the conclusion that the research should not be undertaken.").

78. See, *e.g.*, Beck & Azari, *supra* note 74 and accompanying text.

79. See, *e.g.*, *Natanson*, 350 P.2d at 1106 (noting that as long as a physician's disclosure is "sufficient to assure an informed consent, the physician's choice of plausible courses should not be

The Belmont Report also recognized early on that even what is considered medical treatment inherently blurs at the edges with the research enterprise. The report tried to distill the essential differences between research and therapy:

It is important to distinguish between biomedical . . . research on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review [sic] for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called “experimental” when the terms “experimental” and “research are not carefully defined [T]he term ‘research’ designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is ‘experimental,’ in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective.⁸⁰

Thus it is the requirement that “generalizable knowledge” be sought that distinguishes the research enterprise; the requirement that individual patient benefit be expected is the hallmark of medical treatment. As the next section will show, when IND products are used for therapeutic purposes, this distinction becomes blurred.

V. THE EROSION OF THE RESEARCH/TREATMENT DISTINCTION

A. AIDS, Cancer, and Changes to IND and Approval Rules

Efforts to break down the walls of separation between “research” and “treatment” can be traced to the AIDS epidemic of the 1980s. While the early history of human subjects research was aimed at limiting entry through stringent hurdles, AIDS patients successfully turned this effort on its head by demanding

called into question if it appears, all circumstances considered, that the physician was motivated only by the patient’s best interests”).

80. BELMONT REPORT, *supra* note 48, at 3.

unapproved therapies.⁸¹ Their demands were based on their belief in the therapeutic potential of these IND products and their perception that the barriers to approval of these products were too high.⁸² Those who sought IND products outside research protocols did not necessarily want to be research subjects; rather, they wanted earlier access to what they perceived as beneficial treatments. Some activists even resorted to sabotaging, or threatening to sabotage, research protocols to achieve their goals.⁸³

FDA ultimately created a more flexible regulatory scheme in response to their demands, recognizing that the risk preferences of patients facing life-threatening illnesses should be accorded some deference when deciding when a drug should be made available. The changes made by FDA to drug approval "marked a seminal event in the evolution of new drug approval policy at FDA."⁸⁴ First, in 1987, the agency issued a final rule specifying the conditions under which investigational new drugs could be administered to patients with severe medical conditions.⁸⁵ FDA articulated the purpose of the rule as "facilitat[ing] the availability of promising new drugs to [desperately ill] patients as early in the drug development process as possible [before general marketing begins] and to obtain additional data on the drug's safety and effectiveness."⁸⁶

FDA rule established what the agency termed a "treatment IND." Under the rule, a drug can be used for treatment if:

81. Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL'Y 295, 315-21 (2000); Nancy K. Plant, *Adequate Well-Controlled Clinical Trials: Reopening the Black Box*, 1 WIDENER L. SYMP. J. 267, 285-89 (1996). See also Lisa Terrizzi, *The Need for Improved Access to Experimental Drug Therapy: AIDS Activists and Their Call for a Parallel Track Policy*, 4 ADMIN. L.J. 589, 596-99 (1991) (discussing regulatory changes in FDA policy regarding distribution of experimental drugs to AIDS patients).

82. Greenberg, *supra* note 81; Plant, *supra* note 81. See also Terrizzi, *supra* note 81, at 598 n. 45 (describing arguments regarding the morality of clinical trials aimed at non-terminally ill populations).

83. For example, one AIDS activist group established a method by which patients could have their clinical trial supply analyzed, thus "un-blinding" the study. Plant, *supra* note 81, at 286. At one FDA Advisory Committee meeting concerning early access, AIDS activist Larry Kramer stated: "If we do not get these drugs you will see an uprising, the likes of which you have never seen before since the Vietnam War in this country. We will sabotage all of your Phase I studies." *Id.* at 289 (citing Terrizzi, *supra* note 81, at 622). The term "blinding" refers to procedures that prevent participants in a clinical trial from knowing whether they are receiving the drug being investigated or some other substance (e.g., placebo).

84. Greenberg, *supra* note 81, at 296.

85. Investigational New Drug, Antibiotic, and Biological Drug Product Regulations, 52 Fed. Reg. 19,466, 19,466 (May 22, 1987) (codified at 21 C.F.R. pt. 312) [hereinafter Investigational Drug Regulations]. According to FDA, comments were received from representatives of "virtually every affected constituency," including "consumers, consumer group leaders, health professionals and health care providers, representatives of specific disease and orphan drug organizations, state and local health departments, clinical investigators and research institutions, institutional review boards, pharmaceutical manufacturers, and former FDA officials." *Id.*

86. *Id.*

(i) the drug is intended to treat a serious or immediately life-threatening disease; (ii) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (iii) the drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and (iv) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.⁸⁷

Sponsors seeking to use an IND drug for treatment were required to submit a treatment protocol to FDA containing information such as the rationale for using the drug and the criteria for patient selection.⁸⁸ The sponsor was not required to wait for FDA approval to begin, but rather could begin 30 days after submission unless FDA said otherwise.⁸⁹ Another important component of the rule was that FDA permitted a sponsor or investigator to charge for the drug used in a treatment protocol provided that certain conditions were met.⁹⁰ This was a departure from the prohibition against charging for investigational products, and provided important incentives to companies to provide their investigational products to patients.

The treatment IND demonstrated FDA's willingness to permit seriously ill people to accept more risk in the interest of obtaining potentially beneficial treatments.⁹¹ However, FDA did so while still retaining the "investigational new drug" framework. As a regulatory matter, people receiving products under a treatment IND were still, at least implicitly, research subjects, since the regulations required compliance with the IND provisions. According to the treatment IND regulations:

Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process,

87. Treatment Use of an Investigational New Drug, 21 C.F.R. § 312.34(b)(1)(i)-(iv) (2004). The rule defined "immediately life threatening" to mean "a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment." *Id.* § 312.34(b)(3)(ii). The preamble to the final rule also provided the following illustrative list of diseases fitting this definition: "Advanced cases of AIDS; Advanced congestive heart failure (New York Heart Association Class IV); Recurrent sustained ventricular tachycardia or ventricular fibrillation; Herpes simplex encephalitis; Most advanced metastatic refractory cancers; Far advanced emphysema; Severe combined immunodeficiency syndrome; Bacterial endocarditis; and Subarachnoid hemorrhage." Investigational Drug Regulations, *supra* note 85, at 19,467.

