United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued February 10, 2006 Decided August 11, 2006

No. 05-5137

ALPHARMA, INC.,
APPELLANT

v.

MICHAEL O. LEAVITT, SECRETARY, HEALTH AND HUMAN SERVICES, ET AL.,
APPELLEES

Appeals from the United States District Court
for the District of Columbia
(No. 83cv01603)

Douglas J. Behr argued the cause for appellant. With him on the briefs was *John B. Dubeck.*

Suzette A. Smikle, Attorney, U.S. Department of Justice, argued the cause for appellees. With her on the brief were *Peter D. Keisler*, Assistant Attorney General, *Eugene M. Thirolf*, Director, and *Drake Cutini*, Attorney.

Before: GARLAND, *Circuit Judge*, and SILBERMAN and WILLIAMS, *Senior Circuit Judges*.

Opinion for the court filed by Circuit Judge GARLAND.

Opinion concurring in part and dissenting in part filed by *Senior Circuit Judge* WILLIAMS.

GARLAND, Circuit Judge: This is the second time we have heard an appeal in this matter. In our first opinion, we concluded that the Food and Drug Administration (FDA) had failed to adequately explain why it granted Philips Roxane, Inc.'s "new animal drug application" for bacitracin zinc.[1] *See A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1486 (D.C. Cir. 1995). In this opinion, we conclude that the explanation the FDA offered on remand adequately addressed the questions raised in our first opinion. Nonetheless, we agree with appellant Alpharma, Inc.[2] that the FDA's explanation raises new problems and apparent contradictions that, unfortunately, require yet another remand.

I

The "tortured story" of this case is recounted at length in our previous opinion, *A.L. Pharma*, 62 F.3d at 1486, and in two district court opinions, *A.L. Pharma, Inc. v. Thompson*, No. 83-1603, Mem. Op. (D.D.C. Feb. 4, 2005), and *A.L. Labs. v. Shalala*, No. 83-1603, 1993 U.S. Dist. LEXIS 21357 (D.D.C. Dec. 21, 1993). We retell it only briefly here.

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[1]The parties alternatively refer to the drug as "bacitracin zinc" and "zinc bacitracin." We follow the convention established in our previous opinion, *A.L. Pharma*, 62 F.3d at 1486, and use "bacitracin zinc."

[2]Alpharma brought suit in the district court under the names of its predecessors, A.L. Laboratories, Inc. and A.L. Pharma, Inc. This opinion refers to petitioner by its current name.

Under the Food, Drug, and Cosmetic Act (the "Act"), a manufacturer must apply to the FDA for approval to market a new animal drug. 21 U.S.C. § 360b. To gain approval, a manufacturer must submit a "new animal drug application" (NADA) demonstrating that the drug is both safe and effective under the conditions "prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 360b(d)(1)(A) & (E); *see id*. § 360b(a)(1) & (b)(1); 21 C.F.R. § 514.1.

In the early 1970s, the Animal Health Institute, an industry trade association, coordinated a safety study on bacitracin zinc. There is no dispute that the study provided an adequate basis for the FDA's subsequent conclusion that Philips Roxane's bacitracin zinc product met the Act's safety requirements. *See A.L. Pharma*, 62 F.3d at 1486. The study did not, however, address the statute's efficacy requirement.

The FDA has allowed manufacturers of certain classes of drugs to establish a drug's efficacy by using a "regulatory shortcut" known as "bioequivalency." *A.L. Pharma,* 62 F.3d at 1488. The agency determined that, for those classes, applicants did not need to conduct their own field studies to prove that their products were effective. Instead, an applicant could establish a generic drug's efficacy by demonstrating that it was "bioequivalent" to a "benchmark" drug that the FDA had already found to be effective for the same intended uses. *See id*. at 1487; *see also Tri-Bio Lab., Inc. v. United States*, 836 F.2d 135, 138-39 (3d Cir. 1987).

In July 1970, the FDA found that bacitracin zinc products were effective for increased rate of weight gain and improved feed efficiency in poultry. *See* Bacitracin With or Without Penicillin; Drugs for Veterinary Use; Drug Efficacy Study Implementation, 35 Fed. Reg. 11,531 (July 17, 1970). Based on that finding, the FDA permitted applicants submitting NADAs

for bacitracin zinc intended for those uses to establish the efficacy of their products by showing they were "bioequivalent" to the benchmark drugs upon which the FDA had based its initial finding. *See* New Animal Drugs for Use in Animal Feeds; Bacitracin Zinc; NAS/NRC Update, 46 Fed. Reg. 37,043, 37,044 (July 17, 1981) (codified at 21 C.F.R. § 558.78).

