UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

THOMAS REMPFER, *et al*.,	)	
Plaintiffs,	)	
v.	)	**Civil Action No. 06-2131 (RMC)**
ANDREW C. VON ESCHENBACH, Commissioner Food and Drug Administration, *et al*.,	)	
Defendants.	)	

MEMORANDUM OPINION

Plaintiffs[1] are military personnel subject to orders to take Anthrax Vaccine Adsorbed ("AVA"), the only vaccine in the U.S. licensed as a prophylactic against anthrax. They brought this suit against the Food and Drug Administration (FDA), the Department of Health and Human Services (HHS), and the Department of Defense (DoD)[2] (collectively "Defendants"), challenging (1) the FDA's Final Order, s*ee* 70 Fed. Reg. 75,180 (Dec. 19, 2005), which determined that AVA is safe and effective and not misbranded,[3] and (2) the DoD's decision to reinstate mandatory AVA

[1] Plaintiffs are: Thomas Rempfer, Joshua Cohen, Gareth Harris, Kevin Ferrara, Shameka Edwards, Eric Gearhart, Michael Palmer, and James Hailstone.

[2] The complaint names, in their official capacities, the following: Andrew Von Eschenbach, Commissioner, FDA; Mike Leavitt, Secretary, HHS; and Robert Gates, Secretary, DoD. The FDA is an agent of HHS.

[3] Plaintiffs' counsel here instituted prior litigation, *Doe v. Rumsfeld*, Civ. No. 03-707 (D.D.C.), related to AVA. In that suit, six John and Jane Doe plaintiffs sought to challenge the DoD's immunization program. The court enjoined DoD from inoculating service members, finding that the vaccine was not properly licensed since the FDA had not made a final decision regarding the investigational status of AVA. *Doe v. Rumsfeld*, 297 F. Supp. 2d 119, 131 (D.D.C. 2003). Soon

inoculations. Plaintiffs do not contend that AVA is unsafe or misbranded; instead they allege that there is insufficient evidence that AVA is effective to prevent anthrax infection acquired through inhalation. Defendants move to dismiss. Upon reviewing the pleadings and the administrative record and in deference to the FDA's evaluation of scientific data, Defendants' motion will be granted.

I. BACKGROUND

Anthrax is a bacterial disease caused by spores of Bacillus anthracis. Anthrax spores can cause infection through three routes: skin contact (cutaneous), ingestion, and inhalation. Without antibiotic treatment, inhalation anthrax has the highest fatality rate — estimated to be 45% to 90%. A.R. at 639 (04 AR, Vol. 3).[4] Cutaneous anthrax has an estimated 20% fatality rate, and gastrointestinal anthrax has an estimated fatality rate of 25% to 60%. *Id*. at 638-39. In the U.S., there were eighteen cases of inhalations anthrax from 1900 to October 2001,[5] mostly occurring in textile mill workers. *Id*. at 639. Sixteen of those cases were fatal. Then, from October 4, 2001 to December 5, 2001, there were eleven cases of inhalation anthrax, five of which were fatal. *Id.* The

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after, the FDA issued a final order classifying AVA as safe and effective; as a result the injunction was stayed. *Doe v. Rumsfeld*, 297 F. Supp. 2d 200, 201 (D.D.C. 2004). The Doe plaintiffs then amended their complaint to challenge the FDA's final order. The Court, on cross motions for summary judgment, then determined that the FDA had issued the final order without proper notice and comment. The FDA withdrew the final order and proceeded with notice and comment. The FDA then issued a new Final Order, 70 Fed. Reg. 75,180, the one at issue here.

[4] "A.R." refers to the Administrative Record consisting of 4209 pages originally filed in 2004, *see Doe v. Rumsfeld*, Civ. No. 03-707 (D.D.C.), plus an additional 20,000 pages. The record first filed in 2004 has been refiled here in 15 volumes on a single CD; these documents are secondarily cited as "(04 AR, Vol. ___)". The additional 20,000 pages were filed here in 3 volumes on 3 CDs.

[5] The last case reported in this period occurred in 1976.

2001 cases were all linked to intentional dissemination. *Id*. Regardless of the route of exposure, anthrax is toxic to the body in the same way. The "virulence components" of anthrax include an anitphagocytic capsule and three proteins: protective antigen, lethal factor, and edema factor. The combination of protective antigen with lethal factor causes the formation of cytotoxic lethal toxin, and the combination of protective antigen with edema factor results in edema toxin. *Id*.