88. 21 C.F.R. § 312.25(a) (2004).

89. *Id.* § 312.40(b) (2004).

90. Investigational Drug Regulations, *supra* note 85, at 19,467.

91. For example, in the preamble to the Interim Rule promulgated to expedite treatments for life-threatening or debilitating illnesses, the agency observed that "[t]he procedures contained in this rule reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses." Investigational New Drug, Antibiotic, and Biological Drug Product Regulations, 53 Fed. Reg. 41,516, 41,518 (Oct. 21, 1988) (to be codified at 21 C.F.R. pts. 312 and 314) [hereinafter Investigational Drug Regulations II].

including the regulations governing informed consent (21 CFR part 50) and institutional review boards (21 CFR part 56) and the applicable provisions of part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.⁹²

In 1988, FDA again issued a rule intended to expand access to products for life-threatening⁹³ or severely debilitating⁹⁴ illnesses at an earlier stage of development – this time by reducing the number of research steps that were necessary before a product could be administered. The new rule permitted a departure from the classic phase I, II, III approach.⁹⁵ Instead, FDA stated it would consider approval of the drug following phase II investigational studies, without the need for phase III, which would potentially save a significant amount of time:

FDA believes that if sufficient attention is paid to the quality and amount of data obtained in phase 2, it should be possible to identify early those drugs that represent safe and effective treatments for life-threatening and severely-debilitating diseases – and to develop the evidence needed for their marketing – in the course of carrying out the first controlled trials.⁹⁶

This early approval was predicated on early and frequent meetings between sponsors and FDA reviewers to discuss the design of animal and clinical studies.

92. Treatment Use of an Investigational New Drug, 21 C.F.R. § 312.34(c) (2004).

93. Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses, 21 C.F.R. § 312.81 (2003). The rule defined life threatening diseases as: "(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and (2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival." *Id.*

94. *Id.* The rule defined severely debilitating illnesses as: "diseases or conditions that cause major irreversible morbidity." *Id.*

95. The clinical trial process is typically described as consisting of three pre-approval phases. See Investigational Drug Regulations II, *supra* note 91, at 41,518. During Phase I, the drug is tested on a small number (twenty to eighty) of patients or healthy volunteers to study how the drug is tolerated, metabolized, and excreted. *Id.* Phase I studies are not generally designed to assess drug efficacy although they may provide some initial evidence in this regard. *Id.* Phase II studies are larger, generally comprising 50 to 200 patients, and are the first time when both safety and effectiveness are evaluated. *Id.* Finally, Phase III trials may include between 200 and 1000 patients or more, and are intended to confirm and expand upon the safety and efficacy data obtained from the first two phases. *Id.* These phases are not statutorily required, and they are by no means absolute: indeed, some officials within FDA have tried to get away from the "phase I, II, III" terminology because of concerns that it conveys an unduly "mechanistic" description of the process. Jennifer Kulynych, *Will FDA Relinquish the "Gold Standard" for New Drug Approval? Redefining "Substantial Evidence" in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 143 (1999) (citing International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials, 62 Fed. Reg. 66,113 (Dec. 17, 1997)). For example, a 1997 Guidance Document suggested that a Phase II study be referred to as "therapeutic exploratory" and a Phase III study be referred to as "therapeutic confirmatory." *Id.* Nevertheless, the phase I, II, III terminology appears to remain the standard in the scientific and legal literature and common parlance, as well as FDA's own regulations. Investigational New Drug Application (IND), 21 C.F.R. § 312.21 (2004).

96. Investigational Drug Regulations II, *supra* note 91, at 41,518.

It was anticipated that sponsors would make use of the treatment protocol provisions established in the previous years to administer the drug to patients while preparing the marketing application.⁹⁷ Finally, FDA anticipated that post-marketing (phase IV) studies would be used to obtain additional information about a product's risks, benefits, and optimal use.⁹⁸

Again, while the purpose of this truncated approval process was to speed the approval of therapeutic products to severely ill patients, the mechanism and framework used was the IND regulations. The regulations provided that:

All of the safeguards... designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (§ 312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (§ 312.32), safety update reports during agency review of a marketing application (§ 314.50 of this chapter), and postmarketing adverse reaction reporting (§ 314.80 of this chapter).⁹⁹

FDA therefore created a regulatory "hybrid" under which the recipient of a product pursuant to these regulations could be construed simultaneously as a patient and a research subject. While this hybrid was created to achieve a specific and laudable objective, it has also arguably contributed to the ongoing erosion between the "research" and "treatment" enterprises.

B. Further Erosion During 1991 Gulf War; Confusion in the Aftermath of 9/11

The 1991 Gulf War occurred at a time when traditional distinctions between "research" and "treatment" were being eroded, without explicit regulatory acknowledgment of this shift. Administration of IND products to AIDS patients technically fell within FDA's IND regulations and therefore constituted "research."¹⁰⁰ Consistent with its regulatory context, consent of the recipients was required.¹⁰¹ Yet the intent of permitting the administration of IND products to

97. Treatment Protocols, 21 C.F.R. § 312.83 (2003).

98. Investigational Drug Regulations II, *supra* note 91, at 41,518.

99. Safeguards for Patient Safety, 21 C.F.R. § 312.88 (2004).

100. *See* Investigational Drug Regulations II, *supra* note 91, at 41,517 (using FDA's successful development, evaluation and approval of zidovudine, the first drug approved to treat AIDS, through the use of the four phase clinical trial involving AIDS patients, as an example of how administration to humans of INDs within FDA rules constitutes "research").