On May 28, 1981, Philips Roxane submitted an application to the FDA for approval of its generic version of bacitracin zinc. To establish bioequivalence, Philips Roxane's application, which the FDA designated as NADA 128-550, relied on a 1978 study conducted by Dr. John Prescott of the University of Guelph in Ontario, Canada ("Prescott Study"). Prescott tested the Philips Roxane product alongside a benchmark drug produced by International Minerals & Chemical Corp. The study was designed to determine whether the two were equally effective in treating experimentally-induced necrotic enteritis in a population of chickens when administered at a single dosage. *See* New Animal Drugs for Use in Animal Feeds; Bacitracin Zinc, 47 Fed. Reg. 35,187 (August 13, 1982); *see also* Prescott Aff. ¶ 4 (J.A. 98). Prescott concluded that the two drugs were equally effective for that purpose. *See* Prescott Aff. ¶ 4.

On August 13, 1982, the FDA approved NADA 128-550. Based on the Animal Health Institute study, the agency determined that Philips Roxane's bacitracin zinc product was safe. *See A.L. Pharma*, 62 F.3d at 1486. Based on the Prescott Study, it found that Philips Roxane's product was bioequivalent to the International Minerals benchmark. *See* 47 Fed. Reg. at 35,187. And based on the finding of bioequivalence, the agency concluded that Philips Roxane's bacitracin zinc was effective for increasing weight gain and improving feed efficiency in broiler chickens. *Id*.

Appellant Alpharma manufactures an approved bacitracin zinc product that is similar to the product covered by NADA 128-550. After Philips Roxane's application was granted, Alpharma filed four "citizen petitions" asking the FDA to revoke its approval of NADA 128-550.[3] The agency rejected all four petitions. On June 6, 1983, Alpharma brought suit in the United States District Court for the District of Columbia under the Administrative Procedure Act (APA), 5 U.S.C. § 701 *et seq*., challenging the FDA's approval of NADA 128-550. The district court granted the FDA's motion for summary judgment on December 21, 1993, and Alpharma appealed.

Alpharma's appeal disputed the FDA's conclusion that the Prescott Study established bioequivalence between the Philips Roxane product and the benchmark drug.[4] Alpharma relied on affidavits and letters submitted by sixteen "highly credentialed scientists, all of whom questioned the bioequivalency conclusion." *A.L. Pharma*, 62 F.3d at 1488; *see id*. at 1490. Alpharma asserted that the "unanimous views of these experts conclusively establish[ed] that the FDA acted arbitrarily and thus illegally when it refused to rescind its approval of the NADA." *A.L. Pharma*, 62 F.3d at 1490. Alpharma offered two principal criticisms of the Prescott Study.

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[3]FDA regulations permit any "interested person" to "petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action." 21 C.F.R. § 10.25(a); *see* 21 C.F.R. § 10.30.

[4]Alpharma also contended that the FDA had failed to follow its regulations with respect to the use of certain safety data in Philips Roxane's application. We resolved that issue in the FDA's favor, *A.L. Pharma*, 62 F.3d at 1490, and it is not at issue on this appeal.

Alpharma's first contention was that a comparison of the two products' relative effectiveness for the purpose of fighting a disease (necrotic enteritis) was not a proper measure of bioequivalence for the purpose of promoting growth rates and feed efficiency -- the product's intended use. The FDA responded that it had already determined the benchmark product's efficacy for the latter purpose; hence, the function of a bioequivalence study was not to determine the new product's efficacy for that purpose, but rather to determine "whether the drug's delivery mechanism operates similarly to that of the benchmark product." *Id*. at 1491. The FDA noted that the usual method of establishing bioequivalence, measuring levels of the drug in blood, was not possible for bacitracin zinc. And it further noted that, because "the expected differences [between the performance of drugs in the necrotic enteritis study] are much greater than those for growth experiments," a comparison of "the drugs' abilities to fight disease was perhaps even a better measure of the similarities of their delivery mechanisms than a direct comparison of [their] effects on growth promotion." *Id*. (internal citation and quotation marks omitted). Concluding that this "position reflect[ed] a scientific determination within the scope of the FDA's expertise," we deferred to it. *Id*.

