UNITED STATES OF AMERICA
BEFORE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Iodochlorhydroxyquin and Hydrocortisone	)	Docket No. 80N-0012

POST-HEARING BRIEF FOR CIBA-GEIGY CORPORATION

Joel E. Hoffman
Michael L. Denger
Willard K. Tom
Marguerite E. Trossevin

SUTHERLAND, ASBILL & BRENNAN
1666 K Street, N.W.
Suite 800
Washington, D.C. 20006
(202) 872-7800

Attorneys for
CIBA-GEIGY Corporation

Jeffrey Rudin
CIBA-GEIGY Corporation
Summit, New Jersey 07901

Of Counsel

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Introduction

This hearing concerns the proposal of the Center for Drugs and Biologics (the "Center") of the Food and Drug Administration ("FDA") to withdraw approval of a new drug application (NDA 10-412), held by CIBA-GEIGY Corporation ("CIBA-GEIGY"), for Vioform-Hydrocortisone Cream and Ointment. (49 Fed. Reg. 33173 (Aug. 21, 1984)). Vioform-Hydrocortisone is a topical combination drug preparation consisting of Vioform (iodochlorhydroxyquin), an antifungal and antibacterial agent, and hydrocortisone, an anti-inflammatory and antipruritic agent. (CPF 4-6). 1/

Vioform, a topical drug preparation that has been available in the United States for more than seventy-five years, is generally recognized as safe and effective for antifungal and

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1/ "CPF____" refers (by paragraph number) to the Proposed Findings of Fact Submitted by CIBA-GEIGY Corporation, filed herewith. "Stip. ¶___" refers to paragraphs setting forth uncontroverted facts in the stipulation dated January 11, 1985, among all parties and nonparty participants in this proceeding. Citations to written direct testimony are given by the last name of the witness, the exhibit number, and the page (or paragraph number if the testimony is organized into numbered paragraphs). Citations to other documentary exhibits are given by the exhibit number and page. The hearing transcript is cited as "Tr." followed by the page number.

antibacterial use. 2/ Hydrocortisone, which was approved by FDA in the early 1950's, is generally recognized as a safe and effective topical anti-inflammatory and antipruritic drug. 3/ Vioform-Hydrocortisone Cream, a fixed combination of these two topical drugs, was approved as safe by FDA in 1956. (NDA 10-412). Vioform-Hydrocortisone is used in the treatment of primary fungal infections and secondarily infected steroid-sensitive dermatoses, and has been so used for a material time and to a material extent. (CPF 7). It is safe and has been shown to be safe in such use, and the parties have so stipulated. (CPF 7).

Over the past fifteen years, evidence relating to the effectiveness of Vioform-Hydrocortisone has been reviewed by two separate panels of the National Academy of Sciences-National Research Council (NAS-NRC) and by FDA's OTC Advisory Review Panel on Antimicrobal Drugs (II), each of which found the combination to be effective. (See CPF 185).

Contrary to the conclusions of these advisory panels, as well as of numerous other qualified experts, the Center disagreed that Vioform-Hydrocortisone had been demonstrated to be effective and proposed to withdraw approval of NDA 10-412. 46 Fed. Reg.

2/ For the purposes of this proceeding, the Center did not dispute that Vioform is an effective antifungal agent. Narrative Statement of the Center for Drugs and Biologics, filed October 22, 1984, at 3 n.2.

3/ For the purposes of this proceeding, the Center did not dispute that hydrocortisone is an effective anti-inflammatory agent. Id.

47408 (Sept. 25, 1981). In November 1981, CIBA-GEIGY requested a hearing on the proposal. The request was granted in August 1984.

Three issues have been set for hearing in this proceeding:

> 1. Whether there is evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug;
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> 2. Whether, on the basis of any such adequate and well-controlled investigations that exist, it could fairly and responsibly be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of drugs that the drug products in question satisfy the combination policy set out in 21 CFR 300.50 and will have the effect that they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof (21 U.S.C. 355(d)); and
>
> 3. Whether Vioform-Hydrocortisone is a "new drug" within the meaning of 21 U.S.C. 321(p). 4/

Statement of Facts

The theoretical rationale for using Vioform and hydrocortisone in combination for the indicated conditions is not in dispute. Fungal infections characteristically provoke a significant inflammatory response, and the effectiveness of an antifungal product such as Vioform may be significantly enhanced when combined with an anti-inflammatory agent such as hydrocortisone or

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4/ The first two issues were set forth in the Federal Register notice ordering the hearing. (49 Fed. Reg. 33173, 33176 (Aug. 21, 1984)). The third issue was added by order of the Presiding Officer at CIBA-GEIGY's request, and without objection by the Center, on November 15, 1984.

other corticosteroids. Similarly, a dermatosis complicated by a localized, nonspreading infection may respond more satisfactorily to a corticosteroid/anti-infective combination such as Vioform-Hydrocortisone. (CPF 68; Stip. ¶ 6).

It is also not in dispute that two of the studies submitted by CIBA-GEIGY in this proceeding, the "Carpenter Study" 5/ and the "Brecker Study", 6/ are adequate and well-controlled within the meaning of 21 C.F.R. § 314.111(a)(5)(ii)(1984) (Stip. ¶¶ 1-2), 7/ and it cannot seriously be disputed that the remaining study, the "Vioform-Locorten Study," 8/ is likewise adequate and well-controlled. (CPF 16, 105-114). The qualifications of the experts conducting those investigations have also not been challenged. Indeed the Center's witnesses expressly conceded the qualifications of Drs. Jolly and Maibach, each of whom testified

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5/ Seven Double-Blind Studies of Vioform-Hydrocortisone in Common Dermatologic Disorders. (C-1.2, at 6-71).

6/ A Multicenter Study of Vioform-Hydrocortisone (iodochlorhydroxyquin and hydrocortisone) in Cutaneous Fungal Infections. (C-1.2, at 119-450).

7/ Subsequent to the entry of the stipulation and the submission of written direct testimony, this section of the regulations was recodified as 21 C.F.R. § 314.126(b). References herein and in the Proposed Findings of Fact are to the section as formerly numbered, consistent with the regulation references in the record.

8/ Locorten 0.02%-Vioform 3% Cream Protocol 1: Dermatoses with Infection. (C-6.1). The Vioform-Locorten Study uses a virtually identical protocol and similar statistical methodology as the Carpenter Study. (See CPF 75, 105-06).

in this case on CIBA-GEIGY's behalf and was involved in one of the studies in question. (CPF 25-26). 9/

Since neither the safety of the drug nor the adequate and well-controlled nature of the studies is at issue, the principal issues in this proceeding are (1) whether qualified experts can fairly and responsibly conclude on the basis of these studies that the drug is effective for the indicated conditions, and (2) whether Vioform-Hydrocortisone is a new drug. (See Stip. at pp. 1-2 (issues)). The facts relevant to the first issue are set out in subparts A and B below; additional facts bearing on the "new drug" issue are set forth in Part III of the Argument (pp. 62-65, infra).

A. Primary Fungal Infections

CIBA-GEIGY presented three adequate and well-controlled studies relevant to the effectiveness of Vioform-Hydrocortisone in the treatment of primary fungal infections: the Brecker Study, the Carpenter Study, and the Vioform-Locorten Study. (CPF 83).

1. The Brecker Study

The Brecker Study was a double-blind, randomized, multicenter investigation involving 354 culturally-verified patients with acute cutaneous fungal infections. (CPF 86, 88). The patient population in the Brecker Study was significantly larger than those found in comparable studies. The size of the study, coupled with the fact that the study used a number of investi-

9/ The Center's witnesses also conceded the qualifications of Drs. Urbach and Stoughton, CIBA-GEIGY's remaining medical expert witnesses. (CPF 24, 27).

gators operating under a common protocol, renders the results particularly reliable. (CPF 88).

The Brecker Study compared the effectiveness of Vioform-Hydrocortisone to each of its components and to base cream (placebo) on pathogen conversion, on physician's and patient's global evaluation, and on reduction of erythema (redness), scaling, and pruritus (itching) at visit 2 (after 2 to 3 days of treatment) and visit 3 (after 6 to 8 days of treatment). (CPF 86, 121). The combination's superiority to base cream was demonstrated to a statistically significant degree (using two-tailed p-values) in pathogen conversion, in the physician's and patient's global evaluation at visit 2, and on every variable at visit 3. (CPF 121-23). 10/

The Brecker Study also demonstrated the contribution of each component to the combination's effectiveness. The pathogen conversion rate was 67% for the combination, 23% for hydrocortisone alone, and 30% for placebo, demonstrating Vioform's contribution with a difference that was statistically significant at less than the 0.01 level. (CPF 121, 126). Pathogen conversion is

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10/ Statistical significance, as used herein, refers to a p-value at or below 0.05, the level generally applied by FDA. (CPF 54). Since a p-value is a point on a continuum, any cut-off point is therefore arbitrary and both statistical and medical experts give weight to values somewhat above this point. (See CPF 54-55). P-values refered to herein are based on two-tailed tests, unless otherwise stated, since two-tailed tests were used to report the results of the studies. (CPF 60). A one-tailed value can be derived by dividing the two-tailed value in half (CPF 60). In the case of the studies here involved, it was recognized that use of one-tailed p-values was statistically appropriate. (See CPF 61-69).

an important and the most objective indicator of Vioform's anti-fungal activity. (CPF 126). Vioform's contribution was also shown on the physician's and patient's global evaluation and in reduction of erythema at final visit. (CPF 127). The results are such that the Center has stipulated that the Brecker Study demonstrates the contribution of the Vioform component. (Stip. ¶ 8). The contribution of hydrocortisone was demonstrated at visit 3 in both the physician's global evaluation and in improvement of erythema, the two most important variables and the ones most likely to be susceptible to reliable scoring. (CPF 134-35). The level of statistical significance for the physician's global evaluation was less than 0.01; for erythema it was also less than 0.01. (CPF 134-35).

Seven medical experts testifying as to the Brecker Study concluded that it demonstrated that Vioform-Hydrocortisone is effective in the treatment of primary fungal infections and that each component contributes to the effectiveness of the combination. (CPF 141). These witnesses included one expert testifying for the Center (Dr. Eaglstein), two for the American Academy of Dermatology, a disinterested professional organization representing over 6700 practicing dermatologists (Weary, AAD-1, at ¶1), 11/

11/ Because the Academy witnesses were appearing in support of Vioform-Hydrocortisone, CIBA-GEIGY did not originally request an opportunity to cross-examine them when it filed its Notice of Cross-Examination on April 12, 1985. Subsequently, Academy expert Weary was denied the opportunity to present certain additional oral direct testimony relating to why the data support his conclusion that the combination is effective. Moreover, because the Academy's experts appeared without benefit of counsel, it had no (footnote continued)

and four experts testifying for CIBA-GEIGY. 12/ (CPF 141). Only one witness, Dr. Rosenberg, testified otherwise, but even he indicated that "[i]f there were a replicating study, I would think the combination could be approved." (CPF 142). 13/ Several of the

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opportunity to present redirect testimony in response to the Center's cross-examination. At the hearing, CIBA-GEIGY requested but was denied an opportunity to examine the Academy's witnesses. (Tr. I-49-50, 60-61). CIBA-GEIGY's request was in the interest of fairness (both because the Academy was participating without counsel and because substantial additional testimony and material had been submitted into the record after its experts' written testimony had been prepared) and of developing a clear and accurate record of those experts' views; it would not have prejudiced the Center in any way.

12/ After extensive interviews with each of its four medical expert witnesses, counsel for CIBA-GEIGY prepared the initial drafts of their written direct testimony. The drafts were then submitted to each expert for review, revision and signature. (CPF 24, 27). The experts did not confer or consult with each other. (CPF 24). During cross-examination, counsel for the Center sought, through innuendo, to impugn the credibility, if not indeed the propriety, of this procedure; counsel in no way even attempted, however, to establish that the CIBA-GEIGY experts did not fully and independently subscribe to the statements made in their written direct testimony. The Presiding Officer correctly rejected any inference that the procedure used by CIBA-GEIGY's counsel was in any way improper. (Tr. V-5; see also Committee on Legal Ethics, District of Columbia Bar, Opinion No. 79 (1979) ("a lawyer may properly suggest language as well as the substance of testimony, and may -- indeed, should -- do whatever is feasible to prepare his or her witnesses for examination."). Because the medical experts reviewed the same data and held very similar views, this procedure resulted in their written direct testimony being identical in a number of respects. Because of this similarity, the Presiding Officer ordered exclusion of Drs. Maibach and Jolly so as to insure that each had no prior knowledge of the Center's inquiries of the other on cross-examination. (Tr. V-3-6). The fact that the testimony accurately expresses each individual witness' opinion, reached without collaboration with other witnesses or knowledge of their testimony, was confirmed by the failure of counsel for the Center to obtain any concessions from any of the CIBA-GEIGY experts.

