IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

| | | |
|---|---|---|
| JOHN DOE #1, et al., | ) | |
| | ) | |
| Plaintiffs, | ) | |
| | ) | |
| v. | ) | Civil Action No. 03-707 (EGS) |
| | ) | |
| DONALD H. RUMSFELD, et al., | ) | |
| | ) | |
| Defendants. | ) | |
| | ) | |

**DEFENDANTS' MOTION FOR SUMMARY JUDGMENT**

In accordance with the Court's January 16, 2004 scheduling order, defendants move for summary judgment under Rule 56 of the Federal Rules of Civil Procedure with respect to plaintiffs' claims under the Administrative Procedure Act challenging the Final Order of the Food and Drug Administration ("FDA") categorizing Anthrax Vaccine Adsorbed as a Category I product. FDA's decision is not arbitrary, capricious, or an abuse of discretion and is fully supported by the administrative record. The grounds for this motion are set forth in detail in the accompanying memorandum of points and authorities. Also filed herewith is defendants' statement of material facts under Local Rule 7.1(h).

PETER D. KEISLER
Assistant Attorney General

ROSCOE C. HOWARD, JR.
United States Attorney

BRIAN D. BOYLE
Principal Deputy Associate Attorney General

SHANNEN W. COFFIN
Deputy Assistant Attorney General

*/s/ Craig M. Blackwell*
JOSEPH H. HUNT
VINCENT M. GARVEY
CRAIG M. BLACKWELL, DC Bar # 438758
RONALD J. WILTSIE
ANDREW H. TANNENBAUM
Civil Division
U.S. Department of Justice
P.O. Box 883
Washington, D.C. 20044
Tel: (202) 307-1401
Fax: (202) 616-8470

Attorneys for defendants

Date: March 3, 2004

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

| | | |
|---|---|---|
| JOHN DOE #1, et al., | ) | |
| | ) | |
| Plaintiffs, | ) | |
| | ) | |
| v. | ) | Civil Action No. 03-707 (EGS) |
| | ) | |
| DONALD H. RUMSFELD, et al., | ) | |
| | ) | |
| Defendants. | ) | |
| _____ | ) | |

**MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT**

Respectfully submitted,

PETER D. KEISLER
Assistant Attorney General
ROSCOE C. HOWARD, JR.
United States Attorney
BRIAN D. BOYLE
Principal Deputy Associate Attorney General
SHANNEN W. COFFIN
Deputy Assistant Attorney General
JOSEPH H. HUNT
VINCENT M. GARVEY
CRAIG M. BLACKWELL, DC Bar # 438758
RONALD J. WILTSIE
ANDREW H. TANNENBAUM
Attorneys
Civil Division
U.S. Department of Justice
P.O. Box 883
Washington, D.C. 20044
Tel: (202) 307-1401
Fax: (202) 616-8470

Attorneys for defendants

Date: March 3, 2004

**TABLE OF CONTENTS**

## TABLE OF AUTHORITIES

### CASES

**STATUTES**

**REGULATIONS**

**FEDERAL REGISTER PROVISIONS**



**OTHER SOURCES**

**PRELIMINARY STATEMENT**

In a Final Order dated December 30, 2003, defendant Food and Drug Administration ("FDA") categorized Anthrax Vaccine Adsorbed ("AVA"), a vaccine indicated to provide immunization against disease caused by *Bacillus anthracis* ("*B. anthracis*"), as a Category I product — that is, as safe, effective, and not misbranded. See Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review ("FDA Order" or "Order"), 69 Fed. Reg. 255 (Jan. 5, 2004). *B. anthracis* is the bacterium whose spores cause anthrax, a rare but deadly disease. Anthrax spores can enter the body any of three ways: through the skin (cutaneous), through breathing (inhalation), or through ingestion (gastrointestinal). The Order confirms the use of AVA as a safe and effective vaccine against disease caused by the anthrax bacterium, regardless of the route of exposure. AVA is the only vaccine licensed in the United States for prevention against anthrax.

The FDA Order marks the culmination of study regarding the safety, effectiveness, and labeling of certain bacterial vaccines (including AVA) previously licensed by a predecessor agency. FDA's decision to categorize AVA as "safe, effective, and not misbranded" is consistent with both the Panel on Review of Bacterial Vaccines and Toxoids ("Panel") recommendation that AVA be designated as a Category I product, see Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review, 50 Fed. Reg. 51,002, 51,058-59 (Dec. 13, 1985), and with FDA's proposed order adopting the Panel's Category I recommendation. See id. at 51,104. FDA's categorization of AVA is also consistent with the published findings of an independent, congressionally-mandated study of AVA's safety and effectiveness by the Institute of Medicine. See Institute of Medicine, The Anthrax Vaccine: Is it Safe? Does it Work? (2002). Moreover, as this Court has recognized, FDA's Order "categorizing AVA as safe and effective

for use against inhalation anthrax" addressed the "principle reason" for the Court's earlier injunction in this case. See Order dated January 7, 2004 at 1.

Plaintiffs, six anonymous individuals, challenge the FDA Order with respect to AVA under the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 551, et seq.[1] Notwithstanding the broad language in their Amended Complaint, plaintiffs do not challenge AVA's Category I categorization in its entirety. Plaintiffs, in a recent filing, conceded that AVA is "lawfully approved" — i.e., safe, effective, and not misbranded — for use against cutaneous anthrax. See Reply to Defendants' Memorandum of Law in Opposition to Plaintiffs' Motion to Determine that Class Certification Is Not Required for Program-Wide Injunctive Relief ("Class Cert. Reply") at 4 n.4. Plaintiffs challenge the Order only to the extent it "lawfully approves" AVA for use against inhalation anthrax. This challenge is meritless.

Plaintiffs have not established Article III standing. Plaintiffs claim they have been ordered, or will imminently be ordered, to take AVA as part of their military duties, but eleven months after filing their complaint, plaintiffs themselves have presented no specific facts in support of that claim. Indeed, because plaintiffs are litigating anonymously, defendants have been unable to test plaintiffs' allegations of injury. At this stage of the litigation, having failed to produce evidence of standing, plaintiffs' claims must be dismissed.

Plaintiffs' claims fare no better on the merits. Those claims are reviewed, of course, under the APA's deferential standard. Under that standard, agency action is presumed valid, and the Court must consider only whether the challenged decision was based on a consideration of

---

[1]Plaintiffs' amended complaint raises other claims unrelated to the legality of the Order. Pursuant to the Court's scheduling order, this brief addresses only the "validity of the FDA Order under the Administrative Procedure Act." See Order dated January 16, 2004 at 1-2.

the relevant factors and whether there has been a clear error of judgment; so long as the agency adequately articulates an explanation for its actions, it must be upheld. Indeed, because FDA's determination involves an expert evaluation of scientific data, judicial review is especially deferential. FDA's judgments about safety and effectiveness of drugs and biologics are at the very heart of its expertise.

With respect to safety, plaintiffs have not argued that AVA is unsafe for human use; in fact, plaintiffs affirmatively have *conceded* that AVA is safe for immunization against cutaneous anthrax. Plaintiffs thus effectively have conceded AVA's safety for immunization against inhalation anthrax because AVA is administered in advance of potential exposure to the anthrax bacterium, regardless of whether the intention is to protect against cutaneous or inhalation anthrax. In any event, AVA's safety is evidenced through numerous reports, studies, and data in the record, including the Institute of Medicine report ("IOM report"), and data collected by the Centers for Disease Control ("CDC") during a five-year open-label safety study.[2]

FDA's effectiveness determination is based on the adequate and well-controlled study conducted by Drs. Brachman, Gold, Plotkin, Fekety, Werrin, and Ingraham ("Brachman" or "Brachman study"), and corroborated by, among other things, CDC surveillance data on the occurrence of anthrax in at-risk industrial settings and the IOM report (which concluded that AVA, as licensed, is an effective vaccine to protect humans against inhalation anthrax).

---

[2]Defendants filed the fifteen volume administrative record relating to the portions of the Order involving AVA on February 2, 2004. In this memorandum, we refer to documents in the administrative record by the prefix "AR" followed by the bates-stamp number on the document. As we previously informed plaintiffs, the documents at pages AR681-AR1112 were inadvertently included in the record; these documents relate to portions of the Order not involving AVA.

Plaintiffs' argument that AVA is not effective appears to be based, almost entirely, on a misreading of both the Brachman data and the Panel report.[3] The former did not (as plaintiffs previously have argued) conclude that anthrax vaccine is effective *only* against cutaneous anthrax; the Brachman study calculated the effectiveness of the vaccine to prevent *all* types of anthrax disease combined — regardless of the route of exposure — as 92.5 percent. And the latter did not (as plaintiffs also previously have argued) recommend that AVA be licensed only for use against cutaneous exposure; AVA's label does not specify a route of exposure, and the Panel recommended that AVA, as licensed, be categorized as a Category I product.

In classifying a drug or biological product, FDA must make complex judgments about the quantity and quality of scientific evidence, and must weigh the risks and benefits associated with use. Here, FDA analyzed the evidence, weighed the risks, and decided, consistent with the Panel's recommendation, to classify AVA in Category I. Especially here, where the product at issue is licensed for vaccination against a fatal disease, FDA's expert scientific judgment that the product is safe and effective merits great deference from the Court. FDA's decision is rational, supported by the evidence, and should be upheld.

[3]The Panel report, as noted above, was published in the Federal Register with FDA's proposed order relating to the Panel's recommendations. When citing to the Panel report as published in the Federal Register, we use the shorthand "(Panel)" after the citation. The Panel report is also separately in the administrative record at AR004-600.