101. *See generally* Informed Consent of Human Subjects, 21 C.F.R. § 50.20 (2004) (establishing the requirements for informed consent of human subjects in clinical trials of INDs); Elements of Informed Consent, 21 C.F.R. § 50.25 (specifying the elements that constitute informed consent under the Investigational New Drug clinical trial regulation).

AIDS patients, cancer patients, and others was, at least in part, to improve the health status of the individual recipient. This is generally considered treatment, or medical practice.

DOD further eroded the research/treatment distinction in its request to FDA by seeking a waiver of consent, using a broadened conception of infeasibility. But the military's intent was not to conduct research (i.e., to gain generalizable knowledge), but to protect troops from perceived threats.¹⁰² Indeed, DOD was faulted for not maintaining records that could have permitted better evaluation of the impact of treatment on troops and thus could have led to more generalizable information.¹⁰³

Neither the Nuremberg Code nor FDA's IND regulations contemplated the scenario DOD faced in 1991 and that it faces now: What if, based on all available information, there is a good faith reason to believe that a drug, vaccine, or other medical product *may* be therapeutic, but testing falls below the "gold standard"¹⁰⁴ that we have come to expect? While from a regulatory perspective such a product is "investigational," it does not follow that the motive to administer it is an experimental one – the sole or primary motive may in fact be, as it was in the 1991 situation, to protect troops. In 1991, DOD presented FDA with an investigational product and a therapeutic motivation.¹⁰⁵ This circumstance does not fit the definition of "research," i.e., the pursuit of generalizable knowledge to support a hypothesis.¹⁰⁶ Nor do the words "investigational" or "experimental," at least as they are popularly understood, capture the nature of the enterprise. This is not a merely semantic distinction; the word "experimentation" in particular packs a powerful punch in the popular mind and brings to mind Nuremberg and a host of other atrocities committed against vulnerable populations.

The lack of precise terminology has led not only to distrust of the government, but also to confusion in both the public's mind and in at least one federal court. For example, following 9/11, when anthrax was found in letters sent to members of Congress and others, those civilians at high risk of exposure were offered the anthrax vaccine.¹⁰⁷ Most declined, probably because of concerns about its safety, which may have been exacerbated by the government's unwillingness to

102. RETTIG, *supra* note 1, at 21; *see also* note 15 and accompanying text.

103. RETTIG, *supra* note 1, at 36 (discussing Presidential Advisory Committee Report).

104. The phrase "gold standard" has been used to refer to FDA's high standards for product approval generally as well as to the classic two randomized double-blinded controlled clinical trial standard for drug approval. *See, e.g.*, Kulynych, *supra* note 95.

105. *See* Informed Consent for Human Drugs and Biologics, 55 Fed. Reg. at 52,814.

106. Protection of Human Subjects, 45 C.F.R. § 46.102(d) (2003).

107. *See* Justin Gillis, *FDA Releases Anthrax Vaccine to Military, Approves More*, WASH. POST, Feb. 1, 2002, at A17, available at 2002 WL 10945005; *see also* Clemente Lisi, *Spore Find Raises New Mail Fears*, N.Y. POST, Dec. 30, 2001, at 15, available at 2001 WL 32605665.

provide a recommendation regarding vaccination.¹⁰⁸ The vaccine had also been administered on a mandatory basis to United States troops during the late 1990s.¹⁰⁹ Several hundred military personnel resigned or faced disciplinary proceedings as a result of their refusal to take the vaccine because of concerns about its side effects.¹¹⁰

Contrary to what some critics have claimed and one federal district court recently opined,¹¹¹ the investigational status of the anthrax vaccine when administered to troops on a mandatory basis or to civilians on a voluntary one was by no means clear. The vaccine, named Anthrax Vaccine Adsorbed (AVA), was licensed in 1970¹¹² and used primarily by those in frequent contact with animals through work in agriculture, the wool trade, or laboratory research. FDA-approved labeling for the vaccine does not specify the route of anthrax exposure (inhalational v. cutaneous) that it is intended to prevent.¹¹³ In 1996, the manufacturer submitted an IND to permit an explicit claim against inhalational

108. See Christine Haughney, *Anthrax Vaccine Rejected*, WASH. POST, Jan. 4, 2002, at A13, available at 2002 WL 2518614; see also Sanjay Bhatt, *As Deadline Passes, No New Takers for Anthrax Vaccine*, PALM BEACH POST, Jan. 8, 2002, at 4B, available at 2002 WL 5523247.

109. See Bradley Graham, *Pentagon Plans to Inoculate Troops Against Anthrax Bacteria*, WASH. POST, Dec. 16, 1997, at A23, available at 1997 WL 16224214.

110. Thomas H. Maugh, II, *Science File Vaccinations Problematic Health: Anthrax and Smallpox Shots Present Manufacturing Problems and Dangerous Side Effects*, L.A. TIMES, Oct. 29, 2001, at A14; Jim Ritter, *Anthrax Shot Fears Rise; More Troops Refusing Order to be Vaccinated*, CHI. SUN-TIMES, Nov. 4, 1998, at 3. In addition, an unknown number of National Guard and reserve personnel chose to leave rather than be vaccinated. *Anthrax Vaccine: Hearing on Preliminary Results of GAO's Survey of Guard/Reserve Pilots and Aircrew Members Before the House Comm. on Government Reform*, 101st Congress 1-2 (2000) (statement of Kwai-Cheung Chan, Director, Applied Research and Methods), <http://www.gao.gov/new.items/d0192t.pdf> (last visited Feb. 24, 2005). In 2000, the GAO conducted a survey of 1,253 randomly selected Guard and Reserve Pilots and other aircrew members to assess attitudes about AVIP. *Id.* The survey found that anthrax was a key reason that participants cited for leaving the military or changing their military status. *Id.*

111. *Doe v. Rumsfeld*, 297 F. Supp. 2d 119 (D. D.C. 2003). This case was brought by active duty service members, national guardsmen, and civilian contractors against the Department of Defense after plaintiffs were instructed to submit to anthrax vaccinations without their consent. *Id.* at 122. Plaintiffs argued that the anthrax vaccine was an experimental drug unlicensed for its present use and that the DOD's Anthrax Vaccine Immunization Program (AVIP) violated DOD's regulation, a Presidential Executive Order, and the Administrative Procedure Act. *Id.* at 123. The district court issued a preliminary injunction barring the non-consensual administrations of the vaccine, holding that the vaccine was both an investigational drug and being used for an unapproved purpose. *Id.* A year later, the court granted a stay of the injunction after FDA published a final rule categorizing AVA as safe and effective for use against inhalational anthrax. *Doe v. Rumsfeld*, 297 F. Supp. 2d 200 (D. D.C. 2004).

