Office of Drug Evaluation III
Room 13B45 Parklawn

CDE III

phone 301-827-3144
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DATE: 2/11/97

TO: Director
CDER

FROM: Acting Director
Office of Drug Evaluation III

SUBJECT: exclusivity for propofol with EDTA

Exclusivity for propofol with EDTA is important, because a reviewing division for good scientific reasons asked a sponsor to carry out clinical trials to demonstrate effectiveness and safety. [An advisory committee agreed, in public.] The sponsor was told effectiveness and safety studies were needed for approval. To say later, with the results found reassuring, that the trials weren't needed or were not studies of effectiveness and safety, is not correct.

These clinical investigations were essential to approval; they were new, and they were conducted by the applicant. These are the criteria for granting exclusivity.

I am happy to discuss this further or to provide more information.

Paula Botstein M.D.

cc:
Murray Lumpkin M.D. [with Dr. Wright's memo]
HFD 170/CurtisWright M.D.
HFD 170/David Morgan
Robert Temple M.D.
Roger Williams M.D.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 24, 1997

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Propofol Injectable Emulsion: Exclusivity

TO: Director, Center for Drug Evaluation and Research

There is no doubt raised on anyone's part that the studies carried out by Zeneca to find out whether EDTA added to propofol would affect mineral homeostasis 1) were clinical investigations, 2) were considered essential to approval, and 3) were conducted by the applicant. OGD argues against granting three years of exclusivity on only three possible grounds: that the studies do not meet the test for being new clinical investigations, that the studies may have been, in part, but not entirely, bioavailability studies (with clinical endpoints), and that the five clinical studies might have been "limited confirmatory safety studies" that could have allowed approval of propofol/EDTA as a 505(j) application. The second (bio) argument really is not made strongly because the studies had an undisputed safety component.

1. New clinical investigations

The definition of new clinical investigations in 314.108 is certainly peculiar and its peculiarity seems to have allowed an interpretation by OGD that is incorrect, namely, that because the five Zeneca studies did not address the safety of Diprivan/EDTA in a new patient population, they cannot be "new clinical investigations." That interpretation is not what 314.108, peculiar as it, is, says, as Dr. Wright has also pointed out more tersely than I am about to. We probably need a technical correction of the section.

Section 314.108 is not really about what "constitutes a new clinical investigation;" rather it is about what makes a clinical investigation not a new clinical investigation. Section 314.108 thus defines a new clinical investigation as one never relied on by FDA for providing substantial evidence of effectiveness of a previously

approved drug product for any indication (that is clear enough and perfectly sensible) and also one that has not been relied on to demonstrate safety for a new patient population. That is very odd, because it seems to say that the only way any safety clinical investigation can be considered "not new" is if it was used to show safety in a new population. Taken literally, if a safety study was used to support safety in the original patient population, or the safety of a new (higher) dose, or for any purpose other than safety in a new population, it would still be a new clinical investigation. That is hardly sensible. The rule should simple say that if a safety study was used to support safety of any previously approved drug product for any indication it cannot be a new clinical investigation.

Odd as the language is, however, it does not say that a study of safety in a new population is the only kind of safety study that can be a new clinical investigation, as OGD has read it; rather, it says that the only safety clinical investigation that is not new is one that did study a new population. As the Zeneca studies did not study a new population, they must be bona fide, bulletproof, new clinical investigations, unless they were bio studies or limited conformatory safety studies.

2. Bioavailability studies

It seems fairly clear from the MOR that the clinical studies had certain typical bioavailability components, e.g., examining effects of EDTA on propofol PK in volunteers and pediatric patients. OGD also argues that to the extent the Zeneca studies examined effectiveness of the Propofol/EDTA combination to see if it continued to function as an anesthetic agent equivalent to propofol (same dose, etc.), it is a bio study with clinical endpoints. Presumably the question cannot be fully answered with conventional bio studies (blood levels after a given dose; effect of EDTA on excretion), as these would not need clinical endpoints. Whether the efficacy aspects of the clinical endpoint studies are bio studies seems debatable, and could depend on the reason for concern. If, for example, it was thought that EDTA could affect movement of propofol into various body compartments, an effect not discoverable by measuring blood levels, these could indeed be clinical endpoint bio studies. On the other hand, if it were thought that changes in mineral levels could affect effectiveness on some other basis (membrane effects, perhaps), I would argue that the studies were not bio studies but efficacy studies. I would similarly argue that the clinical trials often needed for CR products to see if very different PK patterns lead to difference in S or E are not bioavailability

studies, but studies of the pharmacodynamic effects of drug. This all may be a discussion for another place.

I do not think the distinction Dr. Wright makes between the effect of propofol vs the effect of the formulation is helpful here; we are in all cases, in considering NDA's of any type, considering the drug product, not the molecule (moiety). A variety of factors could affect the product (inactives, other actives, coatings, etc.). To the extent we are worried about whether there is an effect on rate and extent of absorption or rate and extent of delivery to the active site, the study to show effectiveness is a bio study. But if we know there's a difference in rate and extent (e.g., for a controlled release product) and want to see what difference, if any, that difference makes, it is not a bio study.

In any case OGD agrees that the Zeneca studies were safety studies focussed on mineral homeostasis (but see #4 below).

3. Limited confirmatory safety studies (LCSS's)

As OGD notes, what exactly LCSS's are has never been described, but as a participant in more Petitions Committee meetings than I care to recall, I believe I can say with assurance that no one ever thought that five controlled trials are what it meant.