## BACKGROUND

1. Statutory and Regulatory Framework

a. The PHSA and the FDCA

The Public Health Service Act ("PHSA"), 42 U.S.C. §§ 201, et seq., and the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301, et seq., govern the regulation of biological products in the United States.[4] The PHSA governs licensing of biological products; it grants FDA authority to issue licenses based on a demonstration that the biological product is "safe, pure, and potent," 42 U.S.C. § 262(a)(2)(C)(i)(I), and that the facility in which the product is manufactured "meets standards designed to assure that the biological product continues to be safe, pure, and potent." Id. § 262(a)(2)(C)(i)(II).[5] Biological products, such as vaccines, intended for human use also are "drugs" for purposes of the FDCA, see 21 U.S.C. § 321(g)(1)(B), and, under the FDCA, FDA is charged with approving drugs that are, among other things, safe, effective, and not misbranded. See id. § 355(d).[6] See generally Procedures for Review of Safety,

[4]The PHSA defines biological products as any "virus, therapeutic serum, toxin, antitoxin, vaccine . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i).

[5]Prior to 1997, when the licensing provisions were amended to their current form, the PHSA similarly granted FDA authority to issue licenses "upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products." 42 U.S.C. § 262(d)(1) (1996).

[6]Under the FDCA, as amended in 1962, a drug for human use must be shown to be effective prior to approval. FDA, by regulation, has interpreted "potency" under the PHSA to mean "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." 21 C.F.R. § 600.3(s). Therefore, both biologics under the PHSA and drugs under the FDCA must be demonstrated to be effective before approval. As explained below, see infra p. 9 n.9, in 1972, when FDA initiated a review of the safety and effectiveness of all previously licensed biologics, it stated that proof of effectiveness should consist of "controlled clinical investigations" except in certain limited circumstances. See 21

Effectiveness, and Labeling, 37 Fed. Reg. 16,679, 16,679-80 (Aug. 18, 1972) (explaining interplay between PHSA and FDCA with respect to biologics).

Prior to 1972, the Division of Biologics Standards of the National Institutes of Health ("NIH") implemented PHSA's licensing provisions. See Redelegation of Authority to Administer Certain Provisions of the Federal Food, Drug, and Cosmetic Act, 37 Fed. Reg. 4,004, 4,005 (Feb. 25, 1972). In 1972, the Division of Biologics Standards (now the Center for Biologics Evaluation and Research) was transferred to FDA. See Statement of Organization, Functions, and Delegations of Authority, 37 Fed. Reg. 12,865 (June 29, 1972). That same year, FDA proposed, for notice and comment, regulations establishing procedures for reviewing the safety, effectiveness, and labeling of all biological products previously licensed by NIH. See Procedures for Review of Safety, Effectiveness and Labeling, 37 Fed. Reg. at 16,679. These comprehensive regulations, finalized in 1973, are codified at 21 C.F.R. § 601.25.

b. Section 601.25

Section 601.25 establishes a two-stage process for reviewing biological products licensed prior to July 1, 1972. First, it directs FDA's Commissioner ("Commissioner") to appoint an advisory review panel for each category of biological products to (i) evaluate the safety and effectiveness of the licensed products, (ii) review the labeling of such products, and (iii) advise the Commissioner "on which of the biological products under review are safe, effective, and not misbranded." See 21 C.F.R. § 601.25(a).

In advising the Commissioner, each panel must submit a report containing its conclusions and recommendations. See 21 C.F.R. § 601.25(e). The report must contain a "statement . . .

---

C.F.R. § 601.25(d)(2).

designat[ing] those biological products determined by the panel to be safe and effective and not misbranded," id. § 601.25(e)(1), and this statement "may include any condition relating to active components, labeling, tests required prior to release of lots, product standards, or other conditions necessary or appropriate for their safety and effectiveness." Id. Products in this category are deemed "Category I" products. The report must also contain a statement designating those products determined to be unsafe, ineffective or misbranded ("Category II" products); see id. § 601.25(e)(2); as well as those products for which the available data are insufficient to make the required determination such that further testing is required ("Category III" products). See id. § 601.25(e)(3). Product licenses remain in effect during the review process.

Second, after reviewing the recommendations, the Commissioner must publish in the Federal Register the panel report and a proposed order.[7] See 21 C.F.R. § 601.25(f). The proposed order must contain a statement designating those biological products "determined by the Commissioner . . . to be safe and effective and not misbranded" (i.e., those products in Category I), id. § 601.25(f)(1), as well as a statement designating those products determined to be in Category II and III. See id. § 601.25(f)(2)-(3); see also id. § 601.26 (reclassification procedures for certain Category III products). After reviewing comments on the proposed order, the Commissioner "shall publish . . . a final order on the matters covered" therein, id. § 601.25(g), which shall "constitute final agency action from which appeal lies to the courts." Id.

[7]As FDA noted in the Federal Register notice publishing Section 601.25, "the report of each panel is advisory to the Commissioner, who has the final authority either to accept or to reject the conclusions and recommendations of the panel." Procedures for Review of Safety, Effectiveness and Labeling, 38 Fed. Reg. 4,319, 4,321 (Feb. 13, 1973). Accord FDA Order at 257 ("[t]he Panel's recommendations are not binding but represent the scientific opinions of a Panel of experts").

§ 601.25(i).

Section 601.25(d) establishes the standards for FDA (and the panels) to apply in evaluating safety, effectiveness, and labeling. See 21 C.F.R. § 601.25(d). In the Federal Register notice proposing Section 601.25, FDA noted the "unique problems involved in applying the requirement of 'substantial evidence of effectiveness' to biological products under the [FDCA]," 37 Fed. Reg. at 16,679, and stated that advisory panels, subject to FDA review, would develop "the standard and methodology for effectiveness for a particular class of biological products, taking into account all of the circumstances involved." Id.; see also 50 Fed. Reg. at 51,005 (Panel) ("the judgment concerning safety and efficacy of bacterial vaccines and toxoids presents some complex and knotty overall problems"). The resulting standards, by necessity, thus are not uniform numeric thresholds, but are more in the nature of definitions to guide FDA's expert, case-by-case determinations with respect to particular products. See Berlex Labs., Inc. v. FDA, 942 F.Supp. 19, 25 (D.D.C. 1996) (discussing FDA regulations for determining safety, purity, and potency under the PHSA).

"Safety" is defined in the regulations as:

> the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

See 21 C.F.R. § 601.25(d)(1).[8] This standard is not absolute; it requires only "the relative freedom" from harmful effects. Id. Moreover, as the Panel noted, the standard for safety must

[8]Proof of safety "shall consist of adequate tests by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use." 21 C.F.R. § 601.25(d)(1); see also 21 U.S.C. § 355(d)(1).

"be individualized for each kind of vaccine." 50 Fed. Reg. at 51,006 (Panel).

"Effectiveness" is defined in the regulations as:

> a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological 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).[9] Again, this standard "must be applied separately to each vaccine," according to "current expectations of . . . performance." 50 Fed. Reg. at 51,007 (Panel).

In determining safety and effectiveness, FDA (and the panels) must consider "[t]he benefit-to-risk ratio" of the product under review. 21 C.F.R. § 601.25(d)(3). Risk/benefit analysis, "a fundamental [concept] in a consideration of vaccines," see 50 Fed. Reg. at 51,005 (Panel), requires FDA to determine whether the benefits of the product outweigh the risks of the product for the intended population. See id. at 51,006 (Panel) (noting that "[g]reater risks of adverse effects might be tolerated for a vaccine that provided protection against a lethal disease than for a vaccine against a disease that is basically benign"). Each product "must be assessed individually for its special features that vary from the norm." See id. (Panel).

Finally, with respect to the misbranding determination, FDA (and the panels) must determine whether the product labeling is "clear and truthful in all respects" and not "false or misleading in any particular," 21 C.F.R. § 601.25(d)(5), and whether the labeling complies with applicable statutory and regulatory requirements. See id. (citing 42 U.S.C. § 262, 21 U.S.C. §§

---

[9]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. See 21 C.F.R. § 601.25(d)(2). 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.

352 & 353, 21 C.F.R. §§ 610.60- 610.65, and 21 C.F.R. Part 201, Subpart D).

2. Review of AVA under 21 C.F.R. § 601.25

a. Anthrax disease

Anthrax is an acute bacterial disease caused by infection with spores of *Bacillus anthracis* ("*B. anthracis*"). See 50 Fed. Reg. at 51,058 (Panel). The "reservoir is any of several animal species (cattle, sheep, goats, horses, pigs) and the organism produces extremely resistant spores which may persist in soil and contaminate animals or their products." Id. (Panel).

Anthrax spores may enter the body in three ways: by skin contact (cutaneous), by ingestion (gastrointestinal), and by breathing (inhalation). For cutaneous anthrax, the fatality rate is approximately 20 percent. See AR3363 (Institute of Medicine, The Anthrax Vaccine: Is it Safe? Does it Work? (2002) ("IOM")).[10] For gastrointestinal anthrax, the fatality rate is 25 to 75 percent. See AR3364 (IOM). Until recent terrorist attacks involving anthrax spores, inhalation anthrax was extremely rare;[11] the fatality rate for inhalation anthrax is estimated to be approximately 45 to 90 percent. See AR639 (AVA package insert); see also AR3364 (IOM).

---

[10]In the House Conference Report accompanying the Department of Defense ("DoD") appropriations bill for the fiscal year ending September 30, 2000, Congress directed DoD to "enter into a contract with the National Research Council to independently study the effectiveness and safety of the anthrax vaccine." See H.R. Rep. No. 106-371, at 254 (1999). In October 2000, the Institute of Medicine convened the "Committee to Assess the Safety and Efficacy of the Anthrax Vaccine" ("IOM committee") to prepare this report. See AR3308 (IOM). The IOM report, the substance of which we discuss below, see, e.g., infra p. 22, is in the record at AR3303-3583.

[11]Only eighteen cases of inhalation anthrax were reported in the United States in the twentieth century. See AR3361 (IOM) (noting most cases occur in workers handling animal hides, hairs, or wools). Five of those cases were observed as part of the Brachman study, see id.; AR3734, the well-controlled clinical trial FDA relied upon as the basis for its effectiveness determination. See FDA Order at 259-60. Eleven additional inhalation cases were confirmed in 2001 after letters containing *B. anthracis* spores were sent through the mail. See AR3362 (IOM).

