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No Humans Have Been Injured in the Testing of this Drug: The New Animal Efficacy Rule

Carrie Campbell, Harvard Law School Class of 2004

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Abstract

This paper examines the "Animal Efficacy Rule," a regulation that provides for the approval of products by the FDA when efficacy testing on humans is ethically impossible. It gives a summary of the history of the enactment of this regulation and outlines its structure and major features. Next, the regulation is analyzed in light of statutory authority, ethics, and practicality. Finally the approval of pyridostigmine bromide under the Animal Efficacy Rule is evaluated in light of these concerns to determine whether the rule is acting as intended, illustrating remaining problems in implementation. The article concludes that while the Animal Efficacy Rule meets ethical requirements and is capable of being implemented given careful supervision, the FDA does not have statutory authority to make such regulation and thus a legislative solution is preferable.

In 1944 the United States government asked seventeen-year-old Nathan Schnurman to volunteer to test summer army uniforms, offering him various fringe benefits in exchange for his assistance.[1] When he reported for the testing, Schnurman was sealed in an air-tight chamber and repeatedly exposed to various chemical weapons, including mustard gas.[2] This exposure led to grave health consequences for him and his fellow guinea pigs, including asthma, cancer, and pulmonary disease for which they were never adequately compensated.[3] The government justified their experimentation because it anticipated chemical weapon use by Axis forces during World War II and needed to test clothing to protect against such devastating attacks.[4] Ethical research has always pitted the scientific ideal of controlled trials against the moral respect of human integrity. What happened in 1944 was not the first time America has stretched ethical boundaries for the cause of medical science, and unfortunately it would not be the last. [5]

Human experimentation standards have developed to address these and other problems. Some diseases and toxins, however, present dilemmas that exceed the scope of the current standards. For example, purposely infecting volunteers in a controlled environment is a medically fruitful technique that is nonetheless fraught with ethical problems. Few acceptable methods of drug development remain when a toxin is both rare, making field testing on previously exposed individuals unfeasible, and dangerous, making the intentional infection of human subjects morally suspect. Informed consent requirements may not be a perfect answer as they create non-representative samples in an experiment, hindering the predictive value of research.

This paper examines the way the Food and Drug Administration (FDA) has handled these problems, be-

[1] *Schnurman v. United States*, 490 F. Supp. 429, 430 (E.D. Va. 1980).
[2] *Id.* at 431.
[3] Michael J. O'Connor, *Bearing True Faith and Allegiance? Allowing Recovery for Soldiers Under Fire in Military Experiments that Violate the Nuremburg Code*, 25 Suffolk Transnat'l L. Rev. 649, 658 (2002).
[4] *Schnurman*, 490 F. Supp. at 430.
[5] For a survey of such testing *see* Jonathan D. Moreno, Undue Risk (2000).

ginning with a discussion of the FDA's Gulf War testing policy and its sub-optimal results. This is followed by an analysis of the current FDA regulatory scheme in a statutory, ethical, and practical context. Finally, this paper proposes legislative empowerment of the FDA as a solution that gives the FDA the authority to ethically evaluate drugs that cannot be ethically tested on humans.

Background

The challenges of ethical human testing came into focus in 1990 as the United States prepared for potential biological warfare in Operation Desert Shield. Although anthrax and other exotic diseases are naturally found in the region, Iraq had successfully weaponized lethal biochemical agents as evidenced by its "tests" on Iranian and Kurdish populations. The impending war spurred a serious exploration of biochemical countermeasures; an exploration that quickly conflicted with ethical research standards.

While treatments for some threatening toxins were already available, they involved drugs approved under an "investigational new drug" (IND) protocol.[6] At the IND stage a drug can only be used under certain approved experimentation protocols before full approval. The FDA required informed consent from patients receiving these experimental drugs, but acquiring such consent, already burdensome in a civilian context, presented grave problems in the military context. The stakes could not be much higher. If soldiers refused to take experimental treatments and as a result failed their missions because of illness or death, many additional lives would certainly be lost. Even if consent were achieved, however, the moral issues would remain because the rigid command structure of the military eroded the notion of consent practically to a fiction.[7]

[6] However, none of the IND protocols exactly covered the intended use against biomedical weapons: either the drugs in question were to be used under different conditions than those currently under study in the protocols, or were to be administered in different dosages or by different methods.

[7] *See*, Ruth K. Miller, *Informed Consent in the Military: Fighting a Losing Battle Against the Anthrax Vaccine*, 28 Am.

While preparing for biological war the Department of Defense (DOD) wrote to the FDA requesting a battlefield exception to the IND protocols.[8] This exception would recognize combat occasions where patient consent was "not feasible."[9] In its request, the DOD outlined the dangers to military units and objectives if soldiers were to refuse consent when given an investigational new drug. The letter proposed five limitations on a "military exigency" waiver of informed consent:

> (1) [t]hat drug-by-drug requests for waiver be accompanied by written justification based on the intended uses and the military circumstances involved;
>
> (2) that no satisfactory alternative treatment is available;
>
> (3) that available safety and efficacy data support the proposed use of the drug or biologic product;
>
> (4) that each such request be approved by the applicable [DOD] Institutional Review Board; and
>
> (5) that the waivers be time-limited.[10]

J.L. & Med. 325 (2002).

[8]Letter from Department of Defense Assistant Secretary of Defense for Health Affairs to Department of Health and Human Services Assistant Secretary for Health (Oct. 30, 1990), in 55 Fed. Reg. 52,814 (1990).

[9]55 Fed. Reg. 52814, 52815 (December 21, 1990) [hereinafter "Interim Rule"] (referring to the informed consent guidelines in 21 U.S.C. §§355(i), 357(d) that require consent by recipients of investigational new drugs and new biologics except where not feasible).