13/ The testimony of the remaining Center expert, Dr. Solomon, with respect to the results of the Brecker Study analyzed as a single study was stricken. (CPF 141).

experts specifically explained that, even if the Brecker Study stood alone, experts could fairly and responsibly conclude that Vioform-Hydrocortisone is effective because the Brecker Study was a large multicenter investigation using a common protocol and because of the corroborating evidence that exists. (See CPF 143 (Jolly, Maibach, Urbach, Stoughton, Leyden, and Weary); CPF 173).

2. The Carpenter Study

The Carpenter Study was a double-blind, multicenter study involving 231 patients with secondarily infected steroid-sensitive dermatoses and 47 patients with culturally verified fungal infections. Results for the patients with verified fungal infections were analyzed separately. (CPF 95-96). This analysis of the Carpenter Study demonstrated the superiority of Vioform-Hydrocortisone to base cream on pathogen conversion to a statistically significant degree (one-tailed $p=0.035$), and on the physician's global evaluation at visit 2 (two-tailed $p=0.04$). (CPF 123). This analysis also demonstrated the contribution of each component to the combination's effectiveness. The pathogen conversion rate was 82% for the combination versus 30% for hydrocortisone alone, a difference significant at less than 0.05. (CPF 129). Superiority of the combination over hydrocortisone alone was also shown on physician's global evaluation at visit 2 (two-tailed $p<0.05$) and visit 3 (one-tailed $p=0.03$). (CPF 130). The contribution of hydrocortisone was demonstrated, using two-tailed p-values, in the physician's global evaluation at visit 2 ($p=0.01$) and in erythema at visit 2 ($p=0.03$); statistically significant

results using one-tailed p-values were also obtained for erythema at final visit (p=0.03). (CPF 139). As noted above, these two variables are the most important ones, and the ones most susceptible to reliable scoring. (CPF 167-71).

In light of these results, medical experts testifying in this proceeding were able to conclude that the Carpenter Study (1) was an additional adequate and well-controlled study showing the combination to be better than base cream, (2) confirmed the contribution of Vioform to the effectiveness of the combination, and (3) demonstrated the contribution of hydrocortisone to the effectiveness of the combination in treating primary fungal infections. (Maibach, C-21, at ¶¶ 79, 81, 91-93; Jolly, C-20, at ¶¶ 87-89, 92; Urbach, C-22, at ¶¶ 79, 81, ¶ 91-93; Stoughton, C-24, at ¶¶79, 82, 92-94; Weary, Tr. I-36-39).

3. The Vioform-Locorten Study

The Vioform-Locorten Study was a randomized, double-blind study assessing the effectiveness of Vioform in combination with another corticosteroid, Locorten (flumethasone pivalate). (CPF 16, 105). Because no corticosteroid is qualitatively unique with respect to its therapeutic or toxic effects (CPF 115), and because, in the concentrations used, there is no significant difference between the corticosteroid in the Vioform-Locorten Study and that used in Vioform-Hydrocortisone, the results of the Vioform-Locorten Study are relevant to the effectiveness of Vioform-Hydrocortisone. (CPF 115-19).

The Vioform-Locorten Study confirmed the results of the Brecker and Carpenter Studies. Vioform-Locorten outperformed base cream on pathogen conversion (70% vs. 30%) as well as in the physician's global evaluation at visit 2 (two-tailed p=0.03) and at final visit (two-tailed p=0.02). (CPF 124). Vioform's contribution was demonstrated by the combination's superiority to Locorten alone on pathogen conversion (70% vs. 29%) as well as in physician's global evaluation at final visit (one-tailed p=0.04). (CPF 132).

Thus, the results of three adequate and well-controlled studies are consistent in demonstrating the effectiveness of Vioform-Hydrocortisone in primary fungal infections (see CPF 125, 133, 140, 178-79).

4. Other Confirmatory Evidence

Other evidence and analyses corroborate the effectiveness of Vioform-Hydrocortisone in primary fungal infections.

First, because the Center contended that it was inappropriate to group together for analysis the 40 patients in the Carpenter Study with dermatophyte infections and the 7 patients in whom only Candida albicans was isolated (CPF 97), the Center performed an analysis that excluded the 7 Candida patients. (CPF 97). The alleged necessity for this exclusion, however, was refuted (CPF 98-104). Moreover, even separately analyzed, the data from those 40 patients merely validated the experts' conclusions as to the effectiveness of Vioform-Hydrocortisone. (CPF 123, 125, 129, 133, 139-40, 151-55, 162, 181-82).

Second, the Brecker Study, which originally combined the data from 22 centers into a single pool, was subsequently split into two separate pools on the basis of two different systematic divisions -- odd/even and first eleven/last eleven investigators. (CPF 89). The effect of those splits was equivalent from a statistical standpoint to having conducted two separate studies in the first instance. (CPF 90). The results of this analysis again supported the effectiveness of the combination and the contribution of each of its components. (CPF 122, 128, 138, 143, 161, 173).

Third, while neither the duration and extent of use of a drug nor qualified medical experts' clinical experience with a drug can by themselves provide substantial evidence of effectiveness, such use and experience can corroborate the evidence supplied by adequate and well-controlled studies. They can, for example, enable experts to reach fair and responsible conclusions as to a drug's effectiveness based on fewer adequate and well-controlled studies than would otherwise be the case. (CPF 184). Here, the clinical experience of the experts, and the 30 years of widespread and substantial use of Vioform-Hydrocortisone by dermatologists, strongly support the evidence of effectiveness contained in the Brecker, Carpenter, and Vioform-Locorten Studies. (CPF 184). Similarly, the conclusions of both the Ad Hoc Committee on Steroid Anti-Infective Combination Products of the American Academy of Dermatology ("AAD Ad Hoc Committee") and the FDA's OTC Antimicrobial II Panel (CPF 185), as well as the agency's analo-

gous conclusion that substantial evidence of Neo-Synalar's effectiveness had been presented (CPF 186-90), also confirm that it is fair and responsible to conclude, on the basis of the studies presented in this proceeding, that Vioform-Hydrocortisone is effective in the treatment of primary fungal infections and that each component contributes to effectiveness.

B. Secondarily Infected Steroid-Sensitive Dermatoses

CIBA-GEIGY presented two adequate and well-controlled studies supporting the effectiveness of Vioform-Hydrocortisone, the Carpenter Study and the Vioform-Locorten Study.

1. The Carpenter Study

The 231 patients in the Carpenter Study with culturally verified secondarily infected steroid-sensitive dermatoses were analyzed separately. (CPF 203). That analysis demonstrated that the combination was more effective than base cream to a statistically significant degree in the physician's global evaluation and in reduction of pruritus and burning at visit 2, and on every variable at final visit. (CPF 209). The contribution of hydrocortisone was shown by statistically significant differences, using two-tailed p-values, between the combination and Vioform alone on final visit on the physician's global evaluation ($p<0.001$) and in improvement of erythema ($p<0.01$), pruritus ($p<0.01$), and burning ($p<0.001$), and on visit 2 in improvement of pruritus ($p<0.001$) and burning ($p<0.01$). (CPF 212). The contribution of Vioform was demonstrated by the statistically significant (two-tailed $p=0.03$) superiority of the combination over hydrocortisone alone on physi-

cian's global evaluation (the most important parameter) at visit 2 (the most important visit for discerning the clinically expected benefit of Vioform). (CPF 215). It was also corroborated by the nearly significant difference on global evaluation at visit 3 (one-tailed p=0.055) and by the directional, but not statistically significant, superiority of the combination on every symptom parameter at every visit (CPF 215-16), as well as on pathogen conversion. (CPF 218).

Six of the nine qualified medical experts testifying in the proceeding concluded that the Carpenter Study, standing alone, was sufficient to establish that Vioform-Hydrocortisone is effective in the treatment of secondarily infected steroid-sensitive dermatoses and that each component contributes to the effectiveness of the combination. (CPF 222). Two other experts testifying for the Center, Drs. Rosenberg and Eaglstein, concluded that the Carpenter Study would not be sufficient to establish the combination's effectiveness in the absence of replication. (CPF 224, 226). Dr. Rosenberg's views were based on erroneous assumptions, however (CPF 254-55), and Dr. Eaglstein conceded that he was speaking only of his own view, and not of what other experts could fairly and responsibly conclude. (CPF 256). The Center's remaining expert, Dr. Solomon, based his testimony on the view that the physician's global evaluation is not very reliable and is of little importance. (CPF 257). This view was rejected by every other medical expert in this proceeding, including the other witnesses for the Center, and is not an appropriate basis for

restricting what other qualified experts can fairly and responsibly conclude from the data. (CPF 167-69, 257). 14/

2. The Vioform-Locorten Study

The Vioform-Locorten Study corroborated the results of the Carpenter Study. The combination was more effective than base cream to a statistically significant degree, using two-tailed p-values, on every response measurement at every visit (CPF 210-11), and was superior to Vioform alone on physician's global evaluation at visit 2 ($p=0.02$) and final ($p=0.01$), in improvement of erythema at final visit ($p=0.01$), and in improvement of pruritus at visit 2 ($p=0.01$) and final visit ($p=0.01$). (CPF 213). The superiority to Vioform alone approached statistical significance in the improvement of erythema ($p=0.065$) and burning ($p=0.06$) at visit 2 using one-tailed p-values. (CPF 213). The contribution of Vioform was shown by the combination's superiority to the corticosteroid alone on the physician's global evaluation at visit 2, with a difference extremely close to statistical significance (one-tailed $p=0.052$), as well as by the superiority of the combination on pathogen conversion (two-tailed $p<0.01$). (CPF 219-20). As in the Carpenter Study, the contribution of Vioform was also supported by the directional superiority of the combination over the corticosteroid on every parameter (except improvement of burning) at every visit. (CPF 220).

14/ Dr. Solomon's view that use of a steroid (such as hydrocortisone) is not necessary in the treatment of secondarily infected steroid-sensitive dermatoses is also at odds with the views of all other medical experts testifying in this proceeding. (See CPF 261).

3. Other Confirmatory Evidence

Other evidence also corroborates the findings of the two adequate and well-controlled studies submitted by CIBA-GEIGY regarding the combination's effectiveness in the treatment of secondarily infected steroid-sensitive dermatoses.

First, it was stipulated that the "Byk Study," 15/ although not adequate and well-controlled, may provide corroborative support to the results of other studies showing the effectiveness of Vioform-Hydrocortisone (CPF 17), and the actual results of the Byk Study in fact did so. (CPF 265).

Second, as with primary fungal infections, the duration and extent of use of the drug and the clinical experience of qualified medical experts with the drug corroborate the evidence supplied by the Carpenter and Vioform-Locorten Studies (CPF 267). The conclusions of the AAD Ad Hoc Committee and of five other leading dermatologists who submitted statements to FDA 16/ provide further such corroborative evidence. Their views, along with the agency's Neo-synalar decision, confirm that it is fair and responsible to conclude on the basis of the studies presented in this proceeding that Vioform-Hydrocortisone is effective in the treatment of secondarily infected steroid-sensitive dermatoses and that each component contributes to effectiveness. (CPF 268).

15/ Final Report, Clinical Efficacy Evaluation of Iodochlorhydroxyquin 3% - Hydrocortisone 1% Cream. (G-48, at 36-57).

16/ The views of the five experts are set forth in documents contained in C-1.2, at 72-118. The documents were admitted for the limited purpose of demonstrating that the individuals who made statements took the positions stated therein. Order dated April 19, 1985, at 3 n.3.

Argument

I. THERE IS SUBSTANTIAL EVIDENCE THAT VIOFORM-HYDROCORTISONE IS EFFECTIVE FOR THE TREATMENT OF PRIMARY FUNGAL INFECTIONS.

