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

Civil Action No. 03-707(EGS)

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

2003 U.S. Dist. Ct. Motions 707; 2004 U.S. Dist. Ct. Motions LEXIS 6275

April 21, 2004

Motion for Summary Judgment

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TITLE: REPLY MEMORANDUM IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT

TEXT: PRELIMINARY STATEMENT

Our opening brief established that the Final Order of the Food and Drug Administration ("FDA") categorizing Anthrax Vaccine Adsorbed ("AVA") [**3] as a Category I, safe and effective, biological product, see Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review ("FDA Order" or "Order"), *69 Fed. Reg. 255* (Jan. 5, 2004), is reasonable, supported by the administrative record, and not arbitrary, capricious, or an abuse of discretion for purposes of the Administrative Procedure Act, *5 U.S.C. §§ 551*, et seq. ("APA"). n1 Plaintiffs' short opposition brief offers nothing to rebut our showing. In fact, plaintiffs' opposition is based on a fundamental misunderstanding of the nature of the Court's role in this case.

n1 We refer to the briefs filed thus far as follows: "Def. Br." (for defendants' opening summary judgment brief); "Def. Opp." (for defendants' opposition to plaintiffs' motion for summary judgment); "P1. Br." (for plaintiffs' opening summary judgment brief); and "P1. Opp." (for plaintiffs' opposition to defendants' motion for summary judgment).

Plaintiffs' argument rests almost [**4] *entirely* on an extra-record declaration and unpublished manuscript prepared for plaintiffs for purposes of this litigation by a professor of family studies. The Court may not consider these materials. The claims before the Court on summary judgment arise solely under the APA, and judicial review is limited to the administrative record. Plaintiffs offer no credible reason for supplementing that record with a litigation affidavit attacking the merits of FDA's decision. Nor could they. FDA is the expert agency charged by Congress with reviewing the safety and effectiveness of biological products like AVA, and it is FDA, not plaintiffs' "expert," to which the Court must defer.

Plaintiffs actually chide defendants for reviewing, in our opening brief, the "numbing detail of the alleged FDA review," P1. Opp. at 3, as if the specifics and rationale of FDA's decision, and its underlying scientific basis in the administrative record, are somehow not [*2] relevant here. But again, plaintiffs misunderstand the nature of the Court's review. Under the APA, the focal point for review *is* the agency record, and the only question before the Court is whether the agency has considered the [**5] 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. FDA's licensing decision, we have explained, easily satisfies that standard.

Plaintiffs' challenge in this case has been steadily shrinking since they filed this action over a year ago. Notwithstanding the rhetoric in their brief (see, e.g., P1. Opp. at 1), plaintiffs do not challenge AVA's safety for human use. Plaintiffs also do not challenge AVA's effectiveness for use against cutaneous anthrax. Now, in their latest brief, plaintiffs rest their challenge to AVA's inhalation effectiveness principally on extra-record materials the Court is precluded from considering. Plaintiffs, in the end, simply have no response to defendants' showing that FDA's decision to confirm AVA's license is rational, supported by the administrative record, and certainly not arbitrary or capricious. In its preliminary injunction opinion, the Court stated it could "properly defer" to FDA in determining AVA's status. See *Doe v. Rumsfeld, 297 F. Supp. 2d 119, 133 (D.D.C. 2003);* see also *id at 131* (noting that, [**6] "at bottom," the question of AVA's status "turns on whether the FDA has made a final decision"). FDA has now rendered its decision. The Court, accordingly, should defer to that reasonable decision, and grant defendants' motion for summary judgment.

[*3] **ARGUMENT**

FDA'S EFFECTIVENESS DETERMINATION IS NOT ARBITRARY, CAPRICIOUS, OR AN ABUSE OF DISCRETION

We established in our opening brief that FDA's effectiveness determination is reasonable, supported by the administrative record, and not arbitrary, capricious, or an abuse of discretion. See Def. Br. at 35-42. Plaintiffs offer three brief arguments in response, contending that: (i) the controlled clinical investigation conducted by Drs. Brachman, Gold, Plotkin, Fekety, Werrin, and Ingraham ("Brachman" or "Brachman study") does not support FDA's determination that AVA is effective (see P1. Opp. at 5-8); (ii) FDA improperly "relied" on animal data in support of its effectiveness conclusion (see id. at 8-10); and (iii) AVA is not comparable to the original Department of Defense ("DoD") anthrax vaccine which Brachman, et al., used in their study. See id. at 10-12. Each argument is meritless. [**7]

