

ZENECA INC. v. DONNA SHALALA, et al.

Civil Action WMN-99-307

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MARYLAND

1999 U.S. Dist. LEXIS 12327

August 11, 1999, Decided

DISPOSITION: [*1] Gensia's Motion to Strike GRANTED; Gensia's Motion to Dismiss DENIED as MOOT; Zeneca's Motion for Partial Summary Judgment DENIED; FDA's Motion for Summary Judgment and Motion to Seal GRANTED; Gensia's Motion for Summary Judgment GRANTED; Zeneca's Motion to Strike granted; Zeneca's Request for More Particularized Privilege Log DENIED as moot; FDA's Motion for Protective Order DENIED as moot; judgment ENTERED in favor of Defendants and against Plaintiff.

LexisNexis(R) Headnotes

COUNSEL: For ZENECA INC., plaintiff: Grace E. Speights, Anthony C. Roth, Morgan, Lewis & Bockius, PH, Washington, DC.

For DONNA SHALALA, JANE HENNEY, defendants: Margaret Jane Porter, Food & Drug Administration, Rockville, Md.

For GENZIA SICOR PHARMACEUTICALS, INC., movant: John Thomas Prisbe, E. Anne Hamel, Venable, Baetjer & Howard, Baltimore, MD.

JUDGES: William M. Nickerson, United States District Judge.

OPINIONBY: William M. Nickerson

OPINION:

MEMORANDUM

In this administrative record review case, Plaintiff Zeneca, Inc. ["Zeneca"] challenges a decision of Defendant Food and Drug Administration ["FDA"] approving an Abbreviated New Drug Application ["ANDA"] for a propofol formulation manufactured by Defendant Gensia Sicor Pharmaceuticals, [*2] Inc. ["Gensia"]. In approving Gensia's ANDA, FDA permitted the marketing of

Gensia's propofol product as a generic version of Zeneca's highly successful and profitable propofol product, Diprivan. In its complaint, Zeneca has requested, inter alia, an order vacating that approval.

Cross motions for summary judgment have been filed by all parties, n1 along with several ancillary motions related to the composition of the administrative record, n2 and Gensia's assertion of trade secret protection over portions of the administrative record. n3 All motions are now fully briefed. n4

n1 Zeneca's Motion for Partial Summary Judgment, Paper No. 66; FDA's Motion for Summary Judgment, Paper No. 72; and Gensia's Motion for Summary Judgment, Paper No. 74. Also pending is a motion to dismiss filed by Gensia, Paper No. 29, seeking dismissal of certain Fifth Amendment "takings" claims asserted by Zeneca. Because Zeneca's takings claims are directly related to Zeneca's claim of market exclusivity for its product, an issue that is also raised in the summary judgment motions, the motion to dismiss will be addressed in conjunction with the motions for summary judgment.

[*3]

n2 Gensia's Motion to Strike, Paper No. 28 and FDA's Motion for a Protective Order, Paper No. 84.

n3 Zeneca's Motion to Strike, Paper No. 75; FDA's Motion to Seal, Paper No. 73; and Zeneca's request for a more particularized Privilege Log, Paper No. 76.

n4 The motions are actually more than fully briefed. In responding to Defendants' Summary Judgment motions, Zeneca took the rather unusual step of filing four separate pleadings: a

"Reply Memorandum in Response to FDA's Summary Judgment Memorandum," Paper No. 77; a "Reply Memorandum in Response to Gensia Sicor's Motion for Summary Judgment," Paper No. 78; an "Opposition to FDA's Cross Motion for Summary Judgment," Paper No. 79; and an "Opposition to [Gensia's] Cross Motion for Summary Judgment."

The Local Rules clearly require that where there are cross motions for summary judgment, a party in Zeneca's position should have filed a single memorandum opposing the cross motions and replying to the oppositions to its own motion or, at most, a single memorandum addressed to the arguments of each Defendant. See Local Rule 105(2)(c). Zeneca seeks to excuse its violation of the Local Rules by claiming ignorance of Defendants' intention to file summary judgment motions. See Paper No. 86 at 6 n.4 That claim of ignorance is surprising considering that this is a record review case where it could be safely assumed that cross motions would be filed. If there was uncertainty, the simple resolution would have resulted from a telephone call.

Putting the Local Rules aside, common sense should have dictated a single pleading. As filed, Zeneca's pleadings are incredibly duplicative. Pages 2 through 16 of Paper No. 79 are nearly identical to pages 4 through 17 of Paper No. 80. Large portions, in fact, almost the entirety of Paper Nos. 77 and 78, simply repeat the exact same arguments.

Far from being "illogical" or "draconian" as Zeneca insists, see Paper No. 86 at 6 n.4, the briefing scheme embodied in the Local Rules promotes the most efficient resolution of cross motions for summary judgment. Zeneca's counsels' pleading strategy, adopted for whatever reason, has resulted in a needless waste of the Court's time, opposing counsel's time, and the resources of their client.

