CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64160

CORRESPONDENCE

AADA 64-160

E. Fougera & Co.
Division of Altana, Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

SEP 26 1995

Dear Madam:

Please refer to your abbreviated antibiotic application (AADA) dated August 11, 1995, submitted under Section 507 of the Federal Food, Drug and Cosmetic Act for Clindamycin Phosphate Gel USP, 1 %.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this AADA under 21 CFR 314.101(d)(3) for the following reasons:

> While you have stated that your formulation is qualitatively the same as the reference listed drug, you have failed to provide a side-by-side comparison of the formulation of your proposed drug product with that of the reference listed drug product. You must demonstrate that the proposed drug product is qualitatively and **quantitatively** the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, you must provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(v)]. The information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. ph, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.

Thus, it will not be filed as an abbreviated antibiotic application within the meaning of Section 507 of the Act.

In addition, original signatures are required for certifications submitted for the field copy, the Generic Drug Enforcement Act of 1992, and the list of convictions.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 9/26/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-160
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting 9/7/95 date
HFD-615/HGreenberg, CSO /S/ 9/6/95 date
HFD-610/CHoppes, Actg.Chief, LRB 9/7/95 date
HFD-643/JHarrison, Sup. CSO /S/ 9/26/95 date

AADA Refuse to File!

AADA 64-160

DEC 6 1995

E. Fougera & Co.
Attention: Virginia Carman
60 Baylis RD
Melville, NY 11747

Dear Madam

Reference is made to the bioequivalence data submitted on August 11, 1995, for Clindamycin Phosphate Gel USP, 1%.

The Office of Generic Drugs has reviewed the submitted bioequivalence data and the following comments are provided for your consideration:

1. This product is not eligible for a waiver of in vivo bioequivalence as provided under 21 CFR 320.22(b)(3). In the application volume 1.1 page 48, you have not reiterated the regulations appropriately, they should read as follows:

   The drug product:

   i. Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, or similar other solubilized form.

   ii. Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and

   iii. Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety.

2. Since the product is not eligible for waiver, bioequivalence must be demonstrated using a method described under 21 CFR 320.24. For this product, the Office has typically recommended a bioequivalence study with clinical endpoints.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be considered major and be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

AADA 64-160

E. Fougera & Co.
Division of Altana, Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

OCT 19

Dear Madam:

We acknowledge the receipt of your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated September 26, 1995, and your amendment dated October 4, 1995.

NAME OF DRUG: Clindamycin Phosphate Gel USP, 1%

DATE OF APPLICATION: August 11, 1995

DATE OF RECEIPT: August 14, 1995

DATE ACCEPTABLE FOR FILING: October 6, 1995

We will correspond with you further after we have completed the review of your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Mark Anderson
Consumer Safety Officer
(301) 594-0360

Sincerely yours,

/S/ 10/19/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-160

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

MAR 19 1996

Dear Madam:

This is in reference to your abbreviated antibiotic application dated August 11, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Clindamycin Phosphate Gel USP, 1% (base).

Reference is also made to your amendments dated October 4, 1995 and February 6, 1996.

The application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. Regarding the controls for the ingredients:

   a. Your specification for the active ingredient under "Related substances" is misleading due to the omission of solution (1) and solution (2) (Ref. BP 1993, Volume 1, page 165). Please revise.

   b. Please identify some of the individual impurities for Clindamycin Phosphate.

   c. Is "Carbopol 974P" the synonym of "Carbomer 934P"? Are these two identical in formula and properties?

   d. Since is not included in current USP, please explain the specification source you listed on page 116: "current USP". What is "CTFA"? What is the source of Reference Standard for "Identification"?

2. In your "Composition Statement" for the finished product on page 61, please provide an extra column "kg/ kg" for each ingredient.

3. On Page 198, the information provided for the Altana Inc. facility located at 60 Baylis Road does not contain any description for the QC testing areas. Please clarify.

4. Please confirm that your intended maximum production batch size is kg.

5. From the batch record for Exhibit lot #6453 on page 333, it is noted that the bulk yield is %, below the specified range (%), due to some gel remaining in the equipment. What corrective action has been taken to prevent this from happening again?

6. Please specify the maximum holding period for the gel preparation before filling.

7. Regarding the specifications for the finished product:

   Please identify some of the degradation products and related substances listed under "Others". It is recommended that you complete this effort with some of the test chromatograms.

8. Regarding stability studies:

   a. Please explain why the specification for "Viscosity" is different for release and for stability.

   b. Regarding Degradation Products and Related Substances, we find the results do not justify the proposed high limits (i.e., % for "Clindamycin" and % for "Total"). Please comment.

B. Labeling Deficiencies:

1. CONTAINER: 7.5 g and 30 g

   a. On the 7.5 g label - Relocate "for External Use Only" so that it appears below the equivalency statement.

   b. Include the pH range.

c. We note, the innovator 7.5 gram container is a professional sample size. Do you intend to market this size or is it intended to be used as a professional sample as does the innovator. Please comment and/or revise to include "professional sample" on the label.

2. CARTON

a. See comments under b and c CONTAINER.

b. We encourage you to relocate the "Each gram contains" statement to appear before the storage statement.

