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**Memorandum**      **Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

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**DATE:**      6/24/98

**FROM:**      Paul Leber, M.D.  
                Director,  
                Division of Neuropharmacological Drug Products  
                HFD-120

**SUBJECT:**    NDA 20-414, Pyridostigmine Bromide

**TO:**          File NDA 20-414  
                &  
                Robert Temple, M.D.  
                Director, Office of New Drug Evaluation 1

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**Introduction.**

For several years, the DOD/DOA has sought an NDA for pyridostigmine, a peripherally acting anticholinesterase long marketed for use in the management of myasthenia gravis, for use as a prophylactic component of a multi-drug antidote regimen intended to reduce the incidence of incapacitation and mortality among troops and civilians exposed in combat situations to irreversible cholinesterase inhibitors (i.e., chemical warfare agents, nerve gases, etc.)

The proposed use of pyridostigmine is defended by a reasonably internally coherent set of speculations concerning both the mechanism of action and possible counter-measures that might lessen the impact of these nerve agents, but, and this is the nexus of the problem, there is not one iota of evidence from controlled clinical studies in humans (at least that are known to the agency) to support this theory.

Accordingly, it is not been possible to conclude that there is 'substantial evidence' of pyridostigmine's effectiveness in use, and, as a result, the Division has remained steadfast in its recommendation that this use of the product not be made the subject of an approved NDA.

In March of 1994, the DOD/DOA tried a new approach, submitting an application, NDA 20-414, asking that it be approved under the so-called

Accelerated approval provisions of Subpart H of the agency's regulations (adopted in 1992). The application advanced the argument that inhibition of red cell cholinesterase, a predictable consequence of the oral administration of pyridostigmine to any number of mammalian species, can be viewed as a reasonable surrogate of the drug's value as a component of a multi-drug anti-nerve agent regimen.

(Note, the original DOD application was not filed because it was found to be technically deficient, failing to meet certain CMC requirements; the application was repaired, and resubmitted in May of 1996).

On March 10, 1997, I issued a memorandum explicating why I found red cell cholinesterase not to be a surrogate endpoint "...reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit." Although it is impossible to recapitulate all the points made in that memorandum, the gist of my position was that actions of a drug in a putative model of a human disease (be it a cell culture or a living animal) cannot possibly be assessed in respect to its likelihood to predict an effect in humans because, unlike an observation made in humans that appears to be correlated with an outcome in humans, it is impossible to know whether or not the model, no matter how appealing it may seem to its proponents, has anything whatsoever to do with the human condition it is postulated to represent. Moreover even if the surrogate were predictive in the non-human model, that fact would not mean it would predict anything at all in humans.

In any case, my personal views aside, the agency issued a not approval action on May 27, 1997.

### **Current "submission"**

Not too surprisingly given the absence of a precise enumeration in agency regulations of the attributes that make (or do not make) a surrogate "reasonably likely" to predict clinical benefit, the DOD disagreed with the agency's conclusions. Eventually, but not until March of this year, was a formal request for reconsideration of the agency's decision made (letter of 3/18/98 to Robert Temple from Claudia Bartz, Deputy Chief of Staff for Regulatory Compliance and Quality).

Dr. Temple elected to treat this letter and its accompanying documents, although it provided no new data, as a complete response to the not approval action. Ordinarily a letter of this kind would have been treated as an appeal rather than a resubmission, but in view of the importance of the matter, an exception was made.

The Division was, accordingly, instructed to review the information and arguments made in the letter and its accompanying documents. Although the formal PDUFA action date for the "resubmission" is 9/20/98, the Division was also instructed to prepare a letter responding to the points made in a more timely fashion. I initially suggested that the division might be able to complete its review by June 30, 1998. Unfortunately, that sanguine expectation has been impossible for me to achieve personally because of the press of other PDUFA work.

Unfortunately, the date of June 30, 1998 has been treated by officials at higher echelons within the agency as a firm promise date. To meet their expectations, I am forwarding the action package at a point in its development that is earlier than I would have preferred.

The sections of the letter prepared by the Division includes arguments and positions that the Office Director asked be developed and incorporated into the letter being drafted for his signature. Moreover, the draft letter provided by the Division does not address arguments raised by the DOD concerning the agency's interpretation of what may constitute a surrogate "reasonably likely" to predict clinical benefit. Specifically, the Office Director reserved for himself the construction of this portion of the response.

#### **Conclusion for the administrative record**

This memorandum does not convey an opinion or judgment about the NDA. It is intended primarily to make clear in the administrative record that whatever letter may issue from the Office, I remain persuaded that reliance on a surrogate based on the actions of a drug in animal models is imprudent.

I do acknowledge, however, that a model relying on ex vivo studies on human red blood cell cholinesterase obtained from volunteers exposed to placebo and varying levels of pyridostigmine (one that I suggested, but I am told was also suggested by the DOD's advisory panel), might, and I emphasize, might, be considered as a possible surrogate. Importantly, there are many other matters to be considered in evaluating this approach; for example, any number of enzymes with cholinesterase activity exist throughout the body, and any one or a number of these might be critical to the putative "protection" offered by pyridostigmine. Thus, much preparatory work remains to be done: we do not yet know, for example, how well, if at all, the extent of inhibition (i.e., protection) of red cell cholinesterase activity correlates with 'protection' of these other possible sites of pyridostigmine action.

/s/

✓  
Paul Leber, M.D.

6/24/98

cc NDA 20-414

HFD-101

Temple

HFD-100

Katz

Tresley

Rosloff

Fitzgerald

Nighswander

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:** March 21, 1997  
**FROM:** Nancy Sager, Team Leader, Environmental Assessment Team  
**SUBJECT:** Review of EA and FONSI for NDA 20-414 **/S/**  
**TO:** Janusz Rzeszotarski, HFD-120

The review and FONSI are being returned to you unsigned with the following comment:

**EA:**

I am unable to sign-off on the FONSI because the EA contains incorrect information. Specifically, the drug substance manufacturer identified in the EA is not the one that will be approved. The EA should be revised to identify the correct manufacturer and a certification of compliance with environmental regulations from that manufacturer, in accordance with that described in the Industry Guidance, should be provided.

C.C  
EA file 20-414

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** 19-MAR-97

**FROM:** STANLEY W. BLUM, Ph.D.  
CHEMISTRY TEAM LEADER, DNDC-1 [HFD-120]

**SUBJECT:** "APPROVABLE" for NDA 20-414

**TO:** NDA 20-414 FILES

I have signed off on Dr. Rzeszotarski's brief review for NDA 20-414, the Department of the Army application for Pyridostigmine Bromide Tablets, 30 mg. His review concluded that this should be NA until deficiencies in the two DMFs are corrected [DMF \_\_\_\_\_ for drug product manufacture — DMF \_\_\_\_\_ manufacture]. I do not agree with his conclusion.

I have signed off on his reviews of these two DMFs, and have prepared and signed deficiency letters for each/both of them. The deficiencies for both DMF \_\_\_\_\_ and DMF \_\_\_\_\_ are minor and are not sufficient to preclude approval of NDA 20-414; in fact, they do not require correction until the next annual report for either DMF.

I have attached a copy of the Chemistry Draft Portion for an action letter for NDA 20-414; this was created 16-OCT-96, based on my examination of Dr. Rzeszotarski's DMF and NDA reviews, and conclusion that the DMF deficiencies were minor and would not block approval of the NDA.

There are still two outstanding issues:

- (1) the EA review needs to be checked and signed by Nancy Sager
- (2) we need to get the EER from Compliance.

When these are resolved (satisfactorily) NDA 20-414 will be APPROVABLE for Chemistry.

**/S/**

**Stanley W. Blum, Ph.D., HFD-120**

filename: MEMO\_M-022  
cc: RNighswander  
JRzeszotarski

**Memorandum**      **Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

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**DATE:**      **March 10, 1997**

**FROM:**      **Paul Leber, M.D.**  
                 **Director,**  
                 **Division of Neuropharmacological Drug Products**  
                 **HFD-120**

**SUBJECT:**   **NDA 20-414, Pyridostigmine Bromide**

**TO:**          **File NDA 20-414**  
                 **&**  
                 **Robert Temple, M.D.**  
                 **Director, Office of New Drug Evaluation 1**

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This memorandum conveys and explicates the basis for the Division's recommendation that NDA 20-414, submitted by the Department of the Army [DOA], be declared not approvable.

