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JOHN DOE # 1 et al., Plaintiffs, v. DONALD H. RUMSFELD et al, Defendants.

Civil Action No.: 1:03CV00707(EGS)

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

2003 U.S. Dist. Ct. Motions 707; 2004 U.S. Dist. Ct. Motions LEXIS 8628

March 3, 2004

Motion for Summary Judgment

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TITLE: [**1]

PLAINTIFFS' REPLY TO DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

TEXT: One learns in basic trial advocacy class in law school that when your facts are weak, argue the law, and when the law is weak, argue your facts. When both your facts and law are weak then either shout as loud as possible or ridicule the other side's case. This dispute, however, is not before a law school professor and the defendants' shouting and ridiculing do not diminish the merits of the plaintiffs' case.

Again, the issue before the Court is fairly straightforward -- Is the Anthrax Vaccine Adsorbed vaccine ("AVA") an investigational new drug or a drug unapproved for its intended use following FDA's issuance of its Final Rule and Order? n1 The answer to this question must be a resounding "yes," because, as plaintiffs have demonstrated, the FDA's issuance of its Final Rule, and particularly its inexplicable distortion of the conclusions reached during the only human trial of the vaccine upon which it relies, [*2] represents an example of arbitrary and capricious federal agency action prohibited by the Administrative Procedure Act. *5 U.S.C. § 551* et [**2] seq.

n1 The relevant statute, *10 U.S.C. § 1107*, says nothing about whether a drug or biologic is safe or effective or even licensed. The statute simply prohibits the use of investigational new drugs or drugs unapproved for their intended use on service members without the informed consent of those service members."

The government's misconstrued interpretation of why the plaintiffs primarily chose to pursue obvious procedural violations in their summary judgment motion rather than outline every specific substantive deficiency does nothing to alter the posture of this case. n2 In fact, the Court's determination of the validity of FDA's Final Rule concerning AVA

turns on the incontrovertible fact that there exists no valid human study of the vaccine showing effectiveness against inhalation anthrax. n3

n2 Defendants once again reveal how they have failed to anticipate events in this case. Given that dual summary judgment motions were to be filed there was absolutely no need to simply duplicate substantive arguments in cross-motions, particularly when those arguments should best be addressed at the agency level anyway. Since it was obvious the government was intent on arguing it was entitled to summary judgment purely on substantive grounds, there was more than enough opportunity to prove the fallacy of that position in response to the defendants' Motion while at the same time providing this Court with more than enough evidence that the FDA also violated numerous procedural requirements as part of the plaintiffs' Motion. Either way, whether solely on procedural or substantive grounds or a combination thereof, the government's arguments fail and the plaintiffs have demonstrated why the FDA's Final Rule and Order must be vacated and the injunction reinstated.

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n3 As a substantive matter, the Plaintiffs' Opposition to the Government's Motion for Summary Judgment includes a detailed statistical analysis showing that the vaccine is ineffective against inhalation anthrax. Moreover, the government's contorted effort to twist Brachman's data is statistically invalid. As an aside, the best that can be said based on modern statistical analysis of Dr. Brachman's data is that the vaccine is only probably better than nothing with regard to cutaneous anthrax exposure. See Declaration of Dr. Walter Schumm, Colonel, USAR (Ret.) at PP 6-9 ("Schumm Decl."), attached as Exhibit "1" to Plaintiffs' Opposition to Defendants' Motion for Summary Judgment (filed April 7, 2004).