4. But what safety/minimal homeostasis was being looked for?

Not having any view/knowledge of how realistic a concern about effects of EDTA on mineral metabolism might be, it seemed reasonable to me to accept the word of inside and outside experts that it was realistic. It is also clear from the Fanning/Landow review that mineral effects were, in fact, the primary endpoint in these studies. Imagine my surprise, therefore, to see Dr. Tyler's review, which seems to indicate that concerns about calcium and magnesium were completely misplaced, although effects on Zinc might be a problem (and were not really considered). This raises the interesting possibility that we and the sponsor and the advisory committee all considered certain new clinical studies essential to approval that were not in fact essential.

5. Conclusions

The five controlled investigations of mineral metabolism were undoubtedly demanded by FDA staff and an outside advisory committee and it is clear that we would not have approved Propofol/EDTA without

those data. Dr. Tyler's view, after the fact, certainly needs to be looked into but should not be allowed to alter the history of the development of the drug product nor the Agency's initial view that the studies were needed. Once they are considered essential, it is clear that they <u>are</u> new clinical investigations, are safety, not bioavailibility studies, and are not LCSS's. Three year exclusivity should be granted.

There is a difficult process problem here that needs attention. A sponsor asked to carry out a study has, I think, a right to know whether it is essential, whether it is a bioavailability study, etc., and we should not be altering our view after the study is completed. Although I realize OGD has responsibility for making exclusivity determinations, OGD should ordinarily rely on ORM for determinations of what was needed for approval (always with the right to question a determination, of course). ORM staff also need to understand clearly what kinds of clinical studies might turn out to be bio studies in disguise, so that sponsors will be clear about what they're doing.

Robert Temple, M.D.

cc: Botstein
Wright
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Williams
G. Johnston
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Dickinson

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ROBERT T. ANGAROLA
(1945-1996)

January 22, 1997

BY TELECOPIER/CONFIRMATION COPY WITH ATTACHMENTS BY HAND

Roger L. Williams, M.D.
Deputy Center Director (HFD-3)
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20850

Dear Dr. Williams:

I am writing on behalf of my client, Ohmeda Pharmaceutical Products Division Inc. (Ohmeda). Ohmeda has submitted an abbreviated new drug application (ANDA) for Propofol Injectable Emulsion 1% (ANDA 74-719). Food and Drug Administration (FDA) review of the ANDA is expected to be completed shortly.

Zeneca Pharmaceuticals (Zeneca) is the manufacturer of the reference listed drug (trade name Diprivan®). On or about June 5, 1996, Zeneca received FDA approval of its supplemental new drug application (sNDA) to add the antioxidant EDTA[1/] to Diprivan. We understand that Zeneca has requested that FDA grant three years of marketing exclusivity under the Hatch-Waxman Act

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1/ This letter refers to EDTA as an antioxidant because of its pharmaceutics action, as described in standard pharmaceutical textbooks. See, e.g., The Theory and Practice of Industrial Pharmacy by L. Lachman, H. Lieberman, and J. King, p. 644 (3d ed. 1986), and Pharmaceutical Dosage Forms: Parenteral Medication, K. Avis, H. Lieberman, and L. Lachman, at 194, Vol. 1 (2d ed. 1992). Zeneca refers to EDTA in Diprivan as a "preservative," while qualifying that it is not a preservative by USP standards.

on the ground that Zeneca conducted a clinical study (or studies) in support of the change authorized in the sNDA.

Ohmeda has advised FDA on several occasions that Diprivan contained EDTA prior to the approval of the sNDA. In fact, testing by Ohmeda and an independent laboratory, Magellan Laboratories Inc. (Magellan), showed that Diprivan manufactured as far back as 1992 contained EDTA. Ohmeda's and Magellan's results are presented in Attachment 1. The enclosed data unequivocally demonstrate that EDTA was present in Diprivan well before the sNDA was approved.[2/]

Zeneca's request should be denied for several reasons. First, Zeneca's request is not based on "changes in active ingredient, strength, dosage form, route of administration, or conditions of use," previously identified by FDA as warranting exclusivity. 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994). Rather, the only purported change is the addition of the antioxidant EDTA to Diprivan. The sNDA for Diprivan therefore does not meet the statutory and regulatory requirements for exclusivity.[3/]

Second, EDTA is not new to Zeneca's drug product. Both Ohmeda and an independent laboratory tested Diprivan that was approximately five years old; EDTA was present in that product, as well as in other lots of Diprivan predating approval of the sNDA. See Attachment 1. Thus, at the time the sNDA was submitted to FDA, Zeneca was not proposing to make a qualitative change in product composition, as required by the three-year exclusivity provision.

2/ Ohmeda has provided Diprivan samples to FDA and offered technical support to the laboratory analyzing the samples. Unfortunately, although it was having methodological difficulties, the FDA laboratory was unwilling to discuss its analyses with Ohmeda and refused Ohmeda's offer of assistance. See cover letter to Attachment 1. We wish to emphasize, however, that exclusivity is unwarranted even if EDTA is assumed not to have been present prior to approval of the sNDA.

3/ On October 25, 1996, we sent a letter on behalf of Ohmeda to Douglas L. Sporn, Director, Office of Generic Drugs, stating why Zeneca's sNDA for Diprivan does not meet the statutory and regulatory requirements for marketing exclusivity. See Attachment 2. This letter supplements that letter and sets out additional grounds for denying exclusivity. Rather than repeat the reasoning set out in our October 25, 1996 letter, we incorporate those arguments by reference.

Third, Zeneca has not satisfied the statutory requirement of conducting a clinical trial that was "essential" to the approval of the sNDA. Any clinical trial Zeneca conducted was not "essential" to approving the inclusion of the inactive ingredient EDTA, which is a well-known, well-studied, and widely-used chemical agent in drug products.