[*4]

I. STANDARD OF REVIEW

Zeneca challenges FDA's decision to approve Gensia's ANDA under the Administrative Procedures Act, 5 U.S.C. § 706 ["APA"]. Under the APA, a court shall not set aside an agency action, findings, or conclusions, unless the same are found by the court "to be ... arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law ..." 5 U.S.C. § 706(2)(A). Under this standard, "there is a presumption in favor of the va-

lidity of administrative action," and courts are particularly deferential when an agency is interpreting its own statute and regulations. *United States v. Rutherford*, 442 U.S. 544, 553, 61 L. Ed. 2d 68, 99 S. Ct. 2470 (1979); *Ethicon, Inc. v. FDA*, 762 F. Supp. 382, 386 (D.D.C. 1991). While a reviewing court "is to show a proper deference to the expertise of the agency, the court should make a "searching and careful" inquiry of the record in order to ascertain 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, 28 L. Ed. 2d 136, 91 S. Ct. 814 (1971). [*5] Moreover, under this narrow scope of review, "the court is not empowered to substitute its judgment for that of the agency." *Id.*

An agency is to be accorded particular deference when it is evaluating scientific data within its technical expertise. *FPC v. Florida Power & Light Co.*, 404 U.S. 453, 463, 30 L. Ed. 2d 600, 92 S. Ct. 637 (1972); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995)(FDA's "judgments 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 deference from us."), cert. denied, 516 U.S. 907, 133 L. Ed. 2d 195, 116 S. Ct. 274 (1995); *International Fabricare Inst. v. EPA*, 297 U.S. App. D.C. 331, 972 F.2d 384, 389 (D.C. Cir. 1992) (rationale for deference is "particularly strong" when an agency evaluates scientific evidence within its technical expertise). Nonetheless, deference is not abdication. The court must find that the relevant factors upon which the decision is based are supported by some evidence. *Ritter Transportation, Inc. v. ICC*, 221 U.S. App. D.C. 312, 684 F.2d 86, 88 (D.C. Cir. 1982), [*6] cert. denied, 460 U.S. 1022, 75 L. Ed. 2d 494, 103 S. Ct. 1272 (1983). Lastly and of particular importance in this action, the court must review the administrative record as assembled by the FDA; it does not pursue its own fact finding. *Camp v. Pitts*, 411 U.S. 138, 142, 36 L. Ed. 2d 106, 93 S. Ct. 1241 (1973).

II. PRELIMINARY ISSUES

A. Content of the Administrative Record

Since the commencement of this litigation, Zeneca has attempted to submit to the Court for its consideration evidence which was never submitted to the FDA. Zeneca has produced reports from expert witnesses that were generated for this litigation. Early in this litigation, Zeneca attempted to obtain, through discovery, samples of Gensia's product so that it could submit that product to various tests. The Court denied that request, holding,

even were Zeneca to obtain samples of the product and conduct its own tests as to its safety and efficacy, that evidence would not be admissible in this litigation. Zeneca's protestations to the contrary, notwithstanding, this is an administrative review case. To the extent that Zeneca has now, or will develop in the future, [*7] some new evidence not presented to the FDA, the appropriate course is to submit the evidence to the FDA for reconsideration of its initial determination. New medical evidence will not be reviewed for the first time in this Court.

March 4, 1999 Order at 5-6 n.2.

Nonetheless, after the Court denied that discovery, Zeneca had its employees proceed to create its own version of what it believed Gensia's product to be, tested that product, and then submitted the test results to the Court. Once Zeneca was able to obtain samples of Gensia's actual product, Zeneca had one of its employees conduct additional tests and then Zeneca filed the results of those tests with the Court as well. See Second Declaration of Christopher B. Jones, Ph.D., Ex. A to Zeneca's Reply to FDA's Summary Judgment Motion.

Defendants have motioned for the Court to strike from the complaint all references to materials outside the administrative record, see Paper No. 28, and to disregard any materials submitted with Zeneca's pleadings which were not first submitted to FDA as part of its review of the ANDA. While acknowledging that the Court cannot conduct a de novo review of FDA's decision, Zeneca [*8] argues that the Court can consider the information "for the limited purpose of providing relevant background information necessary to determine whether FDA considered all relevant factors on an appropriate record." Opp. to Gensia's Mot. to Strike at 7-8.

Zeneca's argument creates a distinction without a difference. For the Court to determine whether Zeneca's test results or the issues those results supposedly raise should have been considered by the FDA, would require the Court to make a threshold determination as to the scientific validity of the tests. If, on the one hand, the tests amount to nothing more than "junk science," then the FDA was correct in not considering them. On the other hand, if the tests are scientifically valid, then the FDA may have erred. This determination, however, is precisely the type of scientific determination that FDA is competent and the Court is not competent, to make. If Zeneca truly believed that it had relevant information for FDA to consider, there is no apparent reason why it did

not submit the information to FDA as urged by this Court since the inception of this litigation. n5

n5 The court notes that, while Zeneca submitted these expert opinions and test results with its pleadings, it actually relied on them very little in the pleadings themselves. It would appear that these materials were generated as much for non-litigation purposes as for use in this Court. Zeneca has been widely distributing these materials to the medical community as litigation documents, both through posting them on its website and through direct mailings to health care providers. Were the documents not first made part of the Court record, FDA regulations would have prohibited the distribution of these comparative materials. By couching these materials in terms of "litigation documents," Zeneca believes that it is able to do what it would not have been able to do otherwise.