Section 505(d) of the Federal Food, Drug, and Cosmetic Act ("the Act") defines substantial evidence as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(d).

CIBA-GEIGY submitted the Brecker and Carpenter Studies, each of which was an adequate and well-controlled multicenter clinical trial of Vioform-Hydrocortisone in the treatment of primary fungal infections, as well as an adequate and well-controlled study of Vioform-Locorten for that indication. (CPF 83-119). Thus, the issue under Section 505(d) is whether, based on the results of the Brecker Study, either alone or as confirmed by the Carpenter and Vioform-Locorten Studies, qualified experts could fairly and responsibly conclude, as they did, that Vioform-Hydrocortisone is effective for that indication. If they could so conclude, CIBA-GEIGY has presented "substantial evidence" within the meaning of the statute and has satisfied its burden in this proceeding.

A. The Evidence Shows That Qualified Experts Could Fairly And Responsibly Conclude On The Basis Of The Brecker, Carpenter, and Vioform-Locorten Studies That Vioform-Hydrocortisone Is Effective For The Treatment Of Primary Fungal Infections.

1. Adequate and Well-Controlled Studies Constitute "Substantial Evidence" of Effectiveness If A Reponsible Body of Qualified Experts Concludes From Those Studies That the Drug Is Effective.

a. The experts' conclusions.

In this proceeding, five qualified experts, including participants in both of the studies, testified that they concluded (and that others could so conclude) from the Brecker and Carpenter Studies, as confirmed by the Vioform-Locorten Study, that Vioform-Hydrocortisone is effective for the treatment of primary fungal infections. (CPF 145). Those who so testified included a disinterested expert from the American Academy of Dermatology. In addition, seven of the eight experts who testified (including Dr. Eaglstein testifying for the Center) concluded that the Brecker Study established that Vioform-Hydrocortisone was effective for the treatment of primary fungal infections (CPF 141), and six experts concluded that the Brecker Study by itself was substantial evidence of the combination's effectiveness. (CPF 143). 17/ The bases for and reasoning supporting the experts' conclusions were fully set forth in their testimony. (See CPF 147-83). Without

17/ Even Center expert Rosenberg, the lone dissenter, recognized that the Brecker Study provides "some evidence" of hydrocortisone's contribution (the only disputed issue), and seemed to acknowledge that Brecker could count toward any two-study requirement since he stated that "[i]f there were a replicating study, I would think the combination could be approved." (Rosenberg, G-76, at 22, 23; see CPF 142).

question, a responsible body of experts has fairly and responsibly concluded, and has testified that other experts could so conclude, that the combination has been shown to be effective. That is all the statute requires. 18/

b. The meaning of "substantial evidence."

The statute does not require that the conclusion that a drug is effective be the unanimous or even the preponderant view of experts. Contrary to the position taken by the Center in previous proceedings, which we assume will be taken here as well, the legislative history of the Act demonstrates that a "preponderance of the evidence" standard was rejected by Congress.

(i) The Drug Amendments of 1962 arose out of an investigation by the Senate Judiciary Subcommittee on Antitrust and Monopoly into administered prices in the drug industry. 19/ The concept that approval of a new drug application was to be conditioned upon the drug being "efficacious" as well as safe was first introduced in the original version of S. 1552, 87th Cong.,

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18/ One of the Center's experts testified that the experts who concluded that Vioform-Hydrocortisone was effective were serious people who had reviewed the evidence. (See CPF 146, 228). There is no suggestion in the testimony of the Center's witnesses that those conclusions were unfair or irresponsible. (See CPF 147-83, 230-64). The contrary conclusions of the Center's experts are largely explained by particular views each holds and do not detract from the conclusions of those experts who testified that the CIBA-GEIGY sponsored studies establish that Vioform-Hydrocortisone is effective for its labeled indications. (See CPF 142, 158, 167-69, 199, 225, 254-55, 257, 260-61).

19/ See Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D.Del. 1970).

1st Sess. (1961). The term "efficacious," however, was not defined.

In 1962, the Senate Judiciary Committee adopted amendments to S. 1552 in an effort to clarify what would constitute proof of a drug's effectiveness. These amendments first introduced the concept of "substantial evidence (not necessarily preponderant evidence) that the drug will have the effect claimed for it" as the standard for proof of effectiveness. 108 Cong. Rec. 10108 (June 11, 1962) (Committee summary of the amendments). The purpose of the amendment was to "permit legitimate differences of opinion among responsible clinicians to be resolved by the medical profession in day to day practice, instead of being resolved for all doctors against the effectiveness of the drug by the fiat of the FDA staff." 20/

In analyzing the standard of effectiveness, the Committee stated that:

> The term "substantial evidence" is used to require that therapeutic claims for new drugs be supported by reliable pharmacological and clinical studies. When a drug has been adequately tested by qualified experts and has been found to have the effect claimed for it, this claim should be permitted even though there may be preponderant evidence to the contrary based upon equally reliable studies. 21/

20/ Id. The Committee further noted that "[t]here may be many physicians who would deny the effectiveness simply on the basis of a disbelief growing out of their past experience with other drugs or with the diseases involved." S. Rep. No. 1744, 87th Cong., 2d Sess. 16 (1962).

21/ Id. Indeed, the Center has admitted that adequate and well-controlled studies that demonstrate effectiveness will "suffice even if they are outnumbered by negative studies." In re Oral

(footnote continued)

The Committee went on to explain that its intention was to ensure that "safe new drugs become available for use by the medical profession so long as they are supported as to effectiveness by a responsible body of opinion." S. Rep. No. 1744, note 20 supra, at 16.

In the wake of the thalidomide tragedy, President Kennedy proposed additional amendments providing that approval of a drug could be withdrawn if "there is substantial doubt" as to its safety or efficacy. The "substantial doubt" standard was rejected by Congress, 22/ but the substantial evidence standard was clarified and strengthened by a definition of the quality of evidence that must form the basis for a conclusion that a drug is effective, i.e., the requirement of adequate and well-controlled studies. The Senate Judiciary Committee report explained the amendments, stating that

> [t]he committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels that the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below and evaluated by the Secretary in light of all the information available to him at the time.

Proteolytic Enzymes, Docket No. 75N-0139, Bureau of Drugs' Reply to Companies' Exceptions (July 31, 1981).

22/ Accord, Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 617 (1973) (affirming Hynson, Westcott & Dunning v. Richardson, 461 F.2d 215, 220 (4th Cir. 1972) ("Congress specifically discarded those terms ["preponderant evidence" or "conclusive evidence"] for the milder term 'substantial,' which was understood to embrace the idea, not of a preponderance but rather of a responsible body of qualified opinion.").

S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. 6 (1962). The Committee interpreted the new language as authorizing the Secretary to reject a claim of effectiveness if it were found

> (a) that the investigations were not "adequate"; (b) that they were not "well controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and responsibly be derived from their investigations.

Id. (emphasis added). Thus, Congress intended that drugs would be approved if adequate and well-controlled studies convinced a responsible body of qualified experts -- not a majority of experts or the agency staff or the Commissioner -- that the drug was effective. 23/ Indeed, as stated by the General Counsel of the Department of Health, Education, and Welfare shortly after enactment of the substantial evidence requirement, "there must be a bona fide, responsible and adequately based medical judgment in support of efficacy before a drug may be put on the market, but if this condition is met, a minority opinion may prevail." 24/

23/ Concurrently with the Senate, the House of Representatives was also drafting proposed amendments to the Act. H.R. 11581, 87th Cong., 2d Sess. (1962) also provided that approval of a new drug application would be conditioned upon proof of effectiveness. Originally, the bill permitted the Secretary to withdraw approval of a new drug if there was "substantial doubt" as to its effectiveness. During hearings on the bill, questions repeatedly arose about the quantum of evidence required to approve the marketing of a drug. See, e.g., Hearings on H.R. 11581 before the House Committee on Interstate and Foreign Commerce, 87th Cong., 2d Sess. 214 (1962). Subsequently, the House Commerce Committee amended H.R. 11581 by adopting the amendments proposed in the final version of S. 1552, including the substantial evidence provision.

24/ Alanson W. Wilcox, quoted in National Academy of Sciences, (footnote continued)

(ii) In other proceedings the Center has sought to recharacterize this legislative history as showing that a responsible body of expert opinion is insufficient to justify approval. 25/ Its contention is supported solely by a misreading of the district court's decision in Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301, 308-09 (D.Del. 1970).

In that case, PMA was seeking a declaratory judgment that FDA's regulations particularizing the standard of evidence necessary to demonstrate effectiveness, by specifying the elements of an adequate and well-controlled study, were invalid. PMA argued that a substantial body of expert opinion that a drug was effective satisfied the statutory standard. However, it also argued that clinical experience and investigations other than adequate and well-controlled studies as defined by the regulations should be a sufficient basis for that opinion. Id. at 306.

The court's analysis of the legislative history focused on discussions regarding the need for adequate and well-controlled investigations, id. at 307, and not on whether a preponderance of the evidence standard was appropriate. The position it rejected was that "any drug 'believed by a substantial number of experts' to be effective could be marketed. . .," regardless of the nature of the evidence on which that belief was based. Id. (emphasis

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Drug Efficacy Study: Final Report to the Commissioner of Food and Drugs 8 (1969).

25/ See In re Certain Combination Drugs Containing Antibiotics and Antifungal Agents, Docket No. 82N-0153, Brief of the National Center for Drugs and Biologics at 45 (Aug. 1, 1983).

added). Indeed, the court quoted the portion of the legislative history stating that "a difference of responsible opinion" should not result in disapproval of a claim if it is supported by substantial evidence as defined. Id. at 309. In holding that the "regulations describing the scientific content of adequate and well-controlled clinical investigations . . . reasonably carry out the Congressional mandate that all claims of efficacy for marketed drugs must be supported by substantial evidence," id. at 311, the court did not address the issue of the required degree of consensus among the body of expert opinion which must conclude that such clinical investigations show effectiveness.

(iii) In Antibiotic/Antifungal Combinations, the Center also argued that "whether there is a large or small number of 'such experts'" is irrelevant because the term "such experts" in the latter part of the substantial evidence definition refers only to the experts who participated in the investigations, and that whether those experts' conclusions were fair and responsible is for FDA, and not for other experts to decide. (Docket No. 82N-0153, Brief for the Center at 44-45). The Notice of Hearing in this proceeding, however, clearly construes "such experts" to refer to qualified experts generally. The issue designated for hearing is whether, on the basis of adequate and well-controlled investigations, "it could fairly and responsibly be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of drugs" -- without limitation -- that Vioform-Hydrocortisone is effective. 49 Fed.

Reg. 33173, 33176 (Aug. 21, 1984) (emphasis added). If the Center's contrary interpretation in Antibiotics/Antifungals were correct, it is difficult to imagine why, in this and other proceedings, the Center has gone to the trouble and expense of presenting outside expert witnesses and cross-examining outside experts who did not conduct the studies presented by the sponsor.

Whichever standard applies, however, there can be no doubt here that the investigators were qualified experts, and that they concluded that their studies demonstrate that the drug is effective. (See CPF 25-26; G-3; G54-A; Jolly, C-20; Maibach, C-21). At its narrowest, the issue is whether their conclusions could fairly and responsibly have been reached. Even if that issue be characterized as one for FDA to decide, the testimony of other qualified experts provides the Presiding Officer and ultimately the Commissioner with the evidence on which to make that determination.

c. The meaning of "effective."

To be fair and responsible, expert conclusions must be grounded in studies demonstrating that a drug is effective. The Act does not define "effective" in terms of a particular quantum of relief. To be effective a drug neither has to provide a wonder cure nor must it provide greater relief than other products available for the same indication. An effective drug is one that has "the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the

labeling or proposed labeling thereof . . . ." 21 U.S.C. § 355(d). Thus, an effective drug simply does as much or as little as the labeling claims.