Once inside the body, and regardless of the route of exposure, the virulence of *B. anthracis* derives from three proteins — protective antigen (PA), edema factor (EF), and lethal factor (LF) — and a capsule. See AR3366-67 (IOM). The proteins are not toxic by themselves; rather, to produce active toxins, PA must "bind to cellular receptors and then bind with either EF or LF." AR3367 (IOM). The "resulting edema toxin or lethal toxin can then enter the cell," id., where "the toxins lead to damage." Id. (Figure 2-4).

"The available data indicate that immunity to anthrax is associated with the presence of antibody to protective antigen." AR3328 (IOM); see also AR639 (AVA package insert). AVA contains PA as its principal immunogen. See AR3368 (IOM). It is the only vaccine licensed for active immunization against *B. anthracis*. See AR3308, AR3322, AR3368-69 (IOM).

b. AVA license granted by NIH

"During 1965, it became apparent to many investigators at the National Communicable Disease Center [CDC] and elsewhere tha[t] an anthrax vaccine was needed for human immunization — no such vaccine was available from commercial sources." See AR3764. That year, DoD, through the U.S. Army Biological Laboratories, Fort Detrick, MD, contracted with the Michigan Department of Public Health ("MDPH") to engage in the large-scale production of a PA-based anthrax vaccine. See AR3647-52. Prior to the MDPH contract, the Army had contracted with Merck Sharpe & Dohme ("MS&D") to produce a PA-based vaccine ("MS&D vaccine"); see AR3764, 3831, 3862; prior to that, the Army produced a PA-based vaccine itself ("original DoD vaccine"). See AR3845-46, AR645-50; see also AR3300 (describing the three vaccines).

In 1966, CDC filed with NIH a "Notice of Claimed Investigational Exemption" (file #

DBS-IND-180) for "Anthrax Protective Antigen, Aluminum Hydroxide Adsorbed." See AR3829, AR3665; see also AR3607-3923 (portion of record relating to DBS-IND-180). Under this "investigational new drug" application (or "IND"), CDC began an open-label study designed to collect safety data on anthrax vaccine, the results of which it detailed in annual progress reports to NIH. In 1967, MDPH filed with NIH a product license application ("PLA") for "Anthrax Protective Antigen, Aluminum Hydroxide Adsorbed," see AR3943-50, the vaccine it was producing under contract with the Army. See AR3647; see also AR3924-4030 (portion of record relating to PLA file). During the licensing process, the product name was changed to "Anthrax Vaccine, Adsorbed." See AR3977.

NIH licensed AVA manufactured by MDPH in November 1970. See AR1377; Licensed Biological Products, 36 Fed. Reg. 8,704, 8,705 (May 11, 1971). The NIH committee tasked with reviewing MDPH's application, see AR3974, recommended that a license be granted based on, among other things, the CDC safety data,[12] laboratory tests showing AVA's ability to protect guinea pigs against challenge (potency data),[13] and the development and publication of additional standards relating to production and potency testing for AVA.[14] See AR4021 (Nov. 2, 1970

[12]These data, contained in the five annual progress reports CDC filed under DBS-IND-180, are in the record at AR3668-75 (report #5), AR3676-84 (report #4), AR3685-97 (report #3), AR3781-3820 (report #2), and AR3761-80 (report #1). In the first year of its open-label study, CDC distributed the MS&D and MDPH vaccines. See AR3764. After the first year, the progress reports reflect that CDC distributed only MDPH's product. See reports cited above; see also FDA Order at 260 (noting that approximately 15,000 doses of AVA were used). We discuss the CDC safety data in detail below. See, e.g., infra pp. 14, 19-20.

[13]See, e.g., AR3947 (MDPH describing "time-to-death" animal potency tests based on challenge with injection of *b. anthracis* spores); AR 3684 (potency data); AR3994-95 (potency data comparing AVA and MS&D vaccine).

[14]See AR1138-39. These standards, originally codified at 21 C.F.R. § 620.24, were revoked along with numerous other biologics regulations in 1996. See Revocation of Certain

memorandum from review committee chair); AR3930-31 (June 21, 1968 review committee memorandum); see also AR4022 (letter forwarding product license to MDPH).[15]

The NIH-approved label (or "package insert") recommended immunization with AVA for certain identified classes of persons with a risk of exposure to *B. anthracis* spores. See, e.g., AR3291 (recommending immunization for "individuals who may come in contact with imported animal hides, furs, bonemeal, wool, hair (especially goat hair), and bristles"); see also 50 Fed. Reg. at 51,058 (Panel) (AVA immunization "indicated only for certain occupational groups with risk of uncontrollable or unavoidable exposure to the organism"). It did not recommend that immunization be limited to any particular route of exposure. See AR3291-92 (package insert) ("recommendations for use").

c. Panel review

In 1973, FDA announced the Section 601.25 safety and effectiveness review for "bacterial vaccines and toxoids with standards of potency" — the category of products including AVA — and solicited relevant data and information. See Safety, Effectiveness and Labeling Review; Request for Data Information, 38 Fed. Reg. 5,358 (Feb. 28, 1973). The Panel considering these products (well over 100 products in all) submitted its report in 1980; see AR0001-0600; in 1985, FDA published the report and a proposed order relating to the

---

Regulations; Biological Products, 61 Fed. Reg. 40,153, 40,154 (Aug. 1, 1996).

[15]In various memoranda in the IND and PLA file, the NIH review committee commented that MDPH's vaccine had not itself been employed in a controlled field trial, and that the review committee therefore believed CDC's IND lacked controlled evidence of effectiveness. See, e.g., AR3629 (Sept. 30, 1969 memorandum); AR3630 (Sept. 30, 1969 memorandum). As explained below, however, see infra pp. 18, 21 n.23, & 36 n.31, the original DoD vaccine was used in a well-controlled trial conducted by Brachman, et al., and both the Panel and FDA concluded that, given the similarity between the PA-based vaccines, cf. infra n.19, the Brachman study may be relied upon for proof of AVA's effectiveness.

matters addressed therein. See 50 Fed. Reg. at 51,002.

With respect to AVA, the Panel recommended that it "be placed in Category I" — the category for products deemed safe, effective, and not misbranded — "and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product." 50 Fed. Reg. at 51,059 (Panel). See supra pp. 6-7 (discussing difference between product category designations). FDA, in its proposed order, concurred in the Panel's recommendation, and proposed to adopt the Panel's conclusion. See id. at 51,104. We review the Panel's findings below.

Safety. In determining safety, the Panel reviewed accumulated data from the CDC open-label study. During that study, as explained in the FDA Order, approximately 7,000 at-risk persons were vaccinated with either the MS&D vaccine or the MDPH vaccine and monitored for adverse reactions. See FDA Order at 260. Approximately 15,000 doses of MDPH-manufactured AVA were administered. See id.

Noting that "[i]n general, safety of this product is not a major concern," 50 Fed. Reg. at 51,058 (Panel), the Panel found the CDC data "suggest[] that [AVA] is fairly well tolerated with the majority of reactions consisting of local erythema [i.e., redness] and edema [i.e., swelling]," id. at 51,059 (Panel), and that "[s]evere local reactions and systemic reactions are relatively rare." Id. (Panel); see also id. at 51,058 (Panel) (in summarizing CDC data, noting that ("[l]ocal reactions are typically mild"; "[s]ome individuals may have more severe local reactions with edema, erythema greater than 5x5 cm, induration, local warmth, tenderness and pruritus"; and "[o]nly a few systemic reactions with marked chills and fever have been recorded"). Based on these data, the Panel concluded: "there is substantial evidence of safety . . . for this product." Id.

at 51,059 (Panel).

Effectiveness. In determining effectiveness, the Panel considered two sets of data: (i) the placebo-controlled human field trial conducted by Drs. Brachman, Gold, Plotkin, Fekety, Werrin, and Ingraham in the 1950s (in the record at AR3732-3745); and (ii) surveillance data collected and summarized by CDC. See 50 Fed. Reg. 51,058 (Panel).

The Brachman study involved 1,249 workers in four textile mills in the northeastern United States processing raw imported goat hair.[16] See AR3732, AR3733. A portion of the workers received anthrax vaccine ("vaccine group"), a portion received placebo ("placebo group"), and a portion received no treatment but were monitored for the occurrence of anthrax disease ("observational group"). See AR3734 (Table 2), AR3736 (Table 4); 50 Fed. Reg. at 51,058 (Panel); FDA Order at 259. During the evaluation period, which included an "outbreak" of inhalation anthrax, see AR3733, twenty-six cases of anthrax occurred:

> five of the twenty-six cases were inhalation cases; see AR3736 (Table 4); none of these cases was in the vaccine group; see id.; two were in the placebo group, see id., and three were in the observational group; see id.; four of the five inhalation cases were fatal; see AR3734;
>
> the remaining twenty-one cases were cutaneous; see AR3734; fifteen were in the placebo group (two in persons deemed not completely inoculated), see AR3736 (Table 4), three were in the observational group, see id., and three were in the vaccine group (two in persons deemed not completely inoculated); see id.

Based on the occurrence of a total of fifteen cases of cutaneous and inhalation anthrax in

---

[16] As the Brachman study noted, "[t]he necessary requirements of a well defined, exposed, susceptible population among whom cases of anthrax were reported with some regularity could only be met, in this country, in an industrial area" containing certain types of textile businesses. See AR3732. Brachman, et al., conducted their study in the 1950s. See AR3737 (Figure 1). By 1980, when the Panel submitted its report, this industrial setting was "vanishing, precluding any further clinical studies." 50 Fed. Reg. 51,058 (Panel).

completely inoculated members of the placebo group (some of the workers allocated to the vaccine and placebo groups did not receive the complete vaccination series), see AR3736 & Table 4, Brachman, et al., calculated "[t]he total expected cases" in the completely inoculated vaccine group as 13.35. See AR3737. Given that "only one case was actually observed" in the completely inoculated vaccine group (a cutaneous case), Brachman, et al., calculated the effectiveness of the vaccine against anthrax at 92.5 percent. See id. The authors of the study based their calculation on a comparison with the completely inoculated placebo group, see id., which, as noted above, included both cutaneous (13) and inhalation (2) cases. The calculated effectiveness rate did not include data from the observational group. See id.; AR1381 at n.9.