[10]Interim Rule at 52815.

Less than two months later, the FDA substantially granted the DOD's request in an interim rule[11] (the "Interim Rule") that applied to "specific military operation(s) involving combat or the immediate threat of combat."[12] It adopted the DOD's suggested procedure for granting of waivers, and subjected them to a one year automatic expiration unless renewed at the DOD's request.[13]

The Commissioner of Food and Drugs had final discretion in determining whether to grant such a waiver, and was expected to seek expert advice[14] while weighing the following four factors:

(i) The evidence of drug safety and effectiveness;

(ii) The administering context, e.g., whether a drug is intended for battlefield or hospital settings and whether it will be professionally or self-administered;

(iii) The nature of the targeted medical condition; and

(iv) The nature of the information given to drug recipients concerning the potential benefits and risks treatment.[15]

The FDA eventually granted two Interim Rule waivers for pyridostigmine bromide (PB) and the botulinum toxoid (BT) vaccine.[16] PB is a pre-exposure nerve gas treatment thought to slow damage while the BT

[11] *Id.* at 52817 (codified at 21 C.F.R. §50.23(d)).
[12] *Id.* at 52817 (codified at 21 C.F.R. §50.23(d)(1)).
[13] *Id.* at 52817 (codified at 21 C.F.R. §50.23(d)(4)).
[14] *Id.* at 52817 (codified at 21 C.F.R. §50.23(d)(3)).
[16] 62 Fed. Reg. 40996, 40997-98 (July 31, 1997).

vaccine protects against botulism-based biological weapons.[17] Both products were administered to military personnel during Operation Desert Storm, but since the BT vaccine was administered on a voluntary basis only the PB waiver was used.[18]

Unfortunately, the DOD's subsequent PB waiver administration failed many FDA conditions.[19] Soldiers receiving PB were only partially informed of its proper use[20]due in part to inadequate labeling.[21] Additionally, the DOD did not make reasonable follow-up efforts to discover and report adverse drug-related experiences.[22] The military failed to document which units took PB, when they did so, or under what circumstances.[23] Standard Army follow-up surveys, as well as three subsequent PB safety surveys,[24] fell far short of FDA monitoring and reporting goals under the waiver. While one Journal of American Medicine study found that PB was generally safe as a pretreatment for nerve gas exposure,[25] other studies suggest that PB was linked to Gulf War syndrome.[26] This controversy cannot yet be resolved as efficacy data on PB as a nerve gas defense is unreliable—there are simply too few documented exposures.

The Interim Rule immediately created great controversy. In the thirty-day comment period following its publication, several commentators accused the rule of violating fundamental human rights.[27] Within a month, an anonymous serviceman sued the Department of Health and Human Services and the Department

[17] *Id.* at 40997-98.
[18] *Id.* at 40998.
[19] 64 Fed. Reg. 54180, 54184 (October 5, 1999).
[20] *Id.* at 54184.
[21] *Id.* at 54184.
[22] *Id.* at 54184. This is particularly problematic given the alleged connections between PB and Gulf War Syndrome, *see, e.g.*, GAO/T-NSIAD-97-190, Gulf War Illnesses: Enhanced Monitoring of Clinical Progress and of Research Priorities Needed 8 (1997); H.R. REP. 105-388, 105th Cong., 1st Sess., at p. 35, 67 (1997).
[23] 62 Fed. Reg. 40996, 40998 (July 31, 1997).
[24] For example, Survey II went out to an unspecified number of recipients, making response bias impossible to quantify. Low response rates also
[25] J.R. Keeler et al., *Pyridostigmine Used as a Nerve Agent Pretreatment under Wartime Conditions*, 266 J. Am. Med. Ass'n. 693 (1991)
[26] *See, e.g.*, Beatrice Alexandra Golomb, *A Review of the Scientific Literature as it Pertains to Gulf War Illnesses: Volume 2: Pyridostigmine Bromide* (RAND 1999), available at <http://www.gulflink.osd.mil/library/randrep/pb_paper/>.
[27] 64 Fed. Reg. 53960, 53962 (October 5, 1999) [hereinafter "Proposed Rule"].

of Defense claiming that the procedures outlined in the Interim Rule violated the Federal Food, Drug, and Cosmetic Act (FDCA),[28] the DOD Authorization Act,[29] and Fifth Amendment due process.[30] However, both the district and appellate courts supported the FDA's activity in promulgating the Interim Rule.[31] Despite this victory the reaction to the rule was critical on other fronts: the Presidential Advisory Committee on Gulf War Veterans' Illnesses issued a report describing the problems with the application of the rule by the DOD,[32] and many scholars had weighed in against it.[33] In 1997 the FDA requested comments on the Interim Rule's future that led to its ultimate revocation in 1999.[34] A replacement statute strengthened IRB requirements and outlined waiver qualification guidelines. Most tellingly, the President was now given the sole discretion to issue these military waivers of the informed consent rule.[35]

As it revoked the Interim Rule, the FDA proposed streamlining drug and biological product approval when such items could only be tested ethically on animals. Under the new rule, animal efficacy tests rather than human clinical studies would suffice for drug approval.[36] In the aftermath of the 9/11 terrorist attacks, Congress directed the FDA to facilitate approval of products that counteract chemical, biological, and nuclear threats.[37] The FDA complied by issuing a final rule entitled "Evidence Needed to Demonstrate

[28] 21 U.S.C. § 355.

[29] 10 U.S.C. § 980 (prohibiting the DOD from using its funds for research on involuntary human subjects).