In 1965, DoD contracted with the Michigan Department of Public Health ("MDPH") to produce an anthrax vaccine. A.R. 3647-52 (04 AR, Vol. 13). Before the MDPH contact, DoD had contracted with Merck Sharpe & Dohme to produce an anthrax vaccine and prior to that the Army had produced a vaccine (the "original vaccine" or the "DoD vaccine"). In 1966, the Center for Disease Control ("CDC") filed with the National Institute for Health ("NIH") a "Notice of Claimed Investigational Exemption" for the anthrax vaccine. Under this investigational new drug application, the CDC began an "open label study" to collect safety data on the MDPH vaccine; the study continued from year to year and the CDC provided annual progress reports to the NIH. The next year, MDPH filed a product license application with the NIH for the vaccine it was producing for DoD. During the licensing process, the MDPH vaccine was named AVA.

The NIH licensed AVA in 1970.[6] The NIH-approved package insert recommended AVA immunization for individuals with a risk of exposure to anthrax, those who come into contact with animal hides, bonemeal, and fur, especially goat hair. A.R. 3291 (04 AR, Vol. 12). The

[6] The committee from the NIH that recommended granting the license application based its recommendation on the following: the CDC safety data, potency data from lab tests using AVA in guinea pigs, and additional standards relating to production and potency testing. While the committee noted that MDPH's vaccine had not been used in a controlled field trial, the original vaccine was used in a controlled study. Because the original vaccine and the MDPH vaccine were comparable, the FDA determined that the controlled study could be relied upon for proof of AVA's effectiveness. *See* text *infra* regarding Count III of the First Amended Complaint.

labeling did not recommend immunization be limited to any particular route of exposure. A.R. 3291-92 (04 AR, Vol. 12). AVA was licensed to be given in a six dose regimen: three inoculations, each two weeks apart, and then three more given at six, twelve, and eighteen month intervals thereafter.

In 1973, the FDA announced a safety and effectiveness review for various vaccines, including AVA, and solicited data and information. 38 Fed. Reg. 5,358 (Feb. 28, 1973). The Panel that conducted the review issued a report in 1980. *See* A.R. 0001-0600 (04 AR, Vol. 1-2). In 1985, the FDA published the Panel's report and a proposed order relating to matters in the report. *See* 50 Fed. Reg. 51,002, (Dec. 13, 2005). As to AVA, the FDA agreed with the Panel's recommended that AVA be categorized as safe, effective, and not misbranded. 70 Fed. Reg. at 75,182; *see* 50 Fed. Reg. at 51,059.[7]

To determine whether AVA was effective, the Panel considered: (1) a controlled human field study conducted by Drs. Brachman, Gold, Plotkin, Fekety, Werrin, and Ingraham in the 1950s (the "Brachman Study"), *see* A.R. 3732-3745 (04 AR, Vol. 13), and (2) surveillance data collected by the CDC. *See* 50 Fed. Reg. at 51,058. The Brachman Study involved 1,249 workers in four textile mills that processed raw imported goat hair, a group at risk for anthrax infection.[8] *See*

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[7] There is a two-stage process for reviewing biological products licensed prior to July 1, 1972, such as AVA. *See* 21 C.F.R. § 601.25. First, the FDA Commissioner appoints a Panel of experts to review the safety, effectiveness, and labeling of the biological product at issue and to produce an advisory report. *Id*. § 601.25(a) & (e). Second, the Commissioner publishes the report and a proposed order in the Federal Register and solicits comments. *Id*. § 601.25(f). After reviewing the comments, the FDA publishes a final order, which constitutes final agency action from which appeal may lie to the courts. *Id*. § 601.25(g) & (i).

[8] In order to conduct a study of the effectiveness of the vaccine, the study required a "well defined, exposed, susceptible population among whom cases of anthrax were reported with some regularity." *See* A.R. 3732 (04 AR, Vol. 13). This type of population could only be found in the

AR 3732-33 (04 AR, Vol. 13). The workers were divided into three groups: one received the anthrax vaccine; one received a placebo; and one was simply monitored for anthrax infection. *Id*. at 3732; 50 Fed. Reg. at 51,058. There were 26 cases of anthrax during the study period, five of which were individuals infected through inhalation. *See* AR 3734 (04 AR, Vol. 13); *id*. at 3736 (Table 4). None of the individuals with inhalation anthrax had taken the vaccine, two were in the placebo group, and three were in the observation group. The remaining twenty-one infected workers contracted cutaneous anthrax. Of those, three had taken the vaccine (although two had not been fully inoculated), fifteen were in the placebo group, and three were in the observation group. *Id*. Based on these facts, the Brachman Study concluded the effectiveness of the vaccine at 92.5%, comparing the vaccine group with the placebo group and combining the inhalation and cutaneous cases. *Id*. at 3737. The rate of effectiveness did not include data from the group that was simply monitored. *Id*.; A.R. 1381 at n.9 (04 AR, Vol. 6).