The legislative history of the Drug Amendments of 1962 demonstrates that Congress' concern over the efficacy of drugs related to the protection of consumers from false claims, not to medical breakthroughs or comparative efficacy. During the hearings on the House bill, then FDA Commissioner Larrick testified that requiring effectiveness would not mean that the agency would determine a drug's therapeutic value. He stated that the sole purpose of the amendment was to require a sponsor to show "that the drug will do what he claims it will do." Hearings on H.R. 6245 Before the Antitrust Subcomm. of the House Judiciary Comm., 87th Cong., 2d Sess. 143 (1962). In the hearings on the Senate bill, the Secretary of Health, Education, and Welfare confirmed that the amendments "would not require a showing of relatively greater efficacy than that of other drugs." Hearings on S. 1552 before the Subcomm. on Antitrust and Monopoly of the Senate Comm. on the Judiciary, 87 Cong., 1st Sess. 2585 (1961). The Senate Committee stated that "studies may show that the drug will help a substantial percentage of the patients in a given disease condition, but will not be effective in other cases. What the Committee intends is to permit the claim for this new drug to be made to the medical profession with a proper explanation of the basis on which it rests." S. Rep. No. 1744, 87th Cong., 2d Sess. 16 (1962). Thus, Congress intended that (1) the treating

physician, not the agency, determine whether the effect a drug provides is appropriate for particular patients, and (2) that comparative efficacy be irrelevant in determining whether a drug is effective. 26/

2. The Brecker, Carpenter, and Vioform-Locorten Studies Constitute Substantial Evidence That Vioform-Hydrocortisone Is Effective For the Treatment of Primary Fungal Infections.

(a) A logical corollary to the proposition that the statute does not require unanimity of expert opinion as to the conclusions to be drawn from the studies relied upon to show effectiveness is that the results of the studies can leave room for doubt or disagreement among qualified experts. One expert's conclusion that the data show that a drug is effective is not unfair and irresponsible simply because another expert disagrees. 27/ An expert's conclusion is fair and responsible if it

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26/ Two of the Center's experts who testified that Vioform-Hydrocortisone was not shown to be effective appeared to be applying a relative efficacy or "treatment of choice" standard. (See CPF 198). Evaluation of Vioform-Hydrocortisone's effectiveness under such a standard is irrelevant.

27/ As noted above (see note 26), some of the Center's witnesses evaluated the effectiveness of Vioform-Hydrocortisone under an erroneous relative efficacy standard. As a result, their testimony is not entitled to significant weight. Illustratively, Dr. Rosenberg conceded that the Brecker Study showed statistically significant results in favor of Vioform-Hydrocortisone, but dismissed them because they did not convince him that "it's as effective as what I'm doing, so that maybe I'd want to change . . . ." (Rosenberg, G-76, at 29). Dr. Rosenberg also considered fungal cure to be the physician's primary objective; therefore, he was only interested in results at final visit. (CPF 179). His evaluation disregards the visit 2 data, which demonstrate the early symptomatic relief provided by the combination, and is inconsistent with his view of the "theoretical basis" for having a combination product for primary fungal infections rather than

(footnote continued)

is reasonably supported by the data. As Dr. Eaglstein testified, even "marginal" results in favor of the combination can demonstrate effectiveness. 28/

Seven of eight medical experts, including two from the American Academy of Dermatology and the Center's Dr. Eaglstein, concluded that the results of the Brecker Study establish that Vioform-Hydrocortisone is effective for the treatment of primary fungal infections. 29/ (CPF 141). Six of these experts testified that the Brecker Study alone constitutes substantial evidence of effectiveness (CPF 143); five testified that experts qualified by scientific training and experience could responsibly and fairly conclude, and that they so concluded, that Vioform-Hydrocortisone

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Vioform alone, namely that "the patient gets symptomatic relief a little earlier." (See CPF 179). However, neither Dr. Rosenberg's nor the agency's view regarding the treatment of choice or what clinical benefits are desirable for a certain group of patients is legally relevant or a ground for withdrawing approval of Vioform-Hydrocortisone. Congress specifically left those decisions to the treating physician.

28/ (CPF 141). Although Dr. Eaglstein characterized the results of the Brecker Study as "marginal," he did conclude that the results demonstrate that hydrocortisone contributes to the combination's effectiveness and that, in view of the stipulated contribution of Vioform, the study establishes the combination's effectiveness for the treatment of primary fungal infections. (CPF 141).

29/ CIBA-GEIGY attempted to enter into evidence, either directly or by judical notice, a portion of an internal agency memorandum dated February 13, 1985 (marked as C-33) that established that the Center concurred in the conclusion that the Brecker Study demonstrated that the combination is effective for the treatment of primary fungal infections. Although he admitted a portion of a similar memorandum (C-29) into evidence, the Presiding Officer, without explanation, refused to admit C-33. (Tr. VI-113). C-33 is extremely relevant to the issue of what experts can fairly and responsibly conclude based on the Brecker Study, and there was no basis for its exclusion.

is effective based on the results of the Brecker Study, the Carpenter Study of fungal patients (either 47 or 40-patient analysis), and the Vioform-Locorten Study. (CPF 145). Unquestionably, the data in the Brecker and Carpenter Studies were sufficient to support fair and responsible conclusions as to the combination's effectiveness under the statutory standard.

(b) The results of the Brecker and Carpenter Studies demonstrate that (1) the combination was superior to placebo on virtually every parameter measured; (2) the combination was superior to hydrocortisone and as good as Vioform in eradicating the fungal colony; and (3) the combination was superior to Vioform and as good as hydrocortisone in reducing the symptoms of inflammation. (CPF 120-40). Thus, the studies reasonably support the conclusion that the combination is effective and that each component contributes to that effect.

In the Brecker Study, Vioform-Hydrocortisone was statistically superior to base cream (placebo) on virtually every parameter measured at both visit 2 and final visit. (CPF 121). These results leave no doubt that the combination is effective in the treatment of primary fungal infections. The results of the Carpenter Study are reasonably consistent with those of the Brecker Study and support the conclusion that the combination is effective. Vioform-Hydrocortisone was superior to placebo on the most important measurements of the benefits of its components: pathogen conversion and physician's global evaluation at visit 2. (CPF 123). In view of the small size of the Carpenter Fungal

Study, these results are impressive corroborative evidence of the combination's effectiveness. (See CPF 56).

The Center has stipulated that the pooled data from the Brecker Study demonstrate that Vioform contributes to the effectiveness of Vioform-Hydrocortisone in the treatment of primary fungal infections. (Stip. ¶ 8; CPF 126-28). The Carpenter data are consistent with the Brecker data and confirm that conclusion. As to pathogen conversion rates, the most objective and reliable measurement of the combination's antifungal effect, the results of both the Carpenter 47-patient and 40-patient analyses demonstrate that the combination was statistically superior to hydrocortisone and as good as Vioform on pathogen conversion. (CPF 129). Statistically significant results also demonstrate that the overall condition of patients (physician's global evaluation) treated with Vioform-Hydrocortisone is superior to the condition of patients treated with hydrocortisone alone. (CPF 130). The 47-patient analysis also establishes that patients treated with the combination had greater improvement in erythema (redness) (CPF 130), the most reliably rated individual variable. (CPF 171).

Finally, the Brecker and Carpenter Studies demonstrate the contribution of hydrocortisone. During the first week of treatment, physicians in Brecker observed greater improvement in patients treated with the combination than in those treated with Vioform alone. (CPF 134). The combination in the Brecker Study produced superior results in the reduction of erythema and scaling at final visit. (CPF 135-36). The patient assessments (patient's

global evaluation and improvement of itching) also favored the combination. (CPF 137). In both the 47-patient and 40-patient Carpenter analyses, within the first week of treatment physicians observed greater improvement in patients treated with Vioform-Hydrocortisone than in those treated with Vioform. (CPF 139, 178). In the 47-patient analysis, the physician's global evaluation is corroborated by the superiority of the combination in the reduction of erythema both at visit 2 and final visit ($p=0.03$ and 0.06, respectively). (CPF 139). As noted above, these results are particularly remarkable because of the small size of those studies.

Thus, the data from the Brecker and Carpenter Studies, as corroborated by the Vioform-Locorten Study (see CPF 124, 131-132), reasonably support the conclusion that each component contributes to the combination's effectiveness. The studies show statistically significant results on the most important parameters -- physician's global evaluation, pathogen conversion and improvement of erythema. (CPF 126, 129, 131, 134, 139, 166-171).

3. The Criticisms of the Studies By the Center and Its Witnesses Are Not Such As To Render Conclusions As To Effectiveness Based On Those Studies Unfair Or Irresponsible.

a. The Carpenter Study serves the function of replication and corroborates the Brecker Study.

Despite having stipulated that the Carpenter Study is adequate and well-controlled, the Center has attempted to denigrate its value as a second study through criticisms of various

aspects of the study. The testimony established that these criticisms are not well founded.

(i) The fungal patients in the Carpenter Study included 40 patients whose cultures isolated dermatophyte organisms, primarily T. rubrum, and 7 patients whose cultures isolated Candida albicans. (CPF 96). The Center's witnesses disputed the inclusion of the 7 Candida patients on the grounds that (a) the organisms typically do not produce the same degree of inflammation and (b) few drugs are effective against both organisms. However, the uncontroverted testimony established that the inclusion of the Candida patients was appropriate. (CPF 97-104). The Carpenter Study was conducted in the South and Southwest during the summer months when it is more likely that a T. rubrum infection will be inflammatory. (CPF 102). Moreover, patients are more likely to seek treatment if they are suffering from inflammation. (CPF 102). The patient selection criteria in the Carpenter protocol also required the presence of a primary fungal infection where both anti-inflammatory and antifungal action was indicated. (CPF 101). Because there is absolutely no evidence that the protocol was not followed (CPF 101), it is reasonable to conclude that an anti-inflammatory agent was indicated for the T. rubrum patients selected.

While few drugs are effective against both T. rubrum and Candida, the Center has not disputed that Vioform is a broad spectrum antifungal agent. (CPF 104). The minimum inhibitory concentration ("MIC") of Vioform for T. rubrum and Candida is identical.

(CPF 104). Thus, the contribution of Vioform can be properly evaluated in a study that includes both patients with T. rubrum and patients with Candida. (CPF 104). 30/ Accordingly, the fact that T. rubrum does not ordinarily produce significant inflamation and that most drugs are not effective against both T. rubrum and Candida does not make it inappropriate in the circumstances of the Carpenter Study to include both types of patients. (CPF 97-104).

(ii) The Center also appears to argue that the 10-day Carpenter Study was inadequate because 10 days was insufficient to demonstrate fungal cure. (See CPF 126). While the rate of fungal cure would no doubt have been higher in a longer study (CPF 155), both the Carpenter 47 and 40-patient analyses did in fact produce statistically significant results (using two-tailed p-values) favoring the combination over hydrocortisone on pathogen conversion. (CPF 129). The Center's experts were unaware of this fact (CPF 157) and conceded (except for Dr. Solomon) that such results would be evidence of the combination's effectiveness and the contribution of Vioform. (CPF 158). Their lack of information essential to reaching an informed conclusion about the effect of Vioform renders inaccurate and unreliable the testimony of the Center's witnesses as to the persuasiveness of the Carpenter Study as proof of this component's contribution.

30/ The contrary opinion of the Center's experts is unreliable because they lacked the knowledge necessary to make an informed judgment, i.e., they did not know the MIC of Vioform for T. rubrum and for Candida. (See CPF 104).

(iii) Finally, the Center criticized the Carpenter Study because it did not include a program for standardizing the physicians' ratings. Although standardization procedures are important, failure to use them is not a fatal flaw. As Dr. Maibach testified, standardization techniques provide the advantage of decreasing the variability among investigators' ratings, thus decreasing the number of patients that must be studied in order to observe statistically significant differences. (CPF 176). Conversely, it is more difficult to achieve statistically significant results if standardization procedures have not been used. (CPF 176). Therefore, in view of the absence of standardization procedures, the statistically significant result of the 47-patient and 40-patient Carpenter analyses are more impressive, not less reliable. (See CPF 56, 176).

b. Statistical significance.

The Center's witnesses also criticized the fact that some results on which CIBA-GEIGY's experts relied for corroborating support did not reach statistical significance at the 0.05 level. The Center's statistical experts conceded, however, that the traditional use of p=0.05 as a cut-off point for statistical significance is purely arbitrary. 31/ (CPF 54). As Dr. Rosenberg

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31/ Dr. Stein, the FDA statistician who prepared the Center's statistical review and evaluation of the studies, determined that one-tailed tests of significance are appropriate in reviewing the data on Vioform-Hydrocortisone's effectiveness because the components are known to be effective. (CPF 63). Both the Center's Dr. Johnson and CIBA-GEIGY's statistical expert, Mr. Mantel, concurred. (CPF 63). When one-tailed tests are used, the "cut-off point" is still 0.05, i.e., it does not become 0.025. (See CPF (footnote continued)

testified, "[s]tatistical significance is not a cut and dried issue. . . ." (Rosenberg, G-76, at 6). A p-value of .05 is not a bright line dividing positive and negative results; rather, as Dr. Johnson testified, "clinicians now recognize it as a point on a continuum, which it truly is." (Johnson, G-78, at 7).