[30] *Doe v. Sullivan*, 756 F. Supp. 12 (D.D.C. 1991), *aff'd*, *Doe v. Sullivan*, 938 F.2d 1370 (D.C. Cir. 1991).

[31] *Id.* Both the district court and the appellate majority held that the FDA's decision was reviewable but within FDA's statutory discretion; the lone dissenting justice argued that the case was moot because the conflict during which the drugs had been approved for use was over.

[32] 62 Fed. Reg. 40996-01, 41000 (July 31, 1997).

[33] *See, e.g.*, George J. Annas, *Mengele's Birthmark: The Neuremburg Code in United States Courts*, 7 J. Contemp. Health L. & Pol'y 17, 41 (1991); Suzanne B. Seftel, *Waving for the Flag: Should Informed Consent Rules Apply in the Context of Military Emergencies?*, 60 Geo. Wash. L. Rev. 1387 (1992); Elliot J. Schuchardt, *Distinguishing Between Research and Medical Practice During Operation Desert Storm*, 49 Food & Drug L.J. 271 (1994).

[34] 64 Fed. Reg. 54180-01 (October 5, 1999). FDA received 135 comments on the Interim Rule, of which 119 recommended its revocation and only two favored its retention. *Id* at 54181. FDA's reasons for revoking the rule, addressed in these comments, included problems with DOD oversight and recordkeeping, ethical inadequacy of information and consent to servicemen receiving experimental drugs, and lack of follow-up to assess safety and efficacy of the drugs received. *Id* at 54181, 54183-84.

[35] *See id.;* 10 USC § 1107(f); 21 C.F.R. § 50.23(d)(1).

[36] Proposed Rule at 53960.

[37] Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188 § 123, 116 Stat. 594, 613 (2002).

Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible."[38] This rule would allow for limited approval of products based on animal efficacy tests alone when human efficacy tests are not possible. While the rule presents an ethical solution to the dilemma of drug approval and human testing, it is unfortunately beyond the FDA's authority.

Current Regulations: The Animal Efficacy Rule

Current FDA regulations avoid consent problems in military or emergency situations through limited drug approval based on animal efficacy tests alone (the "Animal Efficacy Rule"). Codified at 21 C.F.R. pt. 314 (drugs) and pt. 601 (biological products), the rules outline the approval process, postmarketing safety and promotional material regulations, and approval revocation.

These sections only apply to products meeting *all* of the following requirements:

(1)

(2)

(3)

[38]67 Fed. Reg. 37988 (May 31, 2002) [hereinafter "Final Rule"].

(4)

(5)

(6)

(7)

The regulations provide additional safeguards by providing for approval withdrawal in certain circumstances. To prevent drug misuse, animal-efficacy-based approval may be withdrawn when postmarketing studies are negligently performed, when marketing restrictions inadequately provide safe public use, or when promotional materials are misleading.[43] Significantly, if postmarketing studies fail to verify the product's efficacy or other data indicate the product is unsafe or ineffective, approval will be revoked.[44] This contrasts with the revocation of an IND, which requires not a mere lack of effectiveness data, but rather "convincing evidence" that the drug is ineffective.[45] The Animal Efficacy Rule's heightened standards better protect the public

[43] *Id.* at 37995, 37997 (codified at 21 C.F.R.§314.620 (a)(3)-(5), §601(a)(3)-(5)).
[44] *Id.* at 37995, 37997 (codified at 21 C.F.R. § 314.620 (a)(1), (a)(6) and §601.92(a)(1), (a)(6))
[45] 21 C.F.R. § 312.44(b)(2)(iii).

when compared to drugs left in approval limbo under an IND protocol.

Are the new regulations a step in the right direction?

Although the 2002 regulations responded to the fiasco created by the Interim Rule,[46] they target a different problem.[47] The Animal Efficacy Rule is broader than the Interim Rule; addressing not only the mass administration of drugs not tested on humans, but also the business model necessary to produce them. The former strategy of granting indefinite IND status to drugs results in dangerously stifled development. Without approval prospects, investigational drug production is likely incapable of supplying large civilian populations, for example after a metropolitan bioterrorism attack. However, *actual* approval possibilities through animal trials would hasten drug research and development that otherwise had little hope of official approval (since we are only considering cases where human trials are prohibited).[48] Approved status also makes animal-tested drugs more quickly available when needed. If these drugs remained investigational, new treatment protocols would need to be cleared by an institutional review board even for life-threatening diseases.[49] If approved these drugs would be available immediately without specific approval.[50]

Drug approval based largely on animal efficacy studies is not unprecedented. In August 2000 the agency approved the use of ciprofloxacin for treating inhalation anthrax without standard clinical studies.[51] Also,

[46] Proposed Rule at 53960.

[47] Waiver of informed consent in military exigencies is still possible, although the rules for doing so were significantly amended during the 1990s. The new regulations delegate this power to the President and provide for more detailed safeguards to follow up on INDs where consent has been waived. 10 U.S.C. § 1107(f); 21 C.F.R. § 50.23(d)(1).

[48] *Cf.* Congress' treatment of orphan drugs, creating incentives to develop such drugs and bring them to market rather than allowing FDA to maintain indefinite "orphan IND" status. Peter Barton Search Term Begin Hutt & Search Term End Richard A. Merrill, Search Term Begin Food Search Term End and Search Term Begin Drug Law 556Search Term End 55655 (2d ed. 1991).

[49] 21 C.F.R. §§ 312.30, 312.34.

[50] *See* Carol Marcus, Ph.D., M.D., Comment on 62 Fed. Reg. 40996 (August 19, 1997), available at <http://www.fda.gov/ohrms/dockets/dockets/98n0237/bkg0001-03-ref0002.pdf> (suggesting that this also could be effected by an "advance buy-in" by national and/or local IRBs).