A. The Brachman Study Provides Proof of AVA's Effectiveness

Plaintiffs claim FDA wrongly relied on the Brachman study for effectiveness because the study produced "insufficient evidence . . . to determine if the [anthrax] vaccine was effective against inhalation anthrax." PL Opp. at 5. This argument is based almost exclusively on an extra-record declaration and unpublished manuscript submitted by Dr. Walter R. Schumm, Professor of Family Studies at Kansas State University. See Pl. Opp., Ex. 1, Declaration of Dr. Walter R. Schumm ("Schumm Dec."); P1. Opp., Ex. 1-A, "A Statistical Reanalysis of the Relationship Between Anthrax Vaccination and Anthrax Infections in Goat Hair Mills in the 1950s" ("Schumm Ms."); P1. Opp., Exs. 1-B, 1-C (extra-record materials attached to Dr. Schumm's declaration); see also Pl. Opp. at 6-8. Dr. Schumm prepared these

materials at [*4] plaintiffs' request for their use in this litigation. See, e.g., Schumm Dec. at 3, P 3 ("I have been asked to comment on the study that serves as the scientific underpinning of the FDA's arguments before this Court on the legal status of the currently licensed anthrax vaccine"). These extra-record [**8] materials are not part of the administrative record and may not be considered by the Court.

It is a fundamental rule of administrative law that, in an APA challenge, "the focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court." *Camp v. Pitts, 411 U.S. 138, 142 (1973).* The D.C. Circuit has "repeatedly applied" this rule "to bar introduction of litigation affidavits to supplement the administrative record." *AT&T Info. Sys., Inc. v. G.S.A., 810 F.2d 1233, 1236 (D.C. Cir. 1987)* (applying rule in review of informal agency proceeding to bar agency attempt to "offer post-hoc rationalizations"). And courts in this district have specifically applied this rule to bar consideration of litigation affidavits in cases involving FDA. See *Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166, 177 & n.7 (D.D.C. 2000)* (refusing to consider extra-record affidavits "showing significant disagreements among scientific experts"); *Berlex Labs., Inc. v. F.D.A., 942 F. Supp. 19, 23 (D.D.C. 1996)* ("affidavits submitted by Berlex have not been considered, [**9] nor are they deemed to be part of the record in this case").

Plaintiffs do not even mention the law on this point. They merely note, half-heartedly and in a footnote, that courts may, in narrow circumstances, permit plaintiffs to "supplement" an agency's administrative record with extra-record materials. See P1. Opp. at 6 n.3. But the grounds plaintiffs cite -- under which courts may permit supplementation where "the agency either deliberately excluded from the record evidence adverse to its position, or was negligent in failing to include such documents" (id) -- have no application here. Dr. Schumm's declaration [*5] and (unpublished) manuscript were prepared in April and March, 2004, respectively, well *after* FDA issued its Order and submitted the administrative record in this case. See FDA Order at 255 (published January 5, 2004); Docket # 33 (February 2, 2004, notice of filing of the administrative record). FDA, *by definition*, could not have considered these materials or included them in the administrative record.

Moreover, plaintiffs have submitted the Schumm materials for the sole purpose of challenging the merits of FDA's effectiveness determination. [**10] See Pl. Opp. at 6-8; Schumm Dec. at 10. Again, it is a basic principle of administrative law that courts may not examine extra-record evidence to determine the correctness of an agency decision. *Environmental Def. Fund, Inc. v. Costle, 657 F.2d 275, 286 & n.37 (D.C. Cir. 1981)* ("a judicial venture outside the record . . . *can never*, under Camp v. Pitts, examine the propriety of the decision itself) (emphasis added): accord *National Treasury Employees Union v. Hove, 840 F. Supp. 165, 169 (D.D.C. 1994)* ("consideration of outside evidence' to determine the correctness or wisdom of the agency's decisions *is not permitted*") (emphasis added) (internal citation omitted); *Doraiswamy v. Secretary of Labor, 555 F.2d 832, 842 (D.C. Cir. 1976)* (affirming denial of discovery where plaintiffs challenged "the correctness" of the agency's decision as opposed to the "fullness of the reasons" given). n2 For all these reasons, the Court may not consider plaintiffs' extra-record materials.

n2 In *Esch v. Yeutter, 876 F.2d 976 (D.C. Cir. 1989),* the D.C. Circuit noted, in dicta, that one instance in which courts have permitted supplementation of an agency record is where "evidence arising after the agency action shows whether the decision was correct or not." See *id. at 991.* The contours of this exception are unclear, but it plainly has no relevance here. Plaintiffs are not seeking to supplement the record with "evidence" arising after FDA issued its Order; rather, they are seeking to add to the record their expert's "reanalysis" of a study published in 1962.