We were unwilling, however, to accept the agency's response to Alpharma's second criticism. Alpharma's experts argued that the Prescott Study could not prove that the two drugs "were equivalent for the purpose of fighting necrotic enteritis, because the two drugs were tested at a single dosage." *Id*. at 1490. To reach the conclusion that the drugs were equivalent, they maintained, "different dosages would have to be tested and dose-response curves for the two products constructed and compared." *Id*. Without the benefit of multi-dosage testing, "there [was] no way to rule out the possibility that one of the drugs barely reached effectiveness at the dosage tested while the other would have been effective against the disease at a fraction

of the dose." *Id*. The FDA's response to this second critique was brief: It "'d[id] not believe that it [was] necessary to test different levels of the drugs and compare dose-response curves' in order to show 'that the biological activity of the two drugs against a known disease organism was not significantly different.'" *Id*. (citing Citizen Pet. Denial at 2).

Finding this response "conclusory," we held that the FDA had "made no attempt to 'cogently explain'" why Alpharma was mistaken in claiming "that a single-dosage study cannot prove bioequivalency." *Id*. at 1492 (quoting *Motor Vehicle Mfr's Ass'n. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 48 (1983)). In light of that failure, we set aside the district court's grant of summary judgment (but not the FDA's approval itself), and remanded the case "so that the FDA may explain what bioequivalency entails in the animal drug context and how the Prescott Study satisfied that standard." *Id*.

The FDA's response to our remand came in the form of an October 27, 1995 letter from Ronald Chesemore, Associate Commissioner for Regulatory Affairs, to counsel for Alpharma. J.A. 208 ("Chesemore Letter"). The FDA advised Alpharma that, "[u]pon review, the agency determined the Prescott study was an appropriate means for evaluating the bioequivalence of the zinc bacitracin product covered by NADA 128-550." Chesemore Letter at 1. In so doing, the FDA reaffirmed its original decision to deny Alpharma's citizen petitions and to approve NADA 128-550. The details of the FDA's explanation are discussed in Parts III and IV below.

On February 4, 2005, the district court held that the Chesemore Letter complied with the terms of our remand, concluding that "the FDA provided an adequate justification for its conclusion that the two drugs are bioequivalent." *A.L. Pharma*, No. 83-1603, Mem. Op. at 5. This appeal followed.

II

We review the district court's grant of summary judgment de novo, "applying the same standards as those that govern the district court's determination." *Troy Corp. v. Browner*, 120 F.3d 277, 281 (D.C. Cir. 1997). We may set aside the FDA's approval of NADA 128-550 only if it was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). That standard requires an agency to "examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" *State Farm*, 463 U.S. at 43 (quoting *Burlington Truck Lines, Inc. v. United States*, 371 U.S. 156, 168 (1962)). The "agency must cogently explain why it has exercised its discretion in a given manner," *id*. at 48, and that explanation must be "sufficient to enable us to conclude that the agency's action was the product of reasoned decisionmaking," *id*. at 52.

We are met at the outset with Alpharma's contention that the Chesemore Letter cannot provide a "satisfactory explanation" because it is a "post-h[o]c rationalization" generated "thirteen years after the relevant decision." Alpharma Br. 24. As Alpharma notes, in *Citizens to Preserve Overton Park, Inc. v. Volpe*, the Supreme Court held that *post hoc* rationalizations "have traditionally been found to be an inadequate basis for review" of agency decisions. 401 U.S. 402, 419 (1971). Nonetheless, in *Overton Park* itself, the Court approved the procedure of remanding so that an agency can provide an explanation for an inadequately articulated decision. *Id*. at 420. Needless to say, if it is appropriate for a court to remand for further explanation, it is incumbent upon the court to consider that explanation when it arrives. And also needless to

say, a letter produced in response to our 1995 remand would have to be "*post hoc*" as measured against an agency decision issued in 1982. *See id*. at 419 (noting, in remanding for an explanation, that "[s]uch an explanation will, to some extent, be a '*post hoc* rationalization'").

