CENTER FOR DRUG EVALUATION AND RESEARCH

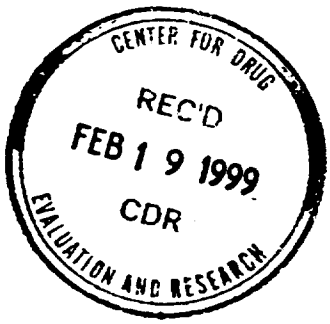
APPLICATION NUMBER:

21-105

CORRESPONDENCE

February 18, 1999

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20857



Attention: HFD-520

RE: NEW DRUG APPLICATION (NDA)
ZOTRIM™ *UTI* THERAPY

Dear Sir/Madam:

Able Laboratories, Inc. herewith submits a new drug application for Zotrim™ *UTI* Therapy pursuant to Section 505 (b) (2) of the Federal Food Drug and Cosmetic Act. All safety and efficacy data is based upon published literature, and therefore, the NDA is considered a "Paper NDA".

In order to support this application, publications related to the following areas were reviewed: compliance with self administration of prescribed treatment regimens, history/use and/or effect of Phenazopyridine Hydrochloride in the treatment of urinary tract infections, history/use and/or effect of Trimethoprim, Sulfamethoxazole, and/or Trimethoprim-Sulfamethoxazole as well as other antibacterial drugs in the treatment of urinary tract infections, non-clinical pharmacology and toxicology studies of Phenazopyridine Hydrochloride, non-clinical pharmacology and toxicology studies using Trimethoprim, Sulfamethoxazole, and/or Trimethoprim-Sulfamethoxazole, non-clinical absorption, metabolism, and excretion studies of Phenazopyridine Hydrochloride, non-clinical absorption, metabolism, and excretion studies of Trimethoprim, Sulfamethoxazole, and/or Trimethoprim-Sulfamethoxazole, human pharmacology of Phenazopyridine Hydrochloride, and human pharmacology of Trimethoprim, Sulfamethoxazole, and/or Trimethoprim-Sulfamethoxazole.

The regulatory aspect of the program was initiated with correspondence to the FDA Division of Anti-Infective Drug Products in November/December of 1996. At that time DynaGen/Able proposed a blister card of Trimethoprim-Sulfamethoxazole DS and Phenazopyridine Hydrochloride for the treatment of urinary tract infection and its symptoms. DynaGen/Able further proposes to purchase Trimethoprim-Sulfamethoxazole DS in bulk and repackage it along with Phenazopyridine Hydrochloride in a single blister card format for the entire treatment regimen.

A Pre-NDA meeting was held with members of the Division of Anti-Infective Drug Products at FDA on March 10, 1997. The following agreements were reached relative to the proposed product:

1) Phenazopyridine Hydrochloride is a Pre-1938 drug with no existing FDA approval under an NDA. The safety and effectiveness of this drug are supported by literature articles which will be submitted in the NDA.

2) The effectiveness for Trimethoprim-Sulfamethoxazole DS has been demonstrated in FDA-approved drugs for 10 and 14 -day treatments.

3) A similar combination product for treatment of urinary tract infection, namely [redacted] which contains Phenazopyridine Hydrochloride and Sulfamethoxazole, has been determined by FDA as an approved NDA drug.

4) Full chemistry sections for Phenazopyridine Hydrochloride, including a letter of authorization for the DMF of Phenazopyridine Hydrochloride raw material need to be provided in the NDA. DynaGen/Able will use referenced CMC data for Trimethoprim-Sulfamethoxazole. Letters of authorization from the drug manufacturer need to be provided for referencing the data.

5) Stability data on the blister card packaging must be submitted. (DynaGen/Able will be submitting at least three batches with at least 6 months (accelerated) stability.

6) Supporting data for existing Trimethoprim-Sulfamethoxazole DS packaging may be referenced. If referenced, authorization letters from the manufacturers will be required. The packaging for the proposed blister card should be at least as good as the referenced packaging. Expiration dating will be based on the lowest component's expiration dating. The dating clock starts at the time of bulk synthesis (*the earliest date of tablet manufacture for either trimethoprim-sulfamethoxazole DS or phenazopyridine hydrochloride*), not at repackaging. Three-month accelerated and real time stability studies should continue.

7) A Pre-approval inspection of the manufacturing site and the analytical laboratories will be required.

8) The review time for a New Drug Application is one year.

9) No exclusivity will be granted to this drug as proposed (10-day/2-day combination).

10) FDA advised DynaGen/Able to conduct drug interaction and bioavailability studies. Literature studies may be sufficient to prove the claim. Further discussion with FDA (Dr. Frank Pelsor) suggested that a prospective drug interaction study would be beneficial and probably less difficult than reviewing the literature for the requested data. Subsequently, the study protocol was discussed with Dr. Pelsor and his suggestions were incorporated and the study was conducted.