3. INSERT

a. DESCRIPTION

i. Include the molecular formula.

ii. First sentence - Clindamycin Phosphate Gel, for topical use, contains...

b. CLINICAL PHARMACOLOGY

i. Delete the second paragraph).

ii. Replace "ml" with "mL". Revise throughout the insert.

c. WARNINGS

Revise the entire section as follows:

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and

mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool cultures for *Clostridium difficile* and stool assay for C. difficile toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin

d. PRECAUTIONS

i. Add the following text after the General subsection:

Drug Interactions:

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution in patients receiving such agents.

ii. Revise the pregnancy subsection heading as follows:

Pregnancy: Teratogenic Effects: Pregnancy Category B

iii. Nursing Mothers -

1) First sentence - "use" rather than "us".

2) Delete the third sentence
Replace it with "Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

iv. Pediatric Use - ... effectiveness in pediatric patients under the...

e. ADVERSE REACTIONS

Revise the entire section as follows:

In 18 clinical studies of various formulations of Clindamycin Phosphate Topical solution using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Number of patients reporting events

Treatment Emergent Adverse Event	Solution n=553(%)	Gel n=148(%)	Lotion n=160(%)
Burning	62(11)	15(10)	17(11)
Itching	36 (7)	15(10)	17(11)
Burning/Itching	60(11)	#(-)	#(-)
Dryness	105(19)	34(23)	29(18)
Erythema	86(16)	10(7)	22(14)
Oiliness/Oily Skin	8(1)	26(18)	12*(10)
Peeling	61(11)	#(-)	11 (7)

not recorded
* of 126 subjects

Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally.

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulation of clindamycin and rarely with topical clindamycin (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as gram-negative folliculitis have also been reported in association with the use of topical formulations of clindamycin.

f. Add the text to appear as the OVERDOSAGE section following the ADVERSE REACTIONS section.

OVERDOSAGE

Topically applied clindamycin topical solution can be absorbed in sufficient amounts to produce system effects (See WARNINGS)

g. HOW SUPPLIED

i. Add "protect from freezing."

ii. Delete the 7.5 gram product size, if it is a professional sample size.

Please revise your labels and labeling, as instructed above, and submit final printed containers labels and carton labeling and draft insert labeling (final print if you prefer).

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this

letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 3/15/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-160

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

AUG 19 1996

Dear Madam:

This is in reference to your abbreviated antibiotic application dated August 11, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Clindamycin Phosphate Gel USP, 1% (base).

Reference is also made to your amendments dated February 6, and July 9, 1996.

The application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

1. We note that you have included revised specifications for In the original submission only was identified as the bulk manufacturer. Please clarify.

2. Please explain in detail the assay procedures for Clindamycin Phosphate potency and for the degradant content of the final product as reported in the stability studies.

3. It is noted that the updated stability data contain results from only the 30 g tube. Please also submit updated stability data for the 7.5 g tube.

4. We await your submission of an in vivo bioequivalence study in response to the letter from our Division of Bioequivalence dated June 27, 1996.

In addition, we request that you send 10 sealed containers of the drug product manufactured from batch # 6453 to the following address for analysis by our laboratory. Each container should contain the appropriate quantity of the drug product as specified in 21 CFR 453.522(b). A copy of the Certificate of Analysis should accompany the samples. Please send the samples to:

Food and Drug Administration
Beltsville Research Facility
Attention: Valerie Flournoy (HFD-910)
8501 Muirkirk Road
Laurel, MD 20708
(301) 827-8054

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/15/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA #64-160
DUP File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-643/M.Shih/8/7/96/ /S/ 8/13/96
HFD-643/J.Harrison/8/7/96 /S/ for J. Harrison 8/14/96
HFD-617/R.West/8/13/96 /S/ 8/14/96

NOT APPROVABLE: MAJOR AMENDMENT

AADA 64-160

JUN 27 1996

E. Fougera & Co.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

Dear Ms Carman:

Reference is made to the Abbreviated Antibiotic Drug Application amendment submitted on February 6, 1996 for Clindamycin Phosphate Gel USP, 1%.

The Office of Generic Drugs has reviewed the submitted bioequivalence data and the following comments are provided for your consideration:

The Office does not agree that the information which you have submitted demonstrates that Clindamycin Phosphate Gel, USP, 1% falls under 21 CFR 320.22(b)(3) of the Bioavailability/ Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study requirements for the product can not be granted for the following reason:

> Clindamycin Phosphate Gel USP, 1% is a post-1962 semisolid topical drug product which requires an *in vivo* bioequivalence study with a clinical end point.

We recommend that a protocol for the clinical bioequivalence study should be submitted to the Division of Bioequivalence for review and consult before any studies are initiated.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

fougera®
a division of Altana Inc.

July 9, 1996

Federal Express

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Re: AADA 64-160
Clindamycin Phosphate Gel USP, 1% (base)
MAJOR AMENDMENT

Dear Mr. Sporn:

Reference is made to a communication of March 19,1996 from Frank Holcombe, Jr., Ph. D., Director, Division of Chemistry II concerning deficiencies in our application.

Each of your concerns is stated and our response immediately follows.

A. Chemistry Deficiencies

1) Regarding the controls for the ingredients:
   a. Comment:
   Your specification for the active ingredient under "Related Substances" is misleading due to the omission of solution (1) and solution (2) (Ref. BP 1993, Volume 1, page 165). Please revise.

   Response:
   The specifications for the active ingredient have been revised to clarify the Related Substances test specification. The revised specification is included in Attachment 1.

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-756-7017

b. Comment:
Please identify some of the individual impurities for Clindamycin Phosphate.

Response:
Potential individual impurities of clindamycin phosphate and their relative retention times (RRT) with respect to clindamycin phosphate are listed below. Retention times were determined by A chromatogram of clindamycin phosphate spiked with the impurities at levels about % is presented in Attachment 2.

Note that the conditions are the same for the assay and the determination of related substances.

RRT	Compound

c. Comment:
Is "Carbopol 974P" the synonym of "Carbomer 934P"? Are these two identical in formula and properties?

Response:
Carbopol 974P is trade name for a type of carbomer 934P NF. also makes Carbopol 934P, which is also carbomer 934P NF. Although both Carbopols have the same chemical properties and conform to the NF monograph for carbomer 934P, is used in the synthesis of Carbopol 974P instead of the used in the synthesis of Carbopol 934P. As a result, Carbopol 974P has trace amounts of instead of the trace amounts of found in Carbopol 934P. Since is potentially more hazardous than and since the materials are otherwise identical, we selected Carbopol 974P as the type of carbomer 934P NF to use in our gel.

Correspondence from confirming this information is presented in Attachment 3.

d. Comment:
Since is not included in current USP, please explain the specification source you listed on page 116: "current USP". What is "CTFA"? What is the source of Reference Standard for "Identification"?

Response:
The source of procedure listed as "Current USP" is in reference to the analytical methods described in the USP General Test chapter (i.e. Loss on Drying section <731> and Residue on Ignition section <733>).

"CTFA" is the abbreviation for the Cosmetic, Toiletry and Fragrance Assn., Inc.

The source for the Allantoin standard is with reference to the CTFA spectrum for identification purposes (See Attachment 4).

2. Comment:
In your "Composition Statement" for the finished product on page 61, please provide an extra column "kg/ kg" for each ingredient.

Response:
The composition statement has been revised to include a column reflecting kg/ kg for each ingredient. This can be found in Attachment 5.

3. Comment:
On Page 198, the information provided for the Altana Inc. facility located at 60 Baylis Road does not contain any description for the QC testing areas. Please clarify.

Response:
A revised facility description which includes a description of the QC testing area is included in Attachment 6.

4. Comment:
Please confirm that your intended maximum production batch size is kg.

Response:
We confirm that the intended maximum production batch size is kg.

5. Comment:
From the batch record for Exhibit lot #6453 on page 333, it is noted that the bulk yield is %, below the specified range (%), due to some gel remaining in the equipment. What corrective action has been taken to prevent this from happening again?

Response:
The yield of % indicates that about kg of product remained in the kettle, transfer lines, transfer pump, and housing for the mesh strainer. This is not an unusual amount. Upon scale up, the kg will represent a smaller percentage of the batch. Gel remaining in the equipment has no adverse effect on the gel which is collected and used. The equipment is cleaned before being used to manufacture subsequent products. Corrective action is therefore not needed.

6. Comment:
Please specify the maximum holding period for the gel preparation before filling.

Response:
As specified in SOP 240.05, all non-emulsion (e.g., ointments, gels and otic solutions), non-sterile topicals and Swim Ear shall be compounded and filled within a six (6) week interval from date of manufacture to initiation of continuous filling. (No interruptions exceeding five (5) days).

7. Regarding the specifications for the finished product:

Comment:
Please identify some of the degradation products and related substances listed under "Others". It is recommended that you complete this effort with some of the test chromatograms.

Response:
Potential degradation products and related substances are listed below; relative retention times (RRT) with respect to clindamycin phosphate are also noted. Retention times were determined by A chromatogram of the gel spiked with the related substances at levels of about % is presented in Attachment 7.

RRT	COMPOUND

The major degradation product of clindamycin phosphate is clindamycin. The major degradation product of methylparaben is
These substances are specifically assayed for in the procedure.

8. Regarding stability studies:
   a. Comment:
   Please explain why the specification for "Viscosity" is different for release and for stability.

   Response:
   The release specifications are tighter than the stability specifications to help ensure that normal changes during the expiry period will not result in test failures.

   The in-process and finished product specifications have been revised to slightly tighten the viscosity specifications. These specifications are presented in Attachments 8 and 9.

   b. Comment:
   Regarding Degradation Products and Related Substances, we find the results do not justify the proposed high limits (i.e., % for "Clindamycin" and % for "Total"). Please comment.

   Response:
   We agree that the limits are too high. Based on the '% clindamycin level found in 30 g tubes after three months at 40° C/75% RH, and allowing % for assay variation, we have tightened the specification for clindamycin to)%, and the specification for total related substances to %.

   We have also tightened the in-process and finished product specifications for clindamycin phosphate, and all specifications for methylparaben

   The revised in process and finished product are presented in Attachments 8 & 9.

   Revised stability specifications are included in Attachment 10.

   Updated stability data can be found in Attachment 11.

B. Labeling Deficiencies

1) Container: 7.5 g and 30 g

a. Comment:
On the 7.5 g label - Relocate "for External Use Only" so that it appears below the equivalency statement.

Response:
The g tube size has been deleted from the proposed marketing plan.

b. Comment:
Include the pH range.

Response:
The pH range has been included on the revised container label.

c. Comment:
We note, the 7.5 gram container is a professional sample size. Do you intend to market this size or is it intended to be used as a professional sample as does the innovator. Please comment and/or revise to include "professional sample" on the label.

Response:
As noted in our response to B.1.a., we have decided to discontinue the proposed 7.5 g tube as either a sample or a marketed package size. Samples (FPL) of the revised container labeling for the 3O g size are included in Attachment 12.

2) CARTON

a. Comment:
See comments under b and c CONTAINER.

Response:
The Carton has been revised to include the pH range. As noted previously, the g tube has been deleted.

b. Comment:
We encourage you to relocate the "Each Gram contains" statement to appear before the storage statement.

Response:
The "contains" statement has been relocated to appear before the storage statement.
Samples (FPL) of the revised carton are included in Attachment 13.

3) INSERT

Comment:

a. DESCRIPTION

i. Include the molecular formula.
ii. First sentence - Clindamycin Phosphate Gel, for topical use, contains...

b. CLINICAL PHARMACOLOGY

i. Delete the second paragraph
ii. Replace "ml" with "mL". Revise throughout the insert.

c. WARNINGS

Revise the entire section as follows:

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool cultures for *Clostridium difficile* and stool assay for C.difficile toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg to 2 grams of vancomycin orally per day in three to four divided doses

administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

d. PRECAUTIONS

i. Add the following text after the General subsection:

Drug Interactions:

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution in patients receiving such agents.

ii. Revise the pregnancy subsection heading as follows:

Pregnancy: Teratogenic Effects:
Pregnancy Category B

iii. Nursing Mothers -

1) First sentence - "use" rather than "us".

2) Delete the third sentence Replace it with "Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

iv. Pediatric Use - ... effectiveness in pediatric patients under the ...

e. ADVERSE REACTIONS

Revise the entire section as follows:

In 18 clinical studies of various formulations of Clindamycin Phosphate Topical solution using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Number of patients reporting events

Treatment Emergent Adverse Event	Solution	Gel	Lotion
	n=553 (%)	n=148 (%)	n=160 (%)
Burning	62 (11)	15 (10)	17 (11)
Itching	36 (7)	15 (10)	17 (11)
Burning/Itching	60 (11)	# (-)	# (-)
Dryness	105 (19)	34 (23)	29 (18)
Erythema	86 (16)	10 (7)	22 (14)
Oiliness/Oily Skin	8 (1)	26 (18)	12* (10)
Peeling	61 (11)	# (-)	11 (7)

not recorded
* of 126 subjects

Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally.

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulation of clindamycin and rarely with topical clindamycin (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as gram-negative folliculitis have also been reported in association with the use of topical formulations of clindamycin.

f. Add the text to appear as the OVERDOSAGE section following the ADVERSE REACTIONS section.

OVERDOSAGE

Topically applied clindamycin topical solution can be absorbed in sufficient amounts to produce system effects (See WARNINGS)

g. HOW SUPPLIED
   i. Add "protect from freezing."
   ii. Delete the gram product size if it is a professional sample size.

Please revise your labels and labeling, as instructed above, and submit final printed containers labels and carton labeling and draft labeling (final print if you prefer).

Response:
The labeling has been revised as requested. Samples of FPL insert labeling are included in Attachment 14.

We trust the enclosed information allays any concerns regarding the proposed drug product. We await the Division of Bioequevalence's decision concerning our request for a bioequevalence waiver for the drug product.

If there are any questions, please contact me at 516 454-7677 ext. 2091.

Sincerely,
E. Fougera & Co.
division of Altana Inc.

/S/
Virginia Carman
Associate Director
Regulatory Affairs

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ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

Federal Express

January 24, 2000

Dr. Vilayat Sayeed
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: ANDA 64-160 TELEPHONE AMENDMENT
Clindamycin Phosphate Gel USP, 1% (base)

Dear Dr. Sayeed:

Reference is made to our Abbreviated New Drug Application dated August 11, 1995 as well as our amendments of October 26, 1999, November 9, 1999 and January 21, 2000.

Reference is also made to our telephone conversation of this date.

As an amendment to our correspondence of January 21, 2000, we wish to confirm that homogeneity testing is performed as follows: Samples are taken at the crimp, middle and top of tube, and assayed individually. This testing is performed at every stability interval.

This information is also being sent in hard copy to the file.

If there are any questions, please contact me at (631) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC/et

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

Federal Express

FA

January 21, 2000

Mr. Bilayat Sayeed
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: ANDA 64-160 TELEPHONE AMENDMENT
Clindamycin Phosphate Gel USP, 1% (base)

Dear Mr. Sayeed:

Reference is made to our Abbreviated New Drug Application dated August 11, 1995 as well as our amendments of October 26, 1999 and November 9, 1999.

Reference is also made to our telephone conversation of this date.

We wish to confirm that homogeneity testing is performed at every stability interval as is indicated in our stability specifications. This is in addition to the analytical assay of the mixed contents of a full tube as we discussed (Point 1 of the October 26, 1999 correspondence).

This information is also being sent in hard copy to the file.

If there are any questions, please contact me at (631) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC/et

ALTANA

tana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

November 24, 1999

NDA ORIG AMENDMENT
N/A

Dale Connor, Ph.D
Division of Bioequivalence (HFD-658)
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: ANDA 64-160 Telephone Amendment
Clindamycin Phosphate Gel USP, 1% (base)

Dear Dr. Connor:

As per the Division's request, please find enclosed in duplicate complete copies of Appendix C, which contain the missing tables, i.e. 3, 5a, 5c, 6b, c, d, 7b, 8b, 9b, 10b, 11b, 12b, 13, 14c, d, g, h, k, l, and 15c, d g, h, k, l.

We apologize for the oversight.

If there are any additional questions, please contact me at (631) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enclosure

VC/et

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

December 17, 1999

Jennifer Fan
Division of Bioequivalence (HFD-658)
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

FA

Re: ANDA 64-160 Telephone Amendment
Clindamycin Phosphate Gel USP, 1% (base)

Dear Ms. Fan:

As per our conversation, please find enclosed the telephone amendment dated November 24, 1999.

Please contact me, if there are any additional questions at (631) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enclosure

VC/et

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

November 11, 1999

Florence S. Fang
Director, Division of Chemistry II
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855-2773

FA

Re: ANDA 64-160 TELEPHONE AMENDMENT

Clindamycin Phosphate Gel USP, 1% (base)

Dear Ms. Fang:

Reference is made a telephone request of November 10, 1999 made by the Division requesting us to address the position of stability samples during the stability studies.

Please find enclosed a revised stability protocol indicating that the samples "will be stored on their sides at 25°C ± 2°c/60% ± 5% RH."

If any further clarification is required, please contact me at (631) 454-7677, ext. 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enclosures

VC/et

NOV

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

November 9, 1999

NDA ORIG AMENDMENT
N/FA

Florence S. Fang
Director, Division of Chemistry II
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855-2773

Re: ANDA 64-160 TELEPHONE AMENDMENT

Clindamycin Phosphate Gel USP, 1% (base)

Dear Ms. Fang:

Reference is made to Altana Inc.'s Abbreviated New Drug Application submitted on August 11, 1995, as well as our amendments of February 6, July 9, 1995 April 26, 1999 and October 26, 1999.

Reference is also made to a telephone conversation between Mr. Mark Anderson and Ms. Maria Shih of the Office and Virginia Carman of Altana Inc. concerning stability samples and results.

Altana was asked as to the position of the stability samples during storage. The Clindamycin Phosphate Gel USP, 1% (base) stability samples were stored on their sides so that the product was in contact with the closure.

We were also requested to comment on our weight loss specification of %, and further as to why there is a weight loss.

Our belief is that there is a slight evaporation of water. If it were due to a leakage through the crimp, there would be a sharp drop in weight, or an inconsistent weight loss over time. In the 30g tubes there is a definite trend indicating evaporation of the water. We propose to tighten the weight loss specification to not more than %. Please see revised stability specification.

We also wish to propose an eighteen-month expiry period for this product.

This information also is being Federal Express to you today.

If there are any further questions; please contact me at (631) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/et

ALTANA

'tana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

Federal Express

November 8, 1999

NEW CORRESP

NC

BIOAVAILABILITY

Mr. Harvey Greenberg
Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: ANDA 64-160 BIOEQUIVALENCE TELEPHONE AMENDMENT
Clindamycin Phosphate Gel USP, 1% (base)

Dear Mr. Greenberg:

As per our telephone conversations of the last several weeks, please find included a data diskette containing the following information:

Basic demographics
Baseline disease severity
Baseline mycologic data
Clinical cure rates
Physician's global assessments
Symptoms
Reasons for discontinuance
Adverse events

I understand that Ms. Aileen Quick from our statistical consultant company spoke with a member of the Office to verify acceptability of the material being submitted on a zip disk in conjunction with another of our submissions, and that this is acceptable.

If there are any problems or any further information is necessary, please contact me at (631) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC/et

Enclosures

ALTANA

Itana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

October 26, 1999

Florence S. Fang
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855-2773

Re: ANDA 64-160 FACSIMILE AMENDMENT

Clindamycin Phosphate Gel USP, 1% (base)

Dear Ms. Fang:

Reference is made to our original Abbreviated New Drug Application dated August 11, 1995, as well as our amendment of April 26, 1999.

Reference is also made to your communication of October 22, 1999 in which several deficiencies were noted. We wish to respond to each point as follows:

1. **Comment**

   For assay analysis, please explain how gel samples are taken from the tubes for release and stability purposes.

   Response

   Samples are extruded directly from the tube for finished product testing. For stability testing the tube is slit and the product is mixed before the analytical sample is taken.

2. **Comment**

   It is not clear regarding the storage position for the stability samples. Are samples stored upright or sideways? Please clarify.

   Response

   All tubes were stored sideways for all stability studies.

3. **Comment**

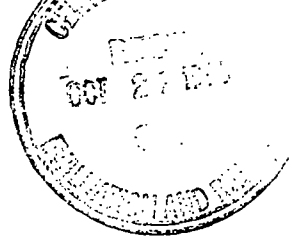
   It is noted that there are significant potency losses for the finished drug product during storage. Please submit additional long-term stability data to support the proposed expiry dating.

   Response

   Long term stability data are included. Based on these data, we are requesting an 18-month expiry date.

4. **Comment**

   Results for seal integrity or leak testing of tubes/caps should be provided.



Response

Leak testing results are included in the stability testing reports under the heading "weight loss".

If any further information is required, please contact me at (516) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC/et

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a division of Altana Inc.

Federal Express

December 4, 1996

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: AADA 64-160
Clindamycin Phosphate Gel USP, 1%

Dear Mr. Sporn:

Reference is made to our letter of October 9, 1996, in which we requested a meeting to discuss the requirement for the performance of an in vivo bioequivalence study as stated in the Division of Bioequivalence's (DOB) letter of June 27, 1996.

As requested in a telephone conversation with a representative of the DOB, we have included for your review a copy of the information which we wish to discuss at the proposed meeting.

We believe that the enclosed information supports the position that our product meets the requirement of 320.22 (b)(3) in that the drug product "i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture or other solubilized form (emphasis added). ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety."

We look forward to your decision concerning our meeting request

Sincerely,
E. Fougera & Co.
division of Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-756-7017

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a division of Altana Inc.

10/25/96
noted this is being handled as controlled correspondence - currently in bio for a response. M. Anderson aware.
Robert Rudolph (SO)

Federal Express

October 9, 1996

RECEIVED
OCT 10 1996
GENERIC DRUGS

BIOAVAILABILITY
NEW CORRESP

Mr. Mark Anderson
Project Manager
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, HFD-650
Rockville, MD 20855-2773

Re: AADA 64-160
Clindamycin Phosphate Gel USP, 1%

Dear Mr. Anderson:

E. Fougera & Co., division of Altana Inc., is requesting a meeting with the Division to discuss the Division's refusal to grant a waiver of the in vivo bioequivalence requirements for the above referenced drug product.

We acknowledge that the drug product is a post-1962 product; however, we believe that the product meets the requirements for a waiver of in vivo bioequivalence contained in 21CFR 320.22 (b)(3). While the drug product is not a true solution, the drug substance is in a solubilized form, and we have generated data to show that the "thickeners" in the vehicle do not affect the release of the product. Also, we can establish that our product demonstrates an in-vitro release profile that is the same as the innovator product, Cleocin T (Upjohn).

The proposed attendees from E. Fougera & Co. are:
Ms. Marcy Adrian - Vice President
Ms. Virginia Carman - Associate Director of Regulatory Affairs
Mr. Dave Pearce - Director of Research & Development
Dr. Joel Zatz - Consultant

Our agenda is to discuss with the Division the issue of the bioequivalence waiver request and for Dr. Zatz and Mr. Pearce to present scientific data supporting our position.

10/25/96

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-756-7017

We wish to meet with the Division as soon as possible. Although this is short notice, Dr. Zatz and Mr. Pearce will be attending a meeting in Washington on October 21, and 22.

If a meeting could be scheduled either the afternoon of October 22, or anytime on the 23rd, it would be greatly appreciated. Otherwise, in order to accommodate Dr. Zatz, Tuesdays, Wednesdays and Fridays are preferable.

Thank you for your consideration of our request.

Sincerely,
E. Fougera & Co.
division of Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC:ch

cc: Dr. R. Patnaik

C:\GINGER\CLIN.P

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

BIOAVAILABILITY

April 26, 1998

Ms. Florence Fang
Director
Division of Chemistry II
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 286
7500 Standish Place
Rockville, Md. 20855-2773

NDA ORIG AMENDMENT

N/A

labeling review drafted 10/13/99 G. Vezza

Re: ANDA 64-160 MAJOR AMENDMENT
Clindamycin Phosphate Gel USP, 1% (base)

Dear Ms. Fang:

Reference is made to Altana Inc.'s Abbreviated New Drug Application submitted on August 11, 1995 in accordance with section 507 of the Federal Food, Drug and Cosmetic Act.

Reference is also made to Altana Inc.'s amendments dated February 6, and July 9, 1996.

Altana Inc. submits this Major Amendment in response to the FDA correspondence dated August 19, 1996, as well as the Division of Bioequivalence's letter of June 12, 1998.

In support of the bioequivalence study submitted herein, we are also including in this response data on the batches of product (active and vehicle) used in the bioequivalence study.

We are also amending the application to include a 60 gram tube presentation.

We wish to respond to each point of your August 19, 1996 letter as follows:

1. Comment
We note that you have included revised specifications for In the original submission only was identified as the bulk manufacturer. Please clarify.

RECEIVED

GENERIC DRUGS

Response

is the only manufacturer of the active drug substance for which approval is sought. The reference to on the raw material specifications has been removed. The "Source of Procedure" is now specified as "Altana/Current USP/Current BP" and the Manufacturer of the drug substance as Included as Attachment 1 are the current raw material specifications for initial release and the "12 Month Extension" specification/analysis report, which specifies the annual retest requirements.

2. Comment

Please explain in detail the assay procedures for clindamycin phosphate potency and for the degrandant content of the final product as reported in the stability studies.

Response

The assay procedures for clindamycin phosphate potency and degradant content of the final product have been updated to include a more detailed explanation. A copy of the procedure has been included for review as Attachment 2.

3. Comment

It is noted that the updated stability data contain results from only the 30 g tube. Please also submit updated stability data for the 7.5 g tube.

Response

One year stability data for the 7.5 g tube is included in Attachment 3. Please note: as previously indicated in our July 9, 1996 response, we are not pursuing approval of the 7.5 g tube.

4. Comment

We await your submission of an in-vivo bioequivalence study in response to the letter from our Division of Bioequivalence dated June 27, 1996.

Response

Included in this submission is a copy of the final study report for an in-vivo bio-equivalence study. This study was conducted in response to Agency correspondence dated June 27, 1996 from the Division of Bioequivalence (DOB) as well as comments from the DOB dated June 12, 1998. Copies of all Agency correspondences concerning the proposed biostudy have been included in Attachment 20 together with the full clinical trial report (last five volumes of this response).

Altana Inc. would also like to acknowledge Agency comments provided by the Chemistry Review to Bio (June 12, 1998).

1. Comment

Please clarify specification sheet on page 191: 1) "Source of Procedure: Current USP, CTFA". 2) under Identification, what is the source of the reference standard?

Response

1) The procedure for testing raw material is obtained from two sources. The current USP chapters are used to perform the Residue on Ignition <281>, Loss on Drying <731> and Infrared Spectrum <851> analyses. The Cosmetic, Toiletry and Fragrance Association (CTFA) Procedures are followed for the Assays of

2) A reference standard for has been obtained from and is used for the Identification test. This information was submitted as part of our response of July 9, 1996.However, an error was noted in the chapter number for Residue on Ignition. A corrected procedure is included in Attachment 4. A representative Certificate of Analysis is also included.

2. Comment

A detailed description section (or flow chart) for the manufacturing process is needed for the actual ANDA.

Response

A manufacturing process flow chart was included as part of the Product Development Report and can be found on pages 261 and 262 of the original ANDA submission.

3. Comment

A detailed section describing Container is needed for the actual ANDA. All information were gathered under Stability section.

Response

A full description of the container/closure system proposed for Clindamycin Phosphate Gel USP, 1% can be found on pages 460 through 520 of the ANDA submission. Information regarding the specifications, DMF authorizations, physico/chemical, biological and routine testing of the components are included.

4. Comment

In the actual ANDA, the section regarding in-process controls has to be expanded and clarified.

Response
Pages 316 through 457 of the ANDA submission contain a copy of the executed batch record, sampling plans and specifications and test procedures for the in-process material, and actual data for the executed batch.

5. Comment
The product specifications on page 388 is for "placebo". The specifications stated are copied from the data sheet (page 392). You need to submit a new specification statement.

Response
Updated finished product specifications have been included as Attachment 5. The specifications for clindamycin phosphate and methylparaben have been tightened from %. The limits for have been reduced from Not More Than % to Not More Than % (relative to methylparaben) and the viscosity limits have been revised from cps.

6. Comment
Please identify some of the degradation products and related substances listed under "Others" for specifications.

Response
Identification of the degradation products and related substances was performed and the results submitted in our July 9, 1996 response to your letter of March 19, 1996.

7. Comment
The limits set for degradation products seem exceptionally high. The actual ANDA will be very carefully reviewed regarding this issue.

Response
As noted above the limits have been revised and submitted as a response in July 1996 to your March 1996 letter.

8. Comment
Under Stability, the same concerns regarding limits of degradants as raised under 5, 6, and 7 apply.

Response
The limits for the clindamycin and total degradation products (relative to clindamycin phosphate) have been tightened to Not More Than % and Not More Than %, respectively. Updated Stability Specifications have been included as Attachment 6.

In addition, as noted in response to several questions the analytical specifications were changed for In-process, Finished Product, and Stability testing. Finished Product and Stability specifications are found in Attachments 5 and 6 respectively. Updated In-process specifications can be found in Attachment 7.

Additional chemistry information is included as follows to support the bioequivalence study. Please note that there have been no changes to the processes and controls previously submitted and reviewed for this drug product unless specifically noted.

1) Clindamycin Phosphate Gel USP, 1%, Lot A313 (Bioequivalence study - test product)

a) Batch record	Attachment 8
b) Active ingredient analysis reports	Attachment 9
c) In-process analytical results	Attachment 10
d) Finished product analytical results	Attachment 11
e) Stability data	Attachment 12

2) Vehicle Control, Lot A312 (Placebo)

a) Batch record	Attachment 13
b) In-process analytical results	Attachment 14
c) Finished product analytical results	Attachment 15

As previously indicated, we also wish to amend the application to include a 60 gram tube presentation. The same procedures and controls used for the filling and packaging of the 30 gram tube apply to the 60 gram tube.

The following information pertinent to the 60 gram tube is included:

1) Specifications and diagrams	Attachment 16
2) Plastics information	Attachment 17
3) Stability data	Attachment 18
4) Proposed container, carton and PI labeling	Attachment 19

Please contact me at (516) 454-7677 ext. 2091 if you require any additional information.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

clingel4-26-99

tougera
Division of Altana Inc.

Certified Mail

February 6, 1996

Keith Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-650)
7500 Standish Place
Rockville, Maryland 20855

RE: AADA 64-160
Clindamycin Phosphate Gel USP, 1%

Dear Dr. Chan:

Reference is made to your letter of December 6, 1995, denying our request for a bioequivalence waiver for the above referenced drug product.

Clindamycin Phosphate Gel is an antibiotic monographed at 21 CFR §453.522b (see attached). As such, we believe that the requirement for conducting *in vivo* bioequivalency testing should be waived.

Additionally, your letter stated that the regulations were not reiterated appropriately and should read as follows:

The drug product:

(i) Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, or similar other solubilized form.

(ii) Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application; and

(iii) Contains no inactive ingredient or other change in the formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety.

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-420-1572

In hindsight, the regulation should have been quoted as above with the appropriate sections highlighted. Our original intent was to emphasize that the drug product is applied to the skin and is in a solubilized form.

It is our belief that the drug product that is the subject of this abbreviated new drug application is eligible for a waiver of the *in vivo* bioequivalence requirements described under 21 CFR §320.24. Our position is based on the facts that the drug product complies with all three of the criteria of 21 CFR §320.22(b)(3), in that: the drug substance, clindamycin phosphate, is in a "solubilized form" within the drug product, Clindamycin Phosphate Gel USP; and, the drug product's formulation is qualitatively and quantitatively identical to the listed drug, therefore, it meets the criteria of citations (ii) and (iii) of §320.22, as well as being a monographed antibiotic.

Therefore, enclosed is a revised bioequivalence waiver request that follows the format and content described in 21 CFR §320.22(b)(3).

We respectfully request that the refusal to grant a bioequivalency waiver for Clindamycin Phosphate Gel USP, 1%, be reconsidered.

We note that your letter did not refer to our submission of October 4, 1995, which contained additional data on the formulation equivalency. This is included to assist in your review.

Sincerely,
E. Fougera & Co.
a division of Altana Inc.

Virginia Carman

Virginia Carman
Associate Director,
Regulatory Affairs

A:\CLINDMGE.124

fougera
Division of Altana Inc.

FEDERAL EXPRESS

October 4, 1995

Mr. Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Metro Park North II, HFD-617 Room 237N
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

RECEIVED
OCT 0 6 1995
GENERIC DRUGS

Re: AADA 64-160
Clindamycin Phosphate Gel USP, 1%

Dear Mr. Phillips:

Reference is made to your communication of September 26, 1995, indicating the Office of Generic Drugs' reasons for refusing to file our application.

Your letter states:

Comment

While you have stated that your formulation is qualitatively the same as the reference listed drug, you have failed to provide a side-by-side comparison of the formulation of your proposed drug product with that of the reference listed drug product. You must demonstrate that the proposed drug product is qualitatively and **quantitatively** the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, you must provide the information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(v)]. The information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. ph, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.

Thus, it will not be filed as an abbreviated antibiotic application within the meaning of Section 507 of the Act.

Response

We wish to respond that although we acknowledge that we did not list a side-by-side

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-420-1572

quantitative comparison between our product and the reference listed product, a qualitative comparison could be found in Section 4.2 and 4.3, pages 0008 and 0009.

Additionally, the quantitative formulation of Cleocin T was determined analytically, and our product was formulated to be quantitatively identical to it. The development report included this analysis and is located in Section 11.1 beginning on page 0209.

We have included herein the original development report as noted above. This report has been prefaced by a report from the Director of Research and Development stating the quantitative comparison of the two drugs, as well as an explanation of the theory and calculations used to determine the formulation of Cleocin T.

As our product is qualitatively and quantitatively identical to the reference drug Cleocin T, there are no issues regarding the safety of the drug product's formulation.

Comment

In addition, original signatures are required for certifications submitted for the field copy, the Generic Drug Enforcement Act of 1992, and the list of convictions.

Response

As requested we've included original signature pages for the field copy, the Generic Drug Enforcement Act of 1992, and list of convictions certifications.

We hereby request that our application for Clindamycin Phosphate Gel USP, 1% be accepted for filing.

Sincerely,
E. Fougera & Co.
division of Altana Inc.

Virginia Carman
Associate Director,
Regulatory Affairs

VC/lae

encl.

C:\MISC\64-160.RES

fougera
Division of Altana Inc.

August 11, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Original Submission
Abbreviated Antibiotic Drug Application
Clindamycin Phosphate Gel USP, 1%

Dear Sir or Madam:

Pursuant to the Regulations contained in 21 CFR §314.94, E. Fougera & Co., division of Altana Inc., is submitting this Abbreviated Antibiotic Drug Application to market a new drug, Clindamycin Phosphate Gel USP, 1%.

The reference listed drug that is the basis for this submission is CLEOCIN T® (NDA 50-165), manufactured by THE UPJOHN CO. The proposed drug, Clindamycin Phosphate Gel USP, 1%, contains the same active ingredient in the same strength and dosage form, has the same indications and usage, and route of administration as the reference listed drug.

The exhibit batch (#6453) included in this application was fully packaged utilizing the 7.5 gram and 30 gram presentations for which approval is currently requested. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this two (2) volume submission, along with Form FDA 356h, is the required Patent Certification and Exclusivity statements, draft Labeling, Bioequivalence Waiver Request, full Components and Composition statements, Raw Materials controls, description of the Manufacturing Facilities, Manufacturing and Processing instructions, In-Process Controls, Filling and Packaging procedures, information on the Container/Closure System, controls for the Finished Dosage Form, Analytical Methods, Finished Dosage Form Stability, Environmental Impact Analysis statement, Certification Requirements of the Generic Drug Enforcement Act of 1992 and Field Copy Certification.

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-420-1572

All regulatory correspondences related to this Abbreviated Antibiotic Drug Application should be addressed to:

Virginia Carman
Associate Director,
Regulatory Affairs
E. Fougera & Co.,
division of Altana Inc.
60 Baylis Road
Melville, NY 11747

A certified copy of this application is being sent to the New York District Office under separate cover.

We trust that this submission will meet your approval. Please advise if you require any additional information.

Sincerely,
E. Fougera & Co.,
division of Altana Inc.

Virginia Carman

Virginia Carman
Associate Director,
Regulatory Affairs

VC:ab

Enclosures