Thirty years ago, we rejected the identical argument that Alpharma raises here. In *Local 814, Int'l Bhd. of Teamsters v. NLRB*, we concluded that we had the authority to consider a supplemental explanation that the NLRB provided in response to our remand. 546 F.2d 989, 992 (D.C. Cir. 1976). We explained the meaning of the "*post hoc* rationalization" rule as follows:

> [The] rule is not a time barrier which freezes an agency's exercise of its judgment after an initial decision has been made and bars it from further articulation of its reasoning. It is a rule directed at reviewing courts which forbids judges to uphold agency action on the basis of rationales offered by anyone other than the proper decisionmakers. Thus the rule applies to rationalizations offered for the first time in litigation affidavits and arguments of counsel. The policy of the *post hoc* rationalization rule does not prohibit [an agency] from submitting an amplified articulation of the distinctions it sees. . . . Moreover, the logic of the rule requires it. If a reviewing court finds the record inadequate to support a finding of reasoned analysis by an agency and the court is barred from considering rationales urged by others, only the agency itself can provide the required clarification.

Id. (internal citations omitted).

There is no question that Associate Commissioner Chesemore is a "proper decisionmaker[,]" *id*., and that his letter represents the considered views of the agency itself. *See* Chesemore Letter at 1 ("Upon review, the *agency* has determined that the Prescott study was an appropriate means for evaluating the bioequivalence of the zinc bacitracin product covered by NADA 128-550.") (emphasis added). The letter is neither a mere "litigation affidavit[,]" nor an "argument[] of counsel." *Local 814*, 546 F.2d at 992. Accordingly, an examination of its contents is perfectly appropriate. In Part III, we consider whether the agency's explanation satisfactorily answered the two questions we posed in our remand order. In Part IV, we address the new problems that arise out of the explanation that the FDA offered.

III

Our remand order instructed the FDA to "explain what bioequivalency entails in the animal drug context and how the Prescott Study satisfied that standard." *A.L. Pharma*, 62 F.3d at 1492. That instruction involved two questions, each of which the FDA addressed in the Chesemore Letter.

A

To paraphrase another (and more famous) poultry case: The first issue is, what is bioequivalence? *Cf. Frigaliment Importing Co. v. B. N. S. Int'l Sales Corp*., 190 F. Supp. 116, 117 (S.D.N.Y. 1960) (Friendly, J.) ("The issue is, what is chicken?"). More precisely, the question we asked on remand was "what characteristics . . . two drugs must share in order to be deemed bioequivalent." *A.L. Pharma*, 62 F.3d at 1491.

The Chesemore Letter set forth, as representing the meaning of bioequivalence during the 1981-82 period in which NADA 128-550 was considered, the following definition:

> A demonstration of bioequivalence involves establishing that two comparable drug formulations, which cannot be presumed to be identical based on chemical equivalence, perform in a similar way in a chosen test system.

Chesemore Letter at 1. Alpharma objects that the FDA's definition is too vague, because it does not clearly explain what it means for two drugs "to perform in a similar way in a chosen test system." Alpharma Br. 34. In context, however, we understand the "chosen test system" to mean experimentally-induced necrotic enteritis, and we understand "perform in a similar way" to mean similarly effective in treating that disease. *See* Chesemore Letter at 3 ("[T]he study demonstrated that [the NADA 128-550] product and the innovator zinc bacitracin product perform in a similar way in the chosen test system (i.e., in the treatment of necrotic enteritis)."). Performance, in turn, was evaluated under the pre-established criteria of mortality, lesions, and weight gain. *See* Memorandum from Dr. Thomas V. Raines to Drs. Malcolm Thomas and Lonnie Luther 1 (Aug. 25, 1981) (describing the evaluation parameters of the Prescott Study) (J.A. 43) ("Raines Memorandum").

In our initial opinion, we acknowledged that "there may be more than one reasonable definition of bioequivalency," and that the FDA was entitled to "latitude in its construction of the term." *A.L. Pharma*, 62 F.3d at 1491-92. Bacitracin zinc is a drug for which "conventional blood level study is not appropriate" because it "does not produce blood levels." Raines Memorandum at 1. As we suggested in our initial opinion, where blood levels could not be used to measure bioequivalence,

it was not unreasonable for the FDA to define bioequivalence in terms of performance -- here, the treatment of a specific disease. *See A.L. Pharma*, 62 F. 3d at 1491 (deferring to the FDA's judgment that a comparison of "the drugs' abilities to fight disease was perhaps even a better measure of the similarities of their delivery mechanisms than a direct comparison of [their] effects on growth promotion").