[*9]

The Court will grant Gensia's motion to strike and, in ruling on the summary judgment motions, will disregard any materials that were not part of the record before FDA.

Zeneca next takes issue with FDA's compilation of the administrative record. Zeneca claims that the record that FDA submitted to the court was not the full administrative record that was before the agency at the time it made its decision. Accordingly, Zeneca has propounded discovery requests to the FDA related to the manner in which the record was assembled and the completeness of the record. Zeneca argues that the Court cannot consider Defendants' cross motions for summary judgment until this discovery is completed and FDA produces the "full record." In response to Zeneca's discovery requests, FDA has filed a motion for a protective order barring discovery.

Because "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, 36 L. Ed. 2d 106, 93 S. Ct. 1241 (1973), discovery is generally not permitted in an APA review case. See *American Canoe Assoc., Inc. v. EPA*, 46 F. Supp. 2d 473 (E.D. Va. 1999). [*10] Courts have, however, recognized a few circumstances where discovery is permitted in such a case: 1) a failure in the record to explain administrative action as to frustrate judicial review; 2) a "substantial showing" that documents considered or relied upon by the agency are absent from the record; 3) a need to supplement the record to explain or clarify technical terms or other difficult sub-

ject matter included in the record; and, 4) a showing of bad faith or improper behavior. *Public Power Council v. Johnson*, 674 F.2d 791 (9th Cir. 1982). These exceptions, however, are limited and narrow, as "the designation of the administrative record, like any established administrative procedure, is entitled to a presumption of administrative regularity. The court assumes the agency properly designated the Administrative Record absent clear evidence to the contrary." *Bar MK Ranches v. Yuetter*, 994 F.2d 735, 740 (10th Cir. 1993)(emphasis added, citations omitted).

Zeneca seeks to rely on the first and second exceptions, identifying several classes of documents that it claims should be included in, but are absent from, the administrative record. Zeneca also [*11] claims, more broadly, that "FDA's whole approach to the compilation of the administrative record in this case is wrong," Opp. to Motion for Prot. Order at 4, in that FDA "appears to have [] 'submitted an administrative record to the Court which contains only documents favoring [FDA's] decision.'" Id. at 3 (quoting *National Wildlife Federation v. Burford*, 677 F. Supp. 1445, 1457 (D. Mont. 1985)).

The Court notes, initially, that Zeneca's claim that FDA only included documents in the record that are favorable to its decision is inconsistent with the position Zeneca has taken in other pleadings. Zeneca argues in moving for summary judgment, not only that there are documents in the record undermining FDA's decision, but that the administrative record as a whole establishes that FDA's decision was arbitrary and capricious. While the Court disagrees with Zeneca's conclusion as to its entitlement to summary judgment, its ability to argue that entitlement belies any conclusion that FDA compiled a sanitized record.

As to the individual classes of documents that Zeneca asserts have been withheld from the record, the Court finds no merit in Zeneca's protestations. The [*12] documents that Zeneca claims are missing are documents that either never existed, exist but are not properly part of the record, or are, in fact, already in the record. For example, Zeneca faults FDA for failing to include a memorandum of meeting for an August 19, 1998 teleconference. As FDA has explained, no memorandum of this meeting was ever created. FDA, in its discretion, did not consider the telephone conference an event that warranted the production of a memorandum to be included in the record. The substance of the conference, however, is included in the record in the form of the pre-conference submissions of Gensia.

Zeneca also protests the absence of a document prepared by an FDA attorney addressing the question of whether the proposed labeling on Gensia's product complied with certain statutory labeling requirements. This

document is clearly a privileged document and, furthermore, as it addresses a purely legal question that the Court must ultimately decide, its inclusion in the record would be unnecessary.

Zeneca's last significant challenge to the record relates to FDA's alleged failure to include documents from outside the FDA's Office of Generic Drugs ["OGD"]. This [*13] allegation is simply false. While the record produced was maintained by OGD, it included consults from other parts of the agency that were added to the record maintained by OGD.

Finding that Zeneca has failed to make the requisite clear and substantial showing that the administrative record is incomplete, the Court will deny Zeneca any further discovery and resolve the pending summary judgment motions based on the administrative record as it now stands. n6

n6 Because this memorandum and order will resolve all outstanding issues and close the case, the Court will deny FDA's motion for a protective order as moot.

The last three preliminary motions relate to FDA's withholding of certain documents in the administrative record on the basis of Gensia's assertion of a trade secret privilege. Early in this litigation, Zeneca filed a motion for a protective order that would have allowed the administrative record to be produced to Zeneca in its entirety, subject to certain restrictions on the use and dissemination of [*14] portions of the material. On March 4, 1999, the Court denied Zeneca's motion, concluding that the need to enforce the statutory protection of Gensia's trade secrets trumped Zeneca's desire for unfettered access for the purpose of this litigation.

On April 30, 1999, this Court issued an order that somewhat modified its March 4, 1999 order. Recognizing that allowing Defendants to rely on those portions of the administrative record withheld from Zeneca might implicate due process concerns, the Court precluded Defendants from using any of the withheld materials in support of their motions or in opposing Zeneca's motion. The Court also allowed the option that Gensia waive its privilege claim and produce the materials pursuant to an appropriate protective order. In the April 30, 1999 Order, the Court also required Gensia to produce a privilege log. Gensia forwarded a copy of a privilege log to Zeneca on May 7, 1999.