Although the Panel relied on the Brachman Study, the Panel found that the study demonstrated effectiveness only against cutaneous anthrax because the inhalation cases "occurred too infrequently to assess the protective effect of [the] vaccine against this form of the disease." Fed. Reg. at 51,058. "Anthrax vaccine poses no serious special problems other than the fact that its efficacy against inhalation anthrax is not well documented. This question is not amenable to study due to the low incidence and sporadic occurrence of the disease." *Id*. Even so, the Panel found the vaccine to be safe and effective for the limited circumstances for which it is employed. *Id*. Further, the Panel did not recommend any change in the "recommendations for use" section of the AVA

U.S. in certain types of textile mills. *Id*. When the Panel submitted its report in 1980, this type of industry was "vanishing, precluding any further clinical studies." 50 Fed. Reg. at 51,058.

label, which recommended AVA for immunization against anthrax, without any specification regarding route of exposure.[9]

In addition to the Brachman Study, the Panel relied on the CDC surveillance data as evidence of effectiveness as follows:

> [The data] were summarized for the period between 1962 to 1974. Twenty-seven cases were identified. Three cases were not mill employees, but worked in or near mills; none of these cases were vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) being unvaccinated. Therefore, no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of this product.

Id. Thus, based on the CDC surveillance data and the Brachman Study, the Panel found "substantial evidence of safety and effectiveness for this product [AVA]." *Id*. at 51,059.

In March of 1998, DoD implemented the Anthrax Vaccine Immunization Program to protect service personnel at risk of contracting anthrax. Congress then directed DoD to contract with the National Research Council to study the safety and effectiveness of AVA. A.R. 3324 (04 AR, Vol. 12). As a result, the Institute of Medicine's Committee to Assess the Safety and Efficacy of the Anthrax Vaccine (the "IOM Committee") conducted an independent study over the course of two years. A.R. 3303-583 (04 AR, Vol. 12). The IOM Committee[10] sought, reviewed, and weighed

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[9] In the Final Order, discussed *infra*, the FDA found that the Panel's conclusion that the Brachman study demonstrated effectiveness only against cutaneous anthrax due to the low incidence of inhalation cases was in error, and that in fact the Brachman Study calculated the vaccine's effectiveness against cutaneous *and* inhalation anthrax. *See* A.R. 3736 (04 AR, Vol. 13 (Table 4); *id*. at 3740-41 (Table 8).

[10] The IOM Committee was composed of ten experts from respected institutions such as Harvard University and the University of Pennsylvania School of Medicine. Their collective knowledge included expertise in microbiology, epidemiology, biostatistics, immunology, and health

"[a]ll available data." *Id*. at 3309. The Committee issued a report finding, "As indicated by evidence from studies in both humans and animals, the committee concluded that AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalational anthrax," and it is "reasonably safe." *Id*. at 3323.

In its 2005 Final Order, the FDA agreed with the report of the IOM Committee and its finding that AVA was effective. 70 Fed. Reg. at 75,183. The FDA disagreed with the Panel's 1985 opinion that the Brachman Study did not have sufficient data to demonstrate the effectiveness of AVA against inhalation anthrax. The FDA explained:

> We do not agree with the Panel's statement that the protection [provided by AVA] was limited to cutaneous anthrax cases. The Brachman [S]tudy's comparison between anthrax cases in the placebo and vaccine groups included both inhalation and cutaneous anthrax cases. Accordingly, the calculated effectiveness of the vaccine to prevent both types of anthrax disease combined was 92.5 percent (lower 95 percent confidence interval = 65 percent) as described in the Brachman, *et al*. report.

Id. *See also* A.R. 3736 (04 AR, Vol. 13 (Table 4)); *id*. at 3740-41 (Table 8). The FDA noted that the CDC surveillance data supported the Brachman Study's findings regarding the effectiveness of AVA.[11]

The FDA received numerous comments relating to its Order. Comments supportive of AVA licensure included a submission by a researcher who discussed in detail "how the pathology

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surveillance, as well as vaccine research, development, manufacture, evaluation, and post-marketing surveillance of adverse events. A.R. 3325 (04 AR, Vol. 12).