The Center's own statistical experts also testified that certain results with a p-value greater than 0.05 should be considered in an overall evaluation of study results. (CPF 55). The appropriate weight to attribute to such results will vary depending on a variety of factors such as the actual p-value, the size of the study, and the presence of discernible trends in related results. For example, there is little, if any, practical differ-

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60-62; see also Review and Evaluation of Clinical Data (Supplement 098) for Stelazine, dated May 30, 1984, at 7). Thus, in reviewing the data for evidence of Vioform-Hydrocortisone's effectiveness, CIBA-GEIGY's medical experts appropriately considered as statistically significant results with either a one- or two-tailed p-value of 0.05 or less. Dr. Levy is the only expert who questioned the appropriateness of using one-tailed p-values. However, his testimony is irrelevant because it it is inconsistent with the facts of this case. Dr. Levy testified that two-tailed tests are appropriate when you are demonstrating that the components of a combination drug are effective individually as well as in combination. (Levy, G-85, at 7-8). However, the Center has conceded that both Vioform and hydrocortisone are known to be effective. (See Narrative Statement, at 3 n.2). The only issue is the effectiveness of the components in combination. In Dr. Levy's opinion, two-tailed tests are also necessary to evaluate any possible antagonism between the components that may nullify the effect of one of the components. (Levy, G-85, at 8). However, there is no evidence of inhibitory activity between the components of this combination. (CPF 68). Finally, Dr. Levy's testimony that the use of one-tailed tests in clinical drug trials is only appropriate if it is known a priori that one treatment is at least as good as the other lacks credibility because it is inconsistent with his own prior practice. (CPF 67-68). Consistent application of his requirements for the use of one-tailed tests would have led Dr. Levy to the conclusion that it is appropriate in the present case.

ence between being 95% certain that a measured result is due to the drug (i.e., p=.05) and being 93% certain (i.e., p=.07).

Moreover, statistical significance is more difficult to achieve in a small study. (CPF 56). In small studies such as the Carpenter Fungal Study, it is therefore particularly appropriate to give weight to results that do not quite reach statistical significance. (CPF 56). Also, results above 0.05, particularly results with p-values between 0.05 and 0.10 that demonstrate a trend consistent with related statistically significant results, are entitled to weight. (CPF 55). 32/

c. It is not necessary to have statistically significant results for every variable measured.

Much of the criticism of the Vioform-Hydrocortisone data voiced by the Center's experts is based on an erroneous understanding of the fixed combination drug policy. The policy requires only that a combination be effective and that "each component makes a contribution to the claimed effects." 21 C.F.R. § 300.50(a) (emphasis added). Such a showing does not require statistically significant results on every parameter measured. (CPF 70-73). A lack of statistical superiority on all of the var-

32/ See also Review and Evaluation of Clinical Data for Stelazine, supra note 29, at n.14 (agency's effectiveness criteria define "favorable trends" as p<0.10). CIBA-GEIGY requested additional oral direct testimony on the issue of statistical significance. (Motion of CIBA-GEIGY Corporation for Additional Oral Direct Testimony, questions 4 and 5 for Drs. Jolly, Maibach, Urbach, and Stoughton and question 4 for Mr. Mantel) (hereinafter "Motion for Additional Oral Direct"). CIBA-GEIGY could not reasonably have anticipated that the Center's witnesses would take a contrary position in their direct testimony.

iables measured is consistent with the synergistic nature of combination drugs such as Vioform-Hydrocortisone. (CPF 70). When the results of the Brecker and Carpenter Studies are analyzed in the context of this synergism, it is apparent that the combination is effective and that each of the components makes a contribution.

The Center's witnesses characterized the study results as "marginal" (e.g., Eaglstein, G-77, at 22) primarily because they failed to take into account the synergistic nature of the combination and therefore believed that there should be statistically significant results on more parameters. (See, e.g., CPF 177). However, a study can demonstrate the effectiveness of a combination drug by producing statistically significant results where medically expected in light of the intended contribution of each component. For example, in the Neo-Synalar decision, FDA concluded that significant results at interim visits evidencing early symptomatic relief were sufficient to demonstrate the contribution of the corticosteroid in anti-infective/corticosteroid combinations. (See C-11, at 2; CPF 190).

The experts also agreed that some parameters may be more important than others in measuring a drug's effectivess. (CPF 167-71). A study may demonstrate effectiveness by producing statistically significant results on the most important parameters and favorable trends (i.e., $p<0.10$) on others. 33/ The relative

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33/ See, e.g., Review and Evaluation of Clinical Data for Stelazine, supra note 29, at 7 (out of six variables measured, agency's effectiveness criteria called for one-tailed p-values of <0.05 on either of two most important variables and p-values of <0.10 ("favorable trends") on the remaining four variables).

importance of the various parameters is a medical, rather than statistical, determination. (CPF 73). With only one exception, the medical experts who testified in this proceeding agreed that the physician's global evaluation was the, or at least one of the, most important variables in measuring the effectiveness of Vioform-Hydrocortisone. (CPF 168-69). Even Dr. Carnot Evans, the Center's medical officer responsible for evaluating studies of Vioform-Hydrocortisone, believes that the physician's global evaluation is the "most important measurement parameter to him." (C-29, at 2). As Dr. Leyden testified, "[t]he global evaluation represents the summation and integration of many signs" and is "the best evaluation a clinician can make and compensates for the many difficulties in scoring individual attributes which go to make up the global impression." (Leyden, AAD-2, at 3-4). 34/ Therefore, it is fair and responsible to conclude that a statistically significant result on the physician's global evaluation is probative evidence of effectiveness, even if it is not supported by statistically significant results on other parameters. 35/

34/ The experts were also in agreement that the "attribute which is most readily amenable to scoring is erythema." (Leyden, AAD-2, at 4; CPF 171). The potential for much greater variability in patient assessments makes it more difficult to achieve statistical significance on patient-evaluated parameters. (CPF 171).

35/ CIBA-GEIGY also requested additional oral direct testmony regarding whether statistically significant results were required on every parameter. (Motion for Additional Oral Direct, question 6). In view of the agency's position with respect to other drugs such as Neo-Synalar, CIBA-GEIGY could not reasonably anticipate that the Center would take a contrary position in this proceeding.

B. The Brecker Study Alone Constitutes Substantial Evidence Of Vioform-Hydrocortisone's Effectiveness For the Treatment Of Primary Fungal Infection.

1. There Is No Statutory Requirement of Two Or More Studies For Each Indication.

The Center has taken the position in this proceeding that the Act requires as a matter of law at least two adequate and well-controlled studies of a drug's effectiveness for each of its indications. 36/ (See Memorandum of Center for Drugs and Biologics in Opposition to CIBA-GEIGY's Motions to Set Aside Stipulation and to Supplement Its 12.85 Submission and In Support of the Center's Motions to Strike, filed March 29, 1985, at 14). The Center's sole basis for the alleged two-study requirement appears to be Congress' use of the plural "investigations" in the

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36/ FDA's official position on the number of studies required to meet the statutory substantial evidence standard was set forth in the preamble to the regulations governing notices of opportunity for hearing, requests for hearing, and grants or denials of hearing requests. 39 Fed. Reg. 9750 (March 13, 1974). FDA stated that pending a decision by the Commissioner to require two studies in all instances, submission of a single study demonstrating effectivenss would be sufficient to preclude immediate summary judgment. Id. at 9755. Accord, SmithKline Corp. v. FDA, 587 F.2d 1107, 1120 n.30 (D.C. Cir. 1978) (existence of a single adequate and well-controlled study renders summary judgment "inappropriate"). If a single adequate and well-controlled study demonstrating effectiveness precludes FDA from concluding as a matter of law that the evidence is insufficient, a fortiori there can be no legal requirement of at least two studies. This follows since FDA need not -- and will not -- hold a hearing if, as a matter of law, the data and information could not justify resolution of the factual issues in the way sought by the sponsor. Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 621 (1973); 21 C.F.R. § 12.24(b)(3). In point of fact, FDA never has proposed to change the regulations to require at least two studies as a prerequisite to a finding of effectiveness.

definition of substantial evidence. However, both the Center 37/ and the agency's senior officials 38/ have publicly stated time and again that neither the Act nor FDA's regulations (which are in relevant part identical) require at least two adequate and well-controlled studies of a drug's effectiveness. 39/

In the face of such statements, the Center's position in this case that as a matter of law two studies are required to establish a drug's effectiveness is plainly nothing but the hyperbole of an overzealous advocate, wholly unsupported by the statute

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37/ The Bureau of Drugs admitted that "[a]lthough FDA commonly asserts that two adequate and well-controlled studies demonstrating effectiveness are necessary for FDA approval, the regulations contain no such requirement." Bureau of Drugs, Investigational and New Drug Regulations, Revisions, Concept Document 180 (Oct. 1979).

38/ Both the Assistant Secretary for Health and the Commissioner of Food and Drugs stated at Congressional hearings in 1982 that FDA has the authority to approve a drug on the basis of a single adequate and well-controlled study, and that the agency has in fact exercised such authority. Assistant Secretary Brandt testified that "[w]hile we have construed our current authority as requiring more than one study, the law does not preclude reliance on a single study when the circumstances warrant." Health and the Environment, Miscellaneous -- Part 7: Hearing Before the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce, 97th Cong., 2d Sess. 319 (1982). Similarly, Commissioner Hayes testified that Section 505(d) of the Act authorizes reliance on a single study to establish a drug's effectiveness, and that there are numerous circumstances in which it is defensible to do so. Id. at 332.

39/ The only reference in FDA's regulations, as they stood at any time in the history of this proceeding, to the number of studies contemplated by the substantial evidence standard appears in Paragraph 12c of the former NDA application form: "Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator. . . ." 21 C.F.R. § 314.1(c)(2) (1984) (emphasis added). In the revision of 21 C.F.R. Part 314, effective May 23, 1985, this sentence was deleted.

or the regulations. 40/ It is necessary in the case of each new drug application to determine, as an issue of fact, whether more than one adequate and well-controlled study is needed for qualified experts to fairly and responsibly conclude that the drug is effective. In the case of Vioform-Hydrocortisone, the evidence shows that qualified experts could fairly and responsibly so conclude on the basis of the Brecker Study alone.

2. Based On the Brecker Study Alone, Experts Could Fairly and Responsibly Conclude That Vioform-Hydrocortisone Is Effective For the Treatment of Primary Fungal Infections.

a. A single large multicenter study such as the Brecker Study is sufficient where, as here, there is consistency across investigators.

In 1974 FDA announced that a single multicenter study, in lieu of two or more single-investigator studies, would be sufficient to establish the effectiveness of anti-infective/corticosteroid combinations such as Vioform-Hydrocortisone which "had wide medical acceptance as useful drugs and appeared, as a class, to be unique." 39 Fed. Reg. 36365 (Oct. 9, 1974). In this Paragraph XIV Notice, the agency required sponsors to submit protocols "for at least two adequate and well-controlled studies by independent investigators or for a multi-clinic study in which the data of at least three investigators can be evaluated independently." 39 Fed. Reg. at 36367 (emphasis added). Products would

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40/ To decide this case on the ground that as a matter of law two studies are always required would be "the essence of arbitrary and capricious action"; even if the agency "would have the power to adopt either of two different approaches to deciding these cases, it cannot adopt one and apply the other." Squaw Transit Co. v. United States, 574 F.2d 492, 496 (10th Cir. 1978).

be upgraded to effective if the data from such a multi-clinic study or separate investigators' studies demonstrated that the provisions of the fixed-combination drug policy (21 C.F.R. § 300.50) had been met. Id. 41/

In accordance with the standards thus enumerated by the agency, CIBA-GEIGY submitted the Brecker Study. It is a large, multicenter investigation in which the results of at least three individual investigators have been analyzed for consistency. (CPF 58). Four years later, the Center announced its criticisms of the Brecker Study and proposed to withdraw approval of the Vioform-Hydrocortisone NDA on the ground that substantial evidence of the drug's effectiveness in, inter alia, primary fungal infections was lacking. 46 Fed. Reg. 47408 (Sept. 25, 1981). Nowhere in this Notice of Opportunity for Hearing did the Center suggest that the alleged lack of substantial evidence might be due to an insufficient number of studies. Much to CIBA-GEIGY's surprise, however (particularly in light of the reiteration of the previously articulated standards in the Notice of Hearing itself, see note 41 supra), the Center subsequently asserted in its October 1984 Narrative Statement that a single multicenter investigation per se

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41/ In the Notice of Hearing in this proceeding, the Commissioner confirmed that CIBA-GEIGY had been required to submit "two single investigator studies (or one multicenter study) designed to show that the product is effective for its claimed indications and that it satisfies FDA's policy for fixed combination prescription drugs . . . ." 49 Fed. Reg. 33173 (Aug. 21, 1984) (emphasis added). Moreover, the Commissioner stated that one of the issues for hearing in this proceding was "[w]hether, on the basis of any such adequate and well-controlled investigations that exist," qualified experts could fairly and responsibly conclude that Vioform-Hydrocortisone is effective. Id. at 33176 (emphasis added).

could not constitute substantial evidence of Vioform-Hydrocortisone's effectiveness.