On May 14, 1999, Zeneca filed a request for a more particularized privilege log. Zeneca complained that the log it received was inadequate in that it: 1) failed to address documents withheld from the Summary Adminis-

trative Record; 2) failed to address documents that had been [*15] produced in a partially redacted form; 3) grouped the materials in too large of units; 4) failed to provide sufficient description of the documents and, 5) failed to specify which privilege was being asserted as to which documents.

On May 28, 1999, Gensia responded to Zeneca's request with a more detailed privilege log and a pleading addressing the concerns raised by Zeneca. As to the Summary Administrative Record documents, Gensia explained that no additional identification is needed as all documents in the Summary Record are also in the full Administrative Record. Gensia acknowledged that it inadvertently failed to include partially redacted documents in the log and rectified that error on the amended log. The amended log also broke the documents down into additional subcategories and provides some additional information regarding the documents. As to Zeneca's last complaint concerning the original log, it seems somewhat disingenuous for Zeneca to claim that it was confused as to the privilege asserted. It should have been clear from the history of this litigation that Gensia was seeking to protect trade secret and confidential commercial information.

Finding that Gensia's response [*16] and amended privilege log adequately address Zeneca's concerns, the Court will deny Zeneca's request for a more particularized privilege log as moot.

On May 14, 1999, Zeneca also moved to strike from Defendant's pleadings any references to undisclosed administrative record materials. In their respective summary judgment pleadings, both Defendants included references to privileged materials that have been withheld from Zeneca. FDA did so deliberately and filed with its pleading a motion to seal, requesting that the Court enter an appropriate protective order allowing release of the privileged materials to Zeneca. Gensia indicates that its reference to privileged materials was inadvertent and asks the Court to rule on the cross motions without reference to the privileged materials referenced by Gensia, or those referenced by FDA. Gensia argues that, even without the withheld documents, the record is sufficient to allow the Court to resolve the cross motions.

The Court agrees that the motions can be resolved without reference to the privileged material. Therefore, the Court will grant Zeneca's motion to strike. FDA's motion to seal, to the extent that it requests release of the withheld [*17] documents pursuant to a protective order, will be denied. n7

n7 The Court will strike those references to the withheld materials in that the Court will not

consider them in resolving the summary judgment motions. The Court will allow the record materials submitted by FDA to remain in the Court file, under seal, to preserve the record for any potential appellate review.

One final note on the privilege issue. As FDA observes, there are difficulties in "artificially confining the Court's review to a partial record." See FDA's Reply in Support of Cross Mot. for Summary Judgment at 8. Unfortunately, those difficulties cannot always be avoided. The goal of conducting a meaningful review of an agency's action will often be in conflict with the need to protect the confidential materials or trade secrets of individual entities involved in that agency action. The Court can certainly imagine situations in which it is not possible to do both -- where the need to protect trade secrets must yield to the need to have an adequate [*18] record for the Court to review. In this instance, however, even on the partial record before the Court, it is clear that there is no merit, whatsoever, to Plaintiff's challenge of FDA's action, as explained below.

III. SUMMARY JUDGMENT MOTIONS

Zeneca proffers seven grounds upon which it argues that FDA's decision to approve Gensia's ANDA was arbitrary and capricious. n8

(1) FDA arbitrarily and capriciously found that disodium edetate ("EDTA") in DIPRIVAN(R) was a preservative and therefore it could approve Gensia Sicor's propofol product using an "abbreviated" review procedure at the same time that it found that EDTA in DIPRIVAN(R) is not a preservative, that EDTA in DIPRIVAN(R) did not meet the accepted United States Pharmacopeia ("USP") definition of a "preservative," and that Zeneca is required to state unequivocally in red letters on DIPRIVAN(R)'s labeling that the product "Contains no preservative."

(2) FDA's medical review of the safety of Gensia Sicor's propofol product was arbitrary and capricious because it was based on a repeated factual error regarding the proposed product's pH range. FDA reviewed the safety of a hypothetical propofol product having [*19] a pH range of 6.0 to 7.5 when the pH range of the proposed, and now approved, Gensia Sicor

product was more than an "order of magnitude" lower at 4.5 to 6.4.

(3) Gensia Sicor admitted, and FDA found, that Gensia Sicor's substitution of sodium metabisulfite ("Sulfite") for EDTA in DIPRIVAN(R) affected the safety of the proposed propofol product so much that a special warning had to be added to the labeling approved for DIPRIVAN(R). FDA nonetheless approved Gensia Sicor's ANDA. In so doing, FDA violated its own regulations which prohibit FDA from approving a drug using its abbreviated review procedures where the applicant, here Gensia Sicor, "fails to provide[] information demonstrating that the differences [between the proposed drug product and the reference listed drug] do not affect the safety of the proposed drug product."

(4) FDA violated the FDCA when it approved Gensia Sicor's ANDA after finding that the presence of Sulfite in Gensia Sicor's propofol product required the addition of a sulfite warning not present in the labeling for DIPRIVAN(R). As FDA has long recognized in its official pronouncements, the FDCA requires rejection of an ANDA "where a proposed change [*20] in a generic drug would jeopardize the safe and effective use of the product so as to necessitate the addition of significant new labeled warnings."