Finally, the presence of EDTA in Diprivan as far back as 1992, presumably without notification to FDA by Zeneca and without an sNDA, precludes FDA from awarding exclusivity in 1997. Zeneca should be deemed to have actually submitted its sNDA once it was statutorily obligated to submit its sNDA, that is, when Zeneca knew, or should have known, that EDTA was present in Diprivan. Accordingly, any exclusivity that Diprivan with EDTA is arguably entitled to has expired.

Analysis

A. Any Changes Made To Diprivan Do Not Merit Three Years Of Exclusivity

The three-year exclusivity provisions of the Hatch-Waxman Act were intended to reward, and thereby encourage, "significant therapeutic" advances in drug therapy. See Statement of Congressman Waxman during House floor debate of Sept. 6, 1984) (Cong. Rec. at H9114); and 59 Fed. Reg. at 50357.[4/]

4/ The exclusivity provisions applicable here -- sections 505(c)(3)(D)(iv) and 505(j)(4)(D)(iv) of the Federal Food, Drug, and Cosmetic Act (FDC Act) -- provide that an sNDA qualifies for three years of marketing exclusivity only if the application "contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the [applicant]." 21 U.S.C. §§ 355(c)(3)(D)(iv) and 355(j)(4)(D)(iv); 21 C.F.R. § 314.108(b)(5). A new clinical investigation is

> an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety

(continued...)

The addition of a well-known, widely-used excipient with some antioxidant effect in a drug product cannot plausibly be characterized as a "significant therapeutic" advance. Nor does it constitute a change in active ingredient, strength, dosage form, or route of administration.

Indeed, as discussed below, addition of EDTA as an antioxidant is considered to be a relatively routine change that generally requires no clinical testing at all. But even if clinical testing were "essential" in the specific case of adding EDTA to Diprivan (and it was not as demonstrated below), the change itself (and, as discussed below, there was no actual "change") must be of a type that has sufficient importance to justify the extraordinary award of three years of market exclusivity. As the Medical Officer Review, at page 2, noted, "EDTA . . . has a long history of safe, FDA-approved use as a preservative in both foods and pharmaceuticals. . . ." Adding an antioxidant to a drug that has been marketed since 1989 does not meet that statutory standard.

Nor is it a valid argument that merely because clinical investigations occurred, the change necessarily justifies the award of exclusivity. It is possible that any change in a drug product, no matter how trivial, might lead to clinical testing to answer minor safety or effectiveness questions. To conclude that the mere performance of clinical testing elevates any change, no matter how trivial, to the status of a "significant therapeutic" advance, however, puts the cart before the horse. To justify three-year exclusivity, a change must be, in the first instance, of a type that is significant -- such as a change in the active ingredient, the strength, the dosage form, or the route of administration -- before it can be considered eligible for the incentive.

This conclusion is confirmed by the *Interim Inactive Ingredients Policy (Policy)*. This document contains a list of "exception excipients," which are those excipients for which FDA allows differences between the proposed generic drug product and the reference listed drug for the purposes of approving an ANDA.

4/ (...continued)

in a new patient population of a previously approved drug product.

21 C.F.R. § 314.108(a). The phrase "essential to approval means, with respect to an investigation, that there are no other data available that could support approval of the application." Id.

A generic drug product can contain an exception excipient and still be approved even though the excipient is not present in the reference listed drug. Antioxidants are identified in the *Policy* as an exception excipient for parenterals. This identification is based on FDA's recognition that the addition of an antioxidant, or the use of a different antioxidant, in a drug constitutes an insignificant change to the product. Such recognition confirms that the addition of the inactive antioxidant EDTA to Diprivan cannot be the sort of change that warrants exclusivity.

Both Congress and FDA have clearly stated that only "significant therapeutic" advances were meant to be rewarded with three years of exclusivity under the Hatch-Waxman Act. FDA's *Policy* demonstrates that even the addition of EDTA to Diprivan cannot be deemed a "significant therapeutic" advance supporting three-year exclusivity, and increasing EDTA levels is entirely undeserving of exclusivity.

Indeed, if companies were awarded exclusivity for a minor change such as adding an inactive antioxidant ingredient to a drug product (or increasing the level of the antioxidant), companies would be encouraged to attempt to extend their product monopolies by making a small change and then conducting unnecessary clinical studies to support the change. This would not serve the purposes of the Hatch-Waxman Act, patients, or the health care system.[5/]

Moreover, as the attached laboratory reports show (Attachment 1), EDTA was present in Diprivan at least as far back as 1992. Thus, even assuming that the addition of an antioxidant such as EDTA could ever be the type of change warranting exclusivity, EDTA was present long before the sNDA was approved. The sNDA did not result in a change in the chemicals present in

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5/ Zeneca may argue that the addition of EDTA was essential for safety reasons. The question is not whether the addition of EDTA provided an "essential" clinical benefit; the question is whether the clinical studies were "essential" to the approval. They were not. Moreover, Zeneca's own conduct belies the "essentiality" of the sNDA. The company did not recall "old" Diprivan products that pre-dated the sNDA, which still are in the marketplace today. For example, samples of Diprivan lot 5326T were obtained from Morristown Memorial Hospital in New Jersey on January 3, 1997, from the hospital's working stock. (The labeling of this lot did not indicate that EDTA was present.) Furthermore, Diprivan was marketed for seven years before the sNDA was approved.

Diprivan. There was, therefore, no "change," even if Zeneca increased the levels of EDTA.