NDA 20-414 provides for the use of pyridostigmine bromide tablets as a component of a multi-drug<sup>1</sup> regimen intended to reduce the incidence of

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<sup>1</sup> The two other components of the regimen are 1) atropine, a muscarinic cholinergic receptor antagonist that serves to reduce the downstream pharmacological effects that would ordinarily accompany excessive synaptic concentrations of acetyl-choline, and 2) pralidoxime, aka pyridine-2-aldoxime methyl chloride or 2-PAM, marketed as Protopam™ Chloride, an agent intended to reverse the inactivation caused by some, but not all, "irreversible" organophosphate cholinesterase inhibitors. 2-PAM's efficacy as a reactivating agent, importantly, depends critically on the rate at which the cholinesterase-inhibitor complex formed undergoes further chemical modification in a process known as "aging." With some organophosphates, notably Soman, the aging step is so rapid that 2-PAM is ineffective. It is in the management of exposure to agents like Soman that pyridostigmine is believed to have a potential to provide a specific and unique benefit. Presumably, pyridostigmine can be administered to humans at doses that cause no impairment in motor or mental performance, but, nonetheless, are sufficient to cause inhibition of some fraction of cholinesterase sites throughout the body. The sites occupied by pyridostigmine are presumably unable to combine with Soman. Accordingly, if Soman exposure is only "transient," and the DOA assumes that this is the most likely scenario given their assumptions about Soman's likely intended mode of use in a combat setting, the cholinesterase sites that were occupied

death and morbidity among individuals exposed to anticholinesterase organophosphates used in chemical weapons systems.

## Introduction/Background

### Why the DOA seeks an NDA

Officials within the Office of the Surgeon General of the Department of the Army have reason to believe, based on evidence adduced in animal models of organophosphate cholinesterase inhibitor poisoning, that pyridostigmine bromide, administered orally at a daily dose of 90 mg (30 mg q 8 h) before and after a chemical weapons attack, may, in combination with the acute administration of atropine and 2-PAM given post exposure, reduce the incidence of death and disability among individuals exposed<sup>2</sup> in the attack.

Although the DOA asserts that it does not seek to market pyridostigmine<sup>3</sup> for the use it proposes, it argues that it is obliged<sup>4</sup>, under existing

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by pyridostigmine will, following elimination of Soman, become available and will be sufficient to sustain life. It is noteworthy in light of this scenario that even if pyridostigmine acts as DOA postulates it does, that its use might, nevertheless, provide little, if any, practical protection under conditions of Soman exposure more intense and/or sustained than those "envisioned" in DOA's scenario.

<sup>2</sup> By implication, pyridostigmine would only contribute to the regimen's protective effects when Soman was among the nerve agents employed.

<sup>3</sup> Pyridostigmine has long been marketed (as Mestinon®) in both parenteral and oral dosage formulations for the treatment of Myasthenia Gravis. The smallest of the marketed oral solid dosage formulations is a 60 mg tablet (twice the amount in DOA's product).

<sup>4</sup> The DOA could, of course, as it did during Desert Storm/Shield, elect to distribute pyridostigmine under an IND protocol. Evidently, the DOA finds this method of distribution cumbersome from a logistic perspective. Perhaps even more troubling is the fact that the use of an investigational drug under an IND requires, unless a waiver is granted by the agency, that informed consent be obtained from all "subjects" to whom the drug is administered. For the DOA, this requirement raises

federal laws, to submit and gain approval of an NDA so that it may legally distribute the product and require its use by military personnel in combat settings as an anti-chemical warfare agent.

### **Why DOA seeks review of the NDA under Subpart H**

The DOA acknowledges that the kind of evidence ordinarily relied upon to support a sponsor's claims of effectiveness in use for a new drug product is not available for pyridostigmine. The DOA asserts, correctly in my view, that both moral and medical risk considerations preclude the conduct of adequate and well controlled clinical investigations that could directly assess pyridostigmine's protective effects in human subjects exposed to the lethal levels of organophosphate nerve agent that are deemed likely to be attained under battlefield conditions following a chemical weapons attack.

The DOA asks the FDA, therefore, to consider its application for pyridostigmine under Subpart H of the agency's NDA regulations [21 CFR 314.500]. These regulations permit the agency, even in the absence of reports of clinical investigations providing evidence bearing directly on the effectiveness of a drug in humans, to consider the evidence bearing on efficacy "substantial," if upon review, the agency determines there is evidence from adequate and well controlled clinical investigations **"establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."**

The DOA argues further that its application for pyridostigmine is not only appropriate for consideration under Subpart H, but must be found approvable under that regulation. In support of this argument, the DOA makes a number of points, among them several that lie within the legal

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the vexing question of whether, in a combat setting, it is in the interest of society to grant to an individual soldier the right to decline to follow a command, albeit one to take a pharmacologically active agent. According to the DOA, once a drug product is approved for use by the FDA, the DOA is no longer obliged to obtain ~~informed~~ consent from those subject to its authority who it 'orders' to take the drug product.

rather than the scientific realm.<sup>5</sup>

### **Is the DOA's NDA appropriate for evaluation under Subpart H**

Whether or not the DOA's NDA for pyridostigmine is suitable for consideration under the provisions of Subpart H is not so clear as DOA contends it is.

The DOA takes red blood cell cholinesterase inhibition [RBC CI] to be a surrogate outcome measure, but provides no clinical or laboratory evidence adduced in humans to show that the extent of RBC CI predicts the extent of survival and/or degree of morbidity among humans exposed to Soman. The DOA argues, however, that, at least insofar as the requirements of Subpart H are concerned, such a level of evidence is not required. It is sufficient to establish that a surrogate is "reasonably likely" to predict clinical benefit.

Thus, the DOA finds RBC CI to be a suitable surrogate endpoint within the meaning of Subpart H because its scientists have concluded that pyridostigmine's capacity to reduce the fatality rate among monkeys and

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<sup>5</sup> The "Integrated Summary of Effectiveness" section of the DOA's NDA offers a number of opinions regarding how the FD&C Act ought to be, or seemingly has been, interpreted in circumstances that the DOA argues are similar to those involving its application for pyridostigmine. In pursuing its arguments, DOA cites prior FDA decisions (e.g., the agency's approval of an NDA for KI as a blocking agent for use in the face of exposure to radioactive iodine and a 1964 approval of an NDA for pralidoxime's use as an antidote for organophosphate poisoning). In my view, it is not within the Division's province, let alone expertise, to determine to what extent, if at all, the cited actions/determinations, should influence the agency's ultimate regulatory determination concerning the approvability of DOA's pending NDA for pyridostigmine. From a purely scientific and epistemological perspective, I see no logical, let alone compelling reason, to consider a decision taken in the past, especially, if the decision was taken in the absence of evidence that I might upon review (now) find inadequate to meet the requirements of the Act. Accordingly, I have elected to restrict the scope of the Division's review to whether or not the evidence and scientific/epistemologic arguments presented in the application would allow a disinterested and informed expert to conclude, fairly and responsibly, that pyridostigmine is effective in use under the conditions of use proposed by DOA.

guinea pigs exposed to Soman under experimental conditions is attributable to its capacity to bind to cholinesterase and, accordingly, it follows that pyridostigmine's capacity to inhibit red cell cholinesterase is "reasonably likely to predict" pyridostigmine's capacity to reduce the risk of death and disability among humans exposed to Soman.

Although Subpart H's provisions do require only that a surrogate be shown to be "reasonably likely" to predict clinical benefit, I believe that DOA's evidence fails to satisfy that requirement. That the DOA and the Division might disagree on this critical point is hardly surprising in light of the fact that the regulations under Subpart H provide no hint as to either the criteria for, or the regulatory process to be employed to evaluate the acceptability of, a surrogate under Subpart H.

I, for one, have concluded that there must, at a minimum, be evidence from human sources that speaks to a putative surrogate's predictive powers before any reasonable person could conclude, responsibly and rationally, that a putative surrogate endpoint was "reasonably likely to predict clinical benefit." I take this view because I believe that it is logically and philosophically impossible to offer an informed opinion about whether or not evidence developed in an animal or mechanistic biological model has any relevance, let alone predictive value, in regard to humans, in the absence of evidence gathered in humans that allows the predictive performance of the surrogate to be assessed.

Before I could responsibly conclude that a measure was, in accord with the requirements of Subpart H, "reasonably likely to predict" the effects of a drug on the future clinical state of patients suffering from a given disease or condition, I would have to be persuaded that observations in humans recording the attained value of the putative surrogate were known to predict in some coherent, quantitative, and reliable fashion, the future clinical state of human subjects in the absence of the drug.