(5) FDA acted arbitrarily, capriciously, and abused its discretion in concluding that Gensia Sicor's propofol product was therapeutically equivalent to DIPRIVAN(R) because, as FDA correctly found, Gensia Sicor's Sulfite-containing propofol product cannot safely be used on a significant portion of the patient population and should not be used on patients whose sulfite sensitivity is unknown.

(6) FDA acted arbitrarily, capriciously and abused its discretion in approving labeling for Gensia Sicor's propofol product which, in violation of FDA's stated requirements, contains only a sulfite "precaution" rather than a full sulfite "warning" and deletes entirely the pancreatitis warning.

(7) FDA violated the FDCA by approving any propofol product prior to June 11, 1999, the current expiration date of FDA's three year market exclusivity grant to DIPRIVAN(R) for a propofol product containing an antimicrobial additive, not just propofol with EDTA.

Motion for Partial Summary Judgment at 2-4 (unnumbered). Each of these grounds [*21] will be addressed, *seriatim*.

n8 Zeneca sought to reserve the right to raise additional issues "after receiving the entire administrative record and/or taking FDA's deposition." Mem. in Support of Part. Summary Judgment at 3 n.2. Because the Court concludes that no additional discovery will be permitted and no additional portions of the record released, Zeneca's challenges to FDA's decision is limited to these seven issues.

A. EDTA and Sodium Metabisulfite as "Preservatives"

Under 21 C.F.R. § 314.94(a)(9)(iii), FDA can approve an ANDA for a generic version of a parenteral drug if the only variance between the innovator drug and the generic drug is a difference in the preservative, buffer, or antioxidant. n9 Zeneca's and Gensia's products contain different antimicrobial agents: Zeneca's Diprivan contains EDTA and Gensia's generic propofol contains sodium metabisulfite. FDA approved the ANDA on the basis that this difference is only a difference in preservatives, Zeneca contends that this reasoning is inconsistent [*22] with FDA's requirement that the labels for both products contain a statement that the product "contains no preservatives."

n9 The regulation reads as follows:

(iii) Inactive ingredient changes permitted in drug products intended for parenteral use. Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an appli-

cant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product.

These positions, however, taken by FDA in these two different contexts, are not inconsistent. The use of the word "preservative" in the context of approval of a generic drug relates to the function of the [*23] inactive ingredient in the formulation. In the labeling requirement, the word refers to the effectiveness of the antimicrobial agent. The FDA explains that neither formulation contains a sufficient concentration of the respective antimicrobial agents so that they can meet applicable preservative effectiveness tests. See SAR at 369-370. Because the level of these agents is insufficient to protect from contamination, FDA requires the labels for both products to contain a statement that the product "contains no preservative" "to diminish the likelihood of continued practitioner misuse and subsequent infections." *Id.* at 370. That does not change the fact that both EDTA and sodium metabisulfite are preservatives, i.e., "substance[s] that prevent[] or inhibit[] microbial growth." *Id.* (citing Remington's Pharmaceutical Sciences at 1286).

B. The pH of the Approved Formulation

Zeneca's Diprivan has a pH range of 7.0 to 8.5. The pH for the product Gensia is marketing has a range of 4.5 to 6.4. Zeneca argues that FDA approved Gensia's product under the mistaken impression that the product would have a pH range of 6.0 to 7.5. Zeneca claim is, in essence, that FDA [*24] simply approved the wrong drug. Because the approval was based on this materially erroneous factual predicate, according to Zeneca, the decision to approve was arbitrary and capricious.

The record belies any claim that FDA was confused as to the pH of Gensia's product. On March 31, 1997, Gensia submitted an ANDA for a generic propofol product containing EDTA, the same antimicrobial agent as found in Diprivan. That product was to have had a pH range of 6.0 to 7.5. On January 16, 1998, however, Gensia amended its ANDA, withdrawing from consideration the formulation containing EDTA and, instead, seeking approval of a formulation using sodium metabisulfite as a preservative. Because the microbial activity of sodium metabisulfite is increased in a more acidic solution, Gensia had to lower the pH of its new formulation to achieve

an antimicrobial effect similar to that of Diprivan. As noted by Gensia, Gensia highlighted throughout the amended ANDA that the new formulation had a pH range of 4.5 to 6.4. See Gensia's Cross Motion at 22 (listing references in the amended ANDA to the pH range). In early June 1998, Dr. Moo Park of FDA noted in his review of the ANDA that "the test product [*25] differs from the reference product in the pH specification," and specifically noted the range as 4.5-6.4. AR at 002905.

In August of 1998, Gensia arranged for a conference call with FDA to discuss various issues related to the amended ANDA. The agenda for the meeting included:

Comparison of Propofol Formulations

...

Differences in Preservation, Packaging Configuration, and pH

...

pH Designated in Formulation

Agenda for August 19, 1998 Meeting (emphasis added), AR 003826. The materials Gensia submitted prior to the telephone conference contained a lengthy discussion of the 4.5 to 6.4 pH specification for the product and Gensia's conclusion that this difference from the originator's formulation would not impact the safety of the generic product. AR at 003827-003829.