The Center cannot, and has made no attempt to, reconcile its litigating position with the express language of the Notices in this proceeding. Its assertion that two studies are required as a matter of law is disingenuous. The Center has conceded that there are cases in which reliance on a single study is justified. Indeed, from the Notices in this proceeding it is obvious that the Center originally concluded that the "unique class" of anti-infective/corticosteroid combinations (39 Fed. Reg. at 36365) presents such a case.

In an effort to sidestep this inconsistency, the Center appears to construe the Paragraph XIV Notice to mean that a drug could be upgraded on the basis of a single multicenter study only if, when separately analyzed, the results from each of at least three centers demonstrate that the drug is effective and superior to its components. (See Narrative Statement of the Center, at 6-7). That is not what the Notice says. It merely says that it must be possible to evaluate the results of three centers independently. Separate analyses of the individual investigators for the purpose of showing statistically significant results is neither necessary nor appropriate. (CPF 58). Indeed, it would be illogical, useless and misleading for FDA to offer sponsors the opportunity to conduct one multicenter study in lieu of two separate studies, but to upgrade only if three individual investigators each produced statistically significant results demonstrating

effectiveness. That would amount to a requirement of three studies demonstrating effectiveness. The only logical reading of the Paragraph XIV Notice is that a single multicenter study is sufficient, provided that at least three individual centers reported results for enough patients to permit an analysis to determine whether the pooled results are consistent across investigators and therefore reliable.

The Center's outside statistical expert, Dr. Levy, testified that a single multicenter study that produced reasonably consistent results across investigators could satisfy the function of replication provided by two studies. (CPF 59). The results of the Brecker Study were analyzed and found to be reasonably consistent across investigators. (CPF 58). Therefore, the Brecker Study satisfies the requirements necessary for a single study to constitute substantial evidence of Vioform-Hydrocortisone's effectiveness.

b. The split analyses of the Brecker Study confirm that the study constitutes substantial evidence.

FDA recently approved a drug, Stelazine, on the basis of a single multicenter study when a split analysis confirmed the pooled results. (See 50 Fed. Reg. 50964 (Dec. 13, 1985); see also Statistical Review and Evaluation, December 19, 1984, at 2, Stelazine Tablets, NDA 11-552 (DESI 9149), Docket No. 76N-0256). The agency also agreed that a one-tailed p-value of 0.05 or less in one subgroup could be corroborated by a one-tailed p-value of 0.10 or less in the other subgroup. (See Review and Evaluation of

Clinical Data (Supplement 098) for Stelazine, May 30, 1984, at 10). The Brecker split analyses conform to these criteria and therefore confirm the results of the pooled data. 42/

In both of the Brecker splits, the combination was statistically superior to placebo on the physician's global evaluation in each subgroup. (CPF 122). In both split analyses the combination was also statistically superior to hydrocortisone in both subgroups on the physician's global evaluation at visit 2, final visit, or both. (CPF 128). Confirmatory results were also obtained showing the combination's superiority to Vioform. (CPF 138).

3. FDA Has Not Imposed A Two-Study Requirement For Comparable Drugs.

FDA announced twelve years ago in this proceeding that one of its goals in evaluating the broad class of anti-infective/corticosteroid combinations is to "deal with all such products . . . in a rational and consistent manner." 39 Fed. Reg. 36365 at 36366 (Oct. 9, 1974) (Paragraph XIV Notice). This commitment

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42/ See CPF 124, 128, 138, 143. The Center's internal statistical expert, Dr. Johnson, did not challenge the propriety of using split analyses. (See Johnson, G-83, at 2). The Center's outside statistical expert, Dr. Levy, hypothesized that the result of such analyses are less reliable because the investigator can gerrymander the data until the most favorable splits are obtained. (CPF 81). There is absolutely no evidence, however, that CIBA-GEIGY did in fact gerrymander the Brecker splits to obtain more favorable results. (See CPF 80-81). On cross-examination, CIBA-GEIGY's witnesses testified that they had not seen and did not know of any other analyses of the Brecker data. (See Maibach, Tr. V-65; Jolly, Tr. V-34; Stoughton, Tr. VI-45; Urbach, Tr. IV-126). The Center's counsel elected not to cross-examine Mr. Mantel, CIBA-GEIGY's statistical expert, who devised the systematic splits that were employed.

merely acknowledges FDA's well-established obligation to apply its standards consistently from one case to another. E.g., United States v. Diapulse Corp. of America, 748 F.2d 56 (2d Cir. 1984). 43/ "Once it channels its discretion in a certain manner . . ., the agency should follow that course consistently or articulate reasons for departure." Rhodia, Inc., Hess & Clark Division v. FDA, 608 F.2d 1376, 1379 (D.C. Cir. 1979). 44/

Thus, a two-study requirement cannot be imposed on CIBA-GEIGY if the agency has approved comparable drugs on the basis of less than two studies demonstrating effectiveness, unless the agency's reasons for departing from its prior practice are explained. This the Center has failed to do. Moreover, its position in this proceeding, i.e., that evidence of the basis for the agency's approval decisions in other cases is irrelevant, cannot be squared with the prohibition against unexplained departure from past precedent.

43/ In Diapulse, FDA sought to deny a manufacturer the right to market its medical device while simultaneously granting another company approval to market a similar device. The Second Circuit rejected this attempt at disparate treatment, holding that FDA must apply its scientific conclusions evenhandedly and not grant to one person a right which it denies to another similarly situated. Id. at 62. The court stated that "[d]eference to administrative discretion or expertise is not a license to a regulatory agency to treat like cases differently." Id. at 62.

44/ In Rhodia, FDA had issued a final order denying a supplemental NADA on the ground that the applicant's use of new bulk suppliers might increase the amount of the drug on the market, thereby posing an increased safety risk. This order was contrary to the agency's approach in similar proceedings. The D.C. Circuit held FDA's order arbitrary and capricious on the ground that the agency had failed to articulate any reason for its departure from prior practice. 608 F.2d at 1379.

(a) Contrary to the Center, the requirement of consistency in administrative adjudication is fundamental. "[T]he concern that animates the consistency requirement -- ensuring 'the evenhanded declaration and application of the law by an administrative authority'" (Delmarva Power & Light Co. v. FERC, 770 F.2d 1131, 1142 n.9 (D.C. Cir. (1985)) 45/ -- lies at the heart of administrative due process principles. An agency's "failure to admit or explain . . . a basic change in the interpretation of a statutory standard to be applied to conduct of the public undermines the integrity of the administrative process." Hatch v. FERC, 654 F.2d 825, 835 (D.C. Cir. 1981). 46/ Thus, reviewing courts unhesitatingly have ruled in case after case after case that an agency's unexplained departure from its own past precedents requires that its order be set aside. 47/

Edison Pharmaceutical Co. v. FDA, 600 F.2d 831 (D.C. Cir. 1979), so frequently cited by the Center, provides no justification for FDA to apply statutory requirements inconsistently

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45/ Quoting Dep't of Treasury v. FLRA, 707 F.2d 574, 581 n.25 (D.C. Cir. 1983).

46/ Citing Atchison, T. & S.F.R. Co. v. Wichita Bd. of Trade, 412 U.S. 800, 807-08 (1973).

47/ In addition to the cases cited elsewhere in this section of our Brief, see, e.g., Airmark Corp. v. FAA, 758 F.2d 685, 691-92 (D.C. Cir. 1985); Ventura Broadcasting Co. v. FCC, 765 F.2d 184, 190 (D.C. Cir. 1985); Greyhound Corp. v. ICC, 551 F.2d 414, 416 (D.C. Cir. 1977); Public Interest Research Group v. FCC, 522 F.2d 1060, 1065 (1st Cir. 1975), cert. denied, 424 U.S. 965 (1976); Office of Communication of the United Church of Christ v. FCC, 560 F.2d 529, 535 (2d Cir. 1977); Frozen Food Express v. United States, 535 F.2d 877 (5th Cir. 1976). See generally Greater Boston Television Corp. v. FCC, 444 F.2d 841, 852 (D.C. Cir. 1970), cert. denied, 403 U.S. 923 (1971).

while shielding its prior actions from scrutiny. In Edison, the sponsor had sought to introduce evidence of "allegedly different treatment rendered by the FDA" to a similar drug. The Court's holding was that "Edison's failure to meet the specific statutory requirements governing NDA approval cannot be excused on the basis of prior action with regard to another drug." Id. at 843. Its ruling that the proffered evidence was properly excluded as irrelevant rested upon its finding that the sponsor had failed to meet "the specific statutory requirements governing approval." 48/

CIBA-GEIGY is not asserting that its product should be approved absent "substantial evidence," as the applicant effectively did in Edison. To the contrary, CIBA-GEIGY's very purpose in proffering evidence regarding other drugs that have been approved as effective is to show what quantum of data the agency in previous cases has deemed to constitute enough "substantial evidence" for approval. Whether inconsistent prior actions of the agency were merely "error" that need not be repeated, as the Center shamelessly argues, is a question that can be answered only after FDA has attempted to "make a rational explanation for its departure." Standard Rate & Data Service, Inc. v. USPS, 584 F.2d 473, 482 (D.C. Cir. 1978). 49/

48/ Two of the "studies" submitted by Edison were only one page long. 600 F.2d at 839-40 n.24. Another "study" was submitted in the form of the transcript of a speech, with handwritten patient forms. 600 F.2d 831, Brief for Respondent FDA, at 11 n.15. None of Edison's studies were "adequate and well controlled," and they failed to establish the drug's effectiveness. 600 F.2d at 840.

49/ The authorities cited by the court in Edison make clear that (footnote continued)

(b) The limited evidence CIBA-GEIGY was allowed to introduce indicates that, without any attempt at explanation, the Center seeks to subject CIBA-GEIGY's product to more stringent standards than those that have been imposed on similar drugs. FDA approved Neo-Synalar, another anti-infective/corticosteroid combination, even though only one of the two studies submitted compared the neomycin component to Neo-Synalar so as to demonstrate the contribution of the corticosteroid. (CPF 186-87). FDA has also approved numerous other drugs on the basis of less than two adequate and well-controlled studies for each indication. (CPF 34-46). Although the agency has articulated certain circumstances which justify reliance on a single study to demonstrate effectiveness (CPF 39-40), many of these approved drugs do not fall within any of these so-called "exceptions" 50/ to the two-

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it is only "inadvertent departures from a generally uniform course of decision" that need not be explained by an agency, Chem-Haulers, Inc. v. ICC, 565 F.2d 728, 730 (D.C. Cir. 1977) (emphasis added), and that prior decisions are not irrelevant where -- as here -- there is a "claim of a deliberate refusal to accord to petitioner a treatment generally accorded to others," Texas Int'l Airlines, Inc. v. CAB, 458 F.2d 782, 785 (D.C. Cir. 1971). It should also be noted that Texas Int'l involved claims to a governmental subsidy, a fact characterized by the Court as "not immaterial" to its affirmance of the challenged agency action. Id.