112. *Vaccine Licensing and the Anthrax Vaccine: Hearing on Vaccine Licensing Before the Senate Comm. on Armed Services*, 101st Cong. (2000) (statement by FDA), <http://www.hhs.gov/asl/testify/t000413d.html> (last visited Feb. 24, 2005).

113. FDA, LABEL OF ANTHRAX VACCINE ADSORBED (BIOTHRAX) (2002), <http://www.fda.gov/cber/label/biopava0131022LB.pdf> (last visited Feb. 24, 2005).

anthrax to be included in the labeled indication.¹¹⁴ But this fact does not by itself indicate that the previous labeling excluded an inhalational indication, only that one could not specifically be claimed. While such a distinction may appear to be analogous to a defense of “no controlling legal authority,” in reality it gets to the heart of the system of drug approval by FDA. FDA approval is based on the “intended use” of the product, as evidenced most clearly by the labeled indication for use.¹¹⁵ Thus the type of data required by the manufacturer for approval is driven by what specific benefit the manufacturer wants to claim for the product. The manufacturer cannot legally promote a product for a use not contained in the labeled indication.¹¹⁶ Therefore, the district court’s inference that an inhalational indication was investigational because DOD sought a labeling change was not necessarily warranted.

Similarly, the use of anthrax for post-exposure prophylaxis, as it was offered to some civilians following the mailing of anthrax-laced letters through the United States mail, was not an investigational use. The label for the vaccine states that its safety and effectiveness “in a post-exposure setting has not been established.”¹¹⁷ Thus, its use for this purpose was, as a technical matter, off-label and not investigational. As discussed above, off-label use of approved drugs is viewed as a legitimate and often indispensable part of ordinary medical practice. While the Byrd Amendment, addressed below, prohibits off-label administration to military personnel without consent, no similar consent requirement is mandated for civilians under either FDA regulations or tort law.

This critique by no means is meant to dismiss as illegitimate the safety concerns that were raised about the anthrax vaccine – criticisms of the laxity with which the vaccine’s manufacturer approached its task as well as FDA’s arguably weak oversight have been discussed elsewhere.¹¹⁸ However, it is meant to point out that the safety and effectiveness of the vaccine should not be judged solely by its regulatory status, nor should those who receive it be classified as human subjects solely on this basis. That a district court could claim in 2003 that administration of AVA constituted a “demand that members of the armed forces

114. John J. Michels, Jr., *The Anthrax Vaccine Controversy*, VA. LAWYER, Dec., 2001, at 20, 21, <http://www.vsb.org/publications/valawyer/dec01/michaels.pdf> (last visited Feb. 24, 2005).

115. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000); *Hanson v. U.S.*, 417 F. Supp. 30, 35 (D. Minn. 1976) (“the ‘intended use’ of a product, within the meaning of the Act, is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source.”).

116. *See* General Requirements on Content and Format of Labeling for Human Prescription Drugs, 21 C.F.R. § 201.56(c) (2003).

117. FDA, *supra* note 113, at 3.

118. Gail H. Javitt, *Drugs and Vaccines for the Common Defense: Refining FDA Regulation to Promote the Availability of Products to Counter Biological Attacks*, 19 J. CONTEMP. HEALTH L. & POL’Y 37, 82-93 (2002).

also serve as guinea pigs for experimental drugs”¹¹⁹ not only reflects a misunderstanding of the FDA approval process, but moreover serves as a red flag that the current regulatory system insufficiently distinguishes between research and treatment, thereby creating confusion, misunderstanding, and distrust among civilians, military personnel, and even the judiciary.

This critique also should not be understood to downplay the particular care that should be taken in evaluating the safety and effectiveness of products administered to military personnel, whether investigational or approved. Military personnel are unique in that they waive their right to consent to medical treatment when they join the military,¹²⁰ and in general agree to submit to decisions by the government about a wide variety of issues affecting their well-being.¹²¹ They also differ from most civilians because a decision made by one soldier may impact the well-being of other military personnel and the success of the military enterprise as a whole. Because of their reduced autonomy to make personal decisions, military personnel must rely on risk-benefit judgments made by others regarding all aspects of their service, in particular with regard to the administration of therapeutic and prophylactic products. Those tasked with such decisions should have adequate expertise and should make such decisions only after careful review of the risks and benefits involved. But this need for expertise and special care inheres regardless of the regulatory status of the product. In all cases, the evidence of a product’s safety and effectiveness must be carefully reviewed, and those with adequate expertise must determine that the potential benefits outweigh the potential risks. Such a determination may be more challenging when dealing with an investigational product if there is incomplete safety and effectiveness information, but the unique status of military personnel demands particular care in all cases.

C. *The Animal Efficacy Rule*

More recent efforts by FDA to speed approval of products to counter bioterrorism similarly demonstrate the need for a new paradigm, but for different reasons. In 2002, FDA issued a final rule, commonly known as the “Animal Efficacy Rule” (AER), which lowers the barriers to market entry of drugs and biological products (including vaccines) by eliminating clinical data requirements to demonstrate a product’s efficacy.¹²² The final rule permits the approval of “appropriate studies in animals in certain cases to provide substantial evidence of

119. *Doe v. Rumsfeld*, 297 F. Supp. 2d 119, 135 (D. D.C. 2003).