[11] The FDA also agreed with the Panel that the safety of AVA was demonstrated by the CDC open label safety study (described *supra*) that was initiated in 1966. 70 Fed. Reg. at 75,183 & 75,188. The CDC open label safety study should not be confused with the CDC surveillance data which corroborated the Brachman Study's findings regarding AVA's effectiveness.

of cutaneous and inhalation anthrax at the cellular level is fundamentally the same, i.e., dependent on the actions of anthrax toxin, such that cytotoxic activities are blocked by antibodies produced in response to AVA in the same manner despite the route of exposure." 70 Fed. Reg. at 75,185. Comments against licensure included the same objections that Plaintiffs raise here. The FDA concluded, "After review of the comments and finding no additional scientific evidence to alter the proposed categorization, FDA accepts the Panel's recommendation . . . and determines AVA to be safe and effective and not misbranded." *Id*. at 75,182.

Counts I, II, and III of the First Amended Complaint challenge the FDA's Final Order. Plaintiffs seek temporary and permanent injunctive relief from DoD's anthrax vaccination program, alleging that the FDA's finding that AVA was effective against inhalation anthrax was arbitrary and capricious in violation of the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701 *et seq*. In Count IV, Plaintiffs seek a declaratory judgment that AVA is being administered in violation of 10 U.S.C. § 1107. Defendants seek dismissal of Counts I, II, and III based on failure to state a claim and on Count IV based on lack subject matter jurisdiction due to lack of standing. Plaintiffs oppose.

II. STANDARD OF REVIEW

A. Failure to State a Claim

A motion to dismiss pursuant to Federal Rule of Civil Procedure 12(b)(6) challenges the adequacy of a complaint on its face, testing whether a plaintiff has properly stated a claim. Although a complaint "does not need detailed factual allegations, a plaintiff's obligation to provide the 'grounds' of his 'entitle[ment] to relief' requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." *Bell Atl. Corp. v. Twombly*, 127 S. Ct. 1955, 1964-65 (2007) (internal citations omitted). The court must treat the complaint's

factual allegations — including mixed questions of law and fact — as true, drawing all reasonable inferences in the plaintiff's favor, *Macharia v. United States*, 334 F.3d 61, 64, 67 (D.C. Cir. 2003); *Holy Land Found. for Relief & Dev. v. Ashcroft*, 333 F.3d 156, 165 (D.C. Cir. 2003), and the facts alleged "must be enough to raise a right to relief above the speculative level," *Twombly*, 127 S. Ct. at 1965. But the court need not accept as true inferences unsupported by facts set out in the complaint or legal conclusions cast as factual allegations. *Browning v. Clinton*, 292 F.3d 235, 242 (D.C. Cir. 2002).

B. Lack of Subject Matter Jurisdiction

Federal courts are courts of limited jurisdiction and the law presumes that "a cause lies outside this limited jurisdiction." *Kokkonen v. Guardian Life Ins. Co. of Am.*, 511 U.S. 375, 377 (1994). Because subject matter jurisdiction is an Article III as well as a statutory requirement, "no action of the parties can confer subject-matter jurisdiction upon a federal court." *Akinseye v. District of Columbia*, 339 F.3d 970, 971 (D.C. Cir. 2003). On a motion to dismiss for lack of subject-matter jurisdiction pursuant to Rule 12(b)(1), the plaintiff bears the burden of establishing that the court has subject matter jurisdiction. *Evans v. B.F. Perkins Co.*, 166 F.3d 642, 647 (4th Cir. 1999); *see also McNutt v. Gen. Motors Acceptance Corp.*, 298 U.S. 178, 182-83 (1936)). Because subject matter jurisdiction focuses on the court's power to hear the claim, however, the court must give the plaintiff's factual allegations closer scrutiny when resolving a Rule 12(b)(1) motion than would be required for a Rule 12(b)(6) motion for failure to state a claim. *Macharia v. United States*, 334 F.3d 61, 64, 69 (D.C. Cir. 2003). To determine whether it has jurisdiction over the claim, the court may consider materials outside the pleadings. *Herbert v. Nat'l Acad. of Scis.*, 974 F.2d 192, 197 (D.C. Cir. 1992).