Even then, I would have continuing doubts about the capacity of the surrogate to predict clinical benefit caused by the drug because a drug might easily affect a surrogate's value through a mechanism irrelevant to the future course of the illness for which the drug was being developed as a treatment. I am mindful, of course, that Subpart H accepts this added

uncertainty as a necessary quid pro quo for accelerating the pace at which effective drug products necessary to the management of serious human diseases that lack effective treatments become available for general use.

To accept as a basis for determining the effectiveness of a drug a surrogate nominated for use on the basis of its predictive power in some animal or mechanistic biological model, a model that itself can only be postulated, and then arguably<sup>6</sup>, to be reflective of some human condition or state, seems, to me, to require a level of toleration for both uncertainty and tenuous extrapolation that cannot be justified under any set of circumstances. Indeed, a decision to rely on such a surrogate is, in my opinion, tantamount to relying on the results of tests conducted in animals to approve a new drug for human use. Such extrapolation is not only unjustified, but is irreconcilable, in my view, with the widely accepted principle that proof of a drug's effectiveness in use derive from adequate and well controlled "clinical" investigations of the drug in patients suffering from the disease being treated.

Thus, in the absence of evidence documenting a predictive quantitative relationship between the extent of RBC CI and the case fatality rate among humans exposed to Soman, I would have chosen, were I acting independently, to refuse to file DOA's NDA on the grounds that it failed to provide reports of adequate and well controlled clinical investigations that by design were capable of assessing the efficacy of pyridostigmine.

Senior agency officials<sup>7</sup> with whom I have shared my views regarding the validity and utility of surrogate endpoints have made clear that they find them, at a minimum, arguable. In light of their views, I concluded that the

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<sup>6</sup> It is impossible to know in any substantive sense whether or not an animal model system for which the putative surrogate is claimed to predict outcome is an apt and valid model of the human condition/disease that is the intended target of treatment in the absence of evidence collected in humans validating the model's predictive powers. We would not rely on a lab test before evaluating its sensitivity, specificity and predictive power; why then we would rely on an outcome measure that might, if the model is flawed, be irrelevant, and worse, misleading?

<sup>7</sup> i.e., officials in organizational units positioned above the Division in the agency's administrative hierarchy .

Division was obliged, my personal beliefs on the subject notwithstanding, to file the NDA and conduct a full review of the arguments and evidence presented by DOA.

### **The Division's review strategy**

If the DOA's NDA is, in fact, suitable for review under Subpart H, the case for the effectiveness of pyridostigmine in use turns on but two issues, one involving a finding of fact, the other a matter of opinion. These issues are, respectively: 1) whether orally administered pyridostigmine predictably inhibits red cell cholinesterase activity in humans and 2) whether the inhibition of RBC cholinesterase activity in animals is a surrogate endpoint that is "reasonably likely" to predict clinical benefit (i.e., decreased mortality and reduced disability in the face of exposure to Soman).

That oral pyridostigmine inhibits red cell cholinesterase in humans has been satisfactorily documented, and, therefore, the truth of the first issue can be taken as a given.

Accordingly, whether or not there is substantial evidence of pyridostigmine's effectiveness (under Subpart H) reduces to whether or not red blood cell cholinesterase inhibition (RBC CI) is an acceptable surrogate endpoint within the meaning of the agency's regulations.

### **Findings of the Division's review**

Based upon its review of reports submitted to DOA's NDA, and other information available in the literature bearing on the question, the Division finds there is a lack of evidence to establish that red cell cholinesterase inhibition "reasonably predicts" clinical benefit.

This conclusion derives primarily from the work of Dr. Barry Rosloff, a senior pharmacologist, who has long served as the Division's expert on cholinesterase inhibition. Why Dr. Rosloff finds the evidence DOA relies upon to support the use of RBC CI as a surrogate lacking is comprehensively summarized in his 7/24/96 review (page 38-44;47-50). I will not review all his arguments here, but I will make some

observations that involve some of them.

Why RBC-CI cannot be employed as a surrogate that is "reasonably likely to predict clinical benefit" is, ironically, documented by the very same experimental findings that establish that pyridostigmine reduces the incidence of death among monkeys given what would otherwise be lethal doses of Soman.

Specifically, Studies A-1 and A-2, which unequivocally show that pyridostigmine reduces the incidence of death among monkeys exposed to Soman (under the experimental conditions studied) fail to establish that a predictable quantitative association exists between the extent of red blood cell cholinesterase inhibition [RBC CI] and the extent of protection provided <sup>8</sup>. Accordingly, the extent of inhibition of red cell cholinesterase cannot be deemed to be a surrogate that reliably predicts<sup>9</sup>

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<sup>8</sup> In Study A-2, for example, the correlation between survival and RBC CI in groups of male rhesus monkeys (N = 10 for each of the 3 dose levels of pyridostigmine; N= 4 for placebo) was evaluated in animals challenged, 45 min after IP pyridostigmine, with a 32 mcg/kg of Soman. All monkeys were treated within a minute of Soman administration with atropine and 2-PAM:

<u>Dose of Pyridostigmine.</u>	<u>Proportion surviving</u>	<u>Percent RBC CI</u>
0 mcg/kg	0%	3%
4 mcg/kg	80%	7%
8.4 mcg/kg	90%	12%
24 mcg/kg	70%	29%

Moreover, further evidence of the apparent dissociation between the percent RBC CI and protection is provided in another phase (IV) of A-2 in which pyridostigmine was administered by gastric intubation. When 40 mcg/kg was given, levels of RBC CI were virtually indistinguishable from those seen in the absence of treatment (e.g., circa 3.5%); nevertheless, 80% protection was obtained in the group. Even more difficult to explain if RBC CI is a surrogate predicting survival is the fact that the 2 monkeys that died in this group of 10 where the ones that had the highest levels of cholinesterase inhibition. (see pages 9, 10c and 10d of Dr. Rosloff's 7/24/96 review)

<sup>9</sup> Documentation that a drug can effect the value of a putative surrogate endpoint in one or more species does not establish the predictive value of the surrogate. The evidence adduced in DOA's experiments, for example, establishes

the protective effects of pyridostigmine. Data collected in experiments with guinea pigs, another species in which pyridostigmine pretreatment has been shown to reduce the incidence of fatalities among animals acutely exposed to Soman, also fail to show a predictive relationship between the degree of protection offered and the extent of RBC CI.

I am mindful that the Division's conclusion that RBC CI is unsuitable for use as a surrogate outcome to assess the efficacy of pyridostigmine's use as a component of a multi-drug regimen to be used against chemical weapons stands in direct contradiction to the assertions of the DOA.

Given the nature of the evidence extant, I am personally unable to understand the basis for the DOA's contrary views unless I assume that the DOA interprets the word "predicts" <sup>10</sup> to mean something quite

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that the extent of RBC CI in rhesus monkeys and humans is quantitatively linked to the dose of pyridostigmine administered. Although these findings are reasonable evidence of pyridostigmine's oral, dose dependent, bioavailability, they in no way speak to whether or not there is a predictive relationship between RBC CI and clinical outcome. The determination that a candidate surrogate is reasonably likely to predict clinical benefit in humans would seem logically to require that there be evidence adduced in animals to show that the surrogate in animals reliably predicts the effect of interest in the animal model. In other words, before someone inclined to rely on such evidence could reasonably conclude that red cell cholinesterase inhibition predicts a clinical benefit in humans, there would have to be evidence showing a correlation between the extent of protection and the extent of RBC CI in at least some animal species. Such evidence has not been provided, however. To be clear, it is always possible to argue that because pyridostigmine is protective in monkeys, it is likely to be protective in humans, but that is a conclusion based on extrapolation across species (from an animal model to man) that has nothing whatsoever to do with the predictive capacity of RBC cholinesterase inhibition.

<sup>10</sup> Perhaps DOA's scientists use the word 'predicts' to mean something substantively different from what I believe it is intended to mean within the context of Subpart H. Given the evidence they rely upon, DOA's usage allows an inference that they intend to use the word 'predict' to denote the condition of 'being associated with.' Clearly, they are correct to assert that when pyridostigmine is present in monkeys in amounts sufficient to inhibit red cell cholinesterase, the risk of death following Soman exposure is generally reduced from what it is in its absence. I do not believe this constitutes surrogacy as intended under Subpart H. I take the term "predict" to imply something more, namely that the quantitative

different than I do.