50/ In this proceeding itself, the Presiding Officer has stated that "there is no question in my mind that if you can carve out the kind of exception [from the two-study requirement] that the Commissioner has set forth in prior decisions, that you would qualify, in his eyes, for that same kind of treatment." Tr. IV-51. In Certain Combination Drugs Containing Antibiotics and Antifungal Agents, Docket No. 82N-0153, the Presiding Officer noted that in the past FDA has considered only one adequate and well-controlled study as substantial evidence of effectiveness in circumstances such as (a) when a disease to be treated is very rare and where it is extremely difficult to obtain the number of sub-
(footnote continued)

study requirement. For example, FDA approved Stelazine (trifluoperazine hydroperazine) for the short-term treatment of generalized non-psychotic anxiety on the basis of a single multicenter study. (CPF 46). Non-psychotic anxiety is not a rare disease; the disease process would not be overly expensive to study experimentally; the study did not consist of "thousands of patients;" and non-psychotic anxiety is not rapidly fatal and alternative therapies exist. 51/

Absent "a reasoned explanation for any failure to adhere to its own precedents," no order withdrawing approval of the Vioform-Hydrocortisone NDA could be upheld "unless the [agency] demonstrates convincingly that the two orders are, in fact, harmonious." Local 32, AFGE v. FLRA, 774 F.2d 498, 502 (D.C. Cir. 1985) (emphasis added). Yet in this proceeding the Center has refused even to attempt either a reconciliation of its actions in

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jects needed for two independent studies; (b) where the disease process would be overly expensive to study experimentally; (c) where a single study is very large, consisting of numerous patients in different centers; and (d) where the disease is rapidly fatal and no alternative therapy exists. Initial Decision, at 10 n.8. This list does not purport to be exhaustive, and FDA has not publicly made known the full range of circumstances under which it has or would find that one adequate and well-controlled study constitutes substantial evidence of effectiveness.

51/ The same considerations apply to Meperidine Hydrocloride (DESI 5010) for relief of moderate to severe pain, to Dexamethasone Sodium Phosphate (DESI 8656) for "relief of inflammatory manifestations of corticosteroid-responsive dermatoses," and to Benoxinate Hydrochloride (DESI 8729) as a short-term topical opthalmic anesthetic. Yet each was found to be effective on the basis of less than two adequate and well-controlled studies. (See CPF 45).

prior cases with its position here, or an explanation of why a different standard should now be applied.

(c) Although the Presiding Officer has authorized CIBA-GEIGY to refer in this Brief to actions of the Center and FDA involving other drugs, official notice still should be taken of the facts pertaining to other drugs approved on the basis of less than two studies, particularly in view of the absence of published decisions articulating the basis for FDA's actions in approving other drugs. Given this paucity of public information, taking official notice of facts relating to previous (as well as contemporaneous) inconsistent positions of the agency as to the need for two adequate and well-controlled studies will obviate a remand to develop the record that will be required for judicial review. CIBA-GEIGY therefore is filing concurrently herewith a Motion specifying the facts that should be noticed.

In support of his earlier refusals to take official notice, the Presiding Officer cited Edison Pharmaceutical Co. v. FDA, 600 F.2d 831 (D.C. Cir. 1979). But nothing in Edison suggests that an agency can evade the requirements of consistency in administrative decisionmaking simply by blinding itself to what its prior actions have been. To the contrary, the Edison court relied on its own earlier decision in Chem-Haulers, Inc. v. ICC, 565 F.2d 728 (D.C. Cir. 1977), which emphasized the importance of making a record that documents any distinctions relied on by the agency in departing from prior practice. Chem-Haulers expressly reiterated the rule that, if changing its policy, the agency "must

vouchsafe its whys and wherefores" with "a reasoned explanation supported by substantial evidence on the record." 565 F.2d at 730, 733. See also Ace Motor Freight, Inc. v. ICC, 557 F.2d 859, 865 (D.C. Cir. 1977).

The Center, when its litigating tactics so require, readily acknowledges that the Presiding Officer may take official notice even of facts that "are not of the kind of which judicial notice could be taken by courts of the United States," but are "peculiarly within the general knowledge of FDA as an expert agency." 52/ Certainly, if the Center considers medical journal articles to be peculiarly within FDA's knowledge, then its own medical and statistical reviews and other records on the effectiveness of drugs clearly must be.

Moreover, this evidence is not otherwise excludable. Under the regulations, evidence may be excluded if it is "irrelevant, immaterial, unreliable, or repetitive." 21 C.F.R. § 12.94(c)(1)(i). This evidence is clearly neither irrelevant nor immaterial to the issue of whether the agency is applying its standards consistently. Nor can it seriously be argued (although the Center has tried) that the agency's medical and statistical reviews and other documents pertaining to the approval of drugs are unreliable. Finally, since there is very little other evidence in the record of prior instances in which the agency has

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52/ See, e.g., In re Isoxsuprine Hydrochloride, Brief of the Center for Drugs and Biologics, at 66 (Sept. 20, 1985) (citing 21 C.F.R. § 12.95(a) in support of the Presiding Officer's judicial notice of medical journal articles).

required less than two studies, the evidence is not repetitive. Unless such evidence is admitted through official notice, there will be no clearly defined basis for the Presiding Officer's determination whether the agency has departed from prior practice and whether any purported basis that counsel may advance for such a departure is simply post hoc rationalization.

4. CIBA-GEIGY Was Not Given Adequate Notice That the Sufficiency of Its Evidence Would Be Measured Against A Two-Study Requirement.

"The right to a hearing embraces not only the right to present evidence but also a reasonable opportunity to know the claims of the opposing party and to meet them." Morgan v. United States, 304 U.S. 1, 18 (1938). Thus, FDA's regulations at the time of the Notice in this proceeding required that "[t]he notice to the applicant . . . of an opportunity for a hearing on a proposal by the Director of the Bureau of Drugs . . . to withdraw the approval of an application will state the reasons for his action and the the grounds upon which he proposes to issue his order." 21 C.F.R. § 314.200(a)(1984). 53/

In the Notice of Opportunity for Hearing in this proceeding, the Center proposed to withdraw approval of Vioform-Hydrocortisone on the ground that neither the Brecker nor the Carpenter Study, respectively, was an adequate and well-controlled study showing the drug to be effective in primary

53/ The present regulation on this matter, 21 C.F.R. § 314.200(a), is to the same effect. The Administrative Procedure Act, 5 U.S.C. § 554(b)(3), provides that persons entitled to notice of an agency hearing "shall be timely informed of . . . the matters of fact and law asserted."

fungal infections and secondarily infected dermatoses. Although the Center set forth in detail its criticisms of the studies, it nowhere suggested that substantial evidence was lacking because "replication" of either study would in any event be required. It was only four years later, in its Narrative Statement -- after CIBA-GEIGY had rebutted those criticisms and its Request for Hearing had been granted -- that the Center advanced for the first time its claim that CIBA-GEIGY had failed to produce substantial evidence "principally" because it had not submitted two studies for each indication. (Narrative Statement, at 3).

"[I]t is well settled that an agency may not change theories in midstream without giving respondents reasonable notice of the change." Rodale Press, Inc. v. FTC, 407 F.2d 1252, 1256 (D.C. Cir. 1968). Notice of new requirements in a proceeding such as this is adequate only if given in time to allow the applicant to "conduct and offer new studies meeting the newly-articulated requirements." American Cyanamid Co. v. FDA, 606 F.2d 1307, 1314 (D.C. Cir. 1977). CIBA-GEIGY's analysis of the Carpenter fungal patients has been received in evidence (over the Center's vehement objection), and it is our position that this is sufficient to meet the Center's newly-articulated two-study requirement with respect to primary fungal infections. But the Center challenges the sufficiency of the Carpenter Study for that purpose. If the Center prevails on this point, its failure to assert the alleged two-study requirement until the eleventh hour will have effectively denied CIBA-GEIGY a meaningful oppor-

tunity to meet it. An additional study obviating the criticisms (however unfounded) that have been leveled against the Carpenter Study by the Center would have been entirely feasible if CIBA-GEIGY had been given timely notice of the Center's theory, as required by the Due Process Clause, the Administrative Procedure Act, and FDA's regulations. But by the time the Center's Narrative Statement was filed, it was far too late for any such study to be undertaken. 54/

As noted above, nothing in this proceeding prior to the filing of the Center's Narrative Statement gave CIBA-GEIGY the slightest reason to believe that anything more than a single adequate and well-controlled multicenter study such as Brecker would be required. The two-study requirement now advocated by the Center thus cannot be imposed on CIBA-GEIGY without giving it a meaningful opportunity to meet that requirement before approval of Vioform-Hydrocortisone is withdrawn. 55/

54/ In point of fact, as promptly as possible after the Center made known its position, CIBA-GEIGY obtained the Center's concurrence in a protocol and commenced such a study. While one phase of the study has been completed (and once again confirms the effectiveness of Vioform-Hydrocortisone in primary fungal infections), time has been too short either to prepare a final report on that phase or to complete the remaining two phases prior to completion of the hearing, much less prior to the deadline for filing evidentiary submissions.

55/ Nor can CIBA-GEIGY be faulted for not anticipating the two-study theory now relied on by the Center as its "principal" ground for seeking withdrawal of approval. As demonstrated above, the statute on its face contains no such requirement. Applicants are not required, at their peril, to guess what theories of statutory interpretation the Center may come up with. Sterling Drug, Inc. v. Weinberger, 503 F.2d 675, 682 (2d Cir. 1974). See also North Alabama Express, Inc. v. United States,
(footnote continued)

II. THERE IS SUBSTANTIAL EVIDENCE THAT VIOFORM-HYDROCORTISONE IS EFFECTIVE FOR THE TREATMENT OF SECONDARILY INFECTED STEROID-SENSITIVE DERMATOSES.

A. Based On The Carpenter And Vioform-Locorten Studies, Experts Could Fairly And Responsibly Conclude That The Combination Is Effective For The Treatment Of Secondarily Infected Steroid-Sensitive Dermatoses.

CIBA-GEIGY submitted the adequate and well-controlled Carpenter and Vioform-Locorten multicenter studies of Vioform-Hydrocortisone's effectiveness for the treatment of secondarily infected steroid-sensitive dermatoses ("infected dermatoses"). (CPF 201-07). Based on the results of the Carpenter Study, either alone or as confirmed by the Vioform-Locorten Study, six experts, including two testifying for the American Academy of Dermatology, concluded that Vioform-Hydrocortisone is effective for the treatment of such dermatoses. (CPF 222, 227).

1. The Carpenter and Vioform-Locorten Studies Constitute Substantial Evidence That Vioform-Hydrocortisone Is Effective For the Treatment of Secondarily Infected Steroid-Sensitive Dermatoses.

The results of the Carpenter and Vioform-Locorten Studies demonstrate that (a) the combination was superior to placebo; (b) the combination was superior to Vioform and as good

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585 F.2d 783, 789 (5th Cir. 1978) ("Notice should not depend on inferences . . ."). Particularly in light of FDA's repeated public acknowledgements that no such requirement exists, its failure to propound such a requirement at any time up to and including the recent rewrite of the NDA regulations (from which even the prior version's comment on what would "ordinarily" be required as adequate has been deleted), and its history of approving new drugs on the basis of fewer than two adequate and well-controlled studies, imposition of a two-study requirement at this stage of the case would be a denial of administrative due process. See, e.g., Port Terminal R.R. Assn. v. United States, 551 F.2d 1336 (5th Cir. 1977).

as the corticosteroid in reducing the symptoms of inflamation; and (c) the combination was superior to placebo and as good as Vioform in eradicating the infection. (CPF 208-21). These results reasonably support the conclusion that the combination is effective and that each of its components contributes to its effectiveness.

In the Carpenter Study, the combination was superior to placebo on virtually every parameter measured. (CPF 209). The Vioform-Locorten Study is almost a carbon copy of the Carpenter Study with the combination being statistically superior to placebo on every parameter. (CPF 210-11). These results overwhelmingly support the conclusion that the combination is effective. (CPF 234).

The Center has stipulated -- and medical experts agree -- that the results of the Carpenter Study further demonstrate that hydrocortisone contributes to the combination's effectiveness. (CPF 212). Once again the Vioform-Locorten results are highly consistent with the Carpenter Study. (CPF 214). The combination was superior to Vioform on the reduction of every inflammatory symptom (with the exception of burning) at visit 2, final visit, or both. (CPF 213).