While relying on the Brachman study for its recommendation of effectiveness, see 50 Fed. Reg. at 51,059 (Panel), the Panel stated the study demonstrated "93 percent . . . protection" only against cutaneous anthrax, and that "[i]nhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease." 50 Fed. Reg. at 51,058 (Panel).[17] This observation, as FDA explained in its Final Order (see FDA Order at 259-60), was erroneous; that is, as noted above, Brachman, et al., calculated the effectiveness of the vaccine to prevent *all* types of anthrax, not just cutaneous. See AR3736 (Table 4); AR3740-41 (Table 8). Nevertheless, and notwithstanding this error, the Panel recommended no change with respect to the "recommendations for use" section of AVA's label (which, as stated supra p. 13,

[17]See also id. at 51,059 (Panel) (describing vaccine as "93 percent protective . . . against cutaneous anthrax" and noting that "[n]o meaningful assessment of its value against inhalation anthrax is possible due to its low incidence"); id. at 51,058 (Panel) (stating that "[a]nthrax vaccine poses no serious special problems other than the fact that its efficacy against inhalation anthrax is not well documented," and that "[t]his question is not amenable to study due to the low incidence and sporadic occurrence of the disease").

recommended AVA for immunization against *B. anthracis*, without specifying a route of exposure). See 21 C.F.R. § 601.25(e)(1) (Category I recommendation "may include any condition relating to . . . labeling" or "other conditions necessary or appropriate for . . . safety and effectiveness"); see also infra n.33.

The Panel also considered surveillance data collected by CDC "on the occurrence of anthrax in at-risk industrial settings." 50 Fed. Reg. at 51,058 (Panel). These data, the Panel observed:

> were summarized for the period 1962-1974. 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.

50 Fed. Reg. at 51,058 (Panel); see also id. at 51,059 (Panel) (reviewing surveillance data). Based on the summarized CDC surveillance data and the Brachman study, the Panel concluded there was "substantial evidence of . . . effectiveness for this product." Id. at 51,059 (Panel).

d. Citizen petition

On October 12, 2001, a group of individuals filed a citizen petition requesting that FDA find AVA ineffective for its intended use, and issue a final order classifying AVA as a Category II product.[18] See AR1313-75. The petitioners argued in part that the Panel had erred in concluding the Brachman study qualified as a well-controlled field trial for purposes of 21 C.F.R.

[18]In late 1995, MDPH became the Michigan Biologic Products Institute (MBPI). See AR1377 at n.1. In September 1998, BioPort, the current manufacturer, purchased MBPI. See id. The petitioners raised other issues relating to AVA's manufacturing by BioPort, which FDA addressed in its response. See AR1385-1392.

§ 601.25(d)(2); see AR1316-17 & n.6; they also argued the vaccine used in the Brachman study was not comparable to AVA. See AR1316 at n.5. In its August 28, 2002 response, FDA explained it was "working to complete [a final order] as soon as possible," and that, given "the pendency of this rulemaking," it could not "evaluate the adequacy of the Panel recommendation." AR1378. Nevertheless, FDA provided its "position at this time" with respect to several issues raised in the petition. See AR1378 (emphasis removed).

For example, FDA explained that the Brachman study qualifies as a well-controlled study under its regulations. See AR1380 (noting the study "permitted a valid comparison of the vaccine with a placebo control group to provide a quantitative assessment of effectiveness"). Relying on the published guidance for determining comparability, see AR1382, FDA also explained that AVA "is comparable to the DOD vaccine used in the Brachman study." See AR1382-84 (reviewing the history of DoD's involvement in the development of all three versions of the PA-based anthrax vaccine).[19] FDA also concluded (contrary to the Panel's observation) that "the efficacy analysis actually conducted in the Brachman study includes all cases of anthrax disease regardless of the route of exposure or manifestation of the disease." AR1381; see also AR4032 (Mar. 4, 1997 letter from DoD to FDA stating DoD's view that "the scope of [AVA's] license . . . include[s] inhalation exposure"); AR4031 (Mar. 13, 1997 response from FDA stating "the current package insert does not preclude this use").

---

[19]The Panel concluded correctly that the vaccine used by Brachman, et al., was "very similar" to AVA, and that the Brachman study could be used to establish AVA's effectiveness. See 50 Fed. Reg. at 51,059 (Panel); see also id. (Panel) (noting that AVA was "patterned after" the vaccine used in the Brachman study). The Panel stated erroneously, however, see id., that Brachman, et al., used the MS&D vaccine; they used the original DoD vaccine. See AR3732. As noted infra n.23, FDA, in its Final Order, explained that AVA is comparable to both predecessor PA-based vaccines.

Finally, FDA noted AVA's package insert had been amended most recently in January 2002, see AR1378 at n.5, and that the amended approved package insert, like the earlier package insert, stated the indication is based on risk of exposure. See AR1377-78; see also AR640 (amended package insert) (AVA indicated for "the active immunization against *Bacillus anthracis* of individuals between 18 and 65 years of age who come in contact with animal products such as hides, hair or bones that come from anthrax endemic areas, and that may be contaminated with *Bacillus anthracis* spores," and "for individuals at high risk of exposure to *Bacillus anthracis* spores such as veterinarians, laboratory workers and others whose occupation may involve handling potentially infected animals or other contaminated materials"). Thus, the current package insert, like the original package insert, see AR3291-92, does not recommend that use of AVA be limited to any particular route of exposure.

e. Final Order

On December 30, 2003, FDA issued a final order under 21 C.F.R. § 601.25(g) regarding the status of the products addressed in the Panel report. See FDA Order at 257-59.[20] With respect to AVA, FDA "adopted Category I" — safe, effective, and not misbranded — "as the final category." See FDA Order at 257 & Table 1. The Order explained in detail FDA's reasoning with respect to its "determination that the data support the safety and efficacy of AVA," id. at 259, and also explained certain "points of disagreement with statements in the Panel report." Id. We review these portions of the Order below.

Safety. FDA, like the Panel, relied on data from CDC's open-label study in finding AVA

[20]The Order also contained a final rule relating to certain additional standards for one of the biological products under review. See FDA Order at 265.

safe. See FDA Order at 260 (noting that, from 1967-1971, approximately 7,000 at-risk persons "were vaccinated with anthrax vaccine and monitored for adverse reactions"; that approximately 15,000 doses of MDPH-manufactured AVA were administered during the study; and that the Panel found the CDC data "'suggests that this product is fairly well tolerated'").

FDA also considered, among other things, the results of a "small, randomized clinical study of the safety and immunogenicity of AVA" conducted by DoD,[21] as well as "post licensure adverse event surveillance data available from the Vaccine Adverse Event Reporting System (VAERS)."[22] FDA Order at 260. These data, FDA noted, "provided the basis for a description of the types and severities of adverse events associated with administration of AVA included in" the FDA-approved amendments to AVA's labeling in 2002. Id.; see also AR641-43.

Effectiveness. FDA cited two principal sources in support of its effectiveness determination: (i) Brachman, et al.'s well-controlled field study; and (ii) the CDC surveillance data. See FDA Order at 259-60. With respect to Brachman, FDA reviewed the nature and scope

---

[21]This study, in the record at AR1407-16, is Phillip R. Pittman, et al., "Anthrax Vaccine: Immunogenicity and Safety of a Dose-Reduction, Route-Change Comparison Study in Humans," 20 *Vaccine* 1412-1420 (2002) ("Pittman"). The study noted, among other things, that local reaction rates associated with AVA are comparable to those associated with other licensed vaccines "in common use today." See AR1414.

[22]VAERS, co-administered by CDC and FDA, is "the nation's principal system for the collection of reports on adverse events following the use of any vaccine licensed in the United States." AR3422 (IOM). It is a passive surveillance system that "relies on spontaneous reporting" of suspected adverse events. AR3425 (IOM). All VAERS reports related to AVA as of December 31, 2001 are in the record at AR1417-AR3244. An FDA summary of VAERS reports related to AVA as of September 30, 2001 is in the record at AR3584-AR3606; the summary notes there is "[n]o clear pattern of association between deaths or serious adverse events and anthrax vaccine." E.g., AR3587. Certain VAERS data related to AVA as of October 30, 2001 also is discussed in the IOM report at AR3433-34; the IOM committee found the data "present no signals of previously undescribed serious adverse reactions associated with exposure to AVA." AR3434 (IOM); see also AR3333 (IOM) (summary of findings relating in part to VAERS data).

of the study, as well as the study's findings. See id. at 259-60; see also discussion supra pp. 15-16. FDA also reviewed the Panel's statement that the study demonstrated a "'93 percent . . . protection against cutaneous anthrax'" and that "'inhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease.'" FDA Order at 259 (quoting Panel report). Explaining its disagreement with these statements by the Panel, FDA concluded:

> [b]ecause the Brachman comparison of anthrax cases between the placebo and vaccine groups included both inhalation and cutaneous cases, FDA has determined that the calculated efficacy of the vaccine to prevent all types of anthrax disease combined was, in fact, 92.5 percent . . . . The efficacy analysis in the Brachman study includes all cases of anthrax disease regardless of the route of exposure or manifestation of disease.

Id. at 259-60.

FDA noted that the five cases of inhalation anthrax reported in the course of the Brachman study, see discussion supra pp. 15-16, were "too few to support an independent statistical analysis." FDA Order at 260. But, FDA continued:

> of these [five] cases, two occurred in the placebo group, three occurred in the observational group, and no cases occurred in the vaccine group. Therefore, the indication section of the labeling for AVA does not specify the route of exposure, and the vaccine is indicated for active immunization against *Bacillus anthracis*, independent of the route of exposure.