We also note -- as did the Chesemore Letter -- that the FDA's "description of bioequivalence is consistent with what Congress later codified in the Generic Animal Drug and Patent Restoration Act of 1988," Pub. L. 100-670, 102 Stat. 3971 (1988)). Chesemore Letter at 1 n.1.[5] Six years after the FDA approved NADA 128-550, Congress provided a statutory definition of bioequivalence for situations (like this one) in which "the Secretary determines that the measurement of the rate and extent of absorption or excretion of the new animal drug in biological fluids is inappropriate or impractical." 21 U.S.C. § 360b(c)(2)(H)(ii)(III). In such circumstances, a new animal drug "shall be considered to be bioequivalent to" an approved new animal drug (i.e., a benchmark drug) if

> an appropriate acute pharmacological effects test or other test of the new animal drug and . . . of the approved new animal drug . . . in the species to be tested . . . does not show a significant difference between the new animal drug and such approved new animal drug when administered at the same dose under similar experimental conditions.

Id. Although Congress' subsequent enactment of a similar bioequivalency standard does not in itself validate the FDA's

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[5]At oral argument, counsel for Alpharma conceded that the 1988 Act could be read as the FDA reads it. Oral Arg. Tape at 50:44.

definition, it does suggest that the concern that prompted our first remand question may not recur.

B

The second issue posed by our remand was "how the Prescott Study satisfied" the FDA's bioequivalency standard. *Id*. at 1492. Specifically, we asked why the FDA viewed a single-dose rather than multiple-dose study as appropriate for establishing bioequivalence. *Id*.

In response, the Chesemore Letter explained that "[b]ioequivalence testing of generic veterinary drugs has historically been conducted using a single dose level; this was the accepted approach at the time NADA 128-550 was approved." Chesemore Letter at 2. "Testing at more than one dosage level," the FDA said, "is necessary only where the drug at issue is a sustained release product or in the rare instance in which the drug has demonstrated nonlinear kinetics." *Id*.[6] Because "neither circumstance existed with zinc bacitracin," the FDA concluded that "a single dose bioequivalence study is sufficient." *Id*.

The FDA's description of its historical practice is entitled to deference in light of the agency's experience and expertise in these matters. *See Fed. Power Comm'n v. Fla. Power & Light Co*., 404 U.S. 453, 463 (1972). To be sure, that description would have been more persuasive had it been accompanied by

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[6] *See* FDA Br. 13 n.5 ("Sustained release drugs are drugs that are manufactured to release a certain amount of an active ingredient in uniform doses at regular intervals over a given period of time. Nonlinear kinetics exists where absorption, distribution, and elimination of a drug cannot be defined by rate constants that are concentration-independent.").

citations. But the plaintiff has not cited anything to contradict the agency's representation, and at oral argument plaintiff's counsel conceded that he did not know of any contrary examples. Oral Arg. Tape 50:01-50:20.

The Chesemore Letter then went on to explain why multiple-dose studies had not historically been required to establish bioequivalence:

> A bioequivalency study is not designed to demonstrate or affirm the efficacy of the product at issue for a given use; instead, . . . its purpose is to demonstrate that two comparable formulations perform similarly in a chosen test system. In contrast, a dose response study is conducted in order to isolate from the range of doses being tested the optimally effective dose of a product for a particular condition or use.

Chesemore Letter at 2.[7] Since the purpose of the Prescott Study was not to determine "the optimally effective dose," Chesemore Letter at 2, but only to determine whether the two drugs would perform in a similar way with respect to necrotic enteritis, the agency's explanation for not employing a multiple-dose study was reasonable. Such a "judgment[] as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of the FDA's expertise and merit[s] deference from us." *A.L. Pharma*, 62 F.3d at 1490 (internal quotation marks omitted); *see Schering Corp. v. FDA*, 51 F.3d 390, 399-400 (3d

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[7]As we noted above, *see supra* Part I, a bioequivalency study is not designed to demonstrate efficacy because the FDA has already determined the benchmark product's efficacy for the given use; the function of a bioequivalency study is only to determine whether the generic "drug's delivery mechanism operates similarly to that of the benchmark product." *A.L. Pharma*, 62 F.3d at 1491.

Cir. 1995) (holding, in the human drug context, that the FDA has "discretion to determine what tests or studies would provide it with appropriate information from which to determine bioequivalence").