B. Studies Of Diprivan With EDTA Were Not Essential

Under the Hatch-Waxman Act, exclusivity can be granted only if the clinical studies were "essential" to approval. Not all clinical studies meet this test. Zeneca's do not, for the reasons discussed below and in our previous letter.

The recent court decision upholding FDA's denial of The Upjohn Company's (Upjohn's) claim of three-year marketing exclusivity for over-the-counter (OTC) sales of Rogaine (minoxidil 2% topical solution) is instructive in analyzing Zeneca's exclusivity request. Upjohn Co. v. Kessler, 938 F. Supp. 439 (W.D. Mich. 1996) (Attachment 3). In this case, Upjohn submitted an sNDA to switch Rogaine from prescription (Rx) to OTC status. Included in Upjohn's sNDA were results of an intravenous (IV) study and an application for a three-year period of exclusivity. Id. at 441. FDA approved Upjohn's sNDA for the Rx-to-OTC switch, but denied the claim of exclusivity on the ground that the IV study was not "essential to approval" of the sNDA. Id. at 443. The court upheld FDA's decision.

"The only issue for the Court's consideration [was] whether there was a rational basis for the FDA's determination that the IV test was not essential to approval." Id. In oral argument before the Court, counsel for FDA explained the agency's denial of exclusivity as follows:

> The [IV] study served to confirm what the agency knew from the other information it had. It gave the agency some comfort. But it was not, as the regulation requires, the only data from which the agency could reach the conclusion that two percent Rogaine was safe to go over-the-counter. And since Upjohn can't satisfy that statutory and regulatory requirement, they don't get the other three years of exclusivity that they want.
>
> . . . [S]ince Upjohn doesn't satisfy the legal requirements for exclusivity, if they were given exclusivity, the absence of competition that would result in would be real harm. Congress again in passing [the Hatch-Waxman Act] determined that the absence of competition was a bad thing. . . .

Transcript of Preliminary Injunction Hearing, Vol II. at 275-76, Upjohn Co. v. Kessler, 938 F. Supp. 439 (W.D. Mich 1996) (No. 4:96-CV-90) (Attachment 4). The Court agreed with the reasoning of FDA's counsel, holding that FDA rationally

> concluded that the IV study did not add significantly to the FDA's ability to reach [a safety] conclusion because (1) the IV study did not add much information about concentration-response relationships . . . and (2) neither the IV or oral studies, as analyzed, shed light on individual responses. . . .
>
> [The Court's] conclusion is that the original clinical data, . . . enhanced by 6 benign (so far as we can tell) years of marketing, and the cohort study, indicate a very satisfactory record of safety, one suitable for an OTC drug. . . . The IV study was not *essential* to [permitting the Rx-to-OTC switch], although it supported it, because concentrations achieved overlapped with those in the study of oral minoxidil and gave little new information.

Upjohn at 444-45.

The Court's decision to uphold FDA's denial of three-year exclusivity to Upjohn's OTC Rogaine product is directly applicable to Zeneca's request for exclusivity. As with the Rx-to-OTC switch of Rogaine, FDA already had sufficient information to conclude that Diprivan with EDTA was safe and effective. EDTA has been used for years as an antioxidant in many kinds of drugs, including injectable drugs.[6/] As with OTC Rogaine, any recently conducted studies on EDTA in Diprivan were confirmatory, and cannot be considered "essential."

Moreover, the *Policy* shows that an ANDA for an EDTA-containing drug can be approved even if the reference listed drug has no EDTA. If an ANDA for an EDTA-containing drug can be approved when the reference listed drug does not contain EDTA, clinical studies were not essential to approving the Diprivan sNDA.

Finally, FDA's own reviews of the clinical data submitted with the Diprivan sNDA demonstrate that the studies were not essential to approval. The Medical Officer Review noted that Zeneca studied calcium and magnesium levels. However, the

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6/ See excerpts from FDA list of inactive ingredients in drug products, which is enclosed with the October 25, 1996 letter to Mr. Sporn (Attachment 2).

Review, at page 3, stated "that Zeneca's concerns regarding [calcium and magnesium] depletion were not well-founded." In other words, there was no need for a clinical study to determine the safety of EDTA with respect to these two ions. The Medical Officer Secondary Review, at page 2, echoed this conclusion.

> As has been well-discussed in Dr. Tyler's primary review, there was little possibility that either of these ions would be affected by ZD0859#1 infusion during either short-term or long-term administration.

The FDA reviewers did note that zinc depletion was a possible concern. However, Zeneca did not measure zinc plasma or urine levels during the study.[7/] FDA's documents demonstrate that, at most, the clinical studies were helpful and corroborative of what was already known -- they were clearly not "essential."

C. Even If The Addition Of EDTA To Diprivan Provided A Colorable Basis For Awarding Exclusivity, The Exclusivity Period Should Be Deemed To Have Already Expired

As demonstrated in Attachment 1, EDTA has been present in Zeneca's Diprivan product since at least 1992, which is over three years before the company obtained sNDA approval for adding this antioxidant to the product. Even assuming *arguendo* that the addition of EDTA to Diprivan provides a basis for awarding marketing exclusivity, FDA should conclude that the exclusivity period commenced at the time EDTA was first present in the product. Under this scenario, the three-year Hatch-Waxman exclusivity period has already expired.

FDA can -- and indeed should -- take equitable factors into account when assessing a company's exclusivity request. The United States Court of Appeals for the District of Columbia has endorsed administrative agencies' reliance upon equitable principles:

> [W]hen an agency is exercising powers entrusted to it by Congress, it may have recourse to equitable conceptions in striving for the reasonableness that broadly identifies the ambit of sound discretion. Conceptions of equity are not a special province of the courts but may properly be invoked

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7/ See Medical Officer Review at 12.