120. See DEP’T OF THE ARMY, *supra* note 16 (discussing command aspects of military care).

121. See, e.g., 10 U.S.C. § 978 (2000) (describing drug and alcohol abuse and dependency testing for new entrants); DEP’T OF THE ARMY, *supra* note 16, Ch. 4 (outlining the standard for appearance and choice of personal relationships).

122. New Drug and Biological Drug Products, 67 Fed. Reg. 37,988, 37,989 (May 31, 2002) (to be codified at 21 C.F.R. pts. 314 & 601).

the effectiveness of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances."¹²³ Approval on this basis is limited to situations where it would be unethical to conduct efficacy studies in humans (because such studies would require exposure of healthy subjects to lethal agents) and for "drug and biological products that are intended to reduce or prevent serious or life-threatening conditions."¹²⁴ The Rule does not waive the requirement for clinical data on product safety.¹²⁵

A product approved pursuant to the AER is not considered to be investigational. Because it is approved with less than the usual amount of data required for drug approval, it is subject to additional requirements. These include the need for postmarketing studies¹²⁶ and for specific patient labeling.¹²⁷ The labeling

[M]ust explain that, for ethical or feasibility reasons, the drug's approval was based on efficacy studies conducted in animals alone and must give the drug's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval.¹²⁸

The labeling must, if possible, be provided to patients prior to administration or dispensing of the drug product.¹²⁹

PB was the first – and, to date, the only – product approved under the AER.¹³⁰ The AER was a significant and unprecedented departure from statutory requirements for product approval – a departure on which there has been few remarks. Section 505(d) of the FD&C Act precludes FDA approval of a new drug application for which "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."¹³¹ The term substantial evidence is defined as:

[E]vidence consisting of adequate and well-controlled investigations, *including clinical investigations*, by experts qualified by scientific

123. *Id.* at 37,988-89.

124. *Id.* at 37,989.

125. *Id.*

126. Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible, 21 C.F.R. § 314.610(b)(1) (2004).

127. *Id.* § 314.610(b)(3).

128. *Id.*

129. *Id.*

130. E-mail from Christopher Colwell, Policy Analyst, U.S. Food and Drug Administration, to Gail H. Javitt, Greenwall Fellow in Bioethics and Health Policy (2000-2002), Johns Hopkins and Georgetown Universities (July 6, 2004, 10:27 EST) (on file with Journal of Health Care Law & Policy).

131. 21 U.S.C. § 355(d) (2000).

training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. (emphasis added).¹³²

On its face, this definition requires clinical efficacy studies as a mandatory component of new drug applications, and this is the manner in which the provision had previously been interpreted, without exception. FDA, in the proposed rule, acknowledged its deviation from the agency's longstanding interpretation of substantial evidence but reasoned that the agency's prior regulations:

[D]id not contemplate situations in which efficacy studies cannot be ethically conducted in humans, and FDA believes that it would be inconsistent with the statute's public health objectives to conclude that FDA cannot use some other basis for considering the efficacy of such products. The legislative history does not address this issue. Concluding that such products cannot ever be approved because human efficacy trials cannot be conducted is contrary to the public interest and inconsistent with the act's purpose of public health protection. Courts have recognized that remedial statutes such as the act are to be liberally construed consistent with the act's overriding purpose to protect the public health.¹³³

In addition, FDA drew a link between investigational and approved products in supporting its decision:

This conclusion is consistent with the recognition by Congress of the importance of ethical behavior in the study of unapproved products. For example, Congress has acknowledged the need: (1) [f]or informed consent in clinical research (section 505(i)(2) of the act); (2) to have due regard for patients in issuing regulations for investigational use of drugs (section 505(k) of the act); and (3) for experts to act "fairly and responsibly" in evaluating efficacy (section 505(d) of the act). Where human efficacy trials cannot be done ethically, experts are without human studies upon which to fairly and responsibly conclude that a product is effective. In the situations described previously, the agency believes that adequate and well-controlled animal studies may provide sufficient data to warrant approval.¹³⁴

FDA noted in the preamble to its final rule that it received no comments "discussing our legal authority to approve new drugs and biological products based

132. *Id.*

133. New Drug and Biological Drug Products, 64 Fed. Reg. 53,960, 53,964 (Oct. 5, 1999) (to be codified at 21 C.F.R. pts 314 & 601) (citing *United States v. An Article of Drug * * * Bacto-Unidisk*, 394 U.S. 784 (1968)).

134. *Id.*

on evidence of effectiveness from studies in animals.”¹³⁵ Perhaps because the AER was viewed as indispensable to providing products to counter bioterrorism, not one comment raised the question of whether FDA had exceeded the scope of its statutory authority, and therefore acted unlawfully, when it promulgated the AER.¹³⁶

The question of whether FDA exceeded its lawful authority in promulgating the AER was also perhaps mooted by Congress’ explicit direction to the agency to finalize the rule – which had been pending in a proposed state from 1999 to 2002. The Public Health Security and Bioterrorism Preparedness Response Act of 2002¹³⁷ directed FDA to complete the process of rulemaking within 90 days of the statute’s enactment.¹³⁸ But the 2002 Act did not amend the FD&C Act definition of substantial evidence, nor did it legislatively codify FDA’s interpretation of this definition. Thus, the question of the legality of the AER, however academic, still stands.

Of more practical import, the AER demonstrates the degree to which FDA has stretched its own statutory authority in the service of approving products for emergent circumstances. Such products may in fact be no more (and may even be less) supported by safety and efficacy data than are products under an IND. This is because an IND product is investigational from the phase I safety trial through the phase III clinical efficacy study, until the actual moment of approval. This is a

135. New Drug and Biological Drug Products, 67 Fed. Reg. at 37,993.

136. It might have been argued, for example, that the “plain meaning” of the statute required human clinical data of efficacy to support FDA approval. If a court agreed that the meaning of the statute was clear, it would likely hold FDA’s action unlawful. *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984) (noting that “if the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress”). If, however, a court determined that the language was ambiguous, it would generally accord significant deference to a reasonable agency interpretation. *Id.* at 843. In this case, a court would also likely note the agency’s departure from longstanding policy, and review whether such a change was adequately explained. *See Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 57 (1983) (“An agency’s view of what is in the public interest may change, either with or without a change in circumstances. But an agency changing its course must supply a reasoned analysis....” (quoting *Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 552 (D.C. Cir. 1970))). Courts accord less deference to an interpretation that constitutes an unexplained departure from a prior consistently held view of the agency. *See, e.g., Smiley v. Citibank*, 517 U.S. 735, 742 (1996); *Good Samaritan Hosp. v. Shalala*, 508 U.S. 402, 417 (1993); *Motor Vehicle Mfrs. Ass’n*, 463 U.S. at 57.