Defendants solitary reliance on the Brachman Study, which categorically states that there is insufficient evidence to show effectiveness of the vaccine against inhalation anthrax, epitomizes the arbitrary and capricious actions of FDA in approving AVA. [*3] FDA's assertion that the conclusions in its Final Rule do not differ from that espoused by the Expert Panel in 1985 is deliberately, [**4] in fact breathtakingly, misleading. The Expert Panel stated categorically that there were insufficient cases of inhalation anthrax to determine whether the vaccine was effective. The FDA's Final Rule says that AVA is effective against all forms of anthrax regardless of route of exposure. How these two recommendations are consistent is unexplained and inexplicable. n4

n4 It cannot be emphasized enough how highly unreasonable it is to believe that the 1985 Expert's Panel could ever have anticipated the scope of use within the military that became prevalent for the anthrax vaccine. The essence of the 1985 determination was specifically grounded on the limited use of the vaccine and a benefit/risk analysis. The Panel stated that the vaccine was to be used by "individuals in industrial settings who come into contact with imported animal hides, furs, wool, hair (especially goat hair), bristles and bone meal, as well as laboratory workers involved in ongoing studies on the organism." *50 Fed.Reg. 51002, 51058* (Dec. 13, 1985). The Panel then recommended that "there is sufficient evidence to conclude that anthrax vaccine is safe and effective *under the limited circumstances* for which this vaccine is employed." *Id. at 51059* (emphasis added). Thus, it is clear that the FDA's 2003 Final Rule and Order, which addresses a situation where millions of people in the military or serving as defense contractors are being forced to take the vaccine, and the 1985 FDA's Expert Panel's recommendations, which understood that the vaccine was being used voluntarily by perhaps a few hundred people, are completely different.

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Because the Government can raise no issue of material fact with regard to its failure to follow the appropriate APA comments procedures, and because the basis of FDA's licensing decision is fundamentally flawed, Plaintiffs' Motion for Summary Judgment should be granted, and Defendants' Motion denied.

ARGUMENT

I.THE FDA'S ISSUANCE OF ITS FINAL RULE AND ORDER REGARDING THE AVA'S STATUS IS REVIEWABLE BY THIS COURT

In yet another attempt by this Administration to avoid any type of judicial review of improper Executive Branch actions, the defendants for the first time now characterize FDA's approval of its 1985 Expert Panel recommendations as an exercise in agency [*4] adjudication (resulting in an Order) versus agency rule making. See Defendants' Memorandum of Points and Authorities in Opposition to Plaintiffs' Motion for Summary Judgment at 3-9 (filed April 7, 2004)("Defs' Opp."). As part of this effort, the defendants spend a substantial portion of their argument contorting generic various case language and statutory definitions to place their square argument into a round hole. The simple truth is that FDA has previously, if not always, considered determinations [**6] like the one issued regarding the AVA as rule making subject to judicial review. Furthermore, FDA specifically considered its actions with regard to AVA an exercise in rule making through the day it issued its decision on December 30, 2003. n5

n5 FDA has routinely failed to extricate itself from judicial review, notwithstanding prior attempts. See e.g., *Community Nutrition Institute v. Young, 818 F.2d 943 (D.C. Cir. 1987)*(action levels were invalid in that they were issued without the requisite notice-and-comment procedures); *Cutler v. Hayes, 818 F.2d 879 (D.C. Cir. 1987)*(FDA failure to review safety and efficacy concerns subject to review); *Upjohn Co. v. Finch, 303 F. Supp. 241, 262 (W.D.MI 1969)*(Commissioner should proceed with all due care and caution and extend to all interested parties a full opportunity to develop and present pertinent information relative to the safety and efficacy of drugs which have been on the market for many years and have been generally and widely prescribed by the medical profession).

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Indeed, the government does not cite to a single specific on-point case that supports its analysis of the FDA's decision making process, and with good reason. A review of comparable FDA determinations demonstrates that this type of FDA action constitutes rule making subject to public comment. Two brief examples will suffice. n6 First, *in Contact Lens Manufacturers Association v. FDA, 766 F.2d 592 (D.C. Cir. 1985),* cert. denied, *474 U.S. 1062 (1986),* a commercial association sued FDA over its decision [*5] to classify contact lenses according to the product's safety effectiveness. n7 *Id. at 594*. In describing the safety and effectiveness of the lenses, the FDA utilized a familiar three class categorization system. Thereafter, contact lens manufacturers, whose products had been placed in a Class III status (product safety and effectiveness could not be reasonably assured and product could not be sold to the general public without FDA pre-marked approval) lobbied to reverse the FDA's proposal to stop a transfer of a category of lenses from Class III to Class I (safety and effectiveness of product is reasonably assured by current [**8] controls). The determinations made by FDA with regard to the product status are virtually identical to the determinations at issue here. Nevertheless, FDA provided extensive comment periods, and even a public hearing on it determination. *Id. at 596-7.*