In the Carpenter Study, the combination was numerically, although not statistically, superior to hydrocortisone in pathogen conversion. (CPF 218). However, the contribution of Vioform was corroborated by the physician's global evaluation. Physicians observed greater improvement in the overall condition

of patients treated with the combination than those treated with hydrocortisone alone. (CPF 215-17). The Vioform-Locorten results confirm the contribution of Vioform. (CPF 219-21). In that study, the combination was statistically superior to the corticosteroid in eradicating the bacterial infection. (CPF 220). These data reasonably support the conclusion that Vioform contributes to the combination's effectiveness. (CPF 236-64).

2. The Vioform-Locorten Study Is Relevant To the Issue of Vioform-Hydrocortisone's Effectiveness.

Because the Vioform-Locorten Study involved a different corticosteroid, the Center's experts challenged its relevance. (CPF 116). In its Neo-Synalar decision (C-11), however, FDA approved a whole range of anti-infective/corticosteroid combinations for the treatment of secondarily infected steroid-sensitive dermatoses on the basis of studies of neomycin (the shared anti-infective) in combination with a single corticosteroid. (CPF 119). "[B]ecause there is no corticosteroid that is unique with respect to therapeutic and toxic effects," the Director of the Center concluded that the studies of Neo-Synalar provided substantial evidence of the effectiveness of neomycin in combination with the other steroids. (C-11, at 2). The Neo-Synalar studies were not simply accepted as corroborative evidence of the effectiveness of the other combinations; they were found to be the equivalent of studies of the other combinations. (See CPF 119).

Nevertheless, the Center's experts have taken the position in this proceeding that the study of Vioform in combination

with the corticosteroid Locorten (flumethasone pivalate) is irrelevant to the issue of the effectiveness of Vioform in combination with the corticosteroid hydrocortisone. (CPF 116). 56/ The Center has failed to articulate any basis for this patent inconsistency in its application of scientific standards.

Under Diapulse, Rhodia, and the numerous other cases cited at pp. 47-52 supra, the agency must apply its scientific judgments consistently unless it articulates a reason for departing from prior practice. The Center has failed to present a shred of evidence that distinguishes the Neo-Synalar decision from the present case. Moreover, the Center cannot seriously argue -- nor has it had the effrontery to do so, except perhaps by innuendo -- that Neo-Synalar was a mistake it need not repeat. The experts most knowledgeable about the relative differences in corticosteroids who testified in this proceeding concluded that the results of a study of an anti-infective agent in combination with one corticosteroid are relevant to assessing the effectiveness of the

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56/ The position of the Center's experts is also contrary to the Center's position in Docket 82N-0153, where it did not not dispute the relevance of various investigations to effectiveness of drugs other than the one studied. Certain Combination Drugs Containing Antibiotics and Antifungal Agents, Docket No. 82N-0153. The Brief for the National Center for Drugs and Biologics, dated August 1, 1983, emphasized that "[t]he Center has announced, from the beginning, that it will not argue that the studies of one combination product in this proceeding are not applicable to another such product." (Brief, at 2). The combination drugs involved contained antibacterial products (either tetracycline or oxytetracyclene) and antifungal agents (either amphotericin B or nystatin), including Mysteclin-F (tetracycline and amphotericin B), Mysteclin V (tetracycline and nystatin), Tetrastatin (tetracycline and nystatin) and Terrastatin (oxytetracycline and nystatin). (Id. at 1-2).

same anti-infective with another corticosteroid (CPF 118), thus establishing that the Director's rationale regarding the Neo-Synalar studies was medically and scientifically sound and that the Vioform-Locorten Study is appropriately considered in assessing the effectiveness of Vioform-Hydrocortisone. 57/ (CPF 117-18, 206-207).

The testimony of the Center-sponsored witnesses, who took the position (unaware of the Neo-Synalar decision) that the results of the Vioform-Locorten Study were irrelevant to Vioform-Hydrocortisone's effectiveness because cortocosteroids of different potencies produce different therapeutic and toxic effects (CPF 115-16, 206), is not probative. These witnesses lacked information essential to reach an informed conclusion. They did not know the relative potency of hydrocortisone and Locorten in the concentrations used in the combinations studied. (CPF 116). Differences in potency can be reduced or eliminated by adjusting the concentrations in which the steroids are used so that they will produce the same therapeutic and toxic effects. (CPF 117). Accordingly, the Center's witnesses could not possibly know whether Locorten and hydrocortisone, in the concentrations used in the combinations, would in fact produce different therapeutic and toxic effects.

57/ This testimony, as well as the Antibiotics/Antifungals and Neo-Synalar precedents, establishes that the Presiding Officer's decision to admit the Vioform-Locorten Study as evidence of the effectiveness of Vioform-Hydrocortisone was appropriate.

The naked speculation comprising the testimony of the Center's witnesses was countered by Drs. Maibach and Stoughton, who have special expertise in the area of the relative potency of corticosteroids. (CPF 117). They established that, in the concentrations used in the combinations, Locorten and hydrocortisone were similar in potency and would have essentially the same therapeutic and toxic effects. (CPF 117). 58/ The Vioform-Locorten Study is thus clearly relevant. (See CPF 115-19, 206-07).

B. Based On The Carpenter Study Alone, Experts Could Fairly And Responsibly Conclude That Vioform-Hydrocortisone Is Effective For The Treatment Of Secondarily Infected Steroid-Sensitive Dermatoses.

As previously noted with respect to primary fungal infections (pp. 39-53 supra), substantial evidence can consist of a single large multicenter study, on the basis of which a responsible body of experts can conclude that the drug is effective.

The Carpenter Study is a large multicenter study in which the results have been analyzed and found to be consistent across investigators. Based on the Carpenter Study alone, six experts concluded that the combination is effective for the treatment of infected dermatoses. (CPF 222). The data from the Carpenter Study discussed above reasonably support that conclusion. (CPF 230-57). Therefore, the Carpenter Study alone consti-

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58/ There is a greater difference in the potency between the class four corticosteroid in Neo-Synalar and the class six corticosteroids (including 1% hydrocortisone) in the other combinations found to be effective on the basis of the Neo-Synalar studies than there is between class five Locorten and class six hydrocortisone. (See CPF 119).

tutes substantial evidence within the meaning of Section 505(d) of the Act. 59/

III. VIOFORM-HYDROCORTISONE IS NOT A NEW DRUG

Section 201(p) of the Act, 21 U.S.C. § 321(p), defines a "new drug" as a drug that "is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" or that has not "been used to a material extent or for a material time under such conditions." In addition, 21 C.F.R. § 314.200(e)(1) states that "[g]eneral recognition of safety and effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information." Thus, under the statute and the regulations, a drug is not a "new drug" if (1) the drug is generally recognized as safe and effective by experts for its labeled indications; (2) such general recognition is based in part upon published studies; and (3) the drug has been used to a material extent and for a material time. Vioform-Hydrocortisone satisfies each of these requirements.

59/ For the reasons stated above with respect to primary fungal infections (supra pp. 53-55), CIBA-GEIGY was not given timely notice of the Center's claim that a second study of secondarily infected dermatoses in addition to Carpenter would be required. Administrative due process therefore would be denied if the Vioform-Locorten Study were deemed not to provide whatever "replication" of Carpenter may be necessary.

A. Experts Generally Recognize Vioform-Hydrocortisone As Safe And Effective For Its Labeled Indications.

The weight of the evidence is that qualified experts generally recognize Vioform-Hydrocortisone's safety and effectiveness. Every expert in the field of dermatology who testified as to Vioform-Hydrocortisone's safety in this proceeding testified that it is safe, and has been shown to be safe, for its labeled indications. (CPF 82, 200; Rosenberg, G-76, at 32-33; Eaglstein, G-77, at 28-29). A substantial majority of the experts testifying in this proceeding concluded that the combination was effective for its labeled indications (CPF 141-46, 191, 222-29, 269), and four of such experts testified that their views were shared by virtually all of their colleagues. (CPF 192, 270). In addition, the American Academy of Dermatology established a panel to review the studies of Vioform-Hydrocortisone's effectiveness. Based on its evaluation of the studies, the Academy concluded that the drug has been shown to be, and is generally recognized as, safe and effective for the stated indications. (Leyden, AAD-2, at 1-4; C-2). 60/ In addition, FDA's OTC Antimicrobial II Panel concluded,

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60/ Dr. Eaglstein, who was a member of the Academy's panel, testified that he did not support their conclusions as to Vioform-Hydrocortisone's effectiveness because he believed that they had not given serious consideration to clinical study results. On cross-examination, however, Dr. Eaglstein admitted that he had not attended the panel's meetings or participated in its discussions. (Eaglstein, Tr. IV-64). His criticism of the panel thus was based solely on hearsay and conjecture; accordingly, his testimony should not be given any weight. (See Tr. IV-64-66). Moreover, Dr. Eaglstein's assessment of the panel's evaluation process was flatly contradicted by Drs. Weary (Tr. I-47) and Leyden (Tr. I-55), who were actively involved as members of the panel. Thus, Dr. Eaglstein's criticism of the panel does not detract in any way
(footnote continued)

on the basis of the Brecker and Carpenter Studies and other data, that Category I antifungal ingredients such as Vioform are generally recognized as safe and effective in combination with hydrocortisone not merely for prescription, but even for over-the-counter use in treating primary fungal infections. (CPF 193). 61/

B. These Conclusions Were Based In Part On Published Studies.

The conclusions of the expert witnesses, the American Academy of Dermatology, and the OTC Panel were based on two adequate and well-controlled clinical studies -- the Carpenter and Brecker Studies -- plus other data and information, all of which confirm the safety and effectiveness of Vioform-Hydrocortisone. The results of the Carpenter Study were published in Current Therapeutic Research, 15:6509 (1973) (G-3), and the results of the Brecker Study were published in the Archives of Dermatology, 114:1773-75 (1978) (G-54A), thus satisfying FDA's requirement that general recognition ordinarily be based on published studies. 62/

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from the significance of the Academy's support for Vioform-Hydrocortisone.

61/ Further corroboration of the general recognition of the safety and effectiveness of Vioform-Hydrocortisone for its labeled indications is provided by widespread use of the combination by AAD members (CPF 196, 273) and by the support expressed for the product by the AAD and the North American Clinical Dermatologic Society (see CPF 195), as well as by the statements of five non-testifying experts (CPF 271) who filed statements with FDA supporting the effectiveness of the combination in earlier stages of this proceeding.

62/ Moreover, the results of the Vioform-Locorten (flumethasone pivalate) Study also have been published: Konopka, et al., "Antimicrobial Effectiveness of Locacorten-Vioform Cream in Secondary Infections of Common Dermatoses," Dermatologica 151:1-8 (1975)
(footnote continued)

C. Vioform-Hydrocortisone Has Been Used To A Material Extent And For A Material Time.

Vioform-Hydrocortisone has been in continuous use since FDA approved it as safe in 1956. The inescapable conclusion is that Vioform-Hydrocortisone has been used to a material extent and for a material time, and the Center has so stipulated. (Stip. ¶5). Thus, the record in this proceeding establishes conclusively that Vioform-Hydrocortisone is not a "new drug" within the meaning of Section 201(p) of the Act.

Conclusion

Based on the evidence in the record as summarized above and set forth more fully in the Proposed Findings of Fact, CIBA-GEIGY respectfully submits that there is substantial evidence that Vioform-Hydrocortisone is safe and effective, and that it is generally recognized as safe and effective, for the treatment of primary fungal infections and for the treatment of secondarily infected steroid-sensitive dermatoses. The proposal of the Center

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(C-7); Miller, "Flumethasone pivalate-iodochlorhydroxyquin cream: a new corticosteroid anti-infective combination," Cutis 14:605-09 (1974) (C-8). These published reports could also form the basis for general recognition of Vioform-Hydrocortisone's safety and effectiveness.

to withdraw approval of the Vioform-Hydrocortisone NDA should be denied.

Respectfully submitted,

Joel E. Hoffman
Michael L. Denger
Willard K. Tom
Marguerite E. Trossevin

SUTHERLAND, ASBILL & BRENNAN
1666 K Street, N.W.
Suite 800
Washington, D.C. 20006
(202) 872-7800

Attorneys for
CIBA-GEIGY Corporation

Jeffrey Rudin
CIBA-GEIGY Corporation

Of Counsel

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