In sum, we conclude that the Chesemore Letter adequately responded to the questions we raised in our remand order. Those responses provide a satisfactory explanation both of what "bioequivalency entails in the animal drug context," and of how the single-dose Prescott Study "satisfied that standard." *A.L. Pharma*, 62 F.3d at 1492.

IV

We would like nothing better than to end this "tortured story" right here. *Id*. at 1486. But the FDA has not made that possible. As Alpharma correctly argues, in the course of responding to our remand, the FDA made new, seemingly contradictory statements that require further clarification before we can conclude that the agency acted reasonably.

The FDA insists that Alpharma's arguments are not properly before us because the company did not raise them on the first appeal. But the arguments that Alpharma asserts here all involve statements that the FDA made for the first time after that appeal, in the Chesemore Letter. Therefore, because they are not arguments that "could have been raised on an initial appeal," it is not "inappropriate to consider [them] on a second appeal following remand." *Northwestern Ind. Tel. Co. v. FCC*, 872 F.2d 465, 470 (D.C. Cir. 1989).

As discussed in Part III, we are satisfied with the FDA's explanation for concluding that "a single dose bioequivalence study is sufficient" for evaluating bacitracin zinc. Chesemore Letter at 2. As Alpharma points out, however, two additional

problems arise out of the agency's further declaration that "a dose of 100 grams/ton of feed" -- the single dose used in the Prescott Study -- "was the appropriate zinc bacitracin dose for control of necrotic enteritis." *Id*. We consider those problems below.

A

The first problem involves an apparent contradiction between the Chesemore Letter's conclusion that 100 grams/ton was the appropriate dose, and its statement that "[h]istorically, the FDA has recommended that, as a general rule, a bioequivalence study be conducted using the highest approved dose." *Id*. As Alpharma notes, 100 grams/ton was not the highest approved dose in the two sources that the Chesemore Letter cites in support of the proposition that 100 grams/ton was the appropriate dose for the Prescott Study. *Id*. One of those sources listed "the approved dose for the water soluble powder form of zinc bacitracin." *Id*. (citing Certifiable Peptide Antibiotic Drugs for Animal Use; Zinc Soluble Powder, 47 Fed. Reg. 24,693, 24,694 (June 8, 1982)). That source fixed the highest approved water-soluble dose for control of necrotic enteritis in chickens at 400 milliliters/gallon, *see* 47 Fed. Reg. at 24,694, which is comparable to 200 grams/ton of feed[8] -- double the dose used in the Prescott Study. The other cited source was for "the approved dose of a related form of bacitracin, bacitracin methylene disalicylate," for use in feed to control necrotic enteritis. Chesemore Letter at 2 (citing 21 C.F.R. § 558.76 (1982)). The highest approved dose for that drug was 200 grams/ton, *see* Animal Drugs, Feeds, and Related Products; Bacitracin Methylene Disalicylate, 47 Fed. Reg. 21,748, 21,749

[8]*See* Alpharma Br. 32. The FDA has not disputed Alpharma's translation of water-soluble doses into feed doses.

(Apr. 14, 1981) (codified at 21 C.F.R. § 558.76) -- again double that used by Prescott.

There is another inconsistency lurking here as well. The Chesemore Letter stated that 100 grams/ton of feed was the appropriate dose for the "control" of necrotic enteritis. Chesemore Letter at 2. But it is not clear from the agency's own description whether Prescott studied the *control* or the *prevention* of necrotic enteritis. As Alpharma points out, the FDA has "described the Prescott Study at times as studying prevention while at other times studying control." Alpharma Br. at 29.[9] This is significant because the two sources cited in the Chesemore Letter listed highest approved doses that were different for prevention than for control -- and that were also different from the 100 grams/ton used in the Prescott Study. Indeed, if the focus of the study was prevention, then the highest approved doses for that purpose were half the 100 grams/ton that Prescott used. *See* 47 Fed. Reg. at 24,694 (listing 100 milliliters/gal, comparable to 50 grams/ton of feed, as the highest approved dose of water-soluble bacitracin zinc for prevention); 47 Fed. Reg. at 21,749 (listing 50 grams/ton of feed as the highest approved dose of bacitracin methylene disalicylate for prevention).