n6 See also *Ethicon, Inc. v. Food & Drug Admin., 762 F. Supp. 382 (D.D.C. 1991)*(Court permitted APA review challenge regarding FDA's reclassification process).
n7 For a drug to be generally recognized as effective, there must be "expert consensus . . . founded upon substantial evidence."' *Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 632 (1973).* "Substantial

evidence" is defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." *21 U.S.C. § 355 (d)*. "In the absence of any evidence of adequate and well-controlled investigation supporting . . . efficacy . . ., [a drug] would be a new drug' subject to the provisions of the [FDC] Act." *Weinberger, 412 U.S. at 629-630*. Thus, the additional information would have to be significant enough to change the view of those experts who previously rejected classification of the drug as effective.

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Second, *in Cutler et al. v. Hayes et al., 818 F.2d 879 (D.C. Cir. 1987),* the FDA engaged in a comprehensive review of the safety and effectiveness of all over-the-counter drugs readily available to consumers without medical supervision. In doing so, FDA used a process virtually identical to the one at issue here. To start, advisory review panels of experts were appointed to analyze existing test data and make recommendations in the form of monographs concerning marketing for the drugs at issue. *Id. at 884*. The [*6] FDA then reviewed the monographs, published them in the Federal Register, and opened a period for public comment, followed by FDA's final recommendation, which was also open for public comment. Id. FDA then promulgated a final determination classifying the drug as either Category I (safe and effective), Category II (drug not generally recognized as safe and effectiveness), or Category III (data is insufficient to justify classification in either Category I or II). FDA's final determination was legally binding as to the drug's status as generally recognized as safe and effective. In making its determination as to the safety and [**10] efficacy of the drugs at issue, FDA invited public comment not once but twice in the process.

Moreover, in the instant matter, FDA and DoD spokesmen have consistently referred to the determination concerning AVA as a "Final Rule." See e.g., Citizens' Petition Response, August 28, 2002, at 1, attached as Attachment "D" to First Amended Complaint (filed January 6, 2004)("We agree that the Food and Drug Administration (FDA or the Agency) should complete the Biologics Review for the anthrax vaccine by issuing a final rule. Due to the pendency of this rule making, at this time we do not know what the result of the rule making will be. In the proposed rule, however, FDA agreed with the Panel on Review of Bacterial Vaccines and Toxoids' (the Panel's) recommendation and conclusion concerning anthrax vaccine and FDA proposed to classify anthrax vaccine in Category I. . . ."); See also Meeting of Armed Forces Epidemiology Board, Feb. 17, 2004, Comments by Colonel John Grabenstein, ("AFEB") found at *www.ha.osd.mil/afeb/meeting/transcript-February172004.pdf* ("and one of the key bases for the Judge's decision was that the Food & Drug Administration had never finalized the 1985 proposed [**11] rule, and therefore, the FDA had made no final statement [*7] with regard to the vaccine status . . . so on December 30, the FDA issued that final rule . . ."). n8

n8 Colonel Grabenstein, a Doctor of Pharmacy and Deputy Director of the Army Anthrax Vaccine Immunization Program, has served in this case as a primary declarant for the defendant Department of Defense ("DoD") on the basis of his overseeing AVA development and DoD's Anthrax Vaccination Immunization Program. 9 The Court should note that the original notice that appeared in the Federal Register on December 30, 2003, described the FDA's action as a final "Rule". Apparently only after hurried review were the words "and order" added by hand. Interestingly, the link on FDA's website to the handwritten annotation version of the Final Rule has been removed, but the plaintiffs preserved a copy. See Exhibit "1".