> by administrative agencies seeking to achieve "the necessities of control in an increasingly complex society without sacrifice of fundamental principles of fairness and justice."

City of Chicago v. Federal Power Comm'n, 385 F.2d 629, 642-43 (D.C. Cir. 1967). See also Gun South, Inc. v. Brady, 877 F.2d 858, 862 (11th Cir. 1989) ("[W]e note that the Supreme Court and other courts have recognized an implied authority in other agencies to reconsider and rectify errors even though the applicable statute and regulations do not expressly provide for such reconsideration.") citing United Gas Improvement Co. v. Callery Properties, 382 U.S. 223, 229 (1965); and American Therapeutics, Inc. v. Sullivan, 755 F. Supp. 1 (D.D.C. 1990) (although there is no FDA regulation or FDC Act provision that contemplates rescission of an FDA drug approval issued by mistake, the court held that FDA has implied authority to correct a mistake).

Under the rationale clearly established by the courts, even if FDA believes that Zeneca may be entitled to exclusivity for adding EDTA to Diprivan, the agency should in fairness take into account the fact that the company has been marketing the product with EDTA for more than three years. Assuming that it was simply a mistake that Zeneca failed to take the measures necessary to support EDTA's inclusion at the time and to ask for any exclusivity it might have entitled it to, that mistake can be corrected by FDA. Failure to do so, by granting exclusivity now, would be inconsistent with the Hatch-Waxman Act. Exclusivity would not reward Zeneca for the development of a new product. Conversely, awarding exclusivity would stifle generic competition for a product that has been on the market for years.

Conclusion

Ohmeda strongly opposes the grant of marketing exclusivity to Zeneca's Diprivan product. Granting exclusivity would violate the explicit language of the Hatch-Waxman Act. Granting exclusivity would also be entirely incompatible with both the intent of the Hatch-Waxman Act to reward "innovation" and with the intent of FDA's implementing regulations. Granting exclusivity would be inconsistent with FDA's own policies and precedents. And, granting exclusivity would be precedent for other manufacturers seeking to obtain extended product monopolies by adding inactive substances and conducting unnecessary clinical studies.

We specifically request that you place this letter, and its attachments, in the administrative record established with

respect to Zeneca's request for exclusivity. We also ask that a copy of this letter and attachments be included in the administrative file for Ohmeda's ANDA.

If you have any questions regarding this letter, please contact me.

Sincerely,

Jeffrey N. Gibbs

JNG/MBN/eal
Attachments
cc: Janet Woodcock, M.D.
Director, Center for Drug
Evaluation and Research (CDER)
Douglas L. Sporn
Director, Office of Generic Drugs, CDER
Gordon Johnston
Deputy Director, Office of Generic Drugs, CDER
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ROBERT T. ANGAROLA
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February 12, 1997

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Roger L. Williams, M.D.
Deputy Center Director (HFD-3)
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20850

Dear Dr. Williams:

On behalf of my client Ohmeda Pharmaceutical Products Division Inc. (Ohmeda), I submit the enclosed **Report on Diprivan® sNDA Clinical Trials** prepared by Dr. Martin Rose, Vice President, Drug Development, Quintiles BRI Worldwide Strategic Consulting. The Report concludes that there were no new clinical investigations that were essential to the Food and Drug Administration's approval (on or about June 5, 1996) of Zeneca Pharmaceuticals' (Zeneca's) supplemental new drug application (sNDA) for Diprivan® containing 0.005% EDTA. Thus, the Report further demonstrates that Zeneca is not entitled to exclusivity.

We specifically request that you place this letter and the enclosed Report in the administrative record established with respect to Zeneca's request for marketing exclusivity for this product under the Hatch-Waxman Act. We also ask that a copy of this letter and the Report be included in the administrative file for Ohmeda's abbreviated new drug application for Propofol Injectable Emulsion 1% (ANDA 74-719).

If you have any questions, please contact me.

Sincerely,

Jeffrey N. Gibbs

JNG/MBN/eal
Attachments

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Douglas L. Sporn
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A wholly owned subsidiary of Quintiles BRI, Inc.

Report on Diprivan® sNDA Clinical Trials

By Martin Rose, M.D., J.D.
Vice President, Drug Development
Quintiles Worldwide Strategic Consulting 1

Introduction

I was asked to prepare a report regarding whether the clinical studies conducted by Zeneca in connection with its supplemental New Drug Application (sNDA) for a new formulation of Diprivan® containing 0.005% EDTA were "essential to approval", as defined by FDA in its regulations regarding marketing exclusivity.

My report begins with a brief summary of my conclusions, followed by a list of the materials reviewed, a discussion of these materials, and a conclusion.

Summary of Conclusions

The materials provided to me regarding the approval of the sNDA for a new formulation of propofol injectable emulsion 1% (Diprivan®), i.e., the releasable reviews for this approval, describe no new clinical investigations that were essential to the approval of the sNDA.

Items Reviewed

Agency documents regarding Zeneca's sNDA for Diprivan® 2

- "Review and Evaluation of Pharmacology and Toxicology Data," by D.H. Jean, Ph.D., dated April 4, 1996 (this is the review date; no stamp date was evident)
- "Pharmacology Review", by D.H. Jean, Ph.D., dated April 22, 1996
- Review and Evaluation of Pharmacology and Toxicology Data," by D.H. Jean, Ph.D., dated May 16 or possibly May 18, 1996, date completed May 14, 1996 (This document is followed by documents from Zeneca regarding a planned in vitro study).
- "Chemist's Review", by M.C. Theodorakis, Ph.D., dated April 12, 1996
- "Medical Officer Review", by I.L. Tyler, Ph.D., M.D., poorly legible stamp date, perhaps April 26, 1996, review completed January 5, 1996

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1 My resume is attached to this report.