137. Pub. L. No. 107-188, 116 Stat. 594 (2002).

138. *Id.* at § 123. This section stated that:

[n]ot later than 90 days after the date of the enactment of this Act, the Secretary of Health and Human Services shall complete the process of rulemaking that was commenced under authority of section 505 of the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act with the issuance of the proposed rule entitled “New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot be Conducted” published in the Federal Register on October 5, 1999 (64 Fed. Reg. 53,960), and shall promulgate a final rule.

wide continuum that encompasses a broad range of information concerning product safety and efficacy. Products approved under the animal efficacy rule and IND products administered for therapeutic purposes therefore share substantive similarities but are, as a regulatory matter, sharply divided. In some cases recipients may be similarly vulnerable to harm. Yet the recipients of products in the former category are considered “patients” while those receiving products in the latter category are “human subjects.” Both require similar regulatory protections and disclosures. While neither should be viewed as “guinea pigs,” heightened safeguards are needed for both to ensure they are fully aware and informed of the risks, limitations, and benefits of the products they are receiving. Additionally, there is a need to monitor those receiving both types of products and for a mechanism to gather retrospective data on their outcomes. Regardless of the regulatory status, and regardless of whether the recipients are civilian or military, data to assess whether the product was protective or therapeutic, or alternatively whether it caused harm, is needed.

D. Project Bioshield and the Emergency Use Authorization Provision

Following the first Gulf War, researchers expected that FDA would finalize its Interim Rule, but the agency did not do so. The Presidential Advisory Committee on Gulf War Veterans’ Illnesses, which operated from 1995-1997, recommended that FDA complete the rulemaking process it had begun.¹³⁹ In response, FDA published a request for comments on the merits of finalizing, modifying, or revoking the Interim Rule.¹⁴⁰ The overwhelming majority of comments FDA received opposed the interim rule and argued that informed consent is essential for military personnel.¹⁴¹

139. See generally PRESIDENTIAL ADVISORY COMMITTEE ON GULF WAR VETERANS’ ILLNESSES, FINAL REPORT, ch. 2 (1996), <http://www.gulfink.osd.mil/gwvi/ch2.html> (last visited Feb. 24, 2005).

140. Accessibility to New Drugs for Use in Military and Civilian Exigencies When Traditional Human Efficacy Studies are Not Feasible, 62 Fed. Reg. 40,996 (July 31, 1997) (to be codified at 21 C.F.R. pt. 50) (request for comments).

141. Human Drugs and Biologics, 64 Fed. Reg. at 54,181. According to FDA, the agency received 134 comments on whether it should revoke or amend the Interim Rule, 119 of which opposed the rule and recommended revocation:

Most of these comments opposed the agency’s continued use of the interim rule after the experience of the Persian Gulf War. Many thought it should never have been used. Specifically, 114 comments stated that informed consent was absolutely essential and that military personnel, like other nonmilitary citizens, should receive adequate information about an investigational product before its use and have the right to refuse to receive it. Seventeen comments stressed the need for followup of possible adverse reactions to investigational products, and 15 comments indicated that DOD could not fulfill its responsibilities even if FDA required adequate followup and other requirements as part of a new regulation. Five comments stated that DOD had shown itself to be incapable of adequate oversight and recordkeeping and three comments noted that the interim rule had not been implemented by DOD as had been intended. Several comments suggested that if the rule were to be used again, there must be an independent board of medical and ethical

Legislation adopted in October 1998 effectively mooted the issue. Known as the Byrd Amendment, the legislation vested the authority to grant waivers of informed consent for the use of an IND product, as well as for a "product unapproved for its applied use" (i.e., off-label use), solely in the President of the United States, based on criteria to be established by FDA.¹⁴² Thereafter, FDA formally revoked the Interim Rule and issued the criteria to be used by the President in reviewing waiver requests.¹⁴³

Since the enactment of the Byrd Amendment, there have been no requests to waive consent. The result of the Amendment has been to prevent DOD, as a practical matter, from using IND products or off-label products for force protection.¹⁴⁴ Critics of the Gulf War episode support this outcome as providing necessary human rights protections to troops.¹⁴⁵ However, this outcome also may have limited DOD's choices in protecting troops from potential threats. In the case of off-label use of drugs, moreover, it has given DOD less latitude in treating its own troops than physicians have in the course of their ordinary medical practice.¹⁴⁶

Project Bioshield, which passed 99-0 in the Senate in May 2004¹⁴⁷ and, in a different version in the House in July 2003,¹⁴⁸ contains a provision aimed at

experts, there must be an institutional review board independent of DOD, and there must be proper monitoring that could only be done by non-DOD personnel.

Id.

142. 10 U.S.C. § 1107 (2000).

143. FDA issued an Interim Final Rule describing these criteria in 1999. See *Human Drugs and Biologics*, 64 Fed. Reg. at 54,181. More recently, the agency announced its intention to issue a final rule by July 2002. See *Unified Agenda of Federal Regulatory and Deregulatory Actions*, 67 Fed. Reg. 33,039, 33,043 (May 13, 2002) (semiannual regulatory agenda).

144. RETTIG, *supra* note 1, at 15; see also DEP'T OF DEFENSE, DIRECTIVE – USE OF INVESTIGATIONAL NEW DRUGS FOR FORCE HEALTH PROTECTION 3 (2000), <http://www.dtic.mil/whs/directives/corres/pdf2/d62002p.pdf> (last visited Feb. 24, 2005).