Given the prevalence of references to the 4.5 to 6.5 pH range in the record, Zeneca acknowledges, as it must, that FDA was apprised of the lower pH range. Zeneca's argument is that, somehow, despite Gensia's repeated reference to the new pH range, FDA never read those materials and became aware of the change in the amended ANDA. As support for this theory, Zeneca cites an April 8, 1998 Memo [*26] from Dr. Mary Fanning in which she mistakenly refers to the pH of Gensia's product as 6.0 to 7.5. Zeneca's Reply to Gensia's Motion at 5 (citing AR 003568).

That Dr. Fanning on one occasion very early in the review process referred to an incorrect pH range is a slim thread to hang the conclusion that FDA repeatedly ignored what was prominently disclosed in Gensia's submissions and conducted this extensive review on the wrong drug. That conclusion is further undermined by the existence of later documents in the record which were provided to Dr. Manning (and on which she "signed off") that contain the correct pH information. See AR 003816, 003824-003831 and 004011-004012; see also, AR 004256 (in labeling review dated Dec. 21, 1998, Koug Lee notes "the pH is now listed as 4.5 - 6.4 compared to 7 to 8.5. The pH difference was found to be ac-

ceptable by Dr. Mary Fanning"). While there may have been some initial confusion, it was certainly clarified long before the ANDA was ultimately approved on January 4, 1999. n10

n10 It is on this issue that the lack of availability of the entire administrative record is the most problematic. FDA's motion cites withheld portions of the record that discuss a October 1998 microbiology review and a December 1998 chemistry review that apparently also reference the proper pH range for the proposed product. Given the other references in the record to FDA's knowledge of the true pH of the proposed formulation, the Court need not consider this withheld material.

[*27]

C. FDA Reliance on Sulfite Warnings in Approving ANDA

It is undisputed that a certain portion of the population is susceptible to adverse reactions to sodium metabisulfite because of sulfite sensitivities or allergies. As a result, in approving-- Gensia's product, FDA required sulfite warnings to be included in its labeling. n11 Zeneca argues that FDA violated § 314.94(a)(9)(iii) of the FDCA by relying on these warnings as part of its safety evaluation of Gensia's product. As stated above, § 314.94(a)(9)(iii) requires that any "differences" related to the use of a different preservative must "not affect the safety of the proposed drug product." As an alternative argument, Zeneca contends that, even if warning labels could be employed to negate new safety concerns related to sodium metabisulfite, the warning labels provided are inadequate to assure the safe use of Gensia's product.

n11 FDA requires the following sulfite warning to appear on any prescription drug product containing a sulfite (except sulfite-containing epinephrine, which must carry a different warning):

"Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general

population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people."

21 C.F.R. § 201.22(a) and (b).

[*28]

As an initial observation, there is nothing novel or unique in FDA's approving a sulfite containing generic drug with appropriate warnings where the pioneer drug did not contain a sulfite. FDA cites three examples of its doing just that. See FDA's Motion for Summary Judgment at 21, n.10, and Exhibit C (listing methocarbamol injection, meperidine hydrochloride injection, and metoclopramide injection as examples). Furthermore, at least one court has found nothing arbitrary or capricious in FDA's approval of a generic by reliance on a warning necessitated by an inactive ingredient in the generic to which a certain portion of the population might be sensitive. See *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996).

In *Bristol-Myers*, the manufacturer of a pioneer drug complained that an FDA-approved generic version of its drug containing aspartame posed a potential public health risk. It was undisputed that aspartame can cause adverse health effects in a certain portion of the population, in this case, those that are unable to metabolize phenylalanine, a component of aspartame. In dismissing the pioneer drug manufacturer's criticism of the FDA [*29] approval, the District Court for the District of Columbia held that "this danger is negated" by the fact that the generic "contains a clear warning label specifying that the drug product contains phenylalanine. The product box also states that it contains aspartame. A treating physician who has a patient who could not metabolize phenylalanine would be on notice, as with other drugs which may have an adverse effect on his or her patients, not to prescribe the drug to phenylketonurics." 923 F. Supp. at 222.

In the instant case, as Gensia correctly observes, in arguing that the approval of Gensia's ANDA was violative of § 314.94(a)(9)(iii), Zeneca is confusing the safety profile of the generic drug with the adverse event profile. See Gensia's Cross Motion at 16. This distinction is explicit in the decision in *Bristol-Myers*. While acknowledging that the approved generic drug "may have an adverse effect" on certain patients, nonetheless, the FDA properly concluded the drug was "safe for its intended use." 923 F. Supp. at 222 (emphasis added). The Court concurs with Gensia that "FDA reasonably concluded that, although the product has a [*30] different risk profile, requiring a warning for sulfite sensitive patients, the

safety of the product was not affected because both Gensia Sicor's product and Diprivan are safe when used as directed." Gensia Cross Motion at 16.