C. APA Review

The APA requires a reviewing court to set aside an agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *Tourus Records, Inc. v. Drug Enforcement Admin.*, 259 F.3d 731, 736 (D.C. Cir. 2001). In making this inquiry, the reviewing court "must consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Marsh v. Oregon Natural Res. Council*, 490 U.S. 360, 378 (1989) (internal quotation marks and citation omitted). At a minimum, the agency must have considered relevant data and articulated an explanation establishing a "rational connection between the facts found and the choice made." *Bowen v. Am. Hosp. Ass'n*, 476 U.S. 610, 626 (1986); *see also Pub. Citizen, Inc. v. Fed. Aviation Admin.*, 988 F.2d 186, 197 (D.C. Cir. 1993) ("The requirement that agency action not be arbitrary or capricious includes a requirement that the agency adequately explain its result."). An agency action usually is arbitrary or capricious if

> the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983); *see also County of Los Angeles v. Shalala*, 192 F.3d 1005, 1021 (D.C. Cir. 1999) ("Where the agency has failed to provide a reasoned explanation, or where the record belies the agency's conclusion, [the court] must undo its action.").

As the Supreme Court has explained, "the scope of review under the 'arbitrary and capricious' standard is narrow and a court is not to substitute its judgment for that of the agency."

Motor Vehicle Mfrs. Ass'n, 463 U.S. at 43; *see Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) ("we might not have chosen the FDA's course had it been ours to chart . . . [b]ut that is hardly the point."). Rather, the agency action under review is "entitled to a presumption of regularity" and the court must consider only whether the agency decision was based on relevant factors and whether there has been a clear error of judgment. *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 415 (1971), *abrogated on other grounds by Califano v. Sanders*, 430 U.S. 99 (1977).

In cases involving scientific or technical decisions within the agency's area of expertise, the agency is entitled to a "high level of deference." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998). When confronted with subject matter characterized by scientific and technological uncertainty, courts " must proceed with particular caution, avoiding all temptation to direct the agency in a choice between rational alternatives." *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 177 (D.D.C. 2000). Judges are not "scientists independently capable of assessing the validity of the agency's determination"; instead of making an independent assessment, courts must hold the agency to the standards of rationality required by the APA. *Serono Labs.*, 158 F.3d at 1327; *accord Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) ("we review scientific judgments of the agency [the EPA] not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality."). The determination of whether a drug is effective "necessarily implicates complex chemical and pharmacological considerations." *Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 654 (1973). The FDA's judgments regarding efficacy fall within the FDA's expertise and thus such judgments merit deference from the courts. *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 220 (D.D.C.

1996). Further, the "FDA's policies and its interpretation of its own regulations will be paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise." *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 25 (D.D.C. 1996).

In reviewing an administration action such as the FDA's Final Order at issue here, the role of the district court is to "sit as an appellate tribunal" and review the case as a matter of law. *Marshall County Health Care Auth. v. Shalala*, 988 F.2d 1221, 1226 (D.C. Cir. 1993). Such review is limited to the administrative record, and "not some new record made initially in the reviewing court." *Camp v. Pitts*, 411 U.S. 138, 142 (1973); *accord Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 177 (D.D.C. 2000). Thus, here the Court reviews the pleadings and the administrative record; the Court may not review any new materials submitted by either party.

III. ANALYSIS

Counts I through III each challenge the FDA's finding that AVA is effective. The standards for the FDA and its Panels to apply in evaluating safety, effectiveness, and labeling are set forth in 21 C.F.R. § 601.25(d). Effectiveness is defined as follows:

> Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biologic product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.

21 C.F.R. § 601.25(d)(2). Proof of effectiveness "shall consist of controlled clinical investigations" as defined in 21 C.F.R. § 314.126, unless this requirement is waived or alternate methods are adequate to substantiate effectiveness. *Id*. Such controlled clinical investigations "may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified

experts, and reports of significant human experience during marketing." *Id*.

A. Counts I and II

Plaintiffs' allegations in Counts I and II of the First Amended Complaint are overlapping. In Count I, Plaintiffs assert that the FDA relied on flawed scientific studies, the Brachman Study and the CDC safety surveillance data, to find that AVA was effective. First Am. Compl. ¶¶ 69-75. In Count II, Plaintiffs assert that there were too few incidents of inhalation anthrax in the Brachman Study to substantiate the vaccine's effectiveness.[12] *Id*. ¶¶ 90-92.