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[*6] Plaintiffs do cite two record sources in support of their assertion that the Brachman study failed to assess the protective effect of the anthrax vaccine against inhalation anthrax -- the Brachman study itself and the report of the Panel on Review of Bacterial Vaccines and Toxoids ("Panel"). See P1. Opp. at 5-6. But with respect to the Brachman study, Brachman, et al., specifically *included* two cases of inhalation anthrax in their effectiveness calculation. See

AR3736-37 & Table 4 (Brachman); see also Def. Br. at 15-17, 36-39 (explaining this point). Thus, far from "repudiat[ing] any conclusion about the effectiveness of AVA against inhalation anthrax" (P1. Opp. at 6), the study authors calculated the effectiveness of the vaccine to prevent all types of anthrax disease, regardless of the route of exposure (which they calculated at 92.5 percent). See FDA Order at 259-60. n3

> n3 Indeed, even plaintiffs' expert acknowledges that "the Brachman field trial is accepted by scholars as the cornerstone of the arguments favoring efficacy of anthrax vaccine for preventing cutaneous or inhalational anthrax in humans." Schumm Ms. at 15; see also id at 4-6 (citing articles, including a recent publication authored in part by Dr. Brachman, observing that the Brachman study showed effectiveness against anthrax generally).

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It is true, as we have explained (see Def. Br. at 16-17), that the Panel, although recommending that AVA be placed in Category I, failed to recognize that Brachman, et al., included inhalation cases in their effectiveness calculation. But that Panel mistake has no relevance here; plaintiffs acknowledge (as they must) that the calculation actually included inhalation cases. See Pl. Opp. at 6. Plaintiffs, in fact, attempt to dismiss the inclusion of inhalation cases as a "mistake." See id But this only shows plaintiffs' continued failure to grasp the significance of Brachman et al.'s analysis.

The Brachman study was designed to gauge the *overall* effectiveness of the vaccine against the anthrax bacterium, *Bacillus anthracis*. Thus, the study was conducted in "a [*7] susceptible industrial population known to be chronically exposed *to anthrax*." AR3732 (Brachman) (emphasis added). There is no question that inhalation was one of the routes of exposure included in the study. See, e.g., AR3736 (Table 4) (categorizing observed anthrax cases in part by the "site of lesion"); AR3740-41 (Table 8) (including inhalation cases in effectiveness calculation). [**13] Indeed, during the study period, there was an "outbreak" of inhalation anthrax (see AR3733), which accounted for *nearly one-third* (five) of the total (eighteen) cases of inhalation anthrax reported in this country in the twentieth century. See AR3361 (IOM). But none of the recipients of the vaccine contracted inhalation anthrax. See AR3736 (Table 4) (Brachman).

At bottom, the most plaintiffs can say is that the number of inhalation cases observed in the Brachman study are too few to support an independent statistical analysis. n4 This is true enough; FDA noted this point in its Order. See FDA Order at 260; see also AR3743 (Brachman) (making a similar observation). But, FDA observed, the inhalation results, viewed separately, are wholly consistent with the cutaneous results (which were independently significant). Of the five reported inhalation cases, "two occurred in the placebo group, three occurred in the observational group, and no cases occurred in the vaccine group." FDA Order at 260. Thus, weighing the evidence in the aggregate, FDA concluded:

> the indication section of the labeling for AVA does not specify the route of exposure, and the vaccine [**14] is indicated for active immunization against *Bacillus* [*8] *anthracis*, independent of the route of exposure.

Id. This conclusion is consistent with Brachman, et al.'s conclusion, n5 and with the pathogenesis of the anthrax bacterium (which suggests that the immune response induced by AVA would be protective regardless of the route of exposure). See Def. Br. at 10-11, 39 n.34. Moreover, there is no contrary clinical data. FDA's determination on this point falls "'squarely within the ambit of [its] expertise and merits deference'" from the Court. *Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 220 (D.D.C. 1996)* (quoting *Schering Corp. v. FDA, 51 F.3d 390, 399* (3d Cir.), cert, denied, *516 U.S. 907 (1995))*. It is reasonable, supported by the administrative record, and should be upheld. n6

> n4 This is the ultimate conclusion of plaintiffs' expert, see Schumm Dec. at 5, P 4.b, although even he acknowledges that the inhalation outbreak was a "more rigorous challenge," Schumm Ms. at 33, which "fortuitously allow[ed] all employees in the experimental group enough time to receive at least three

inoculations before the epidemic began." Id. As we have noted, the vaccine withstood this "rigorous challenge," and none of the employees in the vaccine group contracted inhalation anthrax.