[51] Some animal studies of efficacy were available, as well as assorted human case studies. Medical Review of Ciproflaxin, Application No.: 19-537/S38, 19-847/S24, 19-857/S27, 19-858/S21, & 20-780/S8, approved 8/30/2000, at 32, available at

in November 2001, after a spate of letter-borne anthrax attacks, the FDA allowed doxycycline and penicillin G procaine to be labeled for use as post-exposure protection against inhalation anthrax.[52] The FDA based its decision on rhesus monkey experiments, laboratory studies, and data from a 1979 anthrax outbreak in Sverdlovsk in the former Soviet Union.[53] Although these examples represent a departure from the typical guidelines they remain a precedent for drug approval that relies on animal studies.

The Animal Efficacy Rule seems on the surface to have successfully addressed many of the challenges presented by the Interim Rule by simply codifying and extending a practice FDA had used before: the approval of certain drugs and biological products based on sparse evidence of efficacy in humans. In addressing the flaws of the Interim Rule, the new standards obviate the need for heightened experimental consent because drugs are formally approved and no longer investigational. Additionally, the new standards remove the distinction between military and civilian use because differing safety standards created a perverse incentive to use military personnel as captive subjects for medical testing.[54] Finally, the withdrawal provisions and marketing regulations acknowledge the need for approved drug follow-up and monitoring as problems may arise after widespread use; a lesson learned during the First Gulf War. Nonetheless, this rule is still vulnerable to criticism on statutory, ethical, and practical levels.

Statutory Authority

The Animal Efficacy Rule's clearest vulnerability is its tenuous statutory authority. The FDCA authorizes the FDA to approve drugs based on "substantial evidence," meaning "evidence [of efficacy] consisting of

<http://www.fda.gov/cder/foi/nda/2000/19-537S038_Cipro_medr.pdf>

[52] 66 Fed. Reg. 55679-03 (November 2, 2001).

[53] *Id.* at 55680-81.

[54] Sidney Wolfe, M.D. & Michael Tankersley, Public Citizen Litigation Group, Comment on 62 FR 40996 (October 30, 1997), available at <http://www.fda.gov/ohrms/dockets/dockets/98n0237/bkg0001-07-ref0006.pdf >.

adequate and well-controlled investigations, including clinical investigations, by experts. . . ."[55] "Clinical investigations" have long been understood both by the FDA and by the medical community to include human tests. Approving drugs on the basis of animal studies alone represents a departure from this longstanding interpretation, and it is not clear that the FDA has the authority to make such a drastic change on its own authority.

If a court were reviewing FDA interpretation of the FDCA, it would apply the two-step analysis announced in *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).[56] In the first step of *Chevron*, a court must ascertain whether Congress directly addressed the contested question.[57] In this case, the statute clearly calls for "clinical investigations" which the general medical community and even the FDA itself define as trials performed on *humans,* not animals.[58] Alternatively, if a court deems the statute ambiguous as to human testing requirements, it can defer to novel interpretations of "clinical investigation" but only if it is a "permissible" construction, In our case, only a tortured interpretation of "clinical investigations" can include animals since it goes against both regular usage of the term and the FDA's past practice.[59] Under *Chevron* the FDA cannot redefine statutory terms at will and, consequently, the Animal Efficacy Rule is beyond the FDA's authority.

When the FDA first proposed the Animal Efficacy Rule, it cited *United States v. Article of Drug... Bacto-Unidisk...*[60] in support of its statutory re-reading. *Bacto-Unidisk* gave the FDA authority to interpret its

[55] 21 U.S.C. § 355(d) In the Proposed Rule, the FDA notes that its interpretation of "substantial evidence" has always included human efficacy studies, but implies that this need not be the case. Proposed Rule at 53964.

[56] *See also Doe v. Sullivan*, 756 F. Supp. 12, 15 (D.D.C. 1991) (*citing Chevron* as the appropriate standard of review for the FDA's interpretation of the FDCA).

[57] *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842 (1984)

[58] *See* 21 C.F.R. § 312.3(b) ("Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.").

[59] *Chevron*, 467 U.S. at 843.

[60] 394 U.S. 784, 799 (1969).

enabling statute broadly to effect stated Congressional policy goals.[61] In *Bacto-Unidisk*, a regulated item fell beyond the traditional medical definitions of "drug," but the FDA chose to regulate it as a drug nonetheless.[62] The Court held that, in the context of the FDCA, the word "drug" is a term of art encompassing more than a strict medical definition.[63] If *Bacto-Unidisk* merely stands for the fact that an agency may interpret a statutory term more broadly than its usual meaning, then it is fitting precedent for the FDA's broader interpretation of "clinical investigations" encompassing animal trials. However, the *Bacto-Unidisk* holding is inapplicable for several reasons.

Although the *Bacto-Unidisk* Court noted that statutory definitions may be broader than medical meanings, it still anchored proper interpretation to a term's literal meaning.[64] In our case, the definition of "clinical investigations" is not nearly as ambiguous as "drug." The fact that "drug" is explicitly defined in the FDCA suggests that it is a term of art, further detaching its meaning from the medical community's understanding. "Clinical investigations," however, is not explicitly used as a term of art by the FDCA, and its use before the FDA's recent reinterpretation was unambiguous and uncontested.[65] Furthermore, definitions of "clinical investigations" elsewhere in federal regulations explicitly specify that human subjects must be involved.[66] To interpret animal experiments as "clinical investigations" for a human drug is clearly contradictory to the body of federal regulation.

[61] *United States v. Article of Drug... Bacto-Unidisk...*, 394 U.S. 784, 799 (1969)

[62] The disputed item was a disc that measured patient resistance to certain antibiotics, and arguably falls under the FDCA definitions of either drugs or medical devices.