145. See generally George J. Annas, *Puppy Love: Bioterrorism, Civil Rights, and Public Health*, 55 FLA. L. REV. 1171 (2003) (arguing that forced medical treatment and immunizations are unconstitutional); Philip Alcabes & Ann B. Williams, *Human Rights and the Ethic of Care: A Framework for Health Research and Practice*, 2 YALE J. HEALTH POL'Y L. & ETHICS 229 (2002) (discussing potential risks and benefits for clinical research in human rights context).

146. Off-label use is recognized as a legitimate, and often indispensable, part of medical practice. See Beck & Azari, *supra* note 74, at 76-80.

147. Project Bioshield Act of 2004, S. 15, 108th Cong. (2004), available at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_bills&docid=f:s15es.txt.pdf (last visited Feb. 24, 2005).

148. Project Bioshield Act of 2003, H.R. 2122, 108th Cong. (2003), available at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=108_cong_bills&docid=f:h2122ih.txt.pdf (last visited Feb. 24, 2005). The full House approved its version of Project Bioshield on July 16, 2003. "The largest difference between the bills is how each would fund the purchase of countermeasures. S. 15 authorizes and appropriates for each fiscal year in perpetuity 'such sums as may be necessary' to procure countermeasures. This mandatory funding is not subject to the annual appropriations process. In contrast, H.R. 2122 does not appropriate any money, but establishes a special fund for the purchase of countermeasures and authorizes the appropriation of up to \$5.593 billion total for the fiscal years

facilitating the administration of unapproved and off-label products to both military personnel and civilians in the event of a national security emergency stemming from biological, chemical, radiological or nuclear agents.¹⁴⁹ Bioshield empowers the Secretary of Health and Human Services to authorize the emergency use – defined in statute as “intended for use in an actual or potential emergency”¹⁵⁰ – of medical products that have not yet been approved by FDA or that have been approved for a different indication. Such an authorization may be made upon declaration of emergency by the Secretary of Health and Human Services, which in turn must be based on a determination by the Secretary of Defense or the Secretary of the Department of Homeland Security that “there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a specified biological, chemical, radiological, or nuclear agent or agents;”¹⁵¹ or, authorization may be made upon a determination by the Secretary of Health and Human Services of a “public health emergency under section 319 of the Public Health Service Act that affects, or has a significant potential to affect, national security, and that involves a specified biological, chemical, radiological, or nuclear agent or agents, or a specified disease or condition that may be attributable to such agent or agents.”¹⁵²

To exercise this authority, the Secretary of Health and Human Services must conclude, preferably after consultation with the Director of the National Institutes of Health and the Director of the Centers for Disease Control and Prevention, that:

- (1) the agent for which the countermeasure is designed can cause serious or life-threatening disease;
- (2) the product may reasonably be believed to be effective in detecting, diagnosing, treating, or preventing the disease;
- (3) the known and potential benefits of the product outweigh its known and potential risks;
- (4) there is no adequate alternative to the product that is approved and available; and
- (5) any other criteria prescribed in regulation are met.¹⁵³

Emergency use authorization must be product specific and time limited, lasting no more than one year.¹⁵⁴ The law specifies that, “to the extent practicable,” information must be provided to health professionals and recipients about the known risks, benefits, and alternatives, if any, of the product; that recipients must

2004 to 2013.” FRANK GOTTRON, CRS REPORT TO CONGRESS, PROJECT BIOSHIELD 2 (2003), <http://www.fas.org/irp/crs/RS21507.pdf> (last visited Feb. 24, 2005).

149. S. 15. Most of the Act addresses the creation of incentives to encourage the pharmaceutical industry to research and develop bioterrorism countermeasures. *Id.* The Act authorizes a 10-year, \$6 billion plan under which the government would create and produce vaccines and treatments for anthrax, Ebola, the plague and other potential bio-terrorism agents. *Id.*

150. *Id.* § 4(a).

151. *Id.*

152. *Id.*

153. GOTTRON, *supra* note 148, at 4.

154. S. 15, § 4.

be informed of their option to refuse treatment and the consequences of such refusal; and that adverse event monitoring, reporting, and recordkeeping occur.¹⁵⁵

Bioshield reflects a legislative attempt to work around the problems of administering IND and off-label products to civilians. It creates a mechanism for civilians analogous to the Byrd Amendment's provisions for military personnel. While it is too soon to assess its effectiveness in achieving its objectives, and while its implementation will require careful and thoughtful drafting of regulations, the manner in which the legislation is designed raises some potential concerns. First, given the history of neglect of the Byrd Amendment, it is unclear whether the IND authorization will have any practical effect. In practice, the hurdles to be overcome may be too great. Second, the statute gives no practical guidance on what constitutes an emergency, or what criteria are to be used to determine whether an emergency exists. Indeed, the precise point at which an emergency is upon us, or is likely enough to trigger the Bioshield provisions, is difficult to define. In practice, there may be insufficient time to trigger these provisions, at least in the thoughtful and deliberative way contemplated by the statute.

The inclusion of off-label uses in Bioshield, as it was in the Byrd Amendment, is puzzling. As stated above, off-label use is an accepted part of medical care. Thus, aligning it in these two statutes with IND uses imposes a much higher burden on these products than they are ordinarily subject to. While there may need to be a mechanism to permit physicians, manufacturers, and state and federal public health agencies to endorse the use of a product for an unapproved use, it is unclear why the standards for doing so should be the same as for a product that has never been approved for any indication.

Finally, and perhaps most fundamentally given the premise of this paper, Bioshield does not resolve the inherent regulatory mismatch that currently exists when IND products are used for a therapeutic purpose. Bioshield thus uses the same method for speeding up access that FDA has historically used: namely, creating exceptions to the IND rules without changing the "investigational" terminology. Bioshield therefore does nothing to alleviate, and will likely perpetuate, the confusion that exists when unapproved drugs, or drugs for unapproved uses, are used to combat emergent health threats.