FDA Order at 260.[23]

---

[23]FDA noted the Panel had erred in stating that Brachman, et al., used the MS&D vaccine in their study. See FDA Order at 260; see also supra n.19. Explaining it had "reviewed the historical development of AVA," FDA "concluded that DoD's continuous involvement with, and intimate knowledge of, the formulation and manufacturing processes of all of these versions of the anthrax vaccine" — i.e., the original DoD vaccine, the MS&D vaccine, and the MDPH vaccine — "provide a foundation for a determination that the MDPH anthrax vaccine is comparable to the original DoD vaccine" used in the Brachman study. Id. at 260-61 (citing, e.g., potency data demonstrating that the different vaccines protected rabbits and guinea pigs against

FDA also addressed the summary of the CDC surveillance data considered by the Panel "as supportive of the effectiveness of AVA." FDA Order at 260. These data, the Panel noted, were collected by CDC for the years 1962-1974 on the occurrence of anthrax disease in at-risk industrial settings. See 50 Fed. Reg. at 51,058 (Panel); see also discussion supra p. 17. Reviewing the Panel's discussion, FDA concluded the summary "provide[s] confirmation that the risk of disease still existed for those persons who were not vaccinated and that those persons who had not received the full vaccination series (six doses) were susceptible to anthrax infection, while no cases occurred in those who had received the full vaccination series." FDA Order at 260.

Finally, FDA discussed the congressionally-mandated "independent examination" by IOM of AVA's safety and effectiveness, during which the IOM committee "reviewed all available data, both published and unpublished, [and] heard from Federal agencies, the manufacturer, and researchers." FDA Order at 260. Noting that IOM's published report concluded "that AVA, as licensed, is an effective vaccine to protect humans against anthrax including inhalation anthrax," id.; see also AR3323 (IOM), FDA stated it

> agrees with the report's finding that studies in humans and animal models support the conclusion that AVA is effective against *B. anthracis* strains that are dependent upon the anthrax toxin as a mechanism of virulence, regardless of the route of exposure.

FDA Order at 260; see also id. at n.5.[24]

---

challenge with virulent *B. anthracis* and human data comparing the safety and immunogenicity of the MDPH vaccine and the original DoD vaccine). See also AR3994-95, AR3868, AR3996, AR3732, AR3930, AR3698-3705.

[24]Citing, e.g., P.F. Fellows, et al., "Efficacy of a Human Anthrax Vaccine in Guinea Pigs, Rabbits, and Rhesus Macaques Against Challenge by *Bacillus Anthracis* Isolates of Diverse Geographical Origin," 19 *Vaccine* 3241-47 (2001) ("Fellows") (AR621-27); B.E. Ivins, et al.,

3. Prior Proceedings

Plaintiffs are six anonymous members of the U.S. military and/or DoD contractors who claim they "have been ordered, or will imminently be ordered, to take AVA as part of their military duties or employment obligations." Amended Complaint ("Amd. Compl.") ¶ 1. At the time they filed their original complaint, plaintiffs also sought a preliminary injunction to prevent their inoculation with AVA under DoD's Anthrax Vaccine Immunization Program ("AVIP"), an ongoing program under which DoD vaccinates service members with AVA. See Memorandum in Support of Motion for Temporary Restraining Order and/or Preliminary Injunction ("PI Mem.") at 1. Plaintiffs claimed that inoculation would violate 10 U.S.C. § 1107 and certain implementing regulations/executive orders. See id.

Section 1107 addresses the use of an "investigational new drug" or a "drug unapproved for its applied use" on members of the armed forces. See 10 U.S.C. § 1107(a). It authorizes the President to waive certain (but not other) otherwise applicable FDCA requirements relating to the use of "investigational" drugs upon a determination that obtaining consent is not feasible, contrary to the best interests of the military, or not in the interests of national security. See 10 U.S.C. § 1107(f). Plaintiffs claimed that, because AVA assertedly had not been approved as effective for use against inhalation anthrax, such use was "investigational" within the meaning of Section 1107. See PI Mem. at 1. Plaintiffs did not dispute that AVA has been approved as safe and effective for use against cutaneous anthrax.

---

"Efficacy of a Standard Human Anthrax Vaccine Against *Bacillus Anthracis* Aerosol Spore Challenge in Rhesus Monkeys," 87 *Salisbury Medical Bulletin* 125-26 (1996) ("Ivins, *Salisbury*") (AR628-29); B.E. Ivins, et al., "Comparative Efficacy of Experimental Anthrax Vaccine Candidates Against Inhalation Anthrax in Rhesus Macaques," 16 *Vaccine* 1141-48 (1998) ("Ivins, *Vaccine*") (AR630-37).

On December 22, 2003, the Court enjoined defendants, "[i]n the absence of a presidential waiver [under Executive Order 13139], . . . from inoculating service members [with AVA] without their consent." Doe v. Rumsfeld, — F.Supp.2d —, 2003 WL 22994225 at *14 (Dec. 22, 2003). The Court entered the injunction based upon its conclusion that AVA is "an investigational drug" and a drug unapproved for use against inhalation anthrax. See id. In framing the issue for resolution, the Court stated: "[a]t bottom, this inquiry turns on whether the FDA has made a final decision on the investigational status of AVA[.]" Id. at *10. Noting that "FDA, the only agency that this Court could properly defer to in determining AVA's status as an investigational drug, has failed to provide a formal opinion as to AVA's investigational status," id. at *12, the Court conducted its own inquiry into the "complex" issue regarding "AVA's investigational status." Id.; see also id. at *14 ("because the record is devoid of an FDA decision . . . this Court must determine AVA's status for itself").[25]

After FDA issued its final order on December 30, 2003, defendants immediately requested, among other things, that the Court stay its injunction with respect to persons other than the named plaintiffs. See Docket # 21; Docket # 24. In granting defendants' motion, the Court reiterated that, at the preliminary injunction stage, it had been "persuaded that the record evidence before the Court was devoid of an FDA final decision on the investigational status of [AVA]." See Order dated January 7, 2004 at 1. Noting that "the principle reason for the issuance of the injunction has been addressed" by FDA's Final Order "categorizing AVA as safe

[25]The Court based its conclusion that AVA's "original license" did not "include[] inhalation anthrax" in part on the fact that an IND application filed by AVA's manufacturer in 1996 "remains pending today." 2003 WL 22994225 at *12. We have informed plaintiffs' counsel, and wish to inform the Court, that, after FDA issued its Order relating to AVA, BioPort, in January 2004, withdrew this IND application.

and effective for use against inhalation anthrax," id., the Court stayed its injunction as to all but the six Doe plaintiffs. See id. at 2.

4. Plaintiffs' Amended Complaint

On January 6, 2004, plaintiffs filed an amended complaint adding a count challenging the Order as arbitrary and capricious under the APA. See Amd. Compl. ¶¶ 81-90 (Count IV). Other than this new count, the bulk of the amended complaint simply repeats the claims and allegations in plaintiffs' original complaint, many of which are irrelevant to the legality of FDA's determination.

With respect to the Order, plaintiffs claim FDA's determination to place AVA in Category I "has no rational connection and is unsupported by substantial evidence." See Amd. Compl. ¶ 87. Specifically, plaintiffs claim FDA "distorted or exaggerated the scientific conclusions upon which it relied for its decision," id., "failed to note significant limitations asserted by the authors of anthrax-related studies," id., and inappropriately "reli[ed] on studies involving animal data to support its conclusion that the AVA is effective against inhalation anthrax." Id. ¶ 88. They also claim the Order is "so arbitrary and capricious as to amount to bad faith." Id. ¶ 90; see also id. ¶ 87 ("[i]n issuing its Final rule and final order, the FDA acted in bad faith and excluded evidence adverse to its determination which was known to it at the time of the decisionmaking"). For relief, plaintiffs seek a declaration that the Order "was issued in violation of the [APA], thereby voiding its application," and a remand "to the FDA for further evaluation." Id. at p. 19, ¶ G. Subsequent to filing their amended complaint, however, plaintiffs, in a filing relating to the class certification issue, acknowledged that AVA is "lawfully approved" for use against cutaneous anthrax. See Class Cert. Reply at 4 n.4.

## ARGUMENT

FDA's decision to confirm AVA as a Category I product pursuant to 21 C.F.R. § 601.25 must be upheld under the APA unless that decision is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. See 5 U.S.C. § 706(2)(A). The "arbitrary and capricious" standard is highly deferential to the agency; there is "'a presumption in favor of the validity of administrative action,'" Bristol-Myers Squibb Co. v. Shalala, 923 F.Supp. 212, 216 (D.D.C. 1996) (internal citation omitted), and a reviewing court must consider only whether "the [agency] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 416 (1971); accord Motor Vehicle Mfrs. Ass'n of the United States v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983) ("the agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made'") (internal citation omitted).[26]

A critical component of arbitrary/capricious review is that a court may not "substitute its judgment for that of the agency." State Farm, 463 U.S. at 43; see also, e.g., Vermont Yankee Nuclear Power Corp. v. Natural Res. Def. Council, Inc., 435 U.S. 519, 558 (1978) ("[a]dministrative decisions should be set aside . . . only for substantial procedural or substantive reasons as mandated by statute, not simply because the court is unhappy with the result reached")

[26]The reverse side of this coin, the Supreme Court has noted, is that an agency decision may be deemed arbitrary and capricious only in circumstances where 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." State Farm, 463 U.S. at 43.

(internal citation omitted); 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"). Judicial review, moreover, is limited to the administrative record. See, e.g., Berlex, 942 F.Supp. at 23 (refusing to consider extra-record affidavits submitted by plaintiff); Alliance for Bio-Integrity v. Shalala, 116 F.Supp.2d 166, 177 (D.D.C. 2000) (same).