[63] *Bacto-Unidisk*, 394 U.S. at 793.

[64] *Id.* at 798.

[65] *See, e.g.*, National Institutes of Health, *An Introduction to Clinical Trials* (visited August 14, 2003) <http://www.clinicaltrials.gov/ct/info/whatis#whatis> (clinical trials involve research in "human volunteers"); University of North Carolina at Chapel Hill, *Handbook for the Office of Clinical Trials* pt. I § II (clinical trials defined as involving human subjects).

[66] *See, e.g.*, 21 C.F.R. § 56.102(c) ("Clinical investigation means any experiment that involves a test article and one or more human subjects. . . ."); 21 C.F.R. § 202.1 (noting that the interpretation of "clinical investigations" depends on the intended use of the drug, so that drugs intended for use in humans must be tested in investigations on humans: "as used in this section 'clinical investigations,' 'clinical experience,' and 'clinical significance' mean in the case of drugs intended for administration to man, investigations, experience, or significance in humans, and in the case of drugs intended for administration to other animals, investigations, experience, or significance in the specie or species for which the drug is advertised"); 21 C.F.R. § 314.108(a) ("Clinical investigation means any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.")

The *Bacto-Unidisk* Court based its decision on legislative history supporting a broad "drug" definition as well as the term's inherent ambiguity.[67] Yet the Court warned that a statute should not be interpreted beyond the point where Congress clearly would have it stop.[68] Here there is no indication that Congress gave the FDA power to broaden the definition of clinical trials. On the contrary, the core purpose of the FDCA is to ensure "that every drug or device is safe and effective," not to lower drug approval standards.[69] While the 107th Congress did express approval of the animal efficacy rule by directing FDA to complete the rulemaking process,[70] this is not determinative as to the proper statutory interpretation of the term. The "clinical investigations" language was added as part of the Drug Amendments of 1962, and legislative history of the amendments indicates that Congress always contemplated "clinical investigations" of human, not animal, subjects.[71]

The FDA excuses itself from following the clear statutory language by appealing to the law's public health goals. This argument is very weak. There are innumerable actions that arguably promote public health that the FDA is statutorily barred from pursuing.[72] The FDCA did not give the FDA unbridled discretion to pursue all public health goals but rather bound the FDA closely to the text of its founding document. Even if "a literal reading of a statute would thwart the purposes of Congress," and lead to an absurd result, the FDA "may deviate no further from the statute than is needed to protect congressional intent."[73] Therefore the FDA must argue that its new interpretation of "clinical investigations" is a *necessary* reading of the clear statutory language to prevent an absurd reading of the statute while going no farther than necessary

[67] *Id.* at 798-99.

[68] *Bacto-Unidisk*, 394 U.S. at 800.

[69] *Food and Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000)

[70] Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188 § 123, 116 Stat. 594, 613 (2002).

[71] *See, e.g.*, S. Rep. No. 87-1744, at 15 (1962) (illustrations of clinical trials take place in "hospitals and clinics," which suggests that only human trials were envisioned). ; *Id.* At 58. (This passage quotes the Senate subcommittee testimony of Eugene N. Beesley. Beesley discusses the proper interpretation of "substantial evidence" as clinical trials on "patients," suggesting that humans and not animals were intended.).

[72] For example, the FDA does not have authority to tax harmful items like cigarettes, alcohol, or junk food to reduce consumption.

[73] *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060, 1068 (D.C. Cir. 1998)

to protect Congressional intent. Given the existence of many alternative methods of providing drugs when human tests are unethical,[74] resort to the strained Animal Efficacy Rule interpretation of "clinical trials" clearly amounts to a greater deviation from the plain meaning of the statute than is necessary. Moreover, the FDA's statutory interpretations are governed by the more recent *Chevron* framework, casting *Bacto-Unidisk's* remaining precedential value into question.

The Animal Efficacy Rule is an inappropriate stretch of FDA authority under any possible framework of statutory interpretation, whether following *Bacto-Unidisk* or *Chevron*. If this rule is truly the only viable way to approve drugs that cannot be ethically tested on humans, Congress is free to amend the FDCA to provide an exception to the "clinical investigations" requirements. Congress indicated its support for current regulations by specifically directing the FDA to complete its work on the Animal Efficacy Rule[75] and has even provided fast-track designation to products approved using animal trials alone.[76] Congress has shown a surprising willingness and ability to act quickly in modifying testing guidelines when circumstances warrant. Since Congress cannot and need not abdicate its policy-making role to the FDA, the FDA's unsupported statutory interpretation should not stand.

Ethical Issues

While the average citizen will not be incensed by an overstep of the FDA's statutory authority, ethical violations strike at the heart of the trust Americans put in their government, especially when there is a risk

[74] For example, drugs may be provided via an IND protocol or as off-label uses. While not ideal, these do represent treatment options when human experiments cannot be performed.

[75] Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188 § 123, 116 Stat. 594, 613 (2002).

[76] *Id. at* § 122(b).

that ethical shortcuts may threaten health. The debate about Gulf War drugs gained much prominence and staying power in the media because of allegations of unethical behavior, not because of any technical problems with the regulatory or scientific decisions made. In fact, the perception of even scientific and medical facts can be affected by whether they are viewed as ethical or unethical. It is likely that the association of PB with the Interim Rule, viewed by many as unethical, influenced public opinion of both the danger of PB and the government's trustworthiness when they claimed it was not linked to Gulf War syndrome. The Animal Efficacy Rule will be under scrutiny as a result of its ethically charged history, thus it is important to determine whether it is in fact more ethically acceptable than the Interim Rule.