The Court finds curious Zeneca's related argument that the warnings are ineffective to render Gensia's product safe because physicians will ignore those warnings. See Zeneca's Motion at 35. Regulations related to the labeling and packaging of drugs are a fundamental part of FDA's regulatory scheme. To assume that health care providers would either fail to read or ignore clear warnings would call into question that entire scheme. Zeneca has provided no support for this remarkable assertion. As to Zeneca's claim that the warnings are not sufficiently clear, that they should be printed in a holder print or a different color, that is precisely the kind of specialized determination about which this Court cannot substitute its judgment for that of the regulatory agency. See *Henley v. FDA*, 873 F. Supp. 776, 782 (E.D.N.Y. 1995) ("It is this Court's view that the FDA's determination of what labeling best reflects current scientific information . . . involves a high degree of expert scientific analysis"), *aff'd*, 77 F.3d 616 (2d Cir. 1996).

D. Section 355(j)(2)(A)(v)'s Same Labeling Requirement.

Zeneca also argues that the need to include a sulfite warning on the label of Gensia's product results in a violation of that provision of the FDCA that requires, generally, that the labeling of a generic drug be "the same as" that of the pioneer drug. See 21 U.S.C. § 355(j)(2)(A)(v). n12 Defendants counter that, because the difference in labeling relates to a permissible change in the formulation of the drug, the difference is permissible under an established exception to the "same labeling" requirement, specifically, 21 C.F.R. § 314.94(A)(8)(iv). That regulation, which implements 21 U.S.C. § 355(j)(2)(A)(v), provides,

Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference [*32] listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions

made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

21 C.F.R. § 314.94(A)(8)(iv) (emphasis added).

n12 Section 355(j)(2)(A)(v) provides, in part.

An abbreviated application for a new drug shall contain -

... information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . except for changes required because of the differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers.

[*33]

Zeneca would hold FDA to a very narrow interpretation of this "formulation" exception, essentially limiting it to allowing a listing of product components or ingredients. See Zeneca's Reply to FDA's Motion at 13. In fact, Zeneca appears to question whether Section 314.94(a)(8)(iv)'s allowance for any "formulation" differences is a permissible interpretation of Section 355(j)(2)(A)(v). *Id.* at 13 n.13. Zeneca suggests that Congress intended the "changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers" to be limited to "merely the different name and address of the manufacturer." *Id.*

In one of the few reported decisions interpreting 21 U.S.C. § 355(j)(2)(A)(v), the Court of Appeals for the District of Columbia Circuit took a much broader view of the "same labeling" requirement. *Bristol-Myers Squibb Co. v. Shalala*, 320 U.S. App. D.C. 32, 91 F.3d 1493 (D.C. Cir. 1996). In *Bristol-Myers*, FDA approved an ANDA for a new generic drug even though the label of the generic product did not include one or more indications that appeared on the label of the pioneer drug. 91 F.3d at 1499. [*34] In explaining its approval despite differences in the labeling, FDA relied on § 355(j)(2)(A)(v)'s exception for "changes required . . .

because the new drug and the listed drug are produced or distributed by different manufacturers." The court agreed with FDA's interpretation, finding that only that interpretation "works in harmony with" other provisions of the *FDCA*. 91 F.3d at 1500.

Similarly, in this instance, this Court concludes that FDA's interpretation of the statutory and regulatory "same labeling" provisions is entirely reasonable and most in harmony with other provisions of the *FDCA*. Given that a generic manufacturer is permitted to substitute certain inactive ingredients, including preservatives, see 21 U.S.C. § 355(j)(4)(H), it follows that these different ingredients must be identified in the labeling. Because a change in formulation may also result in other consequences, notice of those consequences must also appear on the label. See 21 C.F.R. § 201.22 (requiring sulfite warnings)

E. FDA's Designation of Gensia's Product as "Therapeutically Equivalent" to Diprivan

Zeneca next takes issue with FDA's decision to list Gensia's [*35] propofol product as therapeutically equivalent to Diprivan in the FDA publication, "Approved Drug Products With Therapeutic Equivalence Evaluations," more commonly known as "the Orange Book." Zeneca argues that FDA's advice in the Orange Book on therapeutic equivalence is inaccurate, and therefore, arbitrary and capricious because the inclusion of a sulfite in Gensia's formulation "may produce severe adverse reactions not associated with Diprivan with EDTA." Zeneca Motion at 43.

Listing in the Orange Book, however, does not imply that the generic drug is automatically interchangeable with the listed drug in all situations. The Orange Book specifies that "drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." Orange Book at viii (emphasis added). Furthermore, the Orange Book specifically cautions health care providers to use due care in prescribing or dispensing generic drugs in that the generic may contain a preservative ingredient, not contained in the pioneer, which might [*36] cause allergic reactions in certain patients. *Id.* at ix. n13

n13 Gensia, relying on *Pharmaceutical Mfrs. Ass'n v. Kennedy*, 471 F. Supp. 1224 (D. Md. 1979), argues that Orange Book ratings are not final agency actions and, therefore, are not reviewable. Because the Court finds that the Orange Book listing was neither arbitrary nor capricious, the Court need not ultimately resolve this

issue. The Court would note, however, that given the increased significance attributed to an Orange Book listing over the years since this Court decided *Pharmaceutical Mfrs.*, it would appear that an Orange Book designation constitutes a final agency action.