In conducting its review of AVA, the FDA acted in a manner consistent with the exercise of rule making. It was not until the government [**12] filed its Memorandum in Opposition that the FDA construed its actions in a different light. It is clear that defendants now seek to recast the entire AVA certification process, much as they seek to recast the

findings of the Brachman study and the Expert Panel's determinations, in order to gain a litigation advantage. See *Louisiana Ass's of Independent Producers & Royalty Owners v. FERC, 958 F.2d 1101, 1123 n.12 (D.C. Cir. 1992)*(Court does not "give an agency the benefit of *a post hoc* rationale of counsel.").

The Court does not have to wade through the pages of irrelevant citations in the Government's brief to determine that the FDA has engaged in rule making in this matter. A simple review of the history of the process, along with a review of similar types of FDA inquiries, shows conclusively that the review conducted by FDA was a rule making exercise and not one resulting in an unreviewable final order. n9

n9 The Court should note that the original notice that appeared in the Federal Register on December 30, 2003, described the FDA's action as a final "Rule". Apparently only after hurried review were the words "and order" added by hand. Interesttingly, the link on FDA's website to the handwritten annotation version of the Final Rule has been removed, but the plaintiffs preserved a copy. See Exhibit "1".

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[*8] **II. FDA'S RULE MAKING PROCESS WAS ARBITRARY AND CAPRICIOUS**

Plaintiffs will give short shrift to Defendants' remarkable argument that FDA has somehow complied with rule making procedures because its determination is in fact "a logical outgrowth" of the proposed rule in 1985.

As a reminder, in 1985, the Expert Panel organized by the FDA acknowledged the fact that there was insufficient evidence for a determination of efficacy against inhalation anthrax. Nevertheless, given the extremely limited use of AVA in industrial settings, they proposed approving the vaccine as labeled. The FDA now proposes to alter this determination by explicitly stating that the vaccine is properly licensed, regardless of route of exposure (for which there is no sufficient clinical evidence) and despite the fact that the vaccine's usage has expanded from a limited industrial setting (perhaps several hundred or a thousand doses annually, if that) to some 4 million doses administered to more than one million people over the last five years. n10

n10 At the AFEB meeting, Colonel Grabenstein, who believes the litigants and counsel in this case are "zealots" (page 52), noted that from March 1998 through February 2004, 3.9 million vaccinations were administered to almost 1.1 million people (page 44). See *http://www.ha.osd.mil/afeb/meeting/021704meeting/Transcript%20-%20February%2017%202004.pdf*.

[**14]

Defendants' tortured analysis notwithstanding, it is clear that they cannot escape the fact that the sole human trial upon which they anchor their determination does not provide a foundation for FDA's Final Rule. Neither can the defendants find support in the recommendations of the Expert Panel. The only way defendants can justify FDA's Final Rule is by relying upon the statistically invalid method of combining results from different routes of exposure and lumping them together into a single group to reach the [*9] desired conclusion n11 or by using invalid animal study data that has no correlation with human effectiveness. Accordingly, there is no issue of material fact regarding the arbitrary and capricious nature of Defendants' actions.

n11 The statistical foolishness of such an approach is properly demonstrated by the analysis discussed in Dr.

Schumm's declaration. See Schumm Decl. at *passim*.

A. The FDA's Improper Use of Animal Efficacy Data

The defendants do not (and cannot) [**15] dispute that there is no correlate of immunity for AVA between animal test subjects and human beings. Accordingly, defendants admit arbitrarily relying on data with virtually no established validity in a clinical setting. The arbitrary nature of FDA's reliance is particularly apparent since it is undisputed that the animal test results are being used to validate the effectiveness of a multiple variation vaccine last tested on human beings more than 40 years ago. In fact, at the time the FDA issued its Final Rule, AVA was still subject to two separate investigational new drug application processes which were trying to determine whether it was possible to establish correlates of immunity for annulations anthrax testing. n12

n12 The two pending IND's were IND 6847, which had been pending since September 1996, and one pursued by the Center for Disease Control, which has been pending (and remains pending) since 2001. Both INDs seek to study the same issue -- whether AVA can be effectively tested in animals through the establishment of correlates of immunity between animals and humans following AVA inoculation.