This ordinary deference may be heightened even further in cases involving scientific or technical decisions. For example, like other agencies operating in highly technical areas, see, e.g., Federal Power Comm'n v. Florida Power & Light Co., 404 U.S. 453, 463 (1972), FDA is entitled to a "'high level of deference'" when its regulatory determination rests on its "'evaluation[] of scientific data within its area of expertise.'" Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (internal citation omitted).[27] The "determination whether a drug is generally recognized as safe and effective within the meaning of [the FDCA] necessarily

[27] Accord id. at 1327 ("Neither we, nor the district judge, are scientists independently capable of assessing the validity of the agency's determination — beyond holding it to the standards of rationality required by the [APA]"); Henley, 77 F.3d at 621 ("FDA possesses the requisite know-how to conduct such analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug, and how those data affect human usage"); Simpson v. Young, 854 F.2d 1429, 1434 (D.C. Cir. 1988) ("[t]his court has 'neither the expertise nor the resources to evaluate complex scientific claims'"; "we cannot decide . . . whether technical evidence beyond our ken supports the proposition it is asserted to support") (internal citation omitted); Alliance for Bio-Integrity, 116 F.Supp.2d at 177 ("'[I]n an area characterized by scientific and technological uncertainty[,] . . . this court must proceed with particular caution, avoiding all temptation to direct the agency in a choice between rational alternatives'") (internal citation omitted) (alterations in original); Bristol-Myers, 923 F.Supp. at 220 ("[t]he parties' dispute is fundamentally a scientific one over which the court lacks expertise and over which the FDA is the expert"); see also Troy Corp. v. Browner, 120 F.3d 277, 283 (D.C. Cir. 1997) (EPA determination) ("[a]s we have said, we review scientific judgments of the agency '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'") (internal citation omitted).

implicates complex chemical and pharmacological considerations." Weinberger v. Bentex Pharms., Inc. 412 U.S. 645, 654 (1973). FDA's "'judgments as to what is required to ascertain the safety and efficacy of drugs'" thus fall "'squarely within the ambit of FDA's expertise and merit deference from' the courts." Bristol-Myers, 923 F.Supp. at 220 (quoting Schering Corp. v. FDA, 51 F.3d 390, 399 (3d Cir.), cert. denied, 516 U.S. 907 (1995)).

Similarly, "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, 942 F.Supp. at 25; accord Bristol-Myers, 923 F.Supp. at 216 ("because this action implicates, in part, an interpretation by the agency of its own regulations, the court must be especially deferential"); cf. Public Citizen v. Foreman, 631 F.2d 969, 975 (D.C. Cir. 1980) (USDA regulation) (traditional deference accorded agency interpretation of its own regulations "especially prudent in areas involving scientific and medical controversies").

With these principles in mind, we turn to the FDA Order, and demonstrate, first, that plaintiffs lack standing,[28] and second, that, even assuming standing, FDA's determination with respect to AVA is reasonable, not arbitrary or capricious, supported by the record, and fully consistent with law.

---

[28]Defendants raised other justiciability arguments at the preliminary injunction stage, which the Court rejected. See, e.g., Defendants' Opposition to Plaintiff's Motion for a Preliminary Injunction at 14-26. Defendants stand by those arguments and incorporate them by reference here, understanding that the Court already has ruled on them. Defendants recognize that the Court found plaintiffs had standing at the preliminary injunction phase of this case, see Doe, 2003 WL 22994225 at *9, but, as explained below, see infra p. 29, that decision does not control whether plaintiffs also have standing at this latter stage of the litigation with respect to their challenge to the Order.

## I. PLAINTIFFS LACK STANDING

The party asserting jurisdiction always has the burden "'clearly to 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) (internal citation omitted). To have standing under the Constitution, a plaintiff must allege: (i) an "actual or imminent" injury-in-fact; (ii) "fairly . . . trace[able] to the challenged action of the defendant"; and (iii) "likely" to be "redressed by a favorable decision." Lujan v. Defenders of Wildlife, 504 U.S. 555, 560-61 (1992) (internal quotations and citations omitted) (alteration in original).

Standing is an "indispensable part of the plaintiff's case," and "must be supported . . . with the manner and degree of evidence required at the successive stages of the litigation." Lujan, 504 U.S. at 561. At the summary judgment stage, "the plaintiff can no longer rest on . . . 'mere allegations,'" id., but must "'set forth' by affidavit or other evidence 'specific facts'" establishing the elements of standing. Id. (quoting Fed. R. Civ. P. 56(e)). Indeed, because summary judgment is the *final* stage with respect to plaintiffs' APA challenge to the FDA Order (i.e., there will be no trial), any facts proffered by plaintiffs to support standing should not be taken as true; rather, defendants should have the opportunity to challenge those facts, and plaintiffs, to establish standing, must demonstrate that their proffered facts are "'supported adequately by the evidence.'" Id. (internal citation omitted).

The Court recognized in its prior ruling that, to establish injury, plaintiffs must demonstrate they have taken, or have been ordered imminently to take, the anthrax vaccine. See Doe, 2003 WL 22994225 at *9. Plaintiffs, in their amended complaint, *allege* they have "been ordered, or will imminently be ordered, to take AVA as part of their military duties or

employment obligations," or have been administered AVA. Amd. Compl. at ¶ 1; see also id. at ¶ 78 (alleging one anonymous plaintiff received "one shot" of AVA). But plaintiffs themselves have presented no "specific facts" in support of these claims. See Fed. R. Civ. P. 56(e). The only "facts" plaintiffs apparently have submitted are contained in a sealed affidavit of plaintiffs' *counsel*, see Docket #1, on which the Court presumably relied in finding standing at the preliminary injunction phase (these facts also were referenced by plaintiffs' counsel at the preliminary injunction hearing). Doe, 2003 WL 22994225 at *9 (noting that "all six plaintiffs have been ordered to appear for the inoculation, and three of the six have already begun the series with more inoculations to follow"). But a lawyer's hearsay affidavit (or statements by a lawyer at a hearing) cannot be sufficient to establish standing at the summary judgment stage. See Fed. R. Civ. P. 56(e) (summary judgment affidavits "shall be made on personal knowledge" and "shall set forth such facts as would be admissible in evidence"). And, even if one or more plaintiffs had filed a party affidavit, plaintiffs could not establish standing (if at all) unless defendants were first provided an opportunity to examine any such affidavit and contest any claim of injury therein.[29]

In fact, while defendants have not seen counsel's sealed affidavit, the information defendants *do* have cuts against standing (at least by implication). After this Court limited its original injunction to the six Doe plaintiffs, defendants' counsel asked plaintiffs' counsel to inform defendants if one of the Doe plaintiffs received an order to report for inoculation (so that defendants would be able to honor the Court's injunction). Plaintiffs' counsel agreed to so inform

[29]Defendants reserve the right to seek discovery in the event plaintiffs proffer facts with respect to standing.

defendants, and, to date, has not alerted defendants that any plaintiff has been ordered to receive the vaccine. For all these reasons, plaintiffs' allegations of injury are not "supported adequately by the evidence," Lujan, 504 U.S. at 561, and their claims, accordingly, should be dismissed for lack of standing.

## II. FDA'S DECISION TO CLASSIFY AVA AS A CATEGORY I PRODUCT IS NOT ARBITRARY, CAPRICIOUS, OR AN ABUSE OF DISCRETION

Even assuming standing, plaintiffs cannot prevail on the merits. FDA categorized AVA as a Category I product under 21 C.F.R. § 601.25 based on its conclusion that AVA is safe, effective, and not misbranded. FDA's determination is reasonable, not arbitrary or capricious, supported by the scientific evidence, and should be upheld.

### A. FDA's Safety Determination Is Not Arbitrary, Capricious, or An Abuse of Discretion

Section 601.25 defines "safety" as "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." 21 C.F.R. § 601.25(d)(1). Proof of safety "shall consist of adequate tests by methods reasonably applicable to show the biological product is safe under the prescribed conditions of use, including results of significant human experience during use." Id.

Safety is not an absolute standard; the regulations require only the "relative freedom" from harmful effects. See 21 C.F.R. § 601.25(d)(1); see also AR3402 (IOM) ("safety is relative, not absolute"); United States v. Rutherford, 442 U.S. 544, 555 (1979) ("[f]ew if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk"). The standard also is not quantitative or measurable; rather, the regulations provide a

definition to guide FDA's expert, case-by-case determinations. See Berlex, 942 F.Supp. at 25 (discussing FDA regulations for determining safety, purity, and potency under the PHSA, including, e.g., the definition of safety in 21 C.F.R. § 600.3(p)). FDA's judgment about what is required to ascertain safety lies at the core of its expertise. See Bristol-Myers, 923 F.Supp. at 220 (citing Schering Corp., 51 F.3d at 399).

Plaintiffs have not argued in this case that AVA is not safe for human use. In fact, plaintiffs have conceded that AVA is "lawfully approved" — i.e., safe, effective, and not misbranded — for use against cutaneous anthrax, see Class Cert. Reply at 4 n.4, and have never argued that AVA's safety somehow varies depending on the route of exposure. Nor would such an argument make sense. AVA is administered *pre*-exposure, see AR640 (package insert) (AVA is indicated for "active immunization" against *B. anthracis*); AR3331, 3402 (IOM), regardless of whether the intention is to protect against cutaneous or inhalation anthrax. If, as plaintiffs acknowledge, AVA is safe for immunization against cutaneous anthrax, then it necessarily also is safe for immunization against inhalation anthrax.

Plaintiffs are right to concede the point, for there is ample scientific evidence in the record to support FDA's determination that AVA meets the safety standard in Section 601.25(d). Significantly, FDA's decision is supported by the accumulated data from CDC's five-year open-label study. These data, discussed in detail above, see supra pp. 14, 19-20, "'suggest[] that [AVA] is fairly well tolerated with the majority of reactions consisting of local erythema and edema," and that "'[s]evere local reactions and systemic reactions are relatively rare.'" FDA Order at 260 (quoting 50 Fed. Reg. at 51,059 (Panel)); accord AR3744 (Brachman) (noting that "[i]ndividual reactions to the vaccine was a relatively minor problem," "[e]dema-producing local

reactions occurred following 2.8 percent of all inoculations," and "[s]ystemic reactions were rare with only 0.2 per cent of inoculations followed by noticeable symptoms"); cf. AR645-49 (early study conducted with DoD vaccine).

Other data and studies in the record corroborate the CDC study. For example, a more recent DoD study of the safety and immunogenicity of AVA found that local reaction rates associated with AVA, although higher than those reported in the CDC data, are comparable to those associated with other licensed vaccines. See AR1414 (Pittman). With respect to more serious adverse events, VAERS reports, reviewed and summarized by FDA from 1990 through September 30, 2001, see AR3584-AR3606, show "[n]o clear pattern of association between deaths or serious adverse events and anthrax vaccine." E.g., AR3587.