Before examining the thorny ethical issues of experimentation, we must first define "experiment." While there are statutory determinations of what constitutes experimental use, ethically this designation is irrelevant. Ethical principles rely not on terminology but on the purpose of a product's use.[77] When a product is used to increase general knowledge about a treatment, it is experimental. On the other hand, if its primary focus is successful individualized patient care, it is therapeutic.[78] At first glance the Animal Efficacy Rule only solves the problem of non-consensual experimentation through creative semantics. The FDA merely changed a product designated "unapproved" under an IND (but used indefinitely) to conditionally approved.[79] However, it is the purpose of an activity, not its bare legal designation, that determines experimental or therapeutic status. Thus off-label drug use,[80] even if unapproved by the FDA, may be

[77] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1979), at pt. A, available at <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm> [herinafter "The Belmont Report"].

[78] James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71, 81 (1998). *See also* The Belmont Report at pt. A.

[79] *See* Carol S. Marcus, Ph.D., M.D., University of California, Los Angeles, Comment on 62 Fed. Reg. 40996 (August 19, 1997), available at <http://www.fda.gov/ohrms/dockets/dockets/98n0237/bkg0001-03-ref0002.pdf> (noting that the risks to human subjects are unchanged if drugs are approved based on animal trials compared to their former status as INDs).

[80] For example, use of most drugs on children is off-label because approval is generally based on adult testing alone. Other drugs may be approved for one purpose and commonly used off-label for another, as occurred in the well-known case of Fen-Phen.

therapeutic when used outside of research protocols and when patient well-being is the primary aim.[81] Just as unapproved off-label uses[82] generally represent state-of-the-art medical practices, drugs approved on animal tests alone may be the cutting-edge for treating otherwise untestable and uncurable diseases.[83] A non-experimental therapeutic use, then, would not trigger the heightened informed consent requirements associated with research but only the usual requirement that a physician notify his patient of material risks involved in a treatment, which applies regardless of how the drug was approved.[84] Naturally the nature of the evidence for a treatment's effectiveness is a factor in the risks that would be discussed with a patient, but it need not affect the kind of consent required. The ethical status of a therapeutic treatment is not related to informed consent like that required for experimentation, but rather to the highly individualized assessment of risks vs. benefits to the patient.

The ethical status of the Animal Efficacy Rule ultimately turns on whether drugs and biological products can in fact be determined to have a favorable risk/benefit ratio based on animal studies alone. Naturally, efficacy cannot be as reliably predicted from animal tests as from human tests. Unsurprisingly, due to the problems inherent in extrapolating from animal data, less than 25% of drugs that are found effective on animals eventually gain FDA approval.[85]. However, given urgent need for treatments against highly lethal agents, a drug need not be 100% effective to be worthwhile. As long as a particular drug's risks are less than (and the benefits greater than) the next-best treatment or no treatment at all, the drug is the optimal therapeutic option.[86] Animal efficacy studies, along with human studies assessing safety, should adequately

[81] Beck & Azari at 82. *See also* The Belmont Report at pt. A.

[82] That is, uses that did not go through the usual four-stage FDA process

[83] For an in-depth discussion of the ethics of off-label use of drugs, see James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71 (1998).

[84] *Cf.* Beck & Azari at 85-86; 21 C.F.R. § 50 (governing informed consent requirements for research).

[85] David Ruppe, *U.S. Response; Some Experts Express Caution on New FDA Measures*,

[86] *See* Juan N. Walterspiel, M.D., Comment on 62 Fed. Reg. 40996 (October 3, 1997), available at <http://www.fda.gov/ohrms/dockets/dockets/98n0237/bkg0001-04-ref0003.pdf>.

determine the risk/benefit ratio for a given drug or biological product.[87] The uncertainty arising from having no human studies would simply be factored into the product's risk, proportionately affecting the predicted benefit.

Some may claim that, despite therapeutic intent to treat, animal-efficacy-approved products should be subject to experimental informed consent rules because the Animal Efficacy Rule mandates close record-keeping of side-effects and evidence of efficacy. Although this practice is broadly consistent with research, it is not sufficient to transform a therapeutic use into an experimental one. The D.C. District Court said as much by noting that mere information collecting does not transform drug efficacy tracking into research.[88] Thus treatments using products approved under the Animal Efficacy Rule are not experimental and need not follow the informed consent requirements associated with human experimentation.[89]

To ensure that patients and doctors properly assess the risk/benefit ratio of newly approved products, complete and accurate labeling is essential. Several comments on the 1998 Proposed Rule addressed significant labeling inadequacies.[90] The FDA responded by requiring explicit labeling disclosing when drugs were approved on animal efficacy studies alone.[91] Commentators also objected to language that only required special labeling of these products "if possible."[92] They believed distributors would be able to use this language to

[87] *See See* Juan N. Walterspiel, M.D., Comment on 62 Fed. Reg. 40996 (October 3, 1997), available at <http://www.fda.gov/ohrms/dockets/dockets/98n0237/bkg0001-04-ref0003.pdf>.

[88] *Doe v. Sullivan*, 756 F. Supp. 12, 16 (D.D.C. 1991).

[89] Under this analysis, it might be noted that the use of PB and botulinum toxoid vaccine by the DOD during the First Gulf War also was not experimental. The goal of the use was not to gather information about the function of the products; this could have been done more effectively by maintaining control populations, monitoring and regulating variables involved and at least by maintaining records of how and when the products were administered. Although these products were used in the context of treatment and thus ethically did not require informed consent beyond that associated with any medical procedure, FDA regulations still provide that treatment using a drug under an IND follow the rules for IND informed consent. Therefore the PB use by the DOD was not unethical because it was an inappropriate experimentation on persons without their consent, but may have run afoul of regular medical consent standards and certainly did not comport with the applicable legal standards.