Another aspect of DOA's NDA deserves note. Much of what the DOA attempts to establish in its NDA seems largely irrelevant to what the Division takes to be the pivotal regulatory question of whether or not RBC CI is a surrogate outcome that could be deemed reasonably likely to predict clinical benefit.

A good part of DOA's efforts, for example, are directed to providing support for their choice of the rhesus monkey as the animal species best suited (i.e., most human like) for using in a model to evaluate the performance of candidate treatments for the management of Soman poisoning. There is a difference, however, between experiments intended to discover which animal species is best suited to serve as a model of some human condition, and those intended to show that a putative surrogate endpoint that can be measured in that species reliably predicts a response to treatment within the model.

To illustrate, the level of carboxylesterase activity in a species is seemingly inversely related to the capacity of pyridostigmine to protect the species in the face of Soman exposure; the rate of regeneration of activity of carbamylated cholinesterase also presumably predicts the utility of pyridostigmine as a treatment for Soman in an animal species. The DOA attempts to make the case that pyridostigmine works best against Soman in the monkey, and that the monkey, in regard to both carboxylesterase activity and decarbamylation rates is most like humans. While evidence of this kind may be used to support the argument that the monkey is the most appropriate among the species evaluated (monkey, guinea pig, rat, rabbit and mouse) to use to model pyridostigmine's protective effects, the evidence in no way speaks to the value of RBC CI as a surrogate measure of pyridostigmine's capacity to protect human subjects.

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value of the surrogate (i.e., its intensity, strength, magnitude) at one point in time quantitatively forecasts the outcome of clinical interest at some future point in time. This postulated distinction in usage may explain why the Division and DOA come to such diametrically opposed conclusions regarding the value and interpretation of the animal data presented in the NDA.

In sum, after considering the evidence submitted, the Division has concluded that there is a lack of evidence from controlled clinical investigations showing that pyridostigmine has an effect on a surrogate endpoint 'reasonably likely' to predict a clinical benefit associated with the use of pyridostigmine.

### **Discussion**

DOA's proposal to administer pyridostigmine as a component of a multi-drug regimen to troops at risk of being exposed to organophosphate cholinesterase inhibitors of the kind employed in chemical weapon systems is not in the least irrational or illogical. To the contrary, the proposed use is scientifically quite plausible, and may well prove beneficial. Indeed, this is the reasoning that led the Division to endorse the DOA's plans to administer pyridostigmine under an IND to troops participating in Desert Shield/Desert Storm. We believed then, and continue to believe now, that the combination of prior clinical experience gained with pyridostigmine as a treatment of myasthenia and the evidence adduced in animal models is sufficient to support, under an IND, the hybrid investigational/treatment use of pyridostigmine in humans in combat settings.

Had the application submitted by DOA provided evidence of a robust correlation between the extent of RBC cholinesterase inhibition produced by pyridostigmine and the extent of protection provided to groups of monkeys exposed to Soman, I would have found the case for pyridostigmine's evaluation under Subpart H at least somewhat more plausible; however, the presence of such a correlation, given my views on the utility and limitations of surrogates developed in animals, would not have persuaded me personally that the case for pyridostigmine's effectiveness had been documented. I would, however, have seen such results as providing further justification for allowing the continued distribution of pyridostigmine under an IND in combat settings.

### **Conclusion and Recommendation.**

Upon review, the Division finds that the reports submitted to NDA 20-414 fail to provide substantial evidence of pyridostigmine's effectiveness for

the use proposed by its sponsor. Accordingly, the Division recommends that the not-approvable action letter conveying this conclusion that is being forwarded for signature by the Office Director, be issued.

*/S/*

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Paul Leber, M.D.

March 10, 1997

NDA 20-414

HFD-101

Temple

HFD-120

Katz

Tresley

Rosloff

Fitzgerald

Nighswander

doc: NA pyrido[3/10/97]

## **MEMORANDUM**

**DATE:** November 13, 1996

**FROM:** Deputy Director  
Division of Neuropharmacological Drug Products/HFD-120

**TO:** File, NDA 20-414

**SUBJECT:** Supervisory Review of NDA 20-414, for the use of  
Pyridostigmine Bromide Tablets as Pre-Treatment for Nerve  
Agent Poisoning

### **BACKGROUND**

On May 24, 1996, the United States Army submitted NDA 20-414 for the use of pyridostigmine bromide tablets as a pre-treatment for organophosphate nerve agent poisoning, in particular Soman. The application was originally submitted on March 4, 1996; however, because of significant chemistry deficiencies, it was not filed at that time. The re-submission of May 24, 1996 was considered sufficiently complete to warrant filing and review.

The past regulatory history of this dosage form (30 mg tablets) is long and complicated. The most immediately relevant aspects relate to the use of the product in the Persian Gulf in 1990 during Operations Desert Shield/Storm. Prior to that conflict, tablets had been stockpiled at military installations around the world, despite the fact that this dosage form was not legally marketed (pyridostigmine bromide is approved for use in patients with myasthenia gravis, as an injectable, syrup and 60 and 180 mg tablets). Around the time of the Persian Gulf war, the Army submitted an IND for the use of the 30 mg tablets. The regimen proposed that, in the face of a predicted attack with nerve gas, soldiers receive 30 mg three times/day for several days prior to the predicted attack and to continue for several days after the attack. In the event of an attack, atropine and 2-PAM were to be administered intramuscularly acutely, in addition to the prophylactically administered pyridostigmine. This regimen was believed, on the basis of animal studies, to decrease the high

mortality expected in the face of a significant nerve agent attack, and justified the fielding of the treatment under an IND (atropine and 2-PAM are approved for use acutely for organophosphate poisoning).

That IND posed a great number of scientific and regulatory questions; perhaps the most vexing related to obtaining informed consent from the troops for the use of pyridostigmine. Ultimately, as is well known, special regulations were promulgated to permit the commissioner to waive the requirement for obtaining informed consent in the face of certain military exigencies. Among the requirements that were imposed, however, was that the Army constitute a plan for capturing adverse event and mortality data in patients who received treatment with pyridostigmine, with and without exposure to nerve agent. It was anticipated that data could have been obtained that would permit an assessment of the treatment's utility should nerve agents be used, by comparing mortality in cohorts that did and did not receive treatment with pyridostigmine.

The current application has been submitted under Subpart H of the NDA regulations. This Subpart, titled **Accelerated Approval of New Drugs for Serious and Life-Threatening Illnesses**, permits drugs to be approved

**...on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.**

In this application, the Army proposes that the NDA be approved on the basis of the drug's effect on red blood cell acetyl-cholinesterase (RBC AChE) inhibition, a marker they believe serves as a surrogate endpoint that predicts survival in patients exposed to nerve agent poisoning.

## **THE ARMY'S POSITION**

The application contains reports of many studies in various animal species intended to document that pretreatment with pyridostigmine, in conjunction with atropine and 2-PAM, increases survival, and, critically, that the increase in survival is predicted by the effects of the treatment on RBC AchE inhibition, in animals. Further, because adequate and well-controlled trials of the ultimate clinical effect in humans have not been, and presumably cannot be, performed, the sponsor believes that showing an effect of the treatment on RBC AchE inhibition in humans, coupled with the presumed documented ability of the effect of the treatment on the surrogate to be reasonably likely to predict the clinical benefit in animals, should be sufficient to approve the treatment for humans. Among other considerations, acceptance of the Army's case would be based on a detailed understanding of what they believe to be the mechanism of pyridostigmine's capacity to protect against nerve agent caused death.

Pyridostigmine, a quaternary carbamate, is a reversible inhibitor of acetylcholinesterase (AChE), the enzyme responsible for the inactivation of acetylcholine, the neurotransmitter at the neuromuscular junction (NMJ). This inhibition results in an increase in the availability of acetylcholine in peripheral tissues, including at the NMJ. While there are clinical settings in which increased cholinergic activity is desirable (e.g., myasthenia gravis), sustained increases in cholinergic stimulation can be life threatening or fatal. In particular, nerve agents of the organophosphate type are **irreversible** inhibitors of AChE, and can be fatal when present in sufficient quantities, presumably due to overstimulation of peripheral cholinergic receptors and resulting respiratory collapse.