First, Plaintiffs allege that the FDA's reliance on the Brachman Study was improper because the study was not "well-controlled" as required by 21 C.F.R. § 601.25(d)(2). The FDA, in its scientific judgment, has found that the Brachman Study was well-controlled. *See* 70 Fed. Reg. at 75,182. This judgment is supported by the record. The Brachman Study was a field study that compared the results in an inoculated group against the results in a placebo control group, and thus by its very definition was a controlled study. AR 3734 (04 AR, Vol. 13); *id*. at 3736 (Table 4). Plaintiffs argue that in 1969 when the NIH reviewed the effectiveness of AVA (the MDPH vaccine), the NIH noted that the studies "did not provide control data whereby the effectiveness of the vaccine could be evaluated." A.R. 3629-30 (04 AR, Vol. 13). In fact, the NIH did not refer to the Brachman Study at all, as the Brachman Study used the earlier version of the vaccine (the DoD vaccine), not

[12] In Count II, Plaintiffs also assert that at the time AVA was licensed in 1970 under the Public Health Service Act ("PHSA"), 42 U.S.C. §§ 201 *et seq.*, it was found to be "potent" as required by the PHSA and it was not found to be "effective" as was required starting in 1972 under the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301 *et seq*. The fact that in 1970 there was no finding of effectiveness is not relevant because in 2005 the FDA in its Final Order did find that AVA is effective. *See* 70 Fed. Reg. 75,180. It is this finding of effectiveness that Plaintiffs challenge in this lawsuit.

the MDPH vaccine that the NIH was reviewing at the time.[13] The NIH documents that Plaintiffs cite discuss data generated from uncontrolled studies of the MDPH vaccine. The NIH was referring to the "Talladega" non-controlled epidemiological data and other uncontrolled studies listed at A.R. 3607-16 (04 AR, Vol. 13). *See* A.R. 3634 (04 AR, Vol. 13) ("The lack of cases of anthrax in an uncontrolled population of approximately 600 persons in the Talladega mill can hardly be accepted as scientific evidence for the efficacy of the vaccine."). In a 1969 letter from the CDC to the NIH, the CDC director indicated, "[t]here have been no controlled evaluation studies with the Michigan [MDPH] anthrax product as was done by Dr. Philip Brachman using the [original/DoD] vaccine." A.R. 1375 (04 AR, Vol. 6).

Second, Plaintiffs allege that the FDA should not have combined statistics regarding cutaneous anthrax cases with inhalation anthrax cases when it evaluated the Brachman Study data. They argue that "modern statistical analysis of Brachman data reveals that there is no statistical correlation between vaccination with AVA and inhalation anthrax protection." Pls.' Resp. at 15. Plaintiffs, in essence, argue that cutaneous and inhalation anthrax are different outcomes and must be tested for separately. If inhalation anthrax had been tested separately in the Brachman Study, the numbers would not have been sufficient for a statistical analysis — the two cases in the placebo group compared to no cases in the vaccinated group were just too few to be statistically significant.

However, the FDA, again in its scientific expertise, determined that the contraction of the anthrax disease was the proper outcome to be tested, regardless of the route of exposure. The Brachman Study compared the incidence of anthrax in a control group with the incidence in an

[13] The FDA concluded in its Final Order that these versions of the vaccine in fact are comparable. *See* discussion of Count III, *infra.*

inoculated group and determined that the vaccine was 92.5% effective against anthrax, combining both cutaneous and inhalation anthrax cases. The FDA determined that this type of statistical analysis was appropriate because the vaccine counteracts the anthrax bacteria in the same manner, no matter how the anthrax was contracted. Regardless of the route of infection, the anthrax bacteria produces the same toxins and the vaccine acts against those toxins in the same manner. The FDA fully explained its analysis:

> The inclusion of both cutaneous and inhalation cases of anthrax in the analysis of the Brachman [S]tudy was appropriate because it was not possible to predict the route of exposure (cutaneous versus inhalation) that would occur within the environmental setting of the woolen mills. With regard to the known pathophysiology of anthrax, the signs and symptoms of disease arise due to the production of toxins by anthrax bacteria growing within the infected individual. The toxins produced by anthrax bacteria do not vary based on route of exposure. The antibodies produced in response to vaccination contribute to the protection of the vaccinated individual by neutralizing the activities of those toxins. Thus, AVA elicits an antibody response to disrupt the cytotoxic effects of toxins produced by anthrax bacteria, regardless of the route of infection.

70 Fed. Reg. at 75,187.

Third, Plaintiffs contend that the fact that inhalation anthrax is more deadly than cutaneous anthrax shows that the bacteria acts differently depending on the route of infection. Pls.' Resp. at 7. Plaintiffs cite no support for this proposition. FDA has explained that inhalation anthrax has a higher fatality rate than cutaneous anthrax because it generally results in a systemic infection whereas cutaneous anthrax generally results in a localized infection. *See, e.g.*, A.R. 3363-64 (04 AR, Vo. 12).