- "Medical Officer Secondary Review," by R.F. Bedford, M.D., stamp date illegible, review completed April 26, 1996
- "Medical Officer Safety Review," by I.L. Tyler, Ph.D., M.D., dated June 7, 1996. This was the 4 month safety review.
- "Clinical Pharmacology and Biopharmaceutics Review", by S. Doddapaneni, Ph.D., poorly legible stamp date, perhaps April 26, 1996, review date March 22, 1996
- (Microbiology) "Review for HFD 170", by P. Stinavage, dated April 17, 1996

Other Documents

- FDCA Sec. 505(j) and its implementing regulations

Discussion

FDCA Sec. 505(j)(4)(D)(iv) provides for a three year period of marketing exclusivity following the approval of an sNDA that was approved after September 24, 1984 (the date of enactment of the relevant provision) which contains "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement ...." Virtually identical language appears in FDA's regulations implementing this statute at 21 CFR 314.108(b)(5). Supplements that do not meet the criteria quoted above are not eligible for exclusivity. The terms "clinical investigation," "new clinical investigation," and "essential to approval" are defined at 21 CFR 314.108(a).

It is my understanding that FDA approved an sNDA for a new formulation of Diprivan® providing for the addition of a new excipient, 0.005% EDTA, on or about June 5, 1996. Five studies described in the various FDA reviews listed above relating to this approval are "clinical investigations" as defined by FDA.3 For the purposes of this discussion, I will assume that all meet the definition of a "new clinical investigation," although I do not know if this is true. However as discussed further below, the reviews suggest that not one of these studies actually was, or was considered by FDA as being, "essential to approval". FDA's regulations define this term as meaning, "with regard to an investigation, that there are no other data available that could support approval of the application." For each study, it appears that the results of the study were highly predictable from other data, and that the studies were essentially superfluous and actually futile. The five clinical studies are discussed serially below. All studies were randomized, double-blind, parallel-group studies.

Trial 1: A Comparison of the Safety, Efficacy, and Pharmacokinetics of ZD0859#1 with Diprivan® in Healthy Subjects.

This study involved 99 subjects. The review indicates that the doses of the new formulation administered were much too low to produce meaningful (or even detectable)

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2 Dates provided are file stamp dates unless otherwise indicated.

3 One proposed study discussed by Dr. Jean in her review completed May 14, 1996, was not a "clinical investigation" as defined by FDA because no study drug was administered to human subjects; instead, propofol was added to human blood after it was drawn from human subjects who not exposed to the drug in any way. In any event, it not clear whether this study was completed.

EDTA-induced reductions in the concentration of Mg^{++} and Ca^{++} in blood, which were monitored. Zinc blood or urine levels were not measured. The safety and pharmacodynamic effects of the two formulations were similar, as expected. Not surprisingly, none were observed; the reviewer states that the negative findings were "as expected". The reviewer also notes that the pharmacokinetics and bioavailabilty of propofol were similar in the two formulations, and that the BUN and creatinine levels (which might be expected to change in the setting of substantial, but not subtle, renal impairment) did not differ between the two formulations; again all these finding were described "as expected". The repeatedly stated theme of the review is that the study had virtually no *a priori* likelihood of detecting a difference between the study groups in any parameter that was actually measured.

Trial 2: ZD0859#1 vs. Diprivan® with High-Dose or Low-Dose Opioid in Cardiac Anesthesia

In this four-way study, 102 cardiac surgery patients were assigned to either the new or old Diprivan® formulation with either high-dose or low-dose opioid anesthesia. Again, the maximum amount of the new formulation used was far below the amount that might produce any observable effect on calcium or magnesium blood levels. Zinc levels were not measured. No notable differences in safety or efficacy were observed between the two formulations.

Trial 3: ZD0859#1 vs. Diprivan® for Maintenance in Children

This study was performed in 37 children undergoing cardiac surgery with nitrous oxide anesthesia. Again, serum calcium and magnesium levels were monitored, but doses of the new formulation were too low to expect any clinical adverse effects of EDTA. Several patients (4 of 19 in the ZD0895#1 group and 1 of 18 in the old Diprivan® formulation group) developed transient, mild, laboratory evidence of hypocalcemia (noted only at the 15 minute measurement); no symptoms were noted. Zinc levels were not measured. No meaningful differences were observed between the formulations.

Trial 4: ZD0859#1 vs. Diprivan® for Sedation in [seventy-five] Post-Surgical ICU Patients [requiring mechanical ventilation]

Trial 5: ZD0859#1 vs. Diprivan® for Long-Term, ICU Sedation [in 52 patients requiring mechanical ventilation]

These two studies were discussed together in Dr. Tyler's first review. He noted that the infusion rates used in these studies made it very unlikely that any effects on cation levels would be observed. Dr. Tyler notes that "as expected", no significant differences between the treatment groups were observed in terms of serum levels of Mg^{++}, Ca^{++}, BUN, or creatinine. The initial study reports contained no data on serum or urinary levels of zinc. However, zinc levels eventually were obtained from stored serum (but not urine) from patients in Study 5 and reviewed in Dr. Tyler's 4 month safety review; they appeared not to be depressed. However, he noted that release of zinc from storage sites in muscle would obfuscate any EDTA-induced reduction of circulating zinc levels in, and

added that "the study methods did not permit their detection" (referring to signs of zinc depletion or subtle renal dysfunction, another possible effect of EDTA). He suggested that microscopic studies of urine sediment (to detect subtle renal dysfunction) and studies of urinary Zn^{++} excretion (along with Cu^{++} and Co^{++} excretion) might answer the relevant scientific questions.