According to the Army, the value of pyridostigmine as a pre-treatment lies in its ability to **reversibly** inactivate AChE. Presumably, pyridostigmine, by reversibly inhibiting the enzyme, "protects" the enzyme from **irreversible** inactivation by the nerve agent. Over time, the nerve agent is detoxified by other mechanisms, and pyridostigmine comes off AChE, thereby restoring (a degree of) normal enzyme function, permitting normal transmission at the NMJ, and thereby preventing death.

Atropine is given acutely to inhibit the effects of overstimulation of the cholinergic receptors, and 2-PAM works to expedite the removal of

inhibitor from AchE.

The Army believes that the application can be approved under Subpart H for the following reasons:

1) the Agency ordinarily considers the risks of the proposed treatments in light of the risks of not treating, and in other circumstances has relied upon surrogate markers and animal data to approve treatments for serious and life threatening diseases

2) adequate and well controlled clinical studies have been performed in humans demonstrating the desired effect on the surrogate marker, and the regulations permit the use of animal data as the "...primary direct evidence of the predictive value of the proposed surrogate endpoint...". The support for the Army's contention that animal data may serve as the primary evidence of the predictive value of the proposed surrogate comes from 2 sources: 1) language in the Federal Register of 12/11/92, page 58944, in which the Agency was responding to comments about the then draft regulations. In discussing past actions, the Agency noted that it had relied on surrogate markers in the past, and, specifically in the case of drugs for hypercholesterolemia, there was evidence from, "...epidemiologic and animal studies...that improving the surrogate would lead to...the desired effects...", and 2) the language in the regulation itself, cited earlier, that includes, "...other evidence" among the types of evidence that may be cited to support the validity of a surrogate measure.

3) RBC AchE levels are at least reasonably predictive of human clinical benefit, and the other requirements of Subpart H have been met (no acceptable alternative treatments are available, clinical studies are not possible, the sponsor is willing to perform those studies that are possible to validate the surrogate in humans after approval, etc.).

Based on the results of animal studies, the Army states that a level of human RBC AchE inhibition of between 20%-40% will be protective in personnel exposed to organophosphate nerve agents. Further, they have performed studies in people demonstrating that this level of inhibition can be achieved reliably with the dose of pyridostigmine that they propose to recommend (i.e., 30 mg TID).

As primary evidence that human RBC AchE inhibition is a valid surrogate marker for survival, the Army has submitted numerous animal studies which they believe establish that the degree of RBC AchE inhibition in animals is reasonably likely to predict clinical benefit in humans, and hence can be considered an acceptable surrogate marker in humans. They then argue that this degree of inhibition in humans will confer protection as well.

The animal data derive from 15 separate studies, performed in monkey, guinea pig, rabbit, mouse, and rat. These studies have been extensively reviewed by Dr. Barry Rosloff, reviewing pharmacologist, in a review dated 7/24/96. As he describes, most of these studies involved pre-treating animals with pyridostigmine, then administering the nerve agent, then treating with atropine and 2-PAM, then measuring survival 24 or 48 hours post nerve agent administration. The primary data on which the Army's conclusions rest are the monkey and guinea pig data, with results in the other species being equivocal. Only the monkey studies were commissioned by the Army; all other animal studies were identified by reports in the scientific literature.

There were 2 monkey studies; A-1 and A-2.

### **Study A-1**

This study involved male rhesus monkeys who were "enrolled" into 1 of 4 treatment groups:

- 1) No treatment
- 2) Atropine and 2-PAM, 2/3 of the total dose given 1 minute after Soman, 1/3 given 10 minutes later.
- 3) Pyridostigmine 1.2 mg/kg po q8 hours x 6 (low dose), with Soman given 5 hours after the last dose and atropine and 2-PAM given as above.
- 4) Pyridostigmine 1.2 mg/kg once followed by 1.8 mg/kg once, followed by 2.4 mg/kg x4, all doses given 8 hours apart (high dose), with Soman,

atropine, and 2-PAM given as above.

In each treatment, doses of Soman were increased until a maximum of 617 mcg/kg, or until death became frequent, in order to determine the LD50 for Soman in the presence of each treatment (each animal received only 1 dose; if a given animal tolerated its dose, the next animal received a higher dose; this procedure was continued until death became frequent, at which point little to no further dose increase occurred. If deaths were not frequent, dose was escalated to a maximum of 617 mcg/kg). Efficacy was determined by a comparison of the Protective Ratio (PR), calculated as the ratio of the LD50 in the presence of treatment to the LD50 in the absence of treatment. Mortality was assessed at 48 hours after Soman exposure, and levels of RBC AchE were obtained in each animal at the time of Soman exposure.

This study enrolled 36 animals in each group 1,3, and 4, and 28 in group 2. The following chart displays the proportion of animals that died and the mean levels of AchE inhibition in each treatment group.

<b>Group</b>	<b>Proportion Dead</b>	<b>Mean AChEI Level</b>
No treatment	17/36 (47%)	0
Atropine/2-PAM	12/28 (43%)	0
Low Dose Pyrido	1/36 (3%)	23%
High Dose Pyrido	3/36 (8%)	37%

PRs could not be calculated for the 2 pyridostigmine treated groups, since LD50's could not be calculated. LD50s for the No treatment and Atropine/2-PAM groups were 15 and 25 mcg/kg, respectively. Clearly, treatment with pyridostigmine (either dose) has a substantial protective effect in this model. Further, the protection conferred is independent of degree of enzyme inhibition. Additional data document that the monkeys continued alive for extended durations, some up to several years.

## STUDY A-2

This study evaluated protection in male rhesus monkeys at lower degrees of enzyme inhibition than those achieved in Study A-1. The study was done in several phases; the relevant ones are described below.

### Phase III

Monkeys were administered pyridostigmine in one of the following doses: 0,4,8.4,, or 24 mcg/kg IP, followed 45 minutes later by a single 32.5 mcg/kg IM Soman injection. Atropine and 2-PAM were given to all animals 1 minute post Soman. The following table displays the results for Proportion Surviving and Percent AchE inhibition (based on a sample taken just before Soman administration):

Pyrido Dose	Proportion Surviving	Percent Inhibition
0 mcg/kg	0/4 (0%)	3%
4 mcg/kg	8/10 (80%)	7%
8.4 mcg/kg	9/10 (90%)	12%
24 mcg/kg	7/10 (70%)	29%

Again, treatment with drug is associated with significant effect on survival, but survival is not correlated with either dose or degree of enzyme inhibition. Further, the degree of inhibition at the low dose is not significantly different from the degree of inhibition in the control (7% vs. 3%).

### Phase IV

Here, 10 monkeys received a single dose of pyridostigmine 10 mcg/kg via nasogastric tube followed 150 minutes later with Soman 32.5 mcg/kg IM. In addition, animals received Atropine and 2-PAM 1 minute after Soman. Survival at 48 hours was 8/10 (80%). RBC AchE inhibition just prior to

Soman administration was 3.5%, essentially identical to that of the control group in Phase III.

### Phase V

In this phase, monkeys were treated with various regimens, described in the table below, which also describes the proportion alive at 48 hours after Soman and the PR for each regimen:

Regimen	N	Proportion Alive (48 Hrs)	PR
Atro/2-PAM	8	4/8 (50%)	1.4
A/2-P/DZP	10	4/10 (40%)	1.7
A/2-P/Pyrido	10	5/10 (50%)	28
A/2-P/Pyr/DZP	10	4/10 (40%)	15

DZP=Diazepam

In this study, the dose of Pyridostigmine was 4 mcg/kg IM, followed 45 minutes later by Soman. Although addition of Pyridostigmine did not increase the proportion of animals alive at 48 hours (in fact, 19/20 pyridostigmine treated animals did not survive to 10 days), it clearly increased the PR compared to Atropine and 2-PAM alone, as well as compared to that of Atropine, 2-PAM, and Diazepam given together. Interestingly, the addition of pyridostigmine to the 3 drug regimen lowered the PR compared to the 3 drug regimen, although the 4 drug regimen still has a PR considerably greater than Atropine and 2-PAM alone.

### Guinea Pig Studies

The Army identified 5 studies from the literature that examined the effects of pyridostigmine in the guinea pig. They are described briefly below:

#### STUDY B-1

This study compared the PRs in animals treated with Atropine and 2-PAM,

Pyridostigmine+Atropine and 2-PAM, and various doses of Ondansetron or Granisetron +Pyridostigmine and Atropine and 2-PAM. Pyridostigmine was given as a single 0.94 mg/kg oral dose, given 45 minutes prior to Soman sc. The study documented PRs of 4-5 with Pyridostigmine+Atropine and 2-PAM, with levels of RBC AchE inhibition of approximately 40% just prior to Soman administration (inhibition data was obtained in different animal than those utilized in this study). Interestingly, at several doses of Ondansetron (in conjunction with Pyrido+Atropine and 2-PAM) levels of AchE inhibition rose to 50-55%, with no greater effect on survival than Pyridostigmine+Atropine and 2-PAM alone. This again demonstrates a lack of correlation between degree of inhibition and protection.