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n5 See AR3737; see also AR3744 (concluding paragraph on effectiveness, which does not specify a route of exposure) ("An anthrax vaccine was clinically and epidemiologically evaluated in an exposed, susceptible, supervised population. Twenty-six cases occurred among the population during the evaluation period. Four cases occurred in individuals who had incomplete inoculations. Of the remaining 22 cases, 15 occurred in placebo-inoculated employees, six in uninoculated employees, and one in a vaccine-inoculated employee. The data indicate that the vaccine has an effectiveness of 92.5 per cent with a lower 95 per cent confidence limit of 65 per cent.").

n6 We note, briefly and for the sake of completeness, that Dr. Schumm's "statistical reanalysis" of the Brachman study in no way undercuts FDA's effectiveness determination. Dr. Schumm does not hold a degree in statistics, see Schumm Dec. at 1, P 1; compare AR3736 (Brachman) (noting that Brachman, et al.'s statistical analysis was performed by the chief of the Statistics Section, Epidemiology Branch, Communicable Disease Center), and his analysis -- which is unpublished, see Schumm Dec. at 4, P 4, and apparently has not been peer-reviewed -- is substantively flawed. For example, his manuscript "reanalyzes" the data in the Brachman study mill-by-mill, concluding that, at three of the four mills participating in the study, the data was not independently "statistically significant." See Schumm Ms. at 28. But there is no indication that the study was designed to produce statistically significant results at each mill; rather, Brachman, et al., likely included multiple sites *precisely because* they wanted a sample size that, *in the aggregate*, would produce statistically significant results. This approach is typical of multi-site clinical trials, where the primary result ordinarily is the overall result, not the result in each site separately. Indeed, Dr. Schumm's analysis of the overall result, although using a different statistical methodology, is fully consistent with Brachman, et al.'s effectiveness calculation. See Schumm Ms. at 29 ("overall, combining all four mills, the Fisher's Exact Test was significant"). Moreover, the site-specific data presented by Dr. Schumm (see id. at 28, Table 11), although perhaps not "statistically significant," are fully supportive of the study's powerful *overall* conclusion, which formed the basis for FDA's effectiveness determination.

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[*9] B. FDA's Consideration of Corroborating Evidence of Effectiveness Was Appropriate

It is not clear why plaintiffs continue to press their point that FDA somehow erred in considering the Institute of Medicine ("IOM") Committee's findings with respect to animal data and the three animal studies cited in the Order. See P1. Opp. at 8-10. n7 Plaintiffs appear to acknowledge -- contrary to the statements in their opening brief (see P1. Br. at 15) -- that FDA relied on the Brachman study for proof of effectiveness under *21 C.F.R. § 601.25(d)(2)*, and considered the IOM Committee's findings and certain animal studies as corroborating evidence of effectiveness. See P1. Opp. at 9; see also FDA Order at 260 ("FDA agrees with the [IOM] report's finding that studies in humans and animal models support the conclusion that AVA is effective against *B. anthracis* . . . regardless of the route of exposure"); Def. Opp. at 19-21 (addressing this point at length).

n7 We reiterate our argument (see Def. Br. at 43 n.38) that, although DoD's vaccination program (AVIP) is not at issue in this brief, Congress specifically charged the IOM Committee with studying AVA's safety and effectiveness, and the Committee specifically concluded that "AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalational anthrax." AR3323 (IOM). Given this IOM Committee conclusion, and the various statutes reflecting Congress's ratification of DoD's mandatory program of

immunization against inhalation exposure (e.g., *10 U.S.C. § 1110* (requiring Secretary of Defense to establish "uniform procedures" for "administrative or medical" exemptions from AVIP); id § 1178 (requiring heads of military departments to track and report to Congress separations of service members due to their refusal to participate in AVIP)), we continue to maintain that the general provisions of *10 U.S.C. § 1107* cannot be applied to constrain DoD's AVIP.

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Having acknowledged this point, plaintiffs' argument is reduced entirely to their contention that, because (they say) the Brachman study does not provide proof of effectiveness, "the government's reliance on animal data for any corroboration is improper." P1. Opp. at 9. [*10] *That* argument, however, is fully answered by our showing supra. Part A. Plaintiffs' contention with respect to FDA's consideration of the IOM Committee's findings and animal studies thus has no independent force, and should be rejected.