Fourth, Plaintiffs contend that the FDA improperly relied on (1) the CDC surveillance data and (2) animal studies. In making a finding of effectiveness, the FDA can rely on a controlled

clinical study such as the Brachman Study, and the controlled clinical study may be "corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing." 21 C.F.R. § 601.25(d)(2). "Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered." *Id.* Under this regulation, the FDA considered the CDC surveillance data as "reports of significant human experience during marketing." Similarly, the FDA found that studies in human and animal models cited in the IOM report supported the conclusion that AVA was effective against anthrax regardless of the route of exposure. 70 Fed. Reg. at 75,183. For example, the IOM Committee noted that the pathology of anthrax in macaques "best mimics that seen in humans after inhalation exposure," A.R. 3385 (04 AR, Vol. 12), and concluded that AVA is effective in protecting macaques from inhalation exposure to the strains of anthrax tested. *Id*. at 3389. Pursuant to section 601.25(d)(2), the FCA cited the IOM's conclusions from animal studies to corroborate the Brachman Study. The FDA's interpretation of its own regulation, as permitting corroboration by the CDC surveillance data and animal studies, was not plainly erroneous and must be afforded deference. *Berlex Labs.*, 942 F. Supp. at 25 (the FDA's interpretation of its own regulations should be paid special deference because of its scientific expertise). Accordingly, the FDA's reliance on the CDC surveillance data and animal studies as corroborating evidence was proper.

B. Count III

In Count III, Plaintiffs assert that the current AVA vaccine, manufactured by the MDPH, was never tested and thus the FDA cannot attest to its efficacy; the Brachman Study tested the original DoD vaccine manufactured by the Army. The FDA may base its approval on studies

done with a prior version of a vaccine if it finds that the two versions are comparable in terms of safety and effectiveness. Products may be comparable, so long as the manufacturers have shared critical manufacturing process information. A.R. 1399-1406 (04 AR, Vol. 6) (FDA comparability policy).

Here, the FDA found that AVA and the original vaccine were comparable under "FDA's long-standing approach to comparability," which permits a manufacturer to make manufacturing changes in producing a product "without performing additional clinical studies to demonstrate the safety and effectiveness of the similar product if data regarding the manufacturing changes support the conclusion that the versions are comparable." 70 Fed. Reg. at 74,184. Applying this approach and after reviewing the development of AVA, the FDA found AVA and the original vaccine were comparable. *Id*. "[C]linical data comparing the safety and immunogenicity of [AVA] vaccine with [the original] vaccine . . reveal[ed] that the serological responses to [AVA] and [the original] vaccine were similar with respect to peak antibody response and seropositivity." *Id*. The FDA concluded that the two versions of the vaccine "are comparable in their ability to protect test animals . . . and their ability to elicit similar immune responses in humans" and thus the data from test studies of the original vaccine could be used to approve AVA. *Id*.

Plaintiffs argue that the FDA may not compare AVA and the original vaccine because the comparability policy only applies to products made by a single manufacturer and AVA and the original vaccine were made by different manufacturers. First Am. Compl. ¶ 99. The FDA comparability policy does not state that it is limited to products made by a single manufacturer.

Further, Plaintiffs claim that the FDA simply "declared" AVA and the original vaccine to be comparable as part of this litigation, that the FDA did not make a legitimate finding

of comparability. This claim is not borne out by the record. As quoted above, the FDA reviewed the development of the anthrax vaccine and examined the clinical data comparing the safety and immunogenicity of AVA and the original vaccine. *See* A.R. 3698-3705 (AR 04, Vol. 13) (clinical data). As the FDA noted in its Final Order, "after a manufacturing change, a manufacturer may use data gathered with a previous version of its product to support the effectiveness of a comparable version of the same product." 70 Fed. Reg. at 75,184; *see also* A.R. 1383-84 (04 AR, Vol. 6) (the FDA's 2002 statement that the DoD vaccine is comparable to the BioPort [aka AVA] vaccine). In sum, the FDA's determination of comparability, based on its review of scientific data, is supported by the record.

C. Count IV

In March of 1998, DoD implemented the Anthrax Vaccine Immunization Program ("AVIP") to protect service personnel at risk of contracting anthrax. Pursuant to this Program, DoD has inoculated active duty and reserve members of the armed forces against anthrax with AVA, via the recommended the six dose regimen: three inoculations, each two weeks apart, and then three more inoculations at six, twelve, and eighteen month intervals thereafter. *See* First Am. Compl. ¶¶ 10 & 25. In July of 2000, DoD suspended the AVIP due to a shortage of AVA. *Id*. ¶ 58. Thus, immunization was interrupted for those military personnel who had not completed the six dose regimen at the time the AVIP was suspended. On October 16, 2006, DoD announced the resumption of the AVIP for military personnel and "emergency-essential" DoD civilians and contractors. *Id*. ¶ 48. Plaintiffs allege:

> As part of this suspension, DoD announced that members of the Armed Forces who had received at least one of the sequences of six vaccinations required by the AVA product license would be subject

> to a modified vaccination schedule that is inconsistent with the vaccination schedule required by the AVA license. Specifically, DoD announced that members who had received one or more vaccinations, but who had not completed the six shot sequence of vaccinations, would not be required to restart the inoculation sequence as long as they received a subsequent shot within two years of their last vaccination.