And the IOM committee, specifically charged by Congress to study AVA's safety, concluded in its published report that AVA is safe. AR3323 (IOM) ("AVA is reasonably safe"). The committee reviewed case reports (primarily from VAERS), see AR3331-32, considered formal epidemiological studies, AR3332, and heard testimony "regarding adverse events following vaccination with AVA." Id. Again, although finding the reactogenicity for AVA higher than that reflected in the CDC data, the IOM committee concluded:

> [w]ithin hours or days following vaccination, it is fairly common for recipients to experience some local events (e.g., redness, itching, swelling, or tenderness at the injection site), while a smaller number of vaccine recipients experience some systemic events (e.g., fever and malaise). But these immediate reactions, and the rates at which they occur, *are comparable to those observed with other vaccines regularly administered to adults*. The [IOM] committee found no evidence that vaccine recipients face an increased risk of experiencing life-threatening or permanently disabling adverse events immediately after receiving AVA, when compared with the general population. Nor did it find any convincing evidence that vaccine recipients face elevated risk of developing adverse health effects over the long term, although data are limited in this regard (as they are for all vaccines).

AR3323 (emphasis added); see also AR3332 (local and systemic reactions associated with AVA occur at rates comparable to those observed with diphtheria and tetanus toxoids and influenza vaccines); AR1414 (Pittman) (local reaction rates for AVA comparable to rates for "other vaccines in common use today," including diphtheria and tetanus toxoids and pertussis vaccine adsorbed); AR641-43 (package insert) (reporting pre- and post-licensure safety data).

No vaccine is one-hundred percent safe.[30] See Rutherford, 442 U.S. at 555. The regulatory standard — "relative freedom from harmful effects" — reflects this reality. See 21 C.F.R. § 601.25(d)(1). FDA, based on its review of the scientific evidence, determined that AVA meets the safety standard in Section 601.25(d). This expert determination, which FDA explained at length in its Order, is rational, supported by the evidence, and should be upheld. See, e.g., Serono, 158 F.3d at 1320 (FDA entitled to a "'high level of deference"' for regulatory determinations resting on "'evaluations of scientific data within its area of expertise"') (internal citation omitted); State Farm, 463 U.S. at 43.

[30]In its preliminary injunction opinion, the Court noted that the "Adverse Reactions" section of AVA's package insert, which describes VAERS data related to AVA from 1990 to October 2001, indicates that VAERS received six reports of fatalities. See Doe, 2003 WL 22994225 at *3; see also AR643 (package insert) (reporting VAERS data and noting that one reported fatality was a suicide). As the package insert states, however, "[b]ecause of the limitations of spontaneous reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is often not possible using VAERS data alone." AR642; accord AR3585 (FDA summary of VAERS data) ("it is usually not possible to determine causal associations between vaccines and adverse events from VAERS reports, unless the event is a well-recognized reaction (e.g., injection site reaction) or confirmatory laboratory results are included (e.g. vaccine strain virus detected in paralytic polio case")). Neither FDA nor the IOM committee found any causal link between AVA and life-threatening events. See AR3587 (FDA summary of VAERS data); AR3323 (IOM).

B. FDA's Effectiveness Determination Is Not Arbitrary, Capricious, or An Abuse of Discretion

Section 601.25(d) defines effectiveness as "a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological 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. See id. 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.

Effectiveness, like safety, must be determined in the context of each vaccine. See 21 C.F.R. § 601.25(d)(2) (requiring a "reasonable expectation" that product will serve a "clinically significant function"); AR3376 (IOM). And, like safety, the regulatory standard provides a definition to guide FDA's expert, case-by-case determinations for particular drugs and products. See Berlex, 942 F.Supp. at 25 (discussing FDA regulations for determining safety, purity, and potency under the PHSA).

Effectiveness determinations, at bottom, require judgments about the quantity and quality of scientific evidence. See Ethicon, Inc. v. FDA, 762 F.Supp. 382, 388 (D.D.C. 1991). These determinations can be quite complex. See 37 Fed. Reg. at 16,679 (FDA noting the "unique problems involved in applying the requirement of 'substantial evidence of effectiveness' to biological products under the [FDCA]," and that standards and methodologies for particular classes of products will "tak[e] into account all of the circumstances involved"); 50 Fed. Reg. at

51,005 (Panel) (noting that "the judgment concerning safety and efficacy of bacterial vaccines and toxoids presents some complex and knotty overall problems"); see also Doe, 2003 WL 229943225 at *12 (noting the "complex[ity]" of the issues in this case). FDA judgments about effectiveness — like its judgments about safety — are at the very heart of FDA's expertise. Bristol-Myers, 923 F.Supp. at 220.

FDA's determination that AVA is effective is amply supported by the record evidence. Most significantly, FDA relied on the well-controlled field study conducted by Brachman, et al., in four textile mills processing raw imported goat hair. See FDA Order at 259-60.[31] The mills provided a natural exposure setting: raw materials (goat hair) were "*Bacillus anthracis*-contaminated," AR3732 (Brachman), and workers were at risk of both cutaneous and inhalation exposure. Indeed, during the course of the study, there was an "outbreak" of inhalation anthrax cases. See AR3733 (Brachman).

During the Brachman trial, twenty-six cases of anthrax were observed; twenty-one

---

[31]As explained supra n.15, when NIH licensed AVA in 1970, the review committee noted there were no clinical trials specifically involving MDPH's vaccine. See, e.g., AR3629. The record indicates the review committee did not rely upon the Brachman trial to provide clinical evidence of effectiveness for MDPH's product. See AR3635 (Jan. 6, 1969 memorandum). Both the Panel and FDA determined that this initial NIH view was incorrect, given the similarity of the PA-based vaccines, and that the Brachman study qualifies as a well-controlled study for purposes of determining AVA's effectiveness. See 50 Fed. Reg. at 51,058-59 (Panel); FDA Order at 259-61; cf. AR621 (Fellows) (Brachman study "demonstrated that a vaccine similar to AVA afforded a significant degree of protection to humans"); AR628 (Ivins, *Salisbury*) (in Brachman study "a vaccine similar to MDPH showed protection against anthrax"). It is FDA's determination, of course, which is due deference in this challenge, see, e.g., Serono, 158 F.3d at 1321 (courts owe deference to the "authorized decisionmaker for the agency on th[e] matter"), and FDA's conclusion is consistent with a 1996 guidance document setting forth FDA policy for accepting clinical trials completed on "comparable" products. See AR1382-83 (response to citizen petition); Berlex, 942 F.Supp. at 25. Indeed, plaintiffs' concession that AVA is effective for cutaneous exposure presumably is based on the Brachman study.

cutaneous and five inhalation. See FDA Order at 259. Of the five inhalation cases (four of which were fatal), "two received placebo and three were in the observational group." Id. None of the vaccinated workers contracted inhalation anthrax. Of the twenty-one cutaneous cases (some of which occurred in persons who were not completely inoculated), fifteen received placebo, three were in the observational group, and three received anthrax vaccine. See id. Comparing anthrax cases between the completely inoculated placebo and vaccine groups, Brachman, et al., calculated the vaccine efficacy at 92.5 percent. See id. As FDA noted, because the placebo group included two inhalation cases, this figure represented the "calculated efficacy of the vaccine to prevent all types of anthrax disease combined" (id.), i.e., "regardless of the route of exposure or manifestation of disease."[32] Id. at 260; accord AR3378 (IOM) ("[t]he overall effectiveness of the vaccine against anthrax infection generally was 92.5 percent"); AR628 (Ivins, *Salisbury*) (Brachman trial "showed protection against anthrax").

The Panel, as discussed above, misread the significance of Brachman, et al.'s effectiveness analysis, believing, erroneously, that the study authors analyzed effectiveness only with respect to cutaneous anthrax. See supra p. 16. Even so, the Panel did not, as this Court stated in its preliminary injunction opinion, find "insufficient data to license [AVA] for use against inhalation anthrax." Doe, 2003 WL 22994225 at *12. When the Panel issued its report, AVA was indicated for persons at risk of exposure to *B. anthracis*, and its label did not specify a

[32]As CDC noted in the original submission of its 1966 IND application, following the Brachman trial, all employees in the mills who received the placebo inoculations subsequently received anthrax vaccine. See AR3840. "No case of anthrax has occurred among individuals who have remained immunized as recommended." Id.

route of exposure. See AR3291-92.[33] The Panel recommended, and FDA agreed, that AVA, *as licensed*, be categorized as a Category I product (i.e. as safe, effective, and not misbranded). The Panel did not, for example, as it did with respect to other products under review, recommend that AVA be placed in different categories depending on its use (i.e., for cutaneous vs. inhalation exposure). Compare, e.g., 50 Fed. Reg. at 51,019 (Panel) (for Diphtheria Toxoid, Fluid, manufactured by Texas Department of Health Resources, recommending Category I "as regards its use for booster immunization" and Category IIIA "as regards its use for primary immunization"); id. at 51,021 (Panel) (for Tetanus Toxoid Adsorbed, manufactured by MDPH, recommending Category I "as regards its use for booster immunization" and Category IIIA "as regards its use for primary immunization") (license revoked in 2000 at request of MDPH); cf. id. at 51,102 (Panel) (for Streptokinase-Streptodornase products, recommending that some indications/presentations be placed in Category I, and other indications/presentations be placed in Category II or III).

Although FDA has noted that the five inhalation cases in the Brachman study "are too few to support an independent statistical analysis," FDA Order at 260; see also AR3743 (Brachman), those five cases accounted for nearly one-third of the total (eighteen) cases of inhalation anthrax reported in this country in the twentieth century. See AR3361 (IOM). And each of the inhalation cases in the Brachman study occurred in the placebo or observational groups. See FDA Order at 261. No vaccinated worker contracted inhalation anthrax (even at the

[33]AVA's package insert was amended in 1979. See Amd. Compl. ¶ 17. It is not clear whether the Panel considered this amended insert in issuing its report, see AR3290-94 (MDPH submitting original package insert to the Panel), but, as plaintiffs' amended complaint makes clear, the 1979 package insert, like the original package insert, stated that AVA was indicated based on risk, and did not specify a route of exposure. See Amd. Compl. ¶ 17.

mill where the outbreak occurred), and FDA concluded, based on this data, that the vaccine protected against inhalation exposure. See id. at 259-60. Thus, weighing the evidence in the aggregate, FDA concluded that the Brachman study provides proof of AVA's claim of effectiveness against *B. anthracis*: "the indication section of the labeling for AVA does not specify the route of exposure, and the vaccine is indicated for active immunization against *Bacillus anthracis*, independent of the route of exposure."[34] Id. at 260. Further clinical investigation of effectiveness, FDA noted, would be either impractical (given the low incidence of anthrax disease in nature) or unethical. Id. at 260 n.4; see also AR3381 (IOM) ("[c]ontrolled trials in which [human] subjects are exposed to potentially lethal agents such as anthrax spores are simply not ethical").

FDA pointed to other data and studies corroborating its effectiveness determination, such as the surveillance data collected by CDC on the occurrence of anthrax in at-risk industrial settings, which CDC summarized and presented to the Panel. See FDA Order at 260. Over thirteen years of observation (1962-1974), CDC identified twenty-seven anthrax cases; no cases (inhalation or cutaneous) were reported in "fully vaccinated" individuals. See 50 Fed. Reg. at 51,058 (Panel summary of CDC data). These data, FDA concluded, "provide confirmation that the risk of disease still existed for those persons who were not vaccinated and that those persons

[34]As noted supra pp. 10-11, the pathogenesis of *B. anthracis* is the same regardless of the route of exposure. That is, however *B. anthracis* enters the body, to produce active toxins, protective antigen binds to cellular receptors which then bind with either edema factor or lethal factor; AR3366-67 (IOM); the resulting toxin (EF or LF) can then enter the cell, leading to damage. Id. at AR3367 & Figure 2-4. AVA creates antibodies to protective antigen. See AR639 (package insert); AR3396 (IOM) ("the available data indicate that immunity to anthrax is associated with the presence of antibodies to PA, such as those stimulated by the anthrax vaccine").

who had not received the full vaccination series (six doses) were susceptible to anthrax infection, while no cases occurred in those who had received the full vaccination series." FDA Order at 260.

FDA's effectiveness determination also is corroborated by the IOM report. The IOM committee, charged by Congress to consider the "inhalation efficacy of the vaccine," H.R. Rep. No. 106-371, at 254 (1999), specifically concluded that "AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalation anthrax." AR3323 (IOM); see also FDA Order at 260. In addition to considering the Brachman study and human serological studies, see AR3377-80, the IOM committee reviewed studies in animal models. See, e.g. AR3385-88 (IOM). After noting that "the pathology of anthrax in nonhuman primates such as macaques best mimics that seen in humans after inhalation exposure to *B. anthracis*," AR3385, the IOM committee concluded: "it appears that AVA is effective in protecting . . . macaques . . . from inhalation exposure to the strains of anthrax tested." AR3387-88 (IOM).

FDA, citing several animal studies in its Order, see FDA Order at 260 n.5, stated its "agree[ment] with the [IOM] report's finding that studies in humans and animal models support the conclusion that AVA is effective against *B. anthracis* strains that are dependent upon the anthrax toxin as a mechanism of virulence, regardless of the route of exposure." Id. at 260; see also AR626 (Fellows) (animal study) ("[t]hese results confirm previous reports showing that AVA is highly protective in this non-human primate animal model [rhesus macaques]"); AR629 (Ivins, *Salisbury*) (animal study) ("[t]he data in this study demonstrates that the MDPH vaccine is

highly efficacious against inhalation anthrax in rhesus monkeys").[35]

Moreover, FDA's determination is fully consistent with the benefit-to-risk ratio FDA generally applies in evaluating the safety and effectiveness of biological products. See discussion supra p. 9 (noting that risk/benefit analysis requires FDA to determine whether the benefits of the product outweigh the risks of the product for the intended population).[36] The benefits of AVA are clear: it is the *only* vaccine licensed to provide immunity against *B. anthracis*, see AR3308, AR3322 (IOM), a rarely-occurring, but potentially deadly, disease; see AR3363-66 (IOM); its effectiveness has been established in a well-controlled field trial; see FDA Order at 259-60; and, while ethical considerations and the "low incidence and sporadic occurrence of anthrax disease" make "further adequate and well-controlled clinical studies of effectiveness not possible," FDA Order at 260 n.4; see also AR1381, strong corroborating data exist. See FDA Order at 260 & n.5. In terms of risk, AVA is associated with local injection site reaction, but, as the IOM report noted, "these immediate reactions, and the rates at which they occur, are comparable to those observed with other vaccines regularly administered to adults."

---

[35]In their amended complaint, plaintiffs allege that "FDA's reliance on studies involving animal data to support its conclusion that the AVA is effective against inhalation anthrax is inappropriate and violates its own regulations." Amd. Compl. ¶ 88. Plaintiffs apparently believe that FDA relied on animal studies to "substantiate [AVA's] effectiveness" for purposes of 21 C.F.R. § 601.25(d)(2). It did not. FDA relied on Brachman, et al.'s controlled clinical investigation as "[p]roof of effectiveness" for purposes of Section 601.25(d)(2). See FDA Order at 259-60. The animal studies, CDC surveillance data, and other supportive data and studies were considered as corroborating evidence.

[36]See also 21 C.F.R. § 601.25(d)(3) (FDA must consider the "benefit-to-risk ratio of a biological product . . . in determining safety and effectiveness"); 50 Fed. Reg. at 51,005 (Panel) ("concept of risks and benefits is a fundamental one in a consideration of vaccines"); id. at 51,006 (Panel) (noting that "[g]reater risks of adverse effects might be tolerated for a vaccine that provided protection against a lethal disease than for a vaccine against a disease that is basically benign").

AR3323 (IOM). Given the highly lethal nature of the anthrax disease, there can be no serious question that AVA's benefits outweigh its risks for the intended population — those at risk of exposure to *B. anthracis*. See, e.g., Rutherford, 442 U.S. at 555 ("the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use").

At bottom, FDA weighed all of the scientific evidence and concluded, based on the data to which it applied its expertise, that AVA is effective for active immunization against *Bacillus anthracis*, regardless of the route of exposure. See FDA Order at 260. We acknowledge that the Court, in its preliminary injunction opinion, suggested a contrary conclusion, but FDA is the expert agency charged by Congress with making effectiveness determinations; having rendered that determination, the Court "may not substitute its own judgment for that of the FDA." Berlex, 942 F.Supp. at 25; see also Doe, 2003 WL 229943225 at *12 (noting the "Court could properly defer to [FDA] in determining AVA's status as an investigational drug"); January 7, 2004 Order at 1 (noting "the principle reason for the issuance of the injunction has been addressed" by FDA's final order "categorizing AVA as safe and effective for use against inhalation anthrax").

FDA plainly has "examined the relevant data and articulate[d] a satisfactory explanation for its action including a rational connection between the facts found and the choice made." Bristol-Meyers, 923 F.Supp. at 219-20 (quoting State Farm, 463 U.S. at 43) (alteration in original) (internal quotations omitted). It considered the relevant factors, and made no "clear error of judgment." State Farm, 463 U.S. at 43. Nothing more is required. Its decision should be upheld.[37]

---

[37]Plaintiffs' assertion (Amd. Compl. at ¶¶ 87, 90) that FDA issued its Order in "bad faith" is meritless. There is a well-established presumption of regularity accorded official acts, including, of course, the acts of agencies. See, e.g., United States Postal Serv. v. Gregory, 534

## CONCLUSION

For all the foregoing reasons, the Court should grant summary judgment for defendants with respect to plaintiffs' APA claims challenging the legality of the FDA Order. Moreover, because the Order confirms the safety and effectiveness of AVA, DoD's use of the vaccine is not subject to 10 U.S.C. § 1107;[38] to the extent plaintiffs challenge DoD's vaccine program based on a claim that AVA's approval is invalid, those claims also must be dismissed.

Respectfully submitted,

PETER D. KEISLER
Assistant Attorney General

ROSCOE C. HOWARD, JR.
United States Attorney

BRIAN D. BOYLE
Principal Deputy Associate Attorney General

---

U.S. 1, 10 (2001) ("a presumption of regularity attaches to the actions of Government agencies"); Bristol-Myers, 923 F.Supp. at 216 (noting the "'presumption in favor of the validity of administrative action'") (internal citation omitted). The presumption of regularity requires that, "in the absence of clear evidence to the contrary, courts presume that [government officials] have properly discharged their official duties." United States v. Chemical Found., Inc., 272 U.S. 1, 14-15 (1926); see also, e.g., United States v. Armstrong, 517 U.S. 456, 464 (1996) (quoting this statement from Chemical Foundation). There is *no* evidence — let alone "clear evidence" — that the challenged portions of the Order were the product of bad faith.

[38]Although DoD's AVIP is not at issue in this brief, we note that Congress has enacted legislation concerning AVIP, and that these laws reflect Congress's acceptance of AVIP's mandatory program of immunization against inhalation exposure. See 10 U.S.C. § 1110 (requiring DoD to establish uniform procedures for exemptions from AVIP for administrative or medical reasons); id. § 1178 (requiring an annual report on the number of military members separated due to refusals to participate in AVIP); id. § 1580a (requiring notification of emergency-essential civilian employees required to participate in AVIP). Indeed, Congress mandated the independent study of AVA's safety and effectiveness in response to "concerns about the anthrax vaccine and AVIP." AR3324 (IOM). The IOM committee, as noted above, specifically concluded that "AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalation anthrax." AR3323 (IOM).

SHANNEN W. COFFIN
Deputy Assistant Attorney General

*/s/ Craig M. Blackwell*
JOSEPH H. HUNT
VINCENT M. GARVEY
CRAIG M. BLACKWELL, DC Bar # 438758
RONALD J. WILTSIE
ANDREW H. TANNENBAUM
Attorneys
Civil Division
U.S. Department of Justice
P.O. Box 883
Washington, D.C. 20044
Tel: (202) 307-1401
Fax: (202) 616-8470

Attorneys for defendants

Date: March 3, 2004