DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Warning Letter

Via FedEx

WL: 320-05-01

FEB 15 2005

Ms. Leslie Drake
President
Germiphene Corporation
1379 Colborne St., East
PO Box 1748
Brantford, Ontario
Canada
N3T 5V7

Dear Ms. Drake:

We have completed our review of the inspection of your pharmaceutical manufacturing facility in Brantford, Ontario, Canada, during the period of October 12-15, 2004. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) Regulations (Title 21 Code of Federal Regulations (CFR), Parts 210 and 211) in the manufacture of drug products. These deviations were listed on an Inspectional Observations (FDA-483) form issued to you at the close of the inspection. These CGMP deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351(a)(2)(B)]. In addition, your products, as described below, are misbranded within the meaning of Section 503(b)(4)(A) of the Act [21 U.S.C. 353(b)(4)(A)] and/or are in violation of Section 505(a) of the Act [21 U.S.C. 355(a)].

Our review also included your November 8, 2004, November 30, 2004, December 23, 2004, and February 1, 2005 responses to the FDA-483 observations. The CGMP deficiencies need more comprehensive corrections than the actions you have proposed or taken.

CGMP Issues

1. Employees engaged in the manufacture, processing, packaging and holding of a drug product lack the education, training and experience required to perform their assigned functions.
   21 CFR 211.25 (a)

Several observations cited a lack of following procedures even though there was documentation that your employees were trained in the procedure. For example, when asked about the procedure for determining the status of equipment prior to use, the employee could only say that the analysts were trained to check the calibration prior to

use. However, the piece of equipment in question was in use and out of calibration for 11 months. Questions were asked of the staff that was reportedly trained, but they could not be answered. For example, one employee could not answer questions regarding the reason some data points on the calibration curve for the [ ] were eliminated, even though she was reportedly trained on the use of this equipment. These observations indicate a serious deficiency in the methods and adequacy of your training efforts. In addition, a lack of a formal training program was cited. Recurring CGMP training was not given to your personnel to keep them updated. Your response indicated that you now have a training program; however, the documentation submitted did not provide a formal procedure. The Training Protocol only provided for training on work instructions. It did not provide for CGMP training on a recurring basis or on the job training for employees. Also, GMP and other training for management as well as an assessment of employees' abilities to perform specific tasks was not included.

2. The use of instruments/apparatus not meeting established specifications was observed.
21 CFR 211.100 (b)

Three instruments were documented to be out of calibration but still in use. The [ ] was out of calibration for two months from the annual calibration as per the sticker, however, the responsible employee indicated that the [ ] