CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-756

APR 1 1999

Dermik Laboratories, Inc.
Attention: Ronald F. Panner
Senior Director, Worldwide Regulatory Affairs
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Dear Mr. Panner:

Please refer to your new drug application (NDA) dated April 9, 1998, received April 10, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BenzaClin (clindamycin 1% and benzoyl peroxide 5% gel) Topical Gel.

We acknowledge receipt of your submissions dated April 24 and 30, June 4 and 19, July 13, October 1, 2, 23, 26 and 27, and December 2 and 9, 1998; and January 8, and 20, February 4 (two) and 25, and March 3 and 26, 1999.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiency may be summarized as follows:

During a recent manufacturing inspection, your ——— was found to be non-compliant with our Good Manufacturing Practice regulations. Satisfactory inspections will be required for all manufacturing and testing facilities before this application may be approved.

Although not the basis for the not approvable action of this application, the following issue should be addressed in any resubmission:

Clindamycin phosphate powder must meet the requirements of the USP monograph. We note that your specifications include an upper limit of ——— for the assay of clindamycin phosphate, which deviates from USP. Please propose a limit that is consistent with usual compendial practice, or provide a rationale for such a high limit.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment

should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Kevin Darryl White, Project Manager, at (301) 827-2020.

Sincerely,

/S/ 1/4/1999

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 50-756
HFD-540/Div. Files
HFD-540/Huene/03.30.99
HFD-540/Walker/03.30.99
HFD-540/Vidra/03.31.99
HFD-540/DeCamp/03.31.99
HFD-540/Mainigi/03.30.99
HFD-540/Jacobs/PCB/03.30.99
HFD-725Farr/RS/03.30.99
HFD-725/Srinivasan/03.30.99
HFD-880Noory/EDB/03.30.99
HFD-880/Bashaw/03.30.99
HFD-540White/03.29.99
HFD-540/Kozma-Fornaro/03.31.99
HFD-002/ORM
HFD-105/ADRA
HFD-95/DDMS
HFD-830/Chen
DISTRICT OFFICE

Drafted by: KDW/March 24, 1999
Initialed by:
final:
filename: N50576LT.WPD

NOT APPROVABLE (NA)

U.S. Food and Drug Administration
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation-III

Addendum Review

To: Kevin Darryl White, Project Manager, HFD-540

From: E. Dennis Bashaw, Pharm.D., DPE-III 3/16/99

Date: 03/16/99

Re: Benzaclin Topical Gel, NDA 50-756

Benzaclin Topical Gel (formerly ——— Topical Gel) is a combination product containing 1% clindamycin phosphate and 5% benzoyl peroxide. In reviewing this NDA the biopharmaceutics portion was found to be deficient due to the fact that the in vivo biostudy was done in a population with healthy skin. It is the policy of the Div. Of Pharm Eval III that topical dermatological studies should be done in subjects with diseased skin, except in those cases where the disease state does not affect the integrity of or the barrier properties of the skin (i.e diseases of pigmentation, etc.) As acne vulgaris has as a major presenting feature localized inflammation, patients with the disease represent the appropriate population for such a study.

At the time of the original review, the clinical portion was also non-approvable and these two elements were to be the primary reasons for non-approval. Since then a re-analysis of the statistical data indicates that the product is indeed clinically efficacious. As the sponsor has previously demonstrated adequate safety, the product is now approvable from a clinical standpoint.

It has been the policy of the DPE-III that when a topical product is clinically approvable and the sponsor has done the incorrect in vivo biostudy, that the results of such a study can be deferred to a post-approval setting. The current in vivo study results, although not strictly relevant will be included in the current package insert as interim labeling with the understanding that the results from the "phase IV study" will be incorporated when they become available.

The requested Phase IV study should include the following general study design elements:

Use of male and female subjects with active acne vulgaris.
Maximal surface area involvement consistent with the approved labeling (eg., face, chest, upper back).
Maximal dosing frequency and amount applied
Study duration of at least 1 week.

The protocol should be submitted to the Agency for review and comment prior to study initiation.

CC: NDA 50-756(ORIG),
HFD-540/DIV File
HFD-540/WhiteK
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 4 PAGE (S)

SUMMARY REPORT

Application: **NDA 50756/000**
Stamp: **10-APR-1998** Regulatory Due: **10-APR-1999**
Applicant: **DERMIK LABS**
500 ARCOLA RD
COLLEGEVILLE, PA 19426

Priority: **4S** Org Code: **540**
Action Goal: District Goal: **09-DEC-1998**
Brand Name: **(BENZOYL PEROXIDE 5%/CLINDAMYCIN**
Established Name:
Generic Name: **BENZOYL PEROXIDE 5%/CLINDAMYCIN 1% TOP**
Dosage Form: **GEL (GEL)**
Strength: **5%/1%**

FDA Contacts: **K. WHITE (HFD-540) 301-827-2023 , Project Manager**
J. VIDRA (HFD-540) 301-827-2065 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:

ACCEPTABLE on 11-FEB-2000 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 06-APR-1999 by R. WOODS (HFD-324) 301-827-0062
WITHHOLD on 30-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 14-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **29-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **01-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: [redacted]

Establishment: **2425129**
RHONE POULENC RORER INC
500 ARCOLA ROAD
COLLEGEVILLE, PA 194260995
DMF No:
AADA No:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: CTL OAI Status: NONE Responsibilities: FINISHED DOSAGE STABILITY TESTER
Last Milestone: OC RECOMMENDATION
Milestone Date 14-JUL-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: 2653125 DMF No:
RHONE POULENC RORER PHARMA AADA No:
SAN JOSE RD 604/COTO NORTE IND
MANATI, PR 00701

Profile: OIN OAI Status: POTENTIAL OAI Responsibilities: FINISHED DOSAGE MANUFACTURER
Last Milestone: OC RECOMMENDATION
Milestone Date 16-JUL-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (949) 798-7600

December 1, 1999

[redacted]

RE: NDA 50-756, Benzoyl Peroxide 5% / Clindamycin 1% Gel (Dermik)

Dear [redacted]

Los Angeles District Office recommended approval to the FDA/Center for Drug Evaluation and Research (CDER) for your role in the above referenced NDA. Previously, a recommendation to withhold approval of the NDA had been made. The most recent inspection, conducted October 19-21, 1999 initially resulted in a continued recommendation to withhold approval of the application, however, corrective actions submitted to the District regarding the deviations have been deemed acceptable.

Please make note that this is only a Los Angeles District recommendation and final Agency approval will be issued from FDA's Center for Drug Evaluation and Research to the applicant, Dermik Labs, Collegeville, PA.

If you have any questions regarding this letter, please contact Terri Dodds, Preapproval Manager at (949) 798-7758.

Sincerely,

[redacted]

/S/

Acting District Director
Los Angeles District

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ATTACHMENT #1

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Clindamycin Palmitate Hydrochloride for Oral Solution taken by the formula:

$$——(F/1000)(W_S/V)(R_U/R_S),$$

in which V is the volume, in mL, of constituted solution from Clindamycin Palmitate Hydrochloride for Oral Solution taken and the other terms are as defined therein.

Clindamycin Phosphate

$C_{18}H_{34}ClN_2O_8PS$ 504.97

Methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, 2-(dihydrogen phosphate), (2*S*-*trans*)-.

Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate) [*24729-96-2*].

» Clindamycin Phosphate has a potency equivalent to not less than 758 μg of clindamycin ($C_{18}H_{33}ClN_2O_5S$) per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Clindamycin Phosphate RS. USP Endotoxin RS.*

Identification, *Infrared Absorption* ⟨197M⟩ (specimen and Reference Standard previously dried at 100° for 2 hours).

Crystallinity ⟨695⟩: meets the requirements.

pH ⟨791⟩: between 3.5 and 4.5, in a solution containing 10 mg per mL.

Water, *Method I* ⟨921⟩: not more than 6.0%.

Other requirements—Clindamycin Phosphate intended for use in making *Clindamycin Phosphate Injection* complies with the requirements for *Bacterial endotoxins* and *Depressor substances* under *Sterile Clindamycin Phosphate.*

Assay—

Mobile phase—Dissolve 10.54 g of monobasic potassium phosphate in 775 mL of water, and adjust with phosphoric acid to a pH of 2.5. Add 225 mL of acetonitrile, mix, and filter. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Ensure that the concentration of acetonitrile in the *Mobile phase* is not less than 22% and not more than 25%, in order to retain the correct elution order.]

Internal standard solution—Prepare a solution of 4′-hydroxyacetophenone in acetonitrile containing about 4 mg per mL. Dilute a volume of this solution with *Mobile phase* to obtain a solution having a concentration of about 0.04 mg per mL.

Standard preparation—Transfer about 24 mg of USP Clindamycin Phosphate RS, accurately weighed, to a 100-mL volumetric flask. Add 25.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer about 24 mg of Clindamycin Phosphate, accurately weighed, to a 100-mL volumetric flask, add 25.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the resolution, R, between the analyte and internal standard peaks is not less than 2.0, and the relative standard deviation for replicate injections is not more than 2.5%.

Procedure—Separately inject equal volumes (about 20 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 1.0 for clindamycin phosphate and 1.2 for 4′-hydroxyacetophenone. Calculate the quantity, in μg, of $C_{18}H_{33}ClN_2O_5S$ in the portion of Clindamycin Phosphate taken by the formula:

$$100CP(R_U/R_S),$$

in which C is the concentration, in mg per mL, of USP Clindamycin Phosphate RS in the *Standard preparation*, P is the potency, in μg of $C_{18}H_{33}ClN_2O_5S$ per mg of the USP Clindamycin Phosphate RS, and R_U and R_S are the ratios of the response of the clindamycin phosphate peak to the response of the internal standard peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Clindamycin Phosphate Gel

» Clindamycin Phosphate Gel contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of clindamycin ($C_{18}H_{33}ClN_2O_5S$).

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Clindamycin Phosphate RS. USP Clindamycin Hydrochloride RS.*

Identification—The retention time of the clindamycin phosphate peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

Minimum fill ⟨755⟩: meets the requirements.

pH ⟨791⟩: between 4.5 and 6.5.

Assay—

Mobile phase—Dissolve 10.54 g of monobasic potassium phosphate in 775 mL of water, and adjust with phosphoric acid to a pH of 2.5. Add 225 mL of acetonitrile, and mix. Filter through a filter having a porosity of 0.5 μm or less, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Prepare a solution in *Mobile phase* containing in each mL about 0.6 mg of USP Clindamycin Phosphate RS and about 0.6 mg of USP Clindamycin Hydrochloride RS.

Standard preparation—Dissolve an accurately weighed quantity of USP Clindamycin Phosphate RS in *Mobile phase* to obtain a solution having a known concentration of about 0.25 mg per mL.

Assay preparation—Transfer an accurately weighed quantity of Gel, equivalent to about 20 mg of clindamycin ($C_{18}H_{33}ClN_2O_5S$), to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and shake by mechanical means for 30 minutes. Centrifuge a portion of the solution thus obtained, and if necessary, filter a portion of the supernatant liquid. Use the clear filtrate as the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed under *Procedure:* the relative retention times are about 1 for clindamycin phosphate and 1.5 for clindamycin, the resolution between the clindamycin phosphate peak and the clindamycin peak is not less than 6.0, the column efficiency is not less than 1700 theoretical plates when calculated by the formula:

$$5.545(t_r/W_{h/2})^2,$$

and the tailing factor is not more than 1.3. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative standard deviation for replicate injections is not more than 2.5%.

Procedure—Separately inject equal volumes (about 20 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of clindamycin ($C_{18}H_{33}ClN_2O_5S$) in the portion of Gel taken by the formula:

ATTACHMENT #2

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B: The contents of the Capsules respond to *Identification* test *B* under *Benzonatate*.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Standard preparation—Transfer about 50 mg of USP Benzonatate RS, accurately weighed, to a 100-mL volumetric flask, dilute with water to volume, and mix.

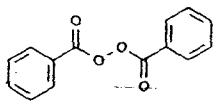
Assay preparation—Mix a number of Capsules, equivalent to about 500 mg of benzonatate, with 40 mL of chloroform in a suitable high-speed blender, and dilute with chloroform to 100.0 mL. Transfer 10.0 mL of this solution, equivalent to about 50 mg of benzonatate, to a 100-mL volumetric flask, and evaporate the chloroform on a steam bath with the aid of a current of air. Dissolve the residue in water, dilute with water to volume, and mix.

Procedure—Transfer 4.0 mL each of the *Standard preparation*, the *Assay preparation*, and water to provide the blank, to separate test tubes. To each tube add in succession 1.0 mL of 1 *M* hydroxylamine hydrochloride and 1.0 mL of 3.5 *N* sodium hydroxide, mixing after each addition. Allow to stand for 10 minutes, accurately timed, then add 1.0 mL of 3.5 *N* hydrochloric acid, mix, add 1.0 mL of ferric chloride solution (8 in 100), and mix. Allow to stand for 30 minutes, accurately timed. Gently swirl the tubes for 1 minute to remove any gas bubbles present, then concomitantly determine the absorbances of the solutions in 1-cm cells, at the wavelength of maximum absorbance at about 500 nm, with a suitable spectrophotometer, using the blank to set the instrument. Calculate the quantity, in mg, of benzonatate ($C_{30}H_{53}NO_{11}$ av.) in the number of Capsules taken by the formula:

$$C(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Benzonatate RS in the *Standard preparation*, and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively.

Hydrous Benzoyl Peroxide



$C_{14}H_{10}O_4$ (anhydrous) 242.23

Peroxide, dibenzoyl.

Benzoyl peroxide [*94-36-0*].

» Hydrous Benzoyl Peroxide contains not less than 65.0 percent and not more than 82.0 percent of $C_{14}H_{10}O_4$. It contains about 26 percent of water for the purpose of reducing flammability and shock sensitivity.

Caution—Hydrous Benzoyl Peroxide may explode at temperatures higher than 60° or cause fires in the presence of reducing substances. Store it in the original container, treated to reduce static charges.

Packaging and storage—Store in the original container, at room temperature. [NOTE—Do not transfer Hydrous Benzoyl Peroxide to metal or glass containers fitted with friction tops. Do not return unused material to its original container, but destroy it by treatment with sodium hydroxide solution (1 in 10) until addition of a crystal of potassium iodide results in no release of free iodine.]

Identification—

A: Prepare a solution in methanol to contain 10 mg of benzoyl peroxide per mL. Apply 5 µL of this solution and 5 µL of a freshly prepared Standard solution of Hydrous Benzoyl Peroxide, previously subjected to the *Assay*, in methanol containing 10 mg per mL on a line parallel to and about 2.5 cm from the bottom of a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Place the plate in a developing chamber containing, and equilibrated with, a mixture of toluene, dichloromethane, and glacial acetic acid (50:2:1). Develop the chromatogram until the solvent front has moved about three-fourths of the length of the plate. Remove the plate, and allow the solvent to evaporate. Observe the plate under short-wavelength ultraviolet light: the R_f value of the principal spot obtained from the solution under test corresponds to that obtained from the Standard solution.

B: Dissolve an accurately weighed quantity in acetonitrile to obtain a solution containing 0.32 mg of benzoyl peroxide per mL. Chromatograph this test solution and a freshly prepared Standard solution of Hydrous Benzoyl Peroxide, previously subjected to the *Assay*, in acetonitrile containing 0.32 mg per mL as directed in the test for *Related compounds* under *Benzoyl Peroxide Gel*: the solution under test exhibits a major peak for benzoyl peroxide, the retention time of which corresponds to that exhibited by the Standard solution.

Chromatographic purity—Calculate the area percentage of each peak in the chromatogram of the test solution prepared as directed in *Identification* test *B*: the sum of the areas of all peaks other than the principal peak does not exceed 2.0% of the total area, and the area of any individual peak other than the principal peak does not exceed 1.5% of the total area.

Assay—Place about 500 mg of previously mixed Hydrous Benzoyl Peroxide in an accurately weighed conical flask fitted with a ground-glass stopper, and weigh again to obtain the weight of the test specimen. Add 30 mL of acetone, and swirl the flask gently to effect solution. Add 5 mL of potassium iodide solution (1 in 5), and mix. Wash the sides of the flask with a few mL of acetone, and allow the solution to stand for 1 minute. Titrate the liberated iodine with 0.1 *N* sodium thiosulfate VS. As the endpoint is approached add 1 drop of starch iodide paste TS, and continue the titration to the discharge of the blue color. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* sodium thiosulfate is equivalent to 12.11 mg of $C_{14}H_{10}O_4$.

Benzoyl Peroxide Gel

» Benzoyl Peroxide Gel is benzoyl peroxide in a suitable gel base. It contains not less than 90.0 percent and not more than 125.0 percent of the labeled amount of $C_{14}H_{10}O_4$.

Packaging and storage—Preserve in tight containers.

Identification—Prepare a *Standard preparation* and an *Assay preparation* as directed in the *Assay*, except to omit the *Internal standard solution*, and chromatograph as directed in the *Assay*: the *Assay preparation* exhibits a major peak for benzoyl peroxide, the retention time of which corresponds to that exhibited by the *Standard preparation*.

pH ⟨791⟩: between 3.5 and 6.0.

Related compounds—

Mobile phase A—Prepare a filtered and degassed mixture of acetonitrile and glacial acetic acid (1000:1).

Mobile phase B—Prepare a filtered and degassed mixture of water and glacial acetic acid (1000:1).

Test preparation—Transfer an accurately weighed quantity of Gel, equivalent to about 100 mg of benzoyl peroxide, to a 50-mL volumetric flask, add 25 mL of acetonitrile, shake vigorously to disperse the specimen, sonicate for 5 minutes, dilute with acetonitrile to volume, mix, and filter.

Standard preparation A—Prepare a solution of benzoic acid in acetonitrile containing 200 µg per mL.

Standard preparation B—Prepare a solution of ethyl benzoate in acetonitrile containing 20 µg per mL.

Standard preparation C—Prepare a solution of benzaldehyde in acetonitrile containing 20 µg per mL.

Standard preparation D—Prepare a solution of hydrous benzoyl peroxide, previously subjected to the *Assay* under *Hydrous Benzoyl Peroxide*, in acetonitrile containing the equivalent of 40 µg of anhydrous benzoyl peroxide per mL.

Resolution solution—Prepare a solution in acetonitrile containing 100 µg of benzoic acid and 60 µg of methylparaben per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector and a 3.9-mm × 15-cm column containing packing L1, and is programmed to provide variable mixtures of *Mobile phase A* and *Mobile phase B*. The system is equilibrated with a mobile phase consisting of a mixture of 18% *Mobile phase A* and 82% *Mobile phase B*. After injection of each *Standard preparation* and the *Test preparation*, the composition of the mobile phase is changed linearly over the next 10 minutes so that it consists of 60% *Mobile phase A* and 40% *Mobile phase B*, and is maintained at that composition until the benzoyl peroxide has completely eluted. The flow rate is about 1.2 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed under *Procedure:* the resolution, *R*, between the benzoic acid and methylparaben peaks is not less than 3.0, and the tailing factors for the benzoic acid and methylparaben peaks are not more than 2.0.

Procedure—[NOTE—Use peak areas where peak responses are indicated.] Separately inject equal volumes (about 10 µL) of the *Standard preparations* and the *Test preparation* into the chromatograph, record the chromatograms by gradient elution (see *Chromatographic system*), and measure the peak responses. The responses of any peaks obtained from the *Test preparation* corresponding to benzoic acid, ethyl benzoate, and benzaldehyde are not greater than those of the main peaks obtained from *Standard preparation A* (10%), *Standard preparation B* (1%), and *Standard preparation C* (1%), respectively, the response of any other impurity peak obtained from the *Test preparation*, other than the main benzoyl peroxide peak, any benzoic acid, ethyl benzoate, benzaldehyde, methylparaben, or propylparaben peak, and any solvent peak, is not more than that obtained from *Standard preparation D* (2%), and the sum of the responses of all the impurity peaks is not more than 6 times that obtained from *Standard preparation D* (12%).

Assay—

Mobile phase—Prepare a solution of acetonitrile in water (about 5 in 10) such that the retention times for ethyl benzoate and benzoyl peroxide are about 7 and 14 minutes, respectively.

Internal standard solution—Dissolve ethyl benzoate in acetonitrile to obtain a solution having a concentration of about 3.6 mg per mL.

Standard preparation—Place a suitable quantity of hydrous benzoyl peroxide, recently subjected to the *Assay* under *Hydrous Benzoyl Peroxide*, in an accurately weighed conical flask fitted with a glass stopper, weigh again to obtain the weight of the specimen, and dissolve quantitatively in acetonitrile to obtain a solution containing a known concentration of about 0.8 mg of benzoyl peroxide per mL. Pipet 10 mL of this solution and 5 mL of *Internal standard solution* into a 25-mL volumetric flask, dilute with acetonitrile to volume, and mix. This *Standard preparation* contains about 0.32 mg of benzoyl peroxide per mL.

Assay preparation—Transfer an accurately weighed quantity of Gel, equivalent to about 40 mg of benzoyl peroxide, to a 50-mL volumetric flask. Add 40 mL of acetonitrile and shake until the material is thoroughly dispersed. Sonicate the mixture for 5 minutes, dilute with acetonitrile to volume, mix, and filter. Pipet 10 mL of the filtrate and 5 mL of *Internal standard solution* into a 25-mL volumetric flask, dilute with acetonitrile to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The high-pressure liquid chromatograph has a detector set at 254 nm and a 4-mm × 30-cm stainless steel column that contains packing L1, and is operated at room temperature. The flow rate is about 1 mL per minute. Chromatograph three replicate injections of the *Standard preparation*, and record the peak responses as directed under *Procedure:* the lowest and highest peak response ratios (R_S) agree within 2.0%, the resolution factor for the ethyl benzoate and benzoyl peroxide peaks is not less than 2.0, and the tailing factors for the ethyl benzoate and benzoyl peroxide peaks are not more than 2.0.

Procedure—Using a microsyringe or sampling valve, chromatograph 10 µL of the *Standard preparation*, and adjust the specimen size and other operating parameters, if necessary, until satisfactory chromatography and peak responses are obtained. Chromatograph equal volumes of the *Standard preparation* and the *Assay preparation*, and measure the peak responses. Calculate the quantity, in mg, of $C_{14}H_{10}O_4$ in the portion of Gel taken by the formula:

$$125C(R_U/R_S),$$

in which *C* is the concentration, in mg per mL, of benzoyl peroxide in the *Standard preparation*, and R_U and R_S are the ratios of benzoyl peroxide peak response to ethyl benzoate peak response obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Benzoyl Peroxide Topical Gel, Erythromycin and— *see* Erythromycin and Benzoyl Peroxide Topical Gel

Benzoyl Peroxide Lotion

» Benzoyl Peroxide Lotion is benzoyl peroxide in a suitable lotion base. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_{10}O_4$.

Packaging and storage—Preserve in tight containers.

Identification—

A: Dilute a quantity of Lotion with acetone to obtain a solution having a concentration of benzoyl peroxide equivalent to 10 mg per mL, and proceed with the solution so obtained as directed in the *Identification* test *A* under *Hydrous Benzoyl Peroxide*, beginning with "Apply 5 µL of this solution." The solution responds to the test.

B: It responds to the *Identification* test under *Benzoyl Peroxide Gel*.

pH ⟨791⟩: between 2.8 and 6.6.

Related compounds—

Mobile phase A, Mobile phase B, Standard preparation A, Standard preparation B, Standard preparation C, Standard preparation D, Resolution solution, and *Chromatographic system*—Proceed as directed in the test for *Related compounds* under *Benzoyl Peroxide Gel*.

Test preparation—Transfer an accurately weighed quantity of Lotion, equivalent to about 100 mg of benzoyl peroxide, to a 50-mL volumetric flask, add 25 mL of acetonitrile, shake vigorously to disperse the specimen, sonicate for 5 minutes, dilute with acetonitrile to volume, mix, and filter.

Procedure—Proceed with Lotion as directed for *Procedure* in the test for *Related compounds* under *Benzoyl Peroxide Gel:* it meets the limits stated.

Assay—

Mobile phase, Internal standard solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Benzoyl Peroxide Gel*.

Assay preparation—Prepare as directed for *Assay preparation* in the *Assay* under *Benzoyl Peroxide Gel*, using Lotion.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Benzoyl Peroxide Gel*. Calculate the quantity, in mg, of $C_{14}H_{10}O_4$ in the portion of Lotion taken by the formula:

$$125C(R_U/R_S),$$

in which *C* is the concentration, in mg per mL, of benzoyl peroxide in the *Standard preparation*, and R_U and R_S are the ratios of

ATTACHMENT #3

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 1 PAGE (S)

ATTACHMENT #4

WITHHOLD 4 PAGE (S)

ATTACHMENT #5

APPEARS THIS WAY
ON ORIGINAL

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CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1074	HFD#	540	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	James D. Vidra				Clindamycin and Benzoyl Peroxide

A. Look-alike/Sound-alike

	Potential for confusion:		
CILOXAN	___ Low	XXX Medium	___ High
LANOXIN	___ Low	___ Medium	XXX High
CLINOXIDE	___ Low	XXX Medium	___ High
CLEOCIN	XXX Low	___ Medium	___ High
	___ Low	___ Medium	___ High

B. Misleading Aspects:

C. Other Concerns:

APPEARS THIS WAY
ON ORIGINAL

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

___ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date

/S/ 11/2/99

ATTACHMENT #6

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 50756/000
Priority: 4S
Org Code: 540
Stamp: 10-APR-1998 Regulatory Due: 10-APR-1999
Action Goal:
District Goal: 09-DEC-1998
Applicant: DERMIK LABS
500 ARCOLA RD
COLLEGEVILLE, PA 19426
Brand Name: BENZOYL PEROXIDE 5%/CLINDAMYCIN
Established Name:
Generic Name: BENZOYL PEROXIDE 5%/CLINDAMYCIN 1% TOP
Dosage Form: GEL (GEL)
Strength: 5%/1%

FDA Contacts:
K. WHITE (HFD-540) 301-827-2023 , Project Manager
J. VIDRA (HFD-540) 301-827-2065 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:

ACCEPTABLE on 11-FEB-2000 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 06-APR-1999 by R. WOODS (HFD-324) 301-827-0062
WITHHOLD on 30-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 14-DEC-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 29-DEC-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 01-DEC-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: [redacted]

Establishment: 2425129
RHONE POULENC RORER INC
500 ARCOLA ROAD
COLLEGEVILLE, PA 194260995
DMF No:
AADA No:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (949) 798-7600

December 1, 1999

[redacted]

RE: NDA 50-756, Benzoyl Peroxide 5% / Clindamycin 1% Gel (Dermik)

Dear [redacted]

Los Angeles District Office recommended approval to the FDA/Center for Drug Evaluation and Research (CDER) for your role in the above referenced NDA. Previously, a recommendation to withhold approval of the NDA had been made. The most recent inspection, conducted October 19-21, 1999 initially resulted in a continued recommendation to withhold approval of the application, however, corrective actions submitted to the District regarding the deviations have been deemed acceptable.

Please make note that this is only a Los Angeles District recommendation and final Agency approval will be issued from FDA's Center for Drug Evaluation and Research to the applicant, Dermik Labs, Collegeville, PA.

If you have any questions regarding this letter, please contact Terri Dodds, Preapproval Manager at (949) 798-7758.

Sincerely,

/S/

Acting District Director
Los Angeles District

APPEARS THIS WAY
ON ORIGINAL

NDA 50-756
[redacted]™(clindamycin phosphate,1% & benzoyl peroxide,5%)

D. ENVIRONMENTAL ASSESSMENT **ACCEPTABLE**

A complete Environmental Assessment (EA) was submitted although after reviewing the Expected Introduction Concentrations (EIC) Section, this sponsor was eligible for a Categorical Exclusion, but did not apply for it. The EIC for clindamycin phosphate and benzoyl proxide was approximately [redacted] and [redacted] respectively. Both drug substances well within the required ≤ 1.00 ppb required for the exclusion. Therefore this EA is RECOMMENDED FOR APPROVAL for a Categorical Exclusion.
Informational Request: That sponsor be made aware of the most recent EA changes as described in 21 CFR 25.31(b). That regulation essentially stated use of the NDA drug substance's estimated concentration at the point of entry into the aquatic environment be below 1 ppb.

E. METHODS VALIDATION **ACCEPTABLE**

Two Methods Validation requests were initiated on 12/7/98 and submitted to both the Philadelphia District Laboratory (Primary Laboratory), HFR-MA160, and the San Juan District Laboratory (Secondary Laboratory), HFR-SE560.

F. LABELING

The trademark, [redacted] was submitted to the LNC for their review on 8/3/98. Their 9/22/98 reply indicated the Established Name of clindamycin phosphate - benzoyl peroxide was ACCEPTABLE, however, the Proprietary Name of [redacted] was UNACCEPTABLE due to a number of look-alike, sound-alike compounds.
A second trademark, BENZACLIN™ Topical Gel, was received on 1/20/99 from sponsor and submitted to the FDA's LNC on 2/2/99. See ATTACHMENT #5 for additional details.

G. ESTABLISHMENT INSPECTION **UNACCEPTABLE**

A total of four sites were submitted for cGMP inspection. The sites were: [redacted], Rhone Poulenc Rorer (CFN #2425129, finished product stability testing) & Rhone Poulenc Rorer (CFN #2650125, drug product manufacturer). The [redacted] was WITHHELD FOR APPROVAL by OC and considered NON-APPROVAL. The 483 for [redacted] was dated 8/19/98 re: CS #57515 (ATTACHMENT #4). Both Rhone Poulenc Rorer sites were ACCEPTABLE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

James J. Leyden, M.D.
Skin Study Center
390 Reed Road
Broomall, PA 19008-4008

Dear Dr. Leyden:

Between November 10 - 24, 1998 Mr. Mike M. Rashti representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of the clinical studies (protocol #DL-6021-9103 and #DL-6021-9301) of the investigational (drug combination of clindamycin 1% and benzoyl peroxide gel) ——— Topical Gel, performed for Dermik Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we found some deviations from federal regulations and/or good clinical practices governing your conduct of clinical investigations. Inspectional observations were made on the Form FDA 483 and were discussed with you at the close of the inspection. The discussion included but was not limited to: (a) enrolling subject #312 in the study despite source documentation of the concomitant use of Retin A, and (b) inadequate record keeping. We acknowledge your responses and your promise to make corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

APPEARS THIS WAY
ON ORIGINAL

We appreciate the cooperation shown Investigator Rashti during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief, Clinical Investigations II
Good Clinical Practice Branch
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

DERMIK LABORATORIES, INC.
Dedicated to Dermatology™
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

New Drug Application No. 50-756
Form FDA 356h
Item 1.B.

———Topical Gel
(clindamycin 1% and
benzoyl peroxide 5% gel)

Item 18.: User Fee Cover Sheet (Form FDA 3397)

In accordance with Section 736(a)(1)(B)(i) of the Prescription Drug User Fee Act of 1992 (PDUFA), as amended by the Food and Drug Administration Modernization Act of 1997 (FDAMA), Dermik Laboratories, Inc. sent a check (Check No. ———) in the amount of $256,846.00 to the Food and Drug Administration, Pittsburgh, Pennsylvnia on March 31, 1998. The Food and Drug Administration assigned the application the User Fee Indentification Number 3442.

The Use Fee Cover Sheet (Form FDA 3397) for this ———Topical Gel (clindamycin 1% and benzoyl peroxide 5% gel) New Drug Application is located on page 7 of Volume 1.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996.

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426-0107

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Ronald F. Panner
Senior Director
Worldwide Regulatory Affairs
Rhône-Poulenc Rorer Pharmaceuticals
500 Arcola Road
Collegeville, PA 19426-0107

3. TELEPHONE NUMBER *(Include Area Code)*
(610) 454-3026

4. PRODUCT NAME
Topical Gel (clindamycin 1% and benzoyl peroxide 5% gel)

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM

6. USER FEE I.D. NUMBER
3442

7. LICENSE NUMBER/NDA NUMBER
No 50756

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☒ NO
(See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Ronald F. Panner	Senior Director Worldwide Regulatory Affairs	April 9, 1998

FORM FDA 3397 (12/93)

BEST POSSIBLE COPY

INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET
FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplement submitted to the Agency on or after January 1, 1994. The prescription drug User Fee Act of 1992, Public Law 102-571, authorizes the collection of the information requested on this form to implement the Act. Failure to complete this form may result in delay in processing the submission.

ITEM NOS.	INSTRUCTIONS
1-3	Self explanatory.
4	PRODUCT NAME - Include the generic name and the trade name, as applicable.
5	If clinical data are required for approval, then the application should be identified as containing clinical data. Please refer to the FDA policy regarding clinical data, Interim Guidance, Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under The Human Prescription Drug User Fee Act of 1992, July 12, 1993. Copies may be obtained from: Food and Drug Administration; Office of Small Business, Scientific and Trade Affairs; 5600 Fishers Lane, HF-50; Rockville, MD 20857. Please include two (2) pre-addressed mailing labels with your request.
6	USER FEE I.D. NUMBER - PLEASE MAKE SURE THIS NUMBER AND THE NUMBER ON THE APPLICATION PAYMENT CHECK ARE THE SAME. FOR APPLICATIONS SUBJECT TO USER FEE PAYMENT, please supply the following identifying information: FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research Central Document Room, at (301) 443-8269. FOR BIOLOGIC PRODUCTS - The first 4 characters are the U.S. License Number, including leading zeros; the second characters are the product code (2 letters followed by 2 numbers); and the last 7 characters are the date on the cover letter of the submission, in the format: DDMONYR. If the facility is unlicensed, or the product code is unknown, a number can be obtained by calling the Center for Biologics Evaluation and Research, at (301) 594-2906. EXAMPLE: For U.S. License Number 4, product code ZZ01, with a document submission date of 8/3/93, the number would be: 0004ZZ0103AUG93.
7	LICENSE NUMBER/NDA NUMBER FOR BIOLOGIC PRODUCTS - Indicate the U.S. License Number. If the facility is unlicensed, leave this section blank. FOR DRUG PRODUCTS - Indicate the NDA number, if known, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 443-0035. EXAMPLE: For NDA99999, the number would be: N099999.
8	EXCLUSIONS - Check the appropriate box if this application is NOT covered by user fees because it is excluded from the definition of "human drug application" as defined in Section 735(1) and (2) of the Prescription Drug User Fee Act. Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); or NOT a new indication for use.
9	WAIVER - Complete this section only if the application has qualified for the small business exception or a waiver has been granted for user fees for this application. A copy of the official FDA notification that the waiver has been granted must be provided with this submission.

DERMIK LABORATORIES, INC.
Dedicated to Dermatology℠
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

New Drug Application No. 50-756
Form FDA 356h
Item 1.G.

Topical Gel
(clindamycin 1% and benzoyl peroxide 5% gel)

Item 16: Debarment Certification

In accordance with Section 306(k)(1) of the Federal Food Drug and Cosmetic Act, we hereby certify that, in connection with this application, Dermik Laboratories, Inc. did not and will not use in any capacity the services of any person debarred under the Mandatory Debarment provisions [Section 306(a)] or the Permissive Debarment provisions [Section 306)b0] of the Federal Food Drug and Cosmetic Act in connection with this application.

DERMIK LABORATORIES, INC.
Dedicated to Dermatology™
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

New Drug Application No. 50-756
Form FDA 356h
Item 1.F.

_____Topical Gel
(clindamycin 1% and
benzoyl peroxide 5% gel)

Items 13 and 14: Patent Information and Patent Certification

Patent information and patent certification information are located in this volume beginning on the next page.

Item 13 -Patent/Exclusivity Information

1)	Active Ingredient(s):	clindamycin and benzoyl peroxide
2)	Strength(s):	1% and 5%
3)	Trademark:	
4)	Dosage Form (Route of Administration):	Topical gel
5)	Application Firm Name:	Dermik Laboratories, Inc.
6)	IND Number:	
7)	NDA Number:	50-756
8)	Approval Date:	N/A
9)	Exclusivity – date first ANDA could be submitted or approved and length of exclusivity period:	Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this application.
10)	Applicable patent numbers and expiration date of each:	5,446,028, Expires August 29, 2012

11) To the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).

A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which we are seeking approval is attached. We have thoroughly searched the scientific literature and, to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which we are seeking approval without reference to the new clinical investigation(s) in the application. The reasons that these studies or reports are insufficient are presented in the attachment as well.

Item 13. Patent Information

1)	Patent number	5,446,028
2)	Date of expiration	August 29, 2012
3)	Type of patent	drug product; method of use
4)	Name of patent owner	Dermik Laboratories, Inc.
5)	U.S. representative	Dermik Laboratories, Inc.

The undersigned declares that Patent No. 5,446,028, covers the formulation, composition, and/or method of use of Applicant's ——— (clindamycin and benzoyl peroxide) product. This product is the subject of this application for which approval is being sought.

Signed: _____ Date: 4/6/98

Name: Ross J. Oehler

Title: Assistant General Counsel, Patents and Trademarks
Rhône-Poulenc Rorer Pharmaceuticals Inc.

EXCLUSIVITY SUMMARY for NDA # 50-756 SUPPL # _____

Trade Name BENZACLIN Generic Name CLINDAMYCIN/BENZOYL PEROXIDE

Applicant Name DERMIK LABORATORIES HFD-540

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 YEARS

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /__/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # — SEE ATTACHED _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

NDA #	API	Drug Name
50-557	Benzoyl peroxide	Benzamycin Erythromycin Gel
50-769	Benzoyl peroxide	Benzamycin Pak
50-162	Clindamycin	Cleocin Capsules
50-163	Clindamycin	Cleocin Solution
50-428	Clindamycin	Cleocin Palmitate Flavored Granules
50-441	Clindamycin	Cleocin Phosphate Solution
50-537	Clindamycin	Cleocin Topical Solution
50-648	Clindamycin	Clindamycin Phosphate injection
50-680	Clindamycin	Cleocin Vaginal Cream
50-767	Clindamycin	Cleocin Vaginal OV
50-782	Clindamycin	Clindamycin Topical

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # DL-6021-9703

Investigation #2, Study # DL-6021-9623

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # DL-6021-9103

Investigation #2, Study # DL-6021-9623

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ _____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

[ ] _____ 11/17/00

Signature
Title: PROJ MGR

Date

[ ] _____ 12/20/00

Signature of Division Director

Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

BEST POSSIBLE

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 50-756 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade and generic names/dosage form: BENZACLIN TOPICAL GEL (CLINDAMYCIN/BPO) Action: (AP) AE NA

Applicant DERMIK Therapeutic Class ANTI ACNE

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate __

Proposed indication in this application ACNE VULGARIS

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__ Neonates (Birth-1month) __ Infants (1month-2yrs) __ Children (2-12yrs) ✓ Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

X 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from MEDICAL OFFICER (e.g., medical review, medical officer, team leader)

/S/ 11/17/00

Signature of Preparer and Title Date

Orig NDA/BLA # 50-756

HFD 540 Div File

NDA/BLA Action Package

HFD-006/ KRoberts

/S/ 11/20/00 /S/ 10/23/00

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

A/BLA # 50-756 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade and generic names/dosage form: BENZACLIN Action: AP AE (NA)

Applicant DERMIK Therapeutic Class ANTI-ACNE

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application FOR THE TOPICAL TREATMENT OF ACNE VULGARIS

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) ✓Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

✓ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.

- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/

_____ _____

Signature of Preparer and Title Date

Orig NDA/BLA #_____
HF_____/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

WITHHOLD 9 PAGE (S)

Draft

Labeling

DERMIK LABORATORIES, INC.
Dedicated to Dermatology
A RHÔNE-POULENC RORER COMPANY

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL: 610-454-8000

New Drug Application No. 50-756
Form FDA 356h
Item 2

——— Topical Gel
(clindamycin 1% and
benzoyl peroxide 5% gel)

Item 2: Labeling

Title: 2.D. ——— Topical Gel Carton Label

Draft carton labeling for ——— (clindamycin 1% and benzoyl peroxide 5% gel) Topical Gel is located in this section on the next page. Both the ——— Topical Gel jar and the ——— vial will be included in the carton when distributed to pharmacies.

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

WITHHOLD 1 PAGE (S)

Draft

Labeling