Conclusion

As discussed above, Dr. Tyler's two reviews indicate that each of the clinical studies was very unlikely to detect any differences between the two formulations in terms of their effects on any clinical laboratory parameter that was actually measured, clinical adverse events, the pharmacodynamics of propofol, its efficacy in clinical use, or its pharmacokinetics. He repeatedly noted that the study results were "as expected". Dr. Bedford, the secondary reviewer (he was then the Acting Director of the Division of Anesthesia and Critical Care Drug Products, which regulates Diprivan®), concurred in his review, where he noted that,

> "As has been well-discussed in Dr. Tyler's primary review, there was little possibility that either of these ions [referring to Ca^{++} and Mg^{++}] would be affected by ZD0895#1 infusion during either short-term or long-term administration. As expected, there was no clinically relevant difference between the 2 propofol formulations in terms of any of the hemodynamic or other vital organ parameters measured during the clinical trials."

These conclusions of Dr. Tyler and Dr. Bedford are not surprising, since the only difference between the new and old formulation was the inclusion of 0.005% EDTA to the new formulation. EDTA is a widely used excipient, and is used at concentrations even higher than 0.005% in many drug products. The most recent version of FDA's *Inactive Ingredient Guide* (January 1996) indicates that the "NDA count" for IM or IV injection containing EDTA at a concentration of 0.01% to 1.0% is 57. The "NDA count" is defined as the "number of approved NDAs in which a particular inactive ingredient currently appears." This source also suggests that there may be as many as 50 other NDAs for products suitable for IV injection containing EDTA at concentrations ranging up to 1.0%. As a general matter, the approval of an sNDA for the addition of a commonly used excipient does not require clinical studies, although on rare occasions FDA might ask for clinical data. In this case, the only plausible reason to require any clinical investigations prior to approval of the sNDA would be to evaluate the safety risks associated with the addition of 0.005% EDTA to the formulation, which FDA believed to be subtle renal dysfunction and zinc depletion.

However, as was noted Dr. Tyler and Dr. Bedford, the studies actually performed could not have done that. None of the trials included the (urinary) clinical laboratory measurements needed to directly address these potential toxicities. Instead, the clinical studies performed by Zeneca addressed scientific questions that did not need to be answered with new clinical data because the answers were already known to a sufficient degree of certainty. Those answers, for each measured parameter, were essentially that the two formulation did not differ in any detectable way. As repeatedly noted by Drs. Tyler and Dr. Bedford, the negative findings of the clinical studies were "as expected," given the known ion binding characteristics of EDTA and the low doses administered in the clinical studies. Thus, the studies performed were superfluous in the sense that they were intended to answer scientific questions that had already been answered, and

futile in the sense that the studies could not possibly show any difference between the two formulations with regard to any parameter that was measured in the studies. Accordingly, none of the studies were "essential to approval" since none addressed scientific questions that needed to be answered by new clinical data. All of the information obtained from these studies could have been provided by or predicted by other sources, including the references discussed by Dr. Tyler in the "Clinical Background" section of his first review and the relevant appendices of that review. The reviews of Drs. Tyler and Bedford note that more rigorous studies of the effects of the new formulation on zinc metabolism or renal dysfunction might have been performed, but were not.4 The supplement was approved nonetheless.

Based on my experience as a primary and secondary reviewer at FDA and subsequent experience in the pharmaceutical industry, and on FDA's reviews of the sNDA for the new formulation of Diprivan® containing EDTA, it is my conclusion that none of the clinical studies contained in that sNDA were essential to its approval.

Martin Rose, M.D., J.D.
Vice President, Drug Development

Date: Feb. 1, 1997

4 Notably, none of the clinical studies attempted to answer the question of whether the addition of EDTA to the formulation provided a clinical benefit to patients by reducing the incidence of post-operative sepsis in patients receiving Diprivan®. To test this hypothesis would require a comparative trial with many thousands of patients. However, I would not expect FDA to require such data, and in fact, it did not.

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EMPLOYMENT

Quintiles Worldwide Strategic Consulting 1994 --
Vice President, Drug Development
Rockville, Maryland

Provide clients with strategic and tactical services regarding drug development, including early-stage go/no-go decisions, pre-clinical development, Phase 1 through Phase 4 clinical development, protocol development, clinical trial execution, regulatory strategy, and drafting and reviewing regulatory submissions. Developed clinical programs for a novel agent for hypertriglyceridemia, an oral anti-diabetic agent, an anti-retroviral agent (including a European trial), an anti-arthritic (including an international multi-center trial), a cardiovascular drug-device combination, and a hormonal agent for prostate cancer. Selected by neuroscience company for clinical portions of NDA and MAA submissions for a novel recombinant agent for a neurodegenerative condition, with submissions planned for 3Q 1996. Planned analysis of safety data for a gastrointestinal OTC monograph product. Provided strategic advice and then planned the development of a vaginal anti-infective product (which is proposed for OTC use) and a novel formulation of a marketed topical steroid. Led BRI and client team writing an NDA that was filed in 2Q 1995 for a 1P cardiovascular drug, and assisted with clinical portions of European submission for the drug, including drafting the clinical expert's report and auditing European clinical sites. Provided strategic development advice to a European company planning to enter the U.S. market with a female hormone replacement product and a U.S. company with an agent for erectile dysfunction. Selected to write clinical portions of NDA for reproductive hormone product, to be filed 1Q 1997. Led team evaluating research portfolio of an Asian biotechnology company. Provided advice and representation at FDA for a client with a novel cardiovascular diagnostic agent that is entering clinical development.