A subsequent communication with Ms. Beth Duvall Miller, Project Manager, in the Division of Anti-Infective Products, outlined the content of the proposed NDA. After review by the Division, the proposed outline was accepted by the Division as communicated to Able Laboratories by Ms. Duvall Miller. Able Laboratories has followed that outline as close as possible in the enclosed application.

Able Laboratories, Inc. certifies that none of the patents identified in the search relative to the components of Zotrim™ *UTI* Therapy, namely, sulfamethoxazole-trimethoprim DS tablets and

phenazopyridine hydrochloride tablets will be infringed by Able Laboratories, Inc. and that all of the patents identified in the search relative to the manufacture of sulfamethoxazole-trimethoprim DS tablets and phenazopyridine hydrochloride have expired.

Able Laboratories, Inc. certifies that the methods, facilities, and controls used for the manufacturing processing, packaging, and holding of the above-mentioned drug products are in conformity with current Good Manufacturing Practices in accord with the Code of Federal Regulations, Title 21, Parts 210 and 211.

Field Copy certification for the application form, Summary Section, and Chemistry, Manufacturing, and Control Section for Able Laboratories, Inc.'s New Drug Application for Zotrim™ *UTI* Therapy may be found in Section XI, "Other". Certification (Form FDA 3454 - Certification: Financial Interests and Arrangements of Clinical Investigators) that Able Laboratories, Inc. has not entered into any financial arrangement with the listed investigator for performance of the Drug Interaction study involving phenazopyridine hydrochloride and trimethoprim-sulfamethoxazole DS. may also be found in Section XI, "Other".

Able Laboratories, Inc. will manufacture the Phenazopyridine Hydrochloride 200 mg tablets component of Zotrim™ *UTI* Therapy; TEVA Pharmaceuticals will provide the Sulfamethoxazole-Trimethoprim DS (sulfamethoxazole: 800 mg; trimethoprim: 160 mg) tablets component of Zotrim™ *UTI* Therapy. Both tablets will be packaged by Packaging Coordinators, Inc. in a single blister card for a complete 10-day regimen for treatment of urinary tract infection. The product will be distributed by [redacted] under license from Able Laboratories, Inc.

Able Laboratories, Inc. commits to perform all tests of the finished product in accordance with the specifications set forth in Section III - Chemistry, Manufacturing, and Controls (Appendix 22).

Able Laboratories, Inc. (formerly, a subsidiary of A.L. Laboratories) was acquired by DynaGen, Inc., a Cambridge, Massachusetts' company, on August 19, 1996. DynaGen, Inc. is a health care company founded in 1988 which develops and markets proprietary and generic therapeutics and diagnostics products for the human health care market. Able Laboratories is in operation as a wholly-owned subsidiary of DynaGen, Inc.

Able Laboratories reiterates its firm commitment to FDA that all manufacturing will be performed in compliance with current regulatory requirements and that all products and services will reflect an uncompromising commitment to continued high quality.

We trust that the enclosed new drug application for Zotrim™ *UTI* Therapy meets your requirements. If you or your colleagues have any questions, please contact me at DynaGen at (617) 491-2527 or fax at (617) 354-3902. Thank you.

Sincerely,

Peter J. Mione, M.S.
Vice President, Clinical and
Regulatory Affairs - DynaGen, Inc.

cc: Ms Janis Picurro - Able laboratories, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-105

MAR 10 1999

Able Laboratories, Incorporated
Attention: Peter J. Mione, M.S.
Vice President, Clinical and Regulatory Affairs
6 Hollywood Court
South Plainfield
New Jersey 07080

Dear Mr. Mione:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zotrim (phenazopyridine HCL tablets 200mg and sulfamethoxazole 160mg-trimethoprim DS tablets 800mg).

Date of Application: February 18, 1999

Date of Receipt: February 19, 1999

Our Reference Number: 21-105

We have not received the appropriate user fee for this application. An application is considered incomplete and can not be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number is on the enclosed check.

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment was received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: Division Document Room
NUMBER
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Attention: Division Document Room
NUMBER
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, contact Ms. Frances V. LeSane, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely,

/S/

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Food and Drug Administration
Rockville MD 20857

Office of the Chief Mediator and Ombudsman
5600 Fishers Lane (HF-7)
Room 14-105
Rockville, MD 20857

ORIG AMENDMENT

N-AR

June 7, 1999

Peter J. Mione
Vice President
Clinical and Regulatory Affairs
DynaGen, Inc.
840 Memorial Drive
Cambridge, MA 02139

Re: Prescription Drug User Fee Act
Small Business Waiver Request
Able Laboratories, Inc.
Our file number: 99.034

Dear Mr. Mione:

This letter responds to your letter, dated March 8, 1999, on behalf of Able Laboratories, Inc. (Able), requesting a waiver of the application fee assessable on the marketing application for Zotrium UTI Therapy (Zotrium), NDA 21-105, as prescribed by the small business waiver provision[1] of the Prescription Drug User Fee Act of 1992, as amended by the Food and Drug Administration Modernization Act of 1997 (User Fee Act).[2] For the reasons stated below, the Food and Drug Administration (FDA) grants Able's request for a waiver of the application fee.