## **STUDY B-2**

Various doses of Pyridostigmine were given to guinea pigs 30 minutes prior to sc Soman. Atropine and 2-PAM were given 1 minute after Soman administration. The actual doses of pyridostigmine were not stated, but doses were chosen to result in various degrees of inhibition based on a preliminary study. The degrees of inhibition achieved in this study was not directly determined; they were, in fact, **assumed**, and reported to be the same as those that occurred in the preliminary study at the same doses given in this trial (again, these doses were not stated). In this study, the PR for Atropine and 2-PAM alone was 2.0, and the only significantly different PR achieved with the addition of Pyridostigmine was 7.1, which occurred at the highest dose, a dose which resulted in 70% AchE inhibition in the preliminary study.

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### STUDY B-3

Animals in this study received increasing doses of Pyridostigmine (0.06 mg/kg-15.0 mg/kg po) 1 hour prior to Soman sc. Atropine and 2-PAM were given 1 minute after Soman. The following table displays the degree of AchE inhibition and Prs achieved:

Pyrido Dose	%Inhibition	PR
0.06 mg/kg	3.1%	4.2
0.12 mg/kg	5.4	5.6
0.23 mg/kg	16.4	5.0
0.47 mg/kg	26.4	6.4
0.94 mg/kg	34.0	5.0
1.90 mg/kg	52.4	5.2
3.75 mg/kg	71.9	5.2
7.50 mg/kg	79.1	6.3
15.0 mg/kg	82.2	6.0

As can be seen, while there is a strong correlation between dose and degree of inhibition, there is no strong correlation between degree of inhibition and PR. The paper does not report if an Atropine/2-PAM (without Pyridostigmine) group existed or, if there was one, what the PR for it was.

### STUDY B-4

In this study, animals received a single dose of Pyridostigmine 0.32 mcmol/kg IM 30 minutes prior to sc Soman, which was followed within 1 minute with Atropine and P2S, (the mesylate salt of 2-PAM), both given IM (some groups also received diazepam). The addition of pyridostigmine (without diazepam) resulted in a PR of 6.8, compared to a PR of 1.7 with just Atropine and P2S. The addition of pyridostigmine to a regimen including diazepam increased the PR to 14, compared to a PR of 2.5 for Atropine/P2S/diazepam without pyridostigmine. AchE inhibition was not measured in this study.

## STUDY B-5

In this study, animals were given doses of either Pyridostigmine 0.47 or 1.9 mg/kg po 60 minutes before exposure to Sarin, VX, or Tabun sc (Soman was not used in this study). Atropine and 2-PAM were given IM 1 minute after exposure to nerve agent. The following table displays the results:

Regimen	Sarin	VX	Tabun
Atropine/2-PAM	36.4	58.8	4.4
A/2-PAM/Pyrido 0.47	34.9	47.1	7.8
A/2-PAM/Pyrido 1.9	23.8	45.3	12.1

As can be seen, the addition of Pyridostigmine at either dose slightly **decreased** the PRs against Sarin or VX compared to those of Atropine and 2-PAM alone, but resulted in a dose related slight increase in it against Tabun. AchE inhibition was not measured in this study, but was predicted to have been approximately 30% at the low dose and 60% at the high dose.

As noted earlier, additional studies were performed in rabbits, mice, and rats. As Dr. Rosloff notes in his review, these studies were equivocal at best, and, where positive, generally documented PRs of about 2, which by the sponsor's own admission represents an inadequate degree of protection.

## SAFETY

As Dr. Richard Tresley, medical officer in the division, notes in his safety reviews dated 8/1/96 and 9/24/96, pyridostigmine has been given chronically to patients with myasthenia gravis for over 40 years, at doses considerably greater than those proposed here. Serious adverse events have been rare.

The sponsor presumably includes reports of over 800 subjects who received pyridostigmine in trials, most of them small, and of quite brief duration. Dr. Tresley has been able to find accounts of approximately 600 of these subjects. A number of these studies examined the effects of pyridostigmine on the functioning of soldiers exposed to extreme environmental conditions (heat, etc.). Few important events occurred, with the possible exception of a seizure 90 minutes after a 30 mg dose. In general, adverse events consisted of well known, relatively mild cholinergic complaints, without systematic changes in vital signs.

Apparently, over 250,000 troops received some treatment with pyridostigmine in the Persian Gulf during Operation Desert Shield/Storm. Approximately 1% of a group of 40,000 soldiers sought medical attention for what they felt were treatment related adverse events. Fewer than 0.1% of patients discontinued the treatment because of adverse events. Two otherwise healthy soldiers experienced hypertension (180-220/110-120 mm Hg); one had a positive re-challenge.

Of course, there has been considerable public speculation about the possible role of pyridostigmine in the genesis of Desert War Syndrome. The "syndrome" is still only vaguely described at this time, and certainly no causative agent or agents have been identified.

Although poorly presented, the safety data do not, not unexpectedly, identify worrisome ADRs.

## **DISCUSSION**

The sponsor asks the Agency to approve the NDA for the pre-treatment of nerve agent exposure with pyridostigmine on the basis of data derived in animals and theoretical arguments that link the findings in animals with the predicted effects of the treatment in humans. The brief outline of their case is as follows: 1) the treatment regimen is effective (decreases mortality) in monkeys, the species which provides the best model for the human experience; 2) in certain circumstances, animal data can provide

the primary basis for a conclusion of effectiveness in humans; 3) RBC AchE inhibition is a surrogate for survival in animals, and in particular in the monkey; 4) RBC AchE inhibition is reasonably likely to predict clinical benefit (can be declared a surrogate) in humans.

I will discuss each of these conclusions in turn.

**1. The treatment regimen decreases mortality in monkeys exposed to nerve agent and this is the species most relevant for exposure of humans to nerve agent**

It is clear that pyridostigmine treatment prior to nerve agent exposure, followed by post-exposure Atropine and 2-PAM, results in a considerable decrease in mortality compared to post-exposure treatment with Atropine and 2-PAM alone in monkeys and guinea pigs. On this point, there is no disagreement with the sponsor. A clear protective effect in the other species has not been as well documented. Indeed, the strongest findings were seen in the monkey studies, by the sponsor's admission, and they acknowledge that in other species the addition of pyridostigmine did not result in a predictable improvement when added to a regimen that includes atropine and 2-PAM given post-exposure.

Having acknowledged that the monkey data provide the strongest data, they have submitted evidence that they feel documents that the monkey is, indeed, the model most relevant to the human situation.

They state that any differences seen in the degree of protection between species can be predicted by, "...known and understood biological differences, such as the rate at which PB-modified AchE undergoes spontaneous decarbamylation, and the presence of species-specific enzymes that ameliorate nerve agent activity, such as carboxylesterase.". They argue that the rate of decarbamylation across species parallels the species specific order of effectiveness, and that monkeys and humans have the fastest rates of decarbamylation of the species examined. Further, they argue that monkeys have little to no carboxylesterase activity, and are more similar to humans than the other species tested in this regard. The sponsor argues that these are the 2 critical processes governing the regeneration of the enzyme which, in turn, is critical for

survival of the organism, and that, of all the species examined, the monkey and human are the 2 species in which the characteristics of these 2 processes are most similar. As noted earlier, Dr. Rosloff offers a critical examination of these claims and the data offered by the sponsor in support of them in his review, pages 32-37k. Suffice it to say here that the exquisite similarity of these 2 processes between monkey and human has not been firmly established, nor has it been established that these are the definitive 2 processes that control survival. Even the language used by the sponsor (i.e., "...biological differences, such as...") implies that these processes do not (necessarily) constitute the complete list of relevant mechanisms.

**2) Animal data, under certain circumstances, can provide the primary data on which to base a conclusion of effectiveness in human**

The sponsor's argument that animal studies may provide the primary basis for a finding of effectiveness in humans is based on 2 lines of reasoning.