Finally, we note that all of these comparisons of highest approved doses are something of a fiction given the FDA's acknowledgment that, at the time of the Prescott Study, there

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[9] *See, e.g.*, Briefing Memorandum on Approval for a New Drug Application 2 (June 30, 1992) (J.A. 66) (describing the Prescott Study as comparing the drugs' "ability to *prevent* necrotic enteritis in broiler chickens") (emphasis added); *see also* Prescott Aff. ¶ 4 ("The study results demonstrated that the two different sources of bacitracin zinc were equally efficacious at the levels used in *preventing* experimentally induced necrotic enteritis.") (emphasis added).

was *no* approved dose of bacitracin zinc for the control of necrotic enteritis. *See* Chesemore Letter at 3 n.4 ("The agency acknowledges that at the time of the approval of NADA-128-550, zinc bacitracin was not approved for use in feed for the control of necrotic enteritis."). The two sources cited by the FDA were for approvals issued well after the Prescott Study was concluded. Yet nothing in the Chesemore Letter explains how Prescott could have appropriately relied on approvals that had not yet been made. Nor does it explain why it was appropriate for him to use a dose different from (either higher or lower than, depending on whether Prescott studied prevention or control) the highest approved dose -- as the FDA had historically recommended.

B

The second problem identified by Alpharma centers around the Chesemore Letter's declaration that 100 grams/ton was the "appropriate zinc bacitracin dose" because it was the "optimally effective dose for controlling necrotic enteritis." Chesemore Letter at 3 n.4. The Letter offers no support for the latter proposition, and, this time, Alpharma points to contradictory indicators. *Compare supra* Part III.B (accepting the FDA's description of its historical practice regarding single-dose studies where plaintiff cited nothing to contradict it).

As Alpharma points out, and as we noted above, the Chesemore Letter concedes that at the time of the approval of NADA 128-550, bacitracin zinc had not been approved for the control of necrotic enteritis at any level, let alone at an optimally effective dose. *See* Chesemore Letter at 3 n.4.[10] Moreover,

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[10]*See also* FDA Br. 23 (acknowledging that "Alpharma correctly states that FDA had not approved zinc bacitracin to control necrotic enteritis at the 100 grams/ton dose level at the time of the Prescott

neither of the two sources discussed in the Chesemore Letter established an optimally effective dose for the control of necrotic enteritis. While 100 grams/ton fell within the range of approved doses for both water-soluble bacitracin zinc and bacitracin methylene disalicylate, neither approval referred to an optimally effective dose. *See* 47 Fed. Reg. at 24,694; 47 Fed. Reg. at 21,749.

The Chesemore Letter flatly declares that "the agency had a clear rationale for its determination that 100 grams/ton would be the optimally effective dose for controlling necrotic enteritis." Chesemore Letter at 3 n.4. The problem is that the letter offers no hint of what that "clear rationale" might have been. Accordingly, we are unable to determine whether it was reasonable.[11]

V

For the reasons discussed in Part III, we conclude that the FDA adequately responded to our initial remand. For the reasons discussed in Part IV, however, we conclude that the agency's response raises questions that leave us unable to conclude that the decision to approve Philips Roxane's new animal drug application "was the product of reasoned decisionmaking." *State Farm*, 463 U.S. at 43. We therefore set

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study").

[11]The FDA's appellate brief proposes a number of reasons why the agency might have accepted the 100 grams/ton dose as appropriate, and why it deviated from its general rule that a bioequivalency study should use the highest approved dose. FDA Br. 22-28. These, however, truly are "*post hoc*" rationalizations "offered for the first time in litigation affidavits and arguments of counsel," and we are "barred from considering" them. *Local 814*, 546 F.2d at 992 (D.C. Cir. 1976) (citations omitted); *see supra* Part II.

aside the district court's grant of summary judgment and remand the case.

Alpharma cannot start counting its chickens just yet. Notwithstanding the problems of the Chesemore Letter, the FDA may still "be able to explain why it reasonably determined that the Prescott Study demonstrated bioequivalence." *A.L. Pharma*, 62 F.3d at 1492. For that reason, and "because no significant harm would result from allowing the approval to remain in effect pending the agency's further explanation,"[12] we leave the approval in place. *Id*. (citing, inter alia, *Allied-Signal, Inc. v. NRC*, 988 F.2d 146, 151 (D.C. Cir. 1993)). The district court is instructed to remand the matter to the FDA for an adequate explanation of its conclusion that a dose of 100 grams/ton was the appropriate bacitracin zinc dose for use in the Prescott bioequivalency study. That explanation must resolve the problems and apparent contradictions highlighted in Part IV.