The small business waiver provision of the User Fee Act entitles a qualified small business to a waiver of the application fee when the business meets two criteria: first, a business must employ fewer than 500 persons, including employees of its affiliates;[3] and second, the marketing application must be the first human drug application, within the meaning of the User Fee Act, that a company or its affiliate submits to FDA for review.[4]

FDA's decision to grant a small business waiver to Able is based on two findings. First, by letter dated April 14, 1999, the Small Business Administration (SBA) determined

[1] 21 U.S.C. § 379h(d)(1)(E)
[2] 21 U.S.C. § 379g et seq.
[3] The term affiliate means a business entity that has a relationship with a second business entity if, directly or indirectly – (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has power to control, both of the business entities. 21 U.S.C. § 379g(9)
[4] 21 U.S.C. § 379h(d)(3).

ORIGINAL

that, as of March 25, 1999, Able had fewer than 500 employees, including employees of its affiliates: DynaGen, Inc.; [redacted] Second, according to FDA records, the marketing application for Zotrium is the first human drug application, within the meaning of the User Fee Act, submitted to FDA by Able or its affiliates.

By letter dated March 10, 1999, FDA informed Able that its NDA for Zotrium was not acceptable for filing because FDA did not receive payment of the application fee. By date of this letter, the marketing application is now considered acceptable for filing. Therefore, FDA will now make a threshold determination of whether the application is sufficiently complete to permit a substantive review (i.e., FDA will file or refuse to file the application). If FDA refuses to file the application or if Able withdraws its application before FDA makes this determination and if Able wishes to resubmit its application, then Able should contact this office. Please contact this office approximately 90 days before resubmitting the application for information about the process for determining whether Able continues to qualify for the small business waiver.

A copy of this letter should be submitted to your marketing application. If any billing questions arise concerning the marketing application, please contact Mr. Michael Jones, Consumer Safety Officer, Center for Drug Evaluation and Research (CDER), at 301-594-2041.

Please note that FDA plans to disclose information about its actions granting or denying waivers, consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If you have any questions about this small business waiver, please contact Ms. Kathleen Locke, of this office, at 301-827-3390.

Sincerely yours,

/S/

Suzanné M. O'Shea
Deputy User Fee Waiver Officer
Office of the Chief Mediator and Ombudsman

ABLE
LABORATORIES
INC. Subsidiary of DynaCen, Inc

July 11, 2000

Ms. Beth Duvall Miller
Food and Drug Administration
Division of Anti-Infective Drug Products
HFD-520
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

Ref.: NDA # 21-105, Zotrim UTI Therapy
Alternate Names

Dear Ms. Duvall:

Pursuant to our conversation of June 21, 2000 and July 11, 2000 we are herewith submitting 2 alternate names to replace the Zotrim UTI Therapy which was deemed unacceptable earlier this year.

Our first choice is: ZoTRAC
Our second choice is: BacTRAC

Per our discussion, a formal submission is being made under separate cover.

Should you require any additional information, or have any questions regarding this correspondence, you may reach me at 908.754.2253 extension 512.

Sincerely,

Iva Klemick

Mrs. Iva Klemick
Director, Regulatory Affairs

6 Hollywood Court ◿ South Plainfield ◿ New Jersey 07080
Telephone 908-754-2253 ◿ Fax: 908-754-2476

NDA 21-105

ABLE Laboratories Inc.
Attention: Shashikant Shah, R.Ph.
Vice President of Quality/Regulatory Affairs
6 Hollywood Court CN1013
South Plainfield, NJ 07080

SEP 5 2000

Dear Mr. Shah:

Please refer to your new drug application (NDA) dated February 18, 1999, received February 19, 1999 (accepted for filing June 7, 1999), submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for a blister card containing twenty trimethoprim/sulfamethoxazole double strength (160 mg/800 mg) tablets and six phenazopyridine hydrochloride 200 mg tablets.

We acknowledge receipt of your submissions dated June 14, 1999, January 24, 2000, and May 24, 2000.

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 deficiencies may be summarized as follows:

Our inspectors could not complete inspection of the [redacted] manufacturing facility in [redacted] for conformance with current good manufacturing practices (cGMP) because the facility was not ready for inspection. A satisfactory inspection will be required before this application may be approved.

We note that at the time of this action your drug product does not have an acceptable proprietary name. If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation. In addition, your submitted draft labeling must be further revised and agreed to prior to the approval of this application.

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.

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, call Beth Duvall-Miller, BS, Regulatory Health Project Manager , at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research