[**16]

Moreover, the Government's assertion that the animal efficacy data is not used to substantiate effectiveness, but merely to "corroborate" effectiveness is both misleading and factually incorrect. See Defs' Opp. at 2. The vaccine was not licensed for inhalation anthrax in any way until no earlier than the 11<th> hour, i.e., when FDA issued its Final Rule on December 30, 2003. Until the fortuitous withdrawal of IND 6847 in February, 2004, the FDA had approved and was reviewing on an annual basis an IND experimental [*10] process specifically designed to obtain an indication for inhalation anthrax on the AVA license. In other words, seven years ago FDA approved an experimental regimen for the vaccine to accomplish what the FDA now says was a foregone conclusion; i.e., that AVA was effective against inhalation anthrax, and indeed, was already licensed for such an indication.

In addition, the animal efficacy data is being used to do more than simply corroborate AVA effectiveness. Because there is no meaningful number of inhalation anthrax cases in any of the human trials of AVA, it is only by animal data that the effectiveness of the vaccine against inhalation anthrax can be [**17] measured in any capacity. The animal tests referred to by defendants are all aerosol anthrax tests against various types of animals. See Defs' Opp. at 17 fn.20. In fact, the animal studies provide the *only* evidence of vaccine effectiveness against inhalation challenge.

Although defendants ignore the plaintiffs' citation to FDA regulations that sanction the use of animal testing data only in very limited circumstances (and which are not present in defendants' cited animal studies), they cite to *21 CFR § 601.25* as authority for their use of animal data. Interestingly, the cited section does not seem to allow for the use of animal data, but rather references various types of studies and "reports a significant human experience during marketing." Indeed, the implication of this section is that FDA may consider data involving human subjects, not animal subjects. Given that the FDA has already spoken on the very limited types of situations where animal data may be used to substantiate effectiveness, it is curious that the government raises an argument that would seem to open the door to any type of unsubstantiated data using unverifiable animal studies, as long as they were [**18] used for "corroboration."

[*11] The defendants' use of unsubstantiated animal testing data is a clear violation of the arbitrary and capricious standard applicable to APA actions. Therefore, the Court should remand this matter for proper consideration.

B. The Current AVA Has Never Been Subject Of Human Testing In Any Form

In their initial Memo of Law, the defendants rely heavily on *Berlex Labs., Inc. v. FDA, 942 F. Supp. 19 (D.D.C. 1996),* to support their assertion that the Brachman study, conducted on the earliest variant of anthrax vaccine, is applicable to the latest AVA variation, notwithstanding the fact that the vaccine has gone through three different manufacturers and four different formulations and manufacturing changes in the interim. However, as noted, Berlex is easily distinguished and has no applicability in the situation here. See Plaintiffs' Opposition to Defendants' Motion for Summary Judgment at 11-12 (dated April 7, 2004)("Pls' Opp."). Yet, defendants now state that because all the changes and manufacturing occurred prior to AVA's licensure by NIH, the plaintiffs' argument somehow fails. See Defs' Opp. at 22.

The defendants [**19] deliberately misconstrue plaintiffs' argument, which is, simply, that the clinical data derived through the Brachman study of the first version of the vaccine, which was manufactured by the Department of Defense in the early 1950s, may not be applied to the fourth version of the vaccine, which has been altered by two other manufacturers and by three variations in formulation and manufacturing technology. These kind of changes typically require either a new license (for already licensed products) or a new clinical study validating the effectiveness of the changes in formula and manufacturing technology. See Pls' Opp. at 16.