So ordered.

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[12]Indeed, the parties advised us that the Philips Roxane drug has never been marketed. *See* Oral Arg. Tape 21:53, 42:23. Perhaps that explains why neither side appears concerned about the length of time it has taken to litigate this case, which was first filed in 1983.

WILLIAMS, *Senior Circuit Judge*: I concur in the court's opinion except Part III.B. I'm not convinced that the FDA adequately explained how a single-dose study satisfied its bioequivalency standard.

In the first appeal of this case, we remanded precisely on this issue, finding that the FDA's "conclusory response to [Alpharma] that it 'does not believe that it is necessary to test different levels of the drugs and compare dose-response curves' [is not] sufficient." *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1492 (D.C. Cir. 1995). We based this ruling on a record containing affidavits and letters of 16 experts arguing, in essence, that a single-dose study was weak support for an inference that the new drug was truly bioequivalent to the benchmark drug. See, e.g., Johnson Aff. ¶ 8 (concluding that "several levels at equally spaced intervals of the drug should be tested and a dose response curve constructed" because "[u]sing a single dose level and finding 100% success only indicates that the drugs are effective at the stated level"). Most of the rest make essentially this point. In response, the FDA's Chesemore Letter offers two substantive reasons that persuade the majority, but I find each defective. (I do not discuss the FDA's historical practice, as practice alone would not constitute an adequate explanation in the face of a serious substantive challenge.)

First, the FDA asserts that multiple dosages are only necessary for sustained release drugs and drugs exhibiting nonlinear kinetics ("SRNK" drugs). But nowhere does the FDA provide an explanation of why *only* SRNK drugs should be tested this way. Nothing in the record establishes that if the benchmark and new drug exhibit linear kinetics and have the same effects at *one dose*, they will have the same effect at *all doses* (or, more pertinently, at all doses likely to be lawfully prescribed in the event of approval).

Indeed, nonlinear kinetics appear to be a complete red herring. We are told by the FDA on brief that "nonlinear kinetics exists where absorption, distribution, and elimination of a drug cannot be defined by rate constants that are concentration-independent." FDA Br. 13 n.5. But the absorption, distribution, and elimination of a drug appear to refer to attributes of a *blood level* study, not a pharmacologic *endpoint* study, which the Prescott Study was. Compare Center for Veterinary Medicine, Bioequivalency Guideline 5-8 (April 12, 1990) (discussing how blood level studies "encompass . . . absorption and depletion (elimination) phases of the drug concentration profiles" and that "a single dose study at the highest approved dose will generally be adequate for the demonstration of bioequivalence"); with *id*. 13-15 (noting that "[w]here the direct measurement of the rate and extent of absorption . . . is inappropriate or impractical, the evaluation of an appropriate pharmacologic endpoint will be acceptable" and that "[d]osage(s) approved for the pioneer product should be used in the study"). Moreover, as with nonlinear kinetics, the FDA provides no discussion of sustained release drugs. The FDA's terse incantation of SRNK drugs thereby provides no basis for an adequate explanation.

Second, the FDA asserts that dose-response studies are designed to choose optimally effective doses. But the fact that multiple-dose testing is required to determine the optimal dose tells us nothing about whether such testing is sensible to show bioequivalence. Moreover, as Alpharma argues, the assertion begs the question of what it means to "perform similarly in a chosen test system," see Chesemore Letter at 2, failing to provide an explanation of how bioequivalence can be established without testing in the ranges that are plausible for the drugs' uses.

The FDA might, though it seems implausible, show that multiple-dose testing affords no material increase in confidence in the bioequivalence of the two drugs. More likely, it might offer some reason to believe that although multiple-dose testing was more accurate, the gain in accuracy wasn't worth the time and cost. Barring some statutory problem, we would properly defer to such a view. Alternatively, of course, the FDA may find that multiple-dose testing is sound as a matter of both science and policy.

In short, the FDA's response to our remand seems completely unilluminating. As the court remands for the FDA to straighten out its explanation of what (single) dose to use, perhaps the agency will seize the occasion to explain its single-dose policy. Users of new drugs would surely find relief in a real explanation.