Id. ¶¶ 59; *see also id*. ¶ 61 & 63 (DoD requires individuals who had their doses deferred must continue with the next dose in the series when directed.) *Id*. ¶ 61.

Thus, Plaintiffs claim that some military personnel will be subject to mandatory immunization under a modified drug regimen schedule that was not approved by the FDA. Because DoD intends to follow a vaccination schedule (for personnel whose vaccine regimen was interrupted) which is inconsistent with AVA's FDA-approved inoculation schedule, in those cases AVA is a drug allegedly unapproved for its applied/intended use. *Id*. ¶ 107. Under 10 U.S.C. § 1107, drugs unapproved for their applied uses may not be given to members of the Armed Forces without their informed consent except in the case of a Presidential waiver. Plaintiffs allege that they have not consented to unapproved anthrax inoculation by the DoD. *Id*. ¶ 111.

Although Plaintiffs allege that for certain military personnel DoD approved a vaccination schedule inconsistent with product instructions, Plaintiffs have not alleged that they themselves have been, or imminently will be, subjected to such a vaccination schedule and thus they lack standing to bring this claim. To withstand a motion to dismiss for lack of standing, a plaintiff must allege facts "demonstrating that he is a proper party to invoke judicial resolution of the dispute." *FW/PBS, Inc. v. City of Dallas*, 493 U.S. 215, 231 (1990). The facts alleged "must be enough to raise a right to relief above the speculative level." *Twombly*, 127 S. Ct. at 1965. To assert standing, an Article III jurisdictional requirement, a plaintiff must allege: (1) an actual or imminent

injury in fact; (2) fairly traceable to the challenged action of the defendant; (3) likely to be redressed by a favorable decision. *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560-61 (1992). Because Plaintiffs have not alleged that they have suffered, or imminently will suffer, an injury due to an off-label inoculation schedule, they lack standing to bring this claim and the Court lacks jurisdiction over it. Count IV will be dismissed.[14]

IV. CONCLUSION

For the reasons explained above, the Court will dismiss Counts I, II, and III, Plaintiffs' APA challenge to the FDA's Final Order. After examining the available scientific data and interpreting the data pursuant to its regulations, the FDA applied its expertise and found that AVA is effective for immunization against anthrax, whether the infection was acquired by inhalation or cutaneously. The FDA did not act arbitrarily or capriciously. It considered the relevant data and articulated an explanation establishing a "rational connection between the facts found and the choice made." *Bowen*, 476 U.S. at 626. The Court will not substitute its own judgment when the FDA made no clear error of judgment. *See Overton Park*, 401 U.S. at 415-16 (the court must consider only whether the agency decision was based on relevant factors and whether there has been a clear error of judgment). In addition, the Court will dismiss Count IV because Plaintiffs lack standing to make a claim of off-label use under 10 U.S.C. § 1107.

[14] Although none of the Plaintiffs is a civilian, Plaintiffs assert that civilian DoD employees and DoD contractors should be covered by 10 U.S.C. § 1107. Pls.' Resp. at 22. Section 1107 expressly applies only to members of the armed forces. 10 U.S.C. § 1107 (this section applies when "the Secretary of Defense requests or requires a member of the armed forces to receive an investigational new drug or a drug unapproved for its applied use"). Even if a civilian were a named plaintiff in this suit, no claim could be stated under section 1107 on behalf of a civilian.

Accordingly, Defendants' motion to dismiss[15] will be granted. Counts I, II, and III will be dismissed for failure to state a claim, and Count IV will be dismissed for lack of standing. A memorializing order accompanies this Memorandum Opinion.

Date: February 29, 2008

_____/s/_____
ROSEMARY M. COLLYER
United States District Judge

[15] Defendants' motion to dismiss [Dkt. # 15] was dismissed without prejudice by Minute Entry Order on August 3, 2007. Defendants renewed their motion to dismiss without amendment by filing a notice of such renewal [Dkt. # 29] on September 17, 2007.