



On the Origin of the Animal Rule New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible

By Paul Aebersold, PhD

"It seems clear that organic beings must be exposed during several generations to new conditions to cause any great amount of variation." While those who deal with government agencies may believe that Charles Darwin's statement, from the opening paragraph of *On the Origin of Species*, must apply to organizations as well as organic beings, the Food and Drug Administration (FDA) has shown itself to be capable of rapid variation in response to new conditions, at least new conditions of war.

On 22 September 1980, Iraq invaded Iran in a war that lasted until 20 August 1988. During the war, Iraq used chemical weapons on Iranian troops and civilians as well as on Iraqi Kurds.

Contemporaneously with the Iraq/Iran war, the US Army was studying pyridostigmine bromide (PB) as a potential protective agent against the nerve agent Soman. PB had been licensed for use since 1955 to treat myasthenia gravis, a rare neurological disorder, but its use as an antidote to Soman was regarded as experimental. In animal models, PB was used as a pretreatment before Soman exposure, followed by atropine and pralidoxime treatment immediately after Soman exposure. Despite promising results, FDA informed the Army in 1988 that it could not approve PB for this indication because there was no regulatory pathway to approve the drug in the absence of human efficacy data.

On 2 August 1990, Iraq invaded Kuwait. In response, a coalition of countries deployed troops to Saudi Arabia. At that time, Iraq was thought to possess biological as well as chemical weapons. Thus, the US Department of Defense (DoD) made preparations to use experimental drugs and vaccines to protect its troops. On 30 October 1990, DoD requested FDA to establish authority to waive the requirement for informed consent for experimental drugs in certain military exigencies.

In the *Federal Register* of 21 December 1990, FDA announced an interim final rule, Informed Consent for Human Drugs and Biologics:

Determination that Informed Consent is Not Feasible. One week later, DoD requested waivers for PB and anthrax vaccine.

On 8 January 1991, FDA granted DoD waivers from informed consent to use the experimental drug and vaccine in combat. On 17 January 1991, Operation Desert Storm, also known as the Gulf War, began. During the Gulf War, an estimated 250,000 to 300,000 troops were required to take PB. A detailed discussion of the interactions between FDA and DoD on waiving of informed consent may be found online in a Rand Corporation monograph.¹

During 1992, to facilitate the development of treatments for AIDS, FDA proposed and issued the final rule, Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (21 CFR Subpart H). This rule provides for approval using a surrogate endpoint that is reasonably likely to predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic or other evidence.

The Army saw in this "Surrogate Marker Rule" a possibility for licensing PB for protection against Soman and therefore investigated PB for inhibition of red blood cell acetylcholinesterase as a surrogate marker for its protection against Soman.

Following the Gulf War, many veterans experienced unexplained illnesses, which collectively came to be known as "Gulf War Syndrome." Chronic fatigue was common. Veterans groups alleged that forced use of investigational drugs had caused these illnesses. A Presidential Advisory Committee on Gulf War Veterans' Illnesses was established in 1995.

On 4 May 1996, the Army submitted a New Drug Application under Subpart H for use of PB as a pretreatment for 2-organophosphate nerve agent poisoning. On 10 March 1997, Dr. Paul Leber, director of the Division of Neuropharmacological Drug Products at FDA, issued a Not-Approvable memorandum. He took issue with the Army's claim that the surrogate endpoint of their clinical trials was "reasonably likely" to predict clinical benefit for the intended military use. He argued that the predictive

power of the Army's surrogate must be shown in humans before any reasonable person could predict benefit.

Meanwhile, the US Department of Veterans Affairs and the British Ministry of Defense were conducting numerous studies on Gulf War veterans. Compared to control groups such as contemporary soldiers who were not deployed to the Persian Gulf, these studies found an increase in four out of the 12 medical conditions reportedly associated with Gulf War Syndrome: fibromyalgia, chronic fatigue syndrome, eczema and dyspepsia.