The first relies on Agency precedent. According to the sponsor, several products have been approved in the past that have not been documented to be effective in humans, and some presumably have relied primarily on animal data. Examples include the use of potassium iodide in the wake of the Three Mile Island accident, as well as the approval of atropine and 2-PAM for organophosphate poisoning, the latter 2 of which the sponsor states were approved on the basis of animal data and anecdotal data in humans.

The second argument involves the specific instance in which a treatment is proposed for approval under Subpart H. The sponsor here makes the case that Agency documents support the conclusion that a product may be approved for use in humans on the basis of its effects on a surrogate found to be reasonably likely to predict clinical benefit in animals.

The sponsor's appeal to Agency precedent is ill founded. The fact that the Agency has presumably taken an action in the past (this presumption is based on the sponsor's account of the events; I have no independent knowledge of the facts in these cases) on the basis of data that might not

ordinarily be interpreted as meeting the Act's requirement for substantial evidence of effectiveness to include data from investigations in humans should not stand as a guide to future Agency actions.

Primary reliance on the effects of a treatment in animals to support the approval of a proposed treatment for humans is fraught with danger; any attempt to do so runs perilously close, in my view, to violating the Act's requirements for evidence of effectiveness derived from clinical investigations. A claim that a specific treatment **cannot** be directly shown to be effective in humans (e.g., due to ethical considerations, as the Army claims is the case here) in no way provides a rationale for approving a treatment on the basis of data that cannot adequately address the question of effectiveness in humans. Approval of an NDA for a treatment in humans means that substantial evidence of effectiveness, derived at least in part in humans, has been submitted and found acceptable by the Agency. It follows logically, then, that if such evidence has not been marshalled, an NDA cannot be approved, regardless of whether or not it is possible to generate such evidence (if the treatment is considered promising, for example, it can be made available under an IND, as has been the case with this product to this point). Even in those instances in which it appears that an "air-tight" case can be made for absolute equivalence of the condition to be treated in animals and humans, and of all the effects of the treatment in animals and humans, numerous (untestable) assumptions would have to be made before concluding that the treatment is effective in humans without direct empirical evidence of the effect (whether a surrogate has been identified or not), making an approval even in this case extremely problematic.

(I am aware that the requirement for human data may, technically, be satisfied under Subpart H by the demonstration, in humans, of the appropriate effect of the treatment on the surrogate marker. However, such a demonstration begs the question of the relevance of the animal model used to justify the choice of the surrogate marker, a question that needs answering before the animal data can be accepted as justifying the use of the surrogate in humans.)

The fact that (some) animals are protected, in and of itself, is insufficient to support a conclusion that the treatment is (or will be)

effective in humans. Almost (if not) all treatments ultimately developed in humans have shown "effectiveness" in animal models someone believes will predict clinical benefit in humans. Obviously, in these circumstances, empirical evidence of benefit in humans is required (both by law and sound reasoning) before an application may be approved. The situation here, with regard to the demonstrated increase in survival in monkeys, is not fundamentally different, although the sponsor might argue that the model being examined in this case (exposure to nerve agent), is, on its face, an essentially exact rendering of the human situation, in contrast to animal models of other illnesses, which are always imperfect. In order for us to accept the proposition that the animal model for nerve agent poisoning is an acceptable model for humans exposed to nerve agents, the sponsor would need to establish that the pathophysiology of the human and animal responses to nerve agent exposure are identical, and that the responses in the various species to the treatment in question are identical, the latter conclusion itself also being dependent on a complete understanding (and, again, identity) of the mechanism(s) of action, both desired and undesired, of the treatment in all species.

Further, as Dr. Rosloff points out in multiple places in his review, in this case, differences in methodologies, descriptions of experimental conditions, unaddressed inter-species differences in biologic processes, and other deficiencies (for example, the question of the reliability of RBC AchE as being reflective of levels at the presumed biologically relevant site, different routes of exposure to nerve agent in animals and humans, etc.) make a comparison of the results of the submitted literature reports difficult at best. The physiologic events underlying death and injury after exposure are complex and not necessarily as well understood as we might hope, nor is the mechanism by which pyridostigmine produces increased survival in a particular species (for example, there is some evidence that pyridostigmine has some central effects, despite the fact that it is generally believed to work peripherally). Even if a case could be made that animal data should serve as the primary data supporting approval in humans, a host of questions (appropriate dosing regimen, etc.) would need to be answered.

In my view, it is clear that, though it may never be appropriate to rely on animal data to provide the primary basis for a conclusion that a treatment

is effective in people, certainly in this case the sponsor has not established that it is appropriate to do so. In particular, the leaps of faith and assumptions necessary to accept animal data as primary in this case, in which the sponsor asks us to accept for use in humans a **surrogate marker** developed in animals, would be even greater than in other cases.

The sponsor's argument that animal studies may, from a strictly **legal** viewpoint, provide the primary data linking the surrogate and clinical benefit appears, at first blush, not entirely without merit, given the language in the regulation and related documents they cite. A strict reading of the regulation, however, reveals that nowhere does it specifically state this to be the case. The regulation itself, when listing the sorts of evidence that may be used to "validate" the surrogate, cites, "...epidemiologic, therapeutic, pathophysiologic, or other evidence...". Presumably, according to the sponsor, "other" evidence could be interpreted to include animal data. They also cite language in the Federal Register, in which the Agency acknowledges that, in the case of a treatment for hypercholesterolemia, "epidemiologic **and animal studies**" (emphasis added) contributed to the conclusion that the surrogate used was acceptable. Note that, at least as far as I can tell from the wording, animal data alone were not relied upon in this case. A strict reading, therefore, of official Agency documents relevant to this issue does not reveal an explicit statement that animal studies alone can support the use of a surrogate in people, although the possibility is also not explicitly excluded.

### **3) RBC AChE inhibition is a surrogate for survival in the monkey**

Having demonstrated, in their view, that the treatment is effective in animals, the sponsor has attempted to make the case that they have established **the degree of RBC AChE** inhibition (in the monkey in particular) as a surrogate marker that is reasonably likely to predict this clinical benefit in animals.

A recent article in the Annals of Internal Medicine by Fleming and DeMets<sup>1</sup> describes the criteria that are necessary to validate a surrogate marker. They point out that it is insufficient for a potential surrogate to be merely correlated with a clinical outcome; the effect of the treatment on the surrogate must **predict** the outcome. As they state, this requirement for prediction can be met only if the surrogate completely "...captures the net effect of treatment on the clinical outcome.". In the absence of this sort of information linking the effects of the treatment on the surrogate and clinical outcome, any number of potential markers may appear to be reasonable choices for surrogates, based on the sponsor's presumed knowledge of the biologic events underlying the condition to be treated as well as the mechanism(s) of the treatment's effects. Indeed, the regulations do not require that a surrogate be validated (i.e., shown to meet the criteria above) for its acceptance under Subpart H; it only need be "reasonably likely" to predict the clinical outcome. In the absence of data designed to validate the surrogate, any number of potential surrogates may appear to be reasonably likely to predict the outcome of interest.

Unfortunately, though, while a correlation of the surrogate with the clinical outcome may be shown readily, the inextricable linkage between the effect of the treatment on the surrogate and the clinical outcome may not be easily demonstrated for many reasons. For example, the treatment may have an effect on the surrogate, but not on the pathophysiologic mechanisms of the clinical outcome (or vice versa), simply because there is a dissociation between the biological events underlying the response of the surrogate and the clinical symptoms of interest. Indeed, the desired drug induced effect on the surrogate may be associated with exactly the opposite effect on the clinical outcome, simply because of the existence of several mechanisms of action of the treatment. There are other reasons for the failure of consistency in the responses of the surrogate and the clinical outcome to the treatment applied, and the article referenced discusses several recent examples in which reliance on the effect of treatment on a surrogate to predict clinical benefit was ill

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<sup>1</sup>Fleming TR, DeMets DL. Surrogate End Points in Clinical Trials: Are We Being Misled? Ann Intern Med. 1996;125:605-613

founded. As the authors conclude, validation of a surrogate requires an almost complete understanding of the pathophysiologic mechanisms underlying the disease process in addition to a complete understanding of the treatment's biologic actions, including those unintended.