Alpha 1 Biomedicals, Inc. 1993 - 1994
Senior Vice President, Clinical and Regulatory Affairs
Bethesda, MD

Had overall responsibility for clinical drug development in the Company. Planned and executed trials of drugs for chronic hepatitis B, chronic hepatitis C, and HIV; planned development of an HIV vaccine; planned development of compound with possible utility in pulmonary and infectious disease applications, including cystic fibrosis, ARDS, and sepsis; and evaluated candidate compounds for in-licensing, including an anti-parkinsonian and an anti-TNF agent. Supervised regulatory and QA functions. Supervised three direct reports and several teams of consultants.

Genentech, Inc. 1988 - 1993
Director, then Senior Director, Government Affairs
Washington, DC

Led development of positions on regulatory policy issues and presented them to Federal agencies and the White House; represented Genentech on the ACTG Pharmaceutical Industry Advisory Panel and in other forums concerned with AIDS drug development; served on AIDS vaccine project team, with responsibility for public and regulatory policy issues; supported DNAse project team, focusing on relations with the Cystic Fibrosis Foundation and the regulatory adequacy of clinical trials; represented Genentech on the industry advisory panel of the Society for the Advancement of Women's Health Research in connection with the Company's breast cancer product; initiated clinical development plan for major new endocrine indication of a marketed recombinant product; consulted with regulatory, clinical, and marketing departments on other development issues as needed; lobbied on legislative matters relating to biotechnology drug development and marketing; and provided legal and strategic assistance to marketing on promotional and reimbursement issues for tPA, hGH, and other Genentech products.

Food and Drug Administration 1983 - 1985 and 1986 - 1988
Group Leader, Division of Cardio-Renal Drug Products
Rockville, MD

From 1986 to 1988, supervised the review of drugs for hypertension, heart failure, and other cardiovascular indications as needed to meet Agency priorities; led group of 10 physicians and support staff. Administratively, functioned as de facto Deputy Division Director. Entered the Division in 1983 as Medical Officer, with responsibility for primary reviews of clinical data.

National Institutes of Health 1985 - 1986
Chief Medical Officer, Office of Medical Applications of Research (OMAR),
Office of the Director
Bethesda, MD

De facto deputy director and medical consultant, with responsibility for the Consensus Development Program, responding to Medicare coverage questions, and advising the NIH director and the offices of the Secretary and Assistant Secretary for Health regarding medical technology assessment-related issues.

Arnold & Porter
Associate Attorney
Washington, D.C.

1981 - 1983

Represented corporate clients in litigation and federal regulatory matters, with an emphasis on representing pharmaceutical manufacturers in matters involving the FDA.

Private Practice of Endocrinology and Internal Medicine
Walnut Creek, CA

1976 - 1977

Provided consultative and primary patient care.

EDUCATION AND MEDICAL TRAINING

University of California, Berkeley, School of Law (Boalt Hall), J.D., 1980; Clerk/Extern, Justice Frank K. Richardson, California Supreme Court, January - May 1980

Endocrine Fellow, University of California, San Francisco -- San Francisco Veterans Administration Hospital, 1974-1976.

Intern and Medical Resident, Saint Mary's Hospital, San Francisco, 1971-1972 and 1973-1974.

University of California School of Medicine, San Francisco, M.D. 1971, B.S. 1968.

Ohio State University, 1966-1967

Massachusetts Institute of Technology, 1964-1965.

CERTIFICATION AND LICENSURE

Member, District of Columbia Bar, 1981 --.
American Board of Internal Medicine, 1975.
California medical license, 1972 (by National Boards), No. G-23558.

ACADEMIC APPOINTMENTS AND PROFESSIONAL SOCIETIES

American Society for Clinical Pharmacology and Therapeutics 1988 -- ; Chair, Section on Clinical Pharmaceutical Development and Regulatory Affairs, 1994 -1997; Member, Government Affairs Committee, 1990 --; member, Publications Committee, 1996 --.

American University, Adjunct Professorial Lecturer of Law, 1984-1986.

UCSF, Clinical Associate in Medicine, 1976-1977.

American College of Physicians, Member, 1975.

TRADE ASSOCIATION AND INDUSTRY ACTIVITIES

PMA User Fee Task Force, 1992.

Institute of Medicine Study on the Use of Advisory Committees by FDA, Industry Liaison Panel, 1992.

FDLI Annual Meeting Planning Committee, 1990, 1992; FDLI Biologics Update Planning Committee, 1992, 1993.

ACTG Pharmaceutical Industry Liaison Panel, 1991 -- .

PMA AIDS Task Force, 1990 -1993.

BIO Drug Regulatory Committee, 1988 --; Chair, 1990 - 1992.

PUBLICATIONS

Rose M., Leibenluft R.F. Antitrust Implications of Medical Technology Assessment. New England Journal of Medicine 1986; 314:1490-1493.

Jacoby I., Rose M. Transfer of Information and its Impact on Medical Practice; the U.S. Experience. International Journal of Technology Assessment in Health Care 1986; 2:107-115.

Rose M., Woodhour A.F. The Orphan Drug Act: Current Perspectives and Future Directions. Regulatory Affairs 1989; 1:119-133.

Rose M., McMahon G.F. Some Problems With Antihypertensive Drug Studies in the Context of the New Guidelines. American Journal of Hypertension: 1990; 3:151-155.

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