[90] *See, e.g.*, Anthony L. Itteilag, NIH Deputy Director of Management, Comment on 64 Fed. Reg. 53960 (May 28 1998), available at < http://www.fda.gov/ohrms/dockets/dockets/98n0237/98n-0237-c000005.pdf>.

[91] 21 C.F.R. § 314.610(b)(3), § 610.91(b)(3).

[92] *Id.*

evade labeling requirements by exaggerating the burden additional labeling would require.[93] In its final promulgation of the Animal Efficacy Rule, the FDA clarified that it would not extend the meaning of "possible" to include cases of mere inconvenience or effort.[94] If the FDA maintains this interpretation, labeling requirements should provide sufficient consumer warning about special approval circumstances.

Drug advertising regulations in this context run a fine line between burdening marketers' free speech rights and protecting consumers from misconstruing FDA approval. The FDA should utilize its pre-approval authority over drug promotional materials[95] to ensure consumer awareness of special circumstances surrounding approval when only animal efficacy tests have been conducted. If properly enforced these restrictions should sufficiently inform patients and doctors of product safety under the Animal Efficacy Rule.

Practical Issues

Much of the implementation of the Animal Efficacy Rule will be similar to procedures already in place for the approval of new drug applications and INDs. Since product safety and efficacy studies in animals are already required to obtain an IND,[96] human safety will presumably be assessed under the Animal Efficacy Rule in substantially the same way. The requirement that the manufacturer perform postmarketing studies addresses the problem of inadequate follow-up on the drugs that were administered during the First Gulf War. The manufacturer obviously has a strong interest in maintaining FDA approval, and therefore will be more motivated to comply with the planned protocols than was the DOD in that case. FDA oversight of

[93] Final Rule at 37992.
[94] *Id.*
[95] 21 C.F.R. § 314.640, § 601.94.
[96] Generally dosage must be determined based on studies in at least three species of animals and preclinical data from animals establishes toxicological and pharmacokinetic properties of the new drug. Report of the Subcommittee on Science, etc. Peter Barton Search Term Begin Hutt & Search Term End Richard A. Merrill, Search Term Begin Food Search Term End and Search Term Begin Drug Law 514Search Term End 55655 (2d ed. 1991).

postmarketing research protocols may also help ensure adequate follow-up testing.

Many practical issues in administrating the 2002 regulations were noted in responses to the 1999 proposed rule including concerns about how certain terms would be defined and how the FDA would determine when a product was well-enough supported and understood to merit approval. In general the Animal Efficacy Rule addressed these concerns. In its final ruling, the FDA clarified many terms that otherwise may have led to confusion and inconsistency in its application, including "lethal,"[97] "permanently disabling,"[98] and "toxic,"[99] providing confidence that the Animal Efficacy Rule would only be applied when human experimentation was truly unethical.

Flexibility built into the Rule is another source of uncertainty. For example, the number of animal species that must be tested before approval is not mandated. While this flexibility is desirable for individualized FDA consideration, pharmaceutical companies may have trouble predicting what studies will be necessary.[100] The Animal Efficacy Rule does however provide some guidance. It suggests that approval based on a single animal model should be limited to cases where the model is "sufficiently well-recognized so as to render studies in multiple species unnecessary."[101] The Rule also notes that the single species approach is best suited for anti-infective products because they have well-known pathophysiological mechanisms and well-characterized animal models.[102] These limitations provide important direction, suggesting that for most products multiple species tests are in fact necessary.

Unfortunately, the Animal Efficacy Rule also never explicitly states the level of pathophysiologic under-

[97] Final Rule at 37990.
[98] *Id.* at 37990.
[99] *Id.* at 37990.
[100] *See* 21 C.F.R. § 214.610 (a)(2); § 601.91 (a)(2).
[101] Final Rule at 37991.
[102] Final Rule at 37991.

standing needed to support animal–efficacy-based approval. This requirement's evaluation is simply left as "a matter of judgment" that may vary from toxin to toxin, infectious organism to infectious organism, or from product to product, even if they are all designed to treat the same condition.[103] This standard will presumably be clarified as the rule is applied, but it does make inconsistent treatment of products almost inevitable.[104] A better solution would be to remove this provision altogether, as the variety of diseases and treatments is such that a consistent standard may be impossible, and a standard that varies on a case-by-case basis is no standard at all.

Despite the FDA's efforts at clarification, the flexibility of the Animal Efficacy Rule presents some real risks for inconsistent treatment of products. Especially in a time when public concern about terrorism is high, the FDA may experience significant pressure to approve products to treat or prevent illnesses from biochemical or nuclear attacks. The open-ended nature of these regulations presents the real possibility that political pressure may influence the FDA to cut corners on animal-efficacy approvals. Until the FDA develops a precedent for application under the Animal Efficacy Rule, the extent of this danger will be difficult to gauge. The current precedent consists of a single drug, approved in February 2003: Pyridostigmine Bromide.

A Test Case: Pyridostigmine Bromine

Ironically, the only drug approved thus far under the Animal Efficacy Rule is the very one whose unethical administration spurred on creation of the rule in the first place: pyridostigmine bromide. Fears about PB, as discussed above, included inadequate information about use of the drug, lack of follow-up by the DOD, and

[103] Final Rule at 37991-92.

[104] *See* lmre Szebik MD. MSc, Clinical Trials Research Group, McGill University, Comment on 64 Fed. Reg. 53960 (December 17, 1999), available at <http://www.fda.gov/ohrms/dockets/dockets/98n0237/98n-0237-c000003.pdf>.

concerns about side effects associated with the drug. While no information about subsequent administration of this drug is yet available, the approval of PB highlights some of the aspects of the new review process, and suggests that added protections of the heightened review may not be very strong.