In this regard, review of the presumably "pivotal" monkey studies reveals that the sponsor's conclusions are clearly incorrect. As has been described here and in Dr. Rosloff's review, the sponsor has demonstrated that monkey survival is enhanced **regardless of the degree of enzyme inhibition achieved**. That is, there is no correlation whatsoever between degree of enzyme inhibition and increased survival. Monkeys appear to have an increased survival of the same magnitude whether their degree of enzyme inhibition is 40%, 20%, or 3%, the latter being **identical to the degree of inhibition seen in the control group**. The sponsor's contention that these findings establish the utility of AchE inhibition as a surrogate marker for increased survival is clearly and definitively contradicted by their own data, which shows that clinical benefit is clearly independent of degree of enzyme inhibition. For this reason, it is obvious that RBC AchE inhibition cannot be considered a validated surrogate for increased survival, because it fails to predict the desired effect on survival.

Although, as noted earlier, the regulation requires that the proposed surrogate only be "reasonably likely" to predict the clinical outcome, it is clear that this standard is applied only in those cases in which data of the kind that would be necessary to validate the surrogate is unavailable. In this case, however, data of the kind necessary to validate the surrogate (in animals) **is available**, so it is reasonable to apply the requirements of validation of the surrogate. As expressed, the proposed surrogate fails this test.

#### **4. RBC AchE inhibition can be used as a surrogate for increased survival in humans**

It is immediately obvious that we cannot accept the Army's contention that RBC AchE inhibition is a surrogate for survival in humans. Their entire argument supporting this use depends primarily and fundamentally

upon a showing that the marker is reasonably likely to predict survival in monkeys; we have seen that it fails to do so. The only conclusion available to us is that, therefore, there is no basis in evidence for accepting its use as a surrogate in humans.

I realize that, at some level, this conclusion seems perhaps unduly negative, even irrelevant. That is, if the treatment "works" in monkeys, why should we care about its effect on this proposed surrogate? Indeed, because the basis for accepting the use of a surrogate is ordinarily theoretical and not necessarily supported by evidence, it seems more reasonable to ignore it and rely on the empirical evidence of "effectiveness" adduced in the monkey study.

This question has already been answered above. Ordinarily, and in this case specifically, we cannot rely on the results of animal studies to establish the effectiveness of a treatment in humans, both because the law appears to prohibit it, and because common sense demands that treatments be declared effective in humans on the basis of evidence gathered in humans. This latter is true because we ordinarily do not (and perhaps never) have sufficient information about the similarity of the condition and the effects of the treatment in animals and humans to permit us to extend a finding in animals to humans (indeed, in this case, for example, the treatment seems not to be effective in certain species, and the sponsor has not established that the monkey is the best model for humans). The appeal of using a surrogate in the case in which the surrogate had been validated in animals and the case had been made beyond doubt that the monkey model predicted the response in humans would presumably lie in its ability to provide appropriate dosing information in humans (that is, knowing what degree of enzyme inhibition is necessary for predicting increased survival would make it possible to devise a dosing regimen in people that would reliably result in that degree of inhibition).

## CONCLUSIONS

The Army has submitted an NDA which proposes that the Agency judge pyridostigmine, 30 mg TID po given several days before and for several days after exposure to organophosphate nerve agent (Soman), coupled with post-exposure atropine and 2-PAM, capable of increasing survival. The primary data on which we are to base this conclusion consists of results of monkey studies, in which such an increase in survival has been demonstrated. Since this effect cannot be directly demonstrated in people, the Army has attempted to establish that the degree of RBC AchE inhibition in the monkey predicts the increased survival in the monkey, and that a similar degree of inhibition in humans will likely result in a similar increase in survival in humans. The dose of pyridostigmine proposed is capable of producing the degree of inhibition thought necessary, based on the animal results.

There are a host of problems with the approach taken by the sponsor. In the first place, it is not at all clear that there can, or should ever, be a case in which animal data serve as the primary data on which a conclusion that a treatment is effective in humans is based. While one reading of the Subpart H regulations suggests that it is possible that a proposed surrogate marker may be validated in animals, this provides (at best) a theoretical possibility only in the legal sense; the scientific rationale for allowing such a conclusion is a more difficult question.

However, aside from all the possible reasons for not permitting animal studies to provide the primary "effectiveness" data, the fundamental flaw in this particular application relates to the sponsor's contention that enzyme inhibition can serve as a surrogate for increased survival in the monkey; that is, it is reasonably likely to predict the clinical outcome.

We have seen that the data do not support this conclusion. Studies in monkeys definitively establish that degree of RBC AchE inhibition is independent of increased survival. Because degree of enzyme inhibition does not predict survival in monkeys, it cannot serve as a valid surrogate (and, of course, therefore, certainly is not "reasonably likely" to predict survival). It follows, of course, that degree of enzyme inhibition cannot

be considered a surrogate for survival in humans.

For these reasons, I recommend that the application be judged Not Approvable, and that a letter outlining the reasons for our judgment be sent to the sponsor.

**/S/**

Russell Katz, M.D.

Cc:

NDA 20-414

HFD-120

HFD-120/Katz/Leber/Tresley/Rosloff/Fitzgerald/Nighswander

rk 11/13/96

E L E C T R O N I C   M A I L   M E S S A G E

Date: 11-Mar-1997 03:34pm EST  
From: Stanley Blum  
BLUMS  
Dept: HFD-120 WOC2 4023  
Tel No: 301-594-5537 FAX 301-594-2859

TO: 3 addressees

CC: 3 addressees

Subject: EER for NDA 20-414 ??

NDA 20-414 [Dept of Defense, for Pyridostigmine Bromide Tablets] has a User Fee Date of 28-MAY-97 --- 5/28/97. However, we are almost ready (like next week) to send the Action Package up to Dr. Temple for his signature. Any word on the compliance status ? Please ? Thanks. STAN

ELECTRONIC MAIL MESSAGE

Date: 03-Sep-1996 07:38am EDT  
From: Melissa Egas  
EGASM  
Dept: HFD-324 MPN1 265  
Tel No: 301-827-0062 FAX 301-827-0145

TO: Stanley Blum ( BLUMS )  
CC: Mark Lynch ( LYNCHM )  
CC: Bruce W. Hartman ( HARTMANB )  
CC: Joseph David Doleski ( DOLESKI )  
CC: Stanley Blum ( BLUMS )  
CC: Charles Hoiberg ( HOIBERG )  
CC: Robbin Nighswander ( NIGHSWANDER )

Subject: RE: EER # 10466 for NDA 20-414

I have the user fee goal date as May 28, 1997 for 20-414. We won't make a date in September, nor will we make a date in November the way the Swiss inspections have been scheduled. If this is an old regulatory clock application, we need to be made aware of this ahead of time.

Mimi

**E L E C T R O N I C M A I L M E S S A G E**

**Date:** 03-Sep-1996 03:43pm EDT  
**From:** Robbin Nighswander  
NIGHSWANDER  
**Dept:** HFD-121 WOC2 4029  
**Tel No:** 301-594-2850 FAX 301-594-2859

**TO:** Melissa Egas ( EGASM )  
**CC:** Stanley Blum ( BLUMS )  
**CC:** Mark Lynch ( LYNCHM )  
**CC:** Bruce W. Hartman ( HARTMANB )  
**CC:** Joseph David Doleski ( DOLESKI )  
**CC:** Stanley Blum ( BLUMS )  
**CC:** Charles Hoiberg ( HOIBERG )

**Subject:** RE: EER # 10466 for NDA 20-414

Melissa:

This application is a "user fee" application which has been given a "Priority" review. Although COMIS may still give the application a 12 month user fee due date from date of receipt (that is - the 5/28/97 date), the Center is committed to reviewing the priority applications within 6 months.

We recognize that the Agency is not committed to reviewing priority applications within 6 months after their submission date until Sept. 30, 1997; however, given the Center's request to attempt to do in 6 months, we are using a date of 11/28/96.

Hopefully, this explains the 11/28/96 date we are working with.

Robbin

ELECTRONIC MAIL MESSAGE

Date: 03-Sep-1996 04:02pm EDT  
From: Melissa Egas  
EGASM  
Dept: HFD-324 MPN1 265  
Tel No: 301-827-0062 FAX 301-827-0145

TO: Robbin Nighswander ( NIGHSWANDER )  
CC: Stanley Blum ( BLUMS )  
CC: Mark Lynch ( LYNCHM )  
CC: Bruce W. Hartman ( HARTMANB )  
CC: Joseph David Doleski ( DOLESKI )  
CC: Stanley Blum ( BLUMS )  
CC: Charles Hoiberg ( HOIBERG )

Subject: RE: EER # 10466 for NDA 20-414

Thanks for the explanation, it's very confusing to us. Even so, we'll still miss the date. We could (probably) make the May 1997 date, if that helps?

Mimi