F. FDA's Approval of "Precaution" versus "Warning" Labeling and Elimination of Pancreatitis Precaution.

Zeneca next makes two claims regarding alleged "erroneous" labeling of Gensia's product: (1) that the sulfite warning was misplaced in the "precautions" section, as opposed the "warnings" section; and, (2) that a pancreatitis precaution found on [*37] Diprivan's labeling, is missing in Gensia's labeling. Neither claim has merit.

Regarding the sulfite warning, it clearly appears in the proper section as evidenced by the sample of the final printed label. Gensia's Cross Motion, Exhibit E. n14 While there is evidence that, at one point, Gensia had placed the warning in the wrong section, FDA identified the error and instructed Gensia to move the warning to the proper place. AR at 004252. As to the pancreatitis warning, Defendants explain that it has been omitted from the generic's label because the warning has yet to be approved for Diprivan. Under 21 U.S.C. § 355(j)(2)(A)(v), "the labeling proposed for the new drug [must be] the same as the approved labeling for the listed drug" (emphasis added). Once the pancreatitis warning is approved for Diprivan, it can be added to Gensia's labeling. n15

n14 21 C.F.R. 201.22(b) requires that the sulfite warning appear in the "Warnings" section.

n15 It is not clear why FDA has yet to issue a formal approval for Diprivan's pancreatitis warning. Zeneca asserts that FDA "dropped the ball." Zeneca Reply to FDA's Motion at 19. Regardless of whether FDA may have made some error with regard to a label approved for Zeneca's product, that is not a ground to withdraw approval of Gensia's ANDA.

[*38]

G. Zeneca's Market Exclusivity Rights

Lastly, Zeneca argues that FDA acted arbitrarily and capricious in approving Gensia's ANDA in that, in so doing, FDA violated certain exclusivity rights granted to Zeneca by FDA. The Court addressed this issue in a recent letter order.

Under 21 U.S.C. § 355(j)(5)(D)(iv), the FDA can grant three years market exclusivity when a pioneer drug manufacturer submits a supplemental NDA containing reports of new clinical investigations "essential to the approval of the supplement." The exclusivity extends only to the "change approved in the supplement," Zeneca's NDA supplement sought authority to add EDTA to Diprivan. The clinical investigations it submitted to the FDA with that supplement were necessitated by specific concerns related to EDTA, not to preservatives in general. Thus, the exclusivity applies to propofol products including EDTA, not to propofol products with other preservatives. As Zeneca itself stated in its exclusivity claim, "the exclusivity claimed is for the innovation represented by the addition of disodium edetate to propofol."

Letter Order dated June 8, 1999.

On this same basis, the Court [*39] will grant summary judgment to Defendants on Zeneca's claim that FDA's approval of the ANDA was arbitrary and capricious because it violated Zeneca's exclusivity rights. Because Zeneca's Fifth Amendment takings claims, Counts V and VI, are premised on the same unsupported assertion of exclusivity rights, summary judgment will be granted as to those claims as well. The Court will then deny Gensia's motion to dismiss those counts as moot.

IV. CONCLUSION

For the above stated reasons, the Court finds FDA did not act arbitrarily or capriciously in approving Gensia's ANDA for its generic version of Diprivan or in listing the product as therapeutically equivalent to Diprivan in the Orange Book. As the viability of each count of the complaint is dependant upon a finding that FDA acted arbitrarily and capriciously, the Court concludes that Defendants are entitled to summary judgment as to all claims.

A separate order consistent with this memorandum will issue.

William M. Nickerson

United States District Judge

Dated: August 11, 1999.

ORDER

In accordance with the foregoing Memorandum and for the reasons stated therein, IT IS this 11th day of August, 1999, by [*40] the United States District Court for the District of Maryland, ORDERED:

1. That Gensia's Motion to Strike, Paper No. 28, is GRANTED;

2. That Gensia's Motion to Dismiss, Paper No. 29, is DENIED as MOOT;

3. That Zeneca's Motion for Partial Summary Judgment, Paper No. 66, is DENIED;

4. That FDA's Motion for Summary Judgment, Paper No. 72, is GRANTED;

5. That FDA's Motion to Seal, Paper No. 73, is GRANTED in that Clerk of Court shall keep the designated materials submitted by FDA with its Motion for Summary Judgment under seal, until the conclusion of any appeal of this matter or the time for such appeal has expired, at which time the Clerk of Court will destroy said materials;

6. That Gensia's Motion for Summary Judgment, Paper No. 74, is GRANTED;

7. That Zeneca's Motion to Strike, Paper No. 75, is granted in that the Court will not consider the objected-to materials, but those materials will remain in the Court file to preserve the record for any appeal, should there be one;

8. That Zeneca's Request for a More Particularized Privilege Log, Paper No. 76, is DENIED as moot;

9. That FDA's Motion for a Protective Order, Paper No. 84, is DENIED as moot;

10. That judgment is hereby [*41] ENTERED in favor of Defendants and against Plaintiff;

11. That this action is hereby CLOSED;

12. That any and all prior rulings made by this Court disposing of any claims against any parties are incorporated by reference herein and this order shall be deemed to be a final judgment within the meaning of Fed. R. Civ. p. 58; and

13 That the Clerk of the Court shall transmit or mail copies of the foregoing Memorandum and this Order to all counsel of record.

William M. Nickerson

United States District Judge