First, while general outlines of the postmarketing studies were submitted, detailed protocols were not to be prepared until later.[105] This suggests that postmarketing research is already a relatively low priority for the manufacturer, and possibly the FDA as well. Unfortunately the usual incentives for a manufacturer to provide detailed postmarketing studies are not really present for PB: the manufacturer is the U.S. Army Medical Research and Material Command, and the drug is only intended for military use. While the military certainly should be concerned about its relationship with the FDA, it has more leverage than a comparable pharmaceutical manufacturer and therefore need not be as solicitous of FDA approval of how it handles postmarketing studies. If the inadequate studies by the DOD after its previous PB use are any indicator, military follow-up leaves much to be desired. It is not at all clear that postmarketing studies under Animal Efficacy Rule approval will be any better than those performed during the First Gulf War.

The provisions for "restricted use" also provided no added protection in the case of PB – the FDA found that distribution need not be restricted. It is not clear what restrictions were originally contemplated by the regulation, but concerns raised about interactions between PB and nicotine or temperature[106] apparently were not felt to be serious,[107] although current research continues to point to PB as a possible factor in

[105] *See* Approval letter from Robert Temple, Director, Office of Drug Evaluation, Center for Drug Evaluation and Research, to Colonel Gere, Commanding General, U.S. Army Medical Research and Material Command, at 4 (February 5, 2003), available at <http://www.fda.gov/cder/foi/appletter/2003/20414ltr.pdf> [hereinafter "Approval Letter"].

[106] *See, e.g.*, Beatrice Alexandra Golomb, *A Review of the Scientific Literature as it Pertains to Gulf War Illnesses: Volume 2: Pyridostigmine Bromide*, ch. 6 (RAND 1999), available at <http://www.gulflink.osd.mil/library/randrep/pb_paper/mr1018.2.chap6.html>

[107] The package insert does, however, note some other drug interactions and their effects. Pyridostigmine Bromide Package Insert, at 5, available at <http://www.fda.gov/cder/foi/label/2003/020414lbl.pdf> [hereinafter "Package Insert].

Gulf War Syndrome.[108] The package insert language limits this drug to military combat use,[109] and no promotional materials were prepared by the manufacturer.[110] While the FDA did not specifically note this in its approval, it is likely that this self-imposed limitation may have made further limitation by the FDA seem unnecessary.

It is interesting to note that additional studies were apparently required by the FDA even after approval.[111] The fact that further study was apparently required by the FDA apart from the regular postmarketing studies required by the regulation raises questions about the quality of evidence available at the time of approval.

The proposed package labeling does seem to address concerns about the use of PB in the First Gulf War, namely that soldiers were not aware of the drug's experimental nature, its possible side-effects, its purpose, or its proper administration. A ten-page physician's package insert provides a great deal of information to the prescribing doctor, including a fairly detailed explanation of the animal efficacy studies performed, the mechanism by which PB is thought to work, its pharmacokinetics, known side effects and interactions, contraindications, administration method, and dosage.[112] This information does not appear to be significantly more detailed than many other prescription drugs apart from the more elaborate explanation of efficacy testing. Patient labeling uses less technical language but still includes information about the animal studies performed, clear instructions for administering the drug, contraindications, and instructions for what to do

[108]Kimberly Sullivan et al., *Cognitive Functioning in Treatment-Seeking Gulf War Veterans: Pyridostigmine Bromide Use and PTSD*, 25 J. Psychopathology & Behav. Assessment 95-103 (2003) (finding that Gulf War veterans who had been exposed to PB performed worse on various psychological and neurological tests that did their unexposed colleagues); J.I. Moss, *Many Gulf War Illnesses may be Autoimmune Disorders Caused by the Chemical and Biological Stressors, Pyridostigmine Bromide, and Adrenaline* 56 Medical Hypotheses, 155–57 (2001).
[109]Package Insert, at 1.
[110]Approval Letter, at 4.
[111]Approval Letter, at 4.
[112]Package Insert, at 1-10.

if side effects are observed.[113] This labeling, if properly given to soldiers along with their dose of PB, makes the proper use of the drug very clear and should address concerns about inadequate patient information during the First Gulf War.

In all, little has changed from the previous approval of PB under the Interim Rule, and many apparent safeguards of the new process seem to be ineffective. Still, the new labeling requirements and the possibility of more FDA oversight in postmarketing testing do represent improvements over the administration of the drug during the First Gulf War. Time will tell whether these new safeguards prove as effective as the FDA hopes.

Conclusion

The current Animal Efficacy Rule represents an ethical solution to a particularly salient problem. Global terrorism coupled with conventional conflict with rogue nations makes an encounter with biological, chemical, and nuclear weapons ever more likely. Although no testing method is free of error, efficacy studies in animals at least provide an approval option for drugs that treat life-threatening conditions. Approval under the Rule will certainly involve difficult decisions, but none that are qualitatively different than the drug approvals the FDA makes on a regular basis. Still, the high-profile nature of many drugs eligible for the rule makes constant monitoring of the rule's application important. While this sort of danger might be overcome with conscientious supervision, the Animal Efficacy Rule still suffers from an important defect: it is likely beyond the FDA's statutory authority. Such an innovative change in practice, even if only applied in limited numbers, is still an inappropriate means to effect change because it transgresses on Congress's policy prerogatives. A legislative solution, even one substantially identical to the current Animal Efficacy Rule, is the best method

[113] Package Insert, at 11-13.

of providing for drug development in while maintaining a commitment to the legal boundaries of agency action.