In the *Federal Register* of 31 July 1997, FDA requested comments on the proposed rule, Accessibility to New Drugs for Use in Military and Civilian Exigencies When Traditional Human Efficacy Studies Are Not Feasible; Determination Under the Interim Rule That Informed Consent is Not Feasible for Military Exigencies.

FDA's rulemaking was rendered moot by the Strom Thurmond *National Defense Authorization Act for Fiscal 1999*, which authorized the president to waive FDA's informed consent requirements in certain military circumstances. Consequently, in the *Federal Register* of 5 October 1999, FDA revoked its 1990 interim final rule and issued a new interim final rule, which established criteria and standards for the president to apply.

In the *Federal Register* of 5 October 1999, FDA also issued a proposed rule, New Drug and Biological 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 and when field trials after accidental or hostile exposure are not feasible. Human safety studies would be needed to support licensure.

The final rule was issued in the *Federal Register* of 31 May 2002, with the revised title, New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible. FDA had received comments on the proposed rule from only two pharmaceutical companies, one physician affiliated with a university and the National Institutes of Health.

On 3 January 2003, the Army resubmitted its New Drug Application to establish that the elements of the new Subpart I had been met. One month later, on 5 February 2003, PB was approved by FDA with indications and usage as:

"Pyridostigmine bromide is indicated for prophylaxis against the lethal effects of Soman nerve agent poisoning. Pyridostigmine is intended to be used in conjunction with protective garments, including a gas mask, and immediate atropine and pralidoxime therapy at the first sign of nerve agent poisoning. Pyridostigmine should be stopped at the first sign of nerve agent poisoning.

The evidence for the effectiveness of pyridostigmine as prophylaxis against Soman-induced toxicity was derived from animal studies alone."

In his memorandum on the basis of approval under the "Animal Efficacy Rule," Dr. Robert Temple, director of the Office of Drug Evaluation I at FDA, noted that there had been discussion and, to a degree, disagreement about whether the expectations of the rule had been met and the relevance of those data to humans, namely:

- the apparent failure of some species (rats, mice, rabbits) to show substantial protection
- the lack of a clear and consistent quantitative relation of a potential surrogate measure of PB effect (inhibition of blood acetylcholinesterase) to protection

Dr. Temple concluded that we do understand "reasonably well" the pathophysiology of the protective effect of PB and that the effect seen in monkeys and guinea pigs is expected to be predictive of an effect in humans. Dr. Temple noted that there had been several external reviews of a possible relationship of PB exposure to the Gulf War Syndrome, but that these concluded that no such relationship was supported by available data. Administrative documents pertaining to this approval of PB are available on FDA's website.²

In 2008, the National Academy of Sciences published evidence suggesting that excessive illnesses in Gulf War veterans can be explained in part by their exposure to acetylcholinesterase inhibitors and pesticides. Also in 2008, the congressionally appointed Research Advisory Committee on Gulf War Veterans' Illnesses reported that exposure to PB and pesticides that were heavily used during the war were implicated as contributing to the illnesses.

The so-called "Animal Rule," a legacy of the Gulf War, was born of the controversy over administration of investigational drugs and biologics to soldiers under military orders without informed consent, under an administrative rule for waiver of informed consent in certain military exigencies. Now that PB has been licensed by FDA under the Animal Rule, should there be future military exigencies in which the use of Soman is anticipated, informed consent would no longer be an issue in ordering soldiers to take the licensed drug as a pretreatment against possible attack.

References

1. Rettig R. *Military Use of Drugs Not Yet Approved by the FDA for CW/BW Defense: Lessons from the Gulf War*. Rand Corporation. Available at www.rand.org/pubs/monograph_reports/MR1018.9/index.html.
2. www.fda.gov, under Drugs, under Spotlight, Drugs@FDA.

Author

Paul Aebersold, PhD, is senior director, Global Regulatory Strategy for Quintiles Consulting.