[*12] Plaintiffs' argument, in fact, relies on FDA's so called comparability policy, which requires a single manufacturer of different variants of a product in order to allow testing data from an earlier version to the applied to a later version. The comparability policy would prohibit the use of the Brachman's study's data to support an efficacy determination on the Bioport vaccine. See AR1400 (FDA comparability guidance). To get around this, the FDA takes the unprecedented step of placing the mantle of "manufacturer" on the DoD. But DoD is not [**20] a commercial vaccine manufacturer despite the FDA's willingness to make it one. There is no evidence anywhere in the administrative record showing a continuous DoD manufacturing presence over the production of the vaccine from 1950 through 19998. Absent such a record, FDA's decision to effectively void its comparability policy is an arbitrary and capricious act.

Therefore, this Court should void FDA's Final Rule and remand the matter for further consideration.

C. A Review Of FDA's Bad Faith Actions And Decisions With Regard To The AVA

Defendants admit that Plaintiffs may properly seek discovery of an agency's decision-making process when there is a strong showing of bad faith or improper behavior, or where discovery provides the only possibility for effective judicial review. See Defs' Opp. at 26. The appropriate bad faith and improper behavior standard is indeed a difficult one to meet, but the plaintiffs believe the facts demonstrate that the standard has been met in this case.

The FDA's decision-making process with regard to AVA has been fundamentally flawed from the initial regulatory actions regarding the vaccine. FDA engaged in invalid statistical gerrymandering [**21] when it asserted that Brachman's data inadvertently included [*13] inhalation anthrax by improperly merging statistical results from two different routes of exposures into one mathematical result. Despite Dr. Brachman's specific contrary comments concerning the validity of his own results regarding inhalation anthrax, FDA used this altered number to reverse the determinations of its own expert panel and issue its Final Rule 18 years later. n13 FDA's administrative record deliberately omits the investigational new drug status of AVA, which began with AVA's manufacturer and defendant DoD applying to properly alter to the license for AVA so that it would provide them with a legal basis to use the vaccine against the inhalation anthrax. FDA deliberately issued a non-binding memorandum letter to DoD in March 1997 in an effort to provide a smoke screen for the AVIP. See AR004031-004032.

n13 The defendants, though informing this Court how they rely upon the conclusions reached by the Institute of Medicine ("IOM"), continue to ignore that the IOM specifically noted that "the small number of inhalational cases in those studies provides insufficient information to allow a conclusion about the vaccine's efficacy against

inhalational infection to be made." See http://books.nap.edu/books/0309083095/html/ 59.html # pagetop. Additionally, Dr. Anna Johnson-Winegar, Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense, presented a briefing on April. 2, 2002, at the Chemical and Biological Arms Control Institute Senior Working Group on "Health as a Global Security Challenge" where she noted that the "Brachman study *suggests* efficacy in humans against inhalational anthrax." See *www.acq.osd.mil/cp/winegarcbaic4-2-02.pdf* (slide 11)(emphasis added).

[**22]

Despite having waited 18 years after the dismantling of the Expert Panel to characterize the AVA, the FDA then hurriedly issues a Final Rule one week after the Court issued its determination that the vaccine was an investigational drug and a drug unapproved for its intended use within the meaning of *10 USC § 1107*. The Final Rule, obviously promulgated for defendants' advantage in this litigation, contained a specific reference to this case, as well as a complete reversal of all prior findings and internal statements.

[*14] These actions epitomize arbitrary and capricious conduct by a federal agency and they form the basis of the plaintiffs' request for discovery should it be determined that summary judgment not be appropriate at this time.

CONCLUSION

For the foregoing reasons, the Court should grant the plaintiffs' Motion for Summary Judgment and invalidate FDA's Final Rule and Order and remand it to the FDA for proper public comment and consideration of additional evidence. n14

n14 To the extent a specific argument of the government has not been addressed, the plaintiffs rely upon, and duly incorporate, their prior submissions filed in support of their Motion for Summary Judgment and in opposition to the defendants' Motion for Summary Judgment.

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Respectfully submitted,

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