VI. AMENDING FDA REGULATIONS TO PERMIT LIMITED PURPOSE APPROVAL

One means to alleviate the confusion regarding unapproved drugs, and to facilitate their use to combat emergent health threats while adequately protecting recipients of these products, is to create a new category of drug approval. This

155. *Id.*

new category, tentatively termed “limited purpose” or “interim” approval, could be used for products about which insufficient data exist regarding safety and effectiveness to warrant full, unrestricted approval, but for which it has been determined that there is a reasonable basis to offer it to populations at high-risk under specific conditions. Such products would not be regulated pursuant to FDA’s investigational new drug regulations. Nevertheless, they would be subject to certain safeguards to ensure adequate monitoring of adverse events and adequate provision of information to recipients concerning risks and benefits. Manufacturers would also be required to conduct “Phase IV” or postmarketing research to bolster the safety and effectiveness data. In addition, their approval would be limited to specific populations or circumstances, depending on the product at issue. Types of limited-purpose approval could be, for example, “For Military Use Only,” or “For Emergency Medical Personnel Only.” Each approval would therefore be carefully tailored to the situation for which its use was contemplated. Furthermore, approval would be time-limited, after which FDA would reevaluate the product in light of reported adverse events and additional data gathered during the time the product was approved.

Under this proposed framework, manufacturers would have to prepare adequate labeling to explain to both providers and patients the risks, limitations, and potential benefits of the product, and the basis upon which it was approved. FDA could help ensure adequate disclosure through the use of “patient package inserts,” which is a mechanism that FDA has previously used for certain types of products where it is especially important to ensure that adequate information is provided to the patient concerning a drug product.

As with other medical treatments, providers would be under a legal obligation to inform patients of the risks and benefits of taking the products. However, unlike products under an IND, the formal regulatory procedures associated with consent would not be required.

VII. CONCLUSION

The philosopher George Santayana is credited with the now famous aphorism that those who do not learn from history are doomed to repeat it.¹⁵⁶ But it is equally the case, though perhaps less often appreciated, that those who draw the wrong lessons from history may make new errors with unforeseen, but similarly damaging, negative consequences.

When considering the issue of the use of investigational therapies in cases of extreme threat – whether that threat is imposed from bioterror agents or “naturally”

156. GEORGE SANTAYANA, *THE LIFE OF REASON* 284 (2d ed. 1927).

originating threats such as SARS, it is important to be guided by history but not misled by it. It is especially important that the atrocities of previous eras not be misinterpreted to preclude the provision of potentially life-saving therapies to military personnel or to the public under the misguided apprehension that such conduct would violate human rights or constitute unethical human experimentation. This is not to ignore the need for rigorous and exacting scientific research and exquisite examination of the risks and benefits to potential recipients of any product that purports to be therapeutic – whether fully “approved” or “investigational.” Nor should it ignore the need to inform the potential recipients of a product of the risks and benefits of the product, to the extent they are known – not because they are considered to be, as a formal legalistic matter, “subjects” of an experiment, but because, as with all medical decisions, they must be adequately informed to make rational choices tailored to their individual needs. But, in considering these issues we should be guided by the facts before us, and the realistic concerns that these facts raise, rather than informed by the specter of the past and labels and categories that may no longer apply.

Of course, a more complex question arises when consent is viewed as infeasible because an individual’s choice *not* to accept a particular therapy has implications for the safety and well-being of others. Some have debated whether and under what circumstances civil liberties may be limited in the face of bioterrorism.¹⁵⁷ Since the case of *Jacobson v. Massachusetts*¹⁵⁸ in the early 1900s, courts have recognized that the government may in certain circumstances require civilians to be vaccinated without their consent to avoid harms to others. Military personnel in general waive their right to consent to standard medical treatment when they enlist,¹⁵⁹ and medical treatment decisions are made not only with the individuals’ well-being in mind, but also with regard to benefit to the military as a whole. Because of this, special safeguards should be in place to ensure that those making the decisions regarding what treatments military personnel receive appropriately consider the risks and benefits to troops and institute adequate measures for monitoring and responding to adverse events. This is particularly important when considering products with incomplete safety and effectiveness information.

157. See generally Lawrence O. Gostin, *When Terrorism Threatens Health: How Far Are Limitations on Personal and Economic Liberties Justified?*, 55 FLA. L. REV. 1105 (2003) (discussing how far personal and economic liberties can be restricted to protect the public health); Annas, *supra* note 145 (arguing that Americans should not tolerate a substantial loss of civil liberties to deal with bioterrorism).

158. 197 U.S. 11 (1905) (upholding a city ordinance requiring citizens to be vaccinated against smallpox as a legitimate exercise of the state’s police power to protect the public health and safety of its citizens).

159. See DEP’T OF THE ARMY, *supra* note 16.

But the question of when, whether, and by whom consent is required should be evaluated separately from the question of whether there is sufficient information concerning a product's potential risks and benefits to warrant its administration for therapeutic or prophylactic purposes. As to this latter question, the need to ensure that benefits outweigh risks exists regardless of whether the product is, as a regulatory matter, classified as "investigational" or "approved."

Unfortunately, the damaging combination of politics, bureaucratic arcana, and inflammatory rhetoric has stymied efforts to clarify and resolve these issues. The attempt by FDA and DOD in 1990 to provide investigational therapies to military troops facing potential biological and chemical warfare threats was superseded by Congress, an action which has resulted in the virtual inability to provide investigational treatments in combat. It is too soon to judge the effectiveness of the emergency use authorization provision in Bioshield, but it too may miss the mark and prove ineffective in practice because it attempts to circumvent the central dilemma rather than squarely address it, and does so in a manner that may have significant practical barriers to its implementation.

This paper has argued for a new category of FDA product, the "interim approval," or "limited purpose approval," to take into account emergent threats stemming from both bioterrorism-mediated and "natural" health threats. Such a system could enhance regulatory clarity and thereby improve public understanding and public trust, while enabling the provision of products with therapeutic potential to prevent or mitigate emergent health threats.