Plaintiffs also acknowledge that FDA considered the Panel's summary of the CDC surveillance data as corroborating evidence of effectiveness. See P1. Opp. at 9; see also FDA Order at 260 (noting these data "provide confirmation"); Def. Br. at 17, 22, 39-40 (describing these data). Nevertheless, plaintiffs, through Dr. Schumm, argue that the summarized surveillance data are "entitled to no weight whatsoever" (P1. Opp. at 7) because they were "much less well controlled than the Brachman" study. Schumm Dec. at 7, P 5.c. This is wrong. FDA may rely on "partially controlled or uncontrolled" data as corroborating evidence of effectiveness, see *21 C.F.R.* [**18] *§ 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"), and its consideration of the Panel's summary of the CDC surveillance data was thus entirely appropriate.

C. FDA Properly Determined That AVA Is Comparable to the DoD Vaccine

Finally, plaintiffs argue that FDA erred in relying on the Brachman study for proof of effectiveness because the Brachman study used a predecessor anthrax vaccine (the DoD vaccine manufactured at Fort Detrick). See Pl. Opp. at 10-12. We have fully addressed this argument in our previous filings, and have explained that FDA properly concluded, based on its review of the record evidence, that AVA is comparable to the original DoD vaccine used in the Brachman study. See FDA Order at 260-61; Def. Br. at 21-22 at n.23; Def. Opp. at 22. We do not repeat those arguments here, but rather address the one new argument plaintiffs raise.

[*11] Plaintiffs acknowledge FDA's comparability policy -- under which a manufacture may use data gathered with a previous version of a product to support [**19] the effectiveness of a comparable version of the same product after a manufacturing change -- but argue that the policy only allows "a *single* manufacturer to make manufacturing changes to a product without performing additional clinical studies." P1. Opp. at 10 (emphasis in original). This is wrong. Although FDA's policy is addressed in parts to manufacturers contemplating a manufacturing change, nothing in the policy states that it is limited to changes undertaken by a single manufacturer. See generally AR1399-1406 (comparability policy). n8 And FDA does not interpret the policy as being limited in this way. See *Berlex, 942 F. Supp. at 25* ("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"). Indeed, in Berlex. which plaintiffs cite in support of their position (see Pl. Opp. at 11), the court upheld FDA's determination to "allow[] Biogen [the product manufacturer] to rely on the results of a clinical study of another company's . . . product." See *942 F. Supp. at 22, 25;* see also [**20] *id. at 22* (noting, as well, that Biogen was a part owner of the other company, a joint venture, which failed and went into receivership).

n8 For example, the policy states generally that, "for manufacturing changes prior to product approval," FDA regulations permit the approval of biological products on the basis of "clinical data generated from a precursor product, made prior to a manufacturing change, so that the manufacturer can demonstrate that the

precursor product is comparable to the manufactured product." AR1402.

As FDA's comparability policy makes clear, the manufacturing process for a biological product is critical, and biological products often are defined by that process. See AR1401. Thus, if two or more entities, working together, share the critical manufacturing process information -- as [*12] Biogen did with the joint venture in Berlex, and as DoD did with Merck Sharp & Dohme and with the Michigan Department of Public Health concerning AVA -- such products may be [**21] deemed comparable under FDA's policy. That, presumably, is why plaintiffs have conceded that AVA is lawfully approved 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 at 4 n.4. Indeed, that concession, which presumably is based on the Brachman study, is hopelessly inconsistent with plaintiffs' argument that AVA is not comparable to the DoD vaccine. For all these reasons, and those we previously have explained, that argument should be rejected. n9

n9 Finally, we note that plaintiffs, in their summary judgment motion, asserted they should be entitled to "discovery before summary judgment is accorded to the defendants" in the event their own motion for summary judgment is denied. See Pl. Br. at 20. In their opposition brief, however, plaintiffs did not argue that they needed discovery in order to oppose defendants' motion for summary judgment (which they opposed on the merits). Nor did plaintiffs follow the procedures in *Fed. R. Civ. P. 56(f)* for seeking such relief. This is yet another reason for rejecting plaintiffs' discovery argument. See *James Madison Ltd. v. Ludwig, 82 F.3d 1085, 1096 (D.C. Cir. 1996),* cert denied, *519 U.S. 1077 (1997);* see also Def. Opp. at 25-30 (setting forth defendants' other arguments for rejecting plaintiffs' discovery contention).

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[*13] **CONCLUSION**

For all the foregoing reasons, the Court should grant defendants' motion for summary judgment.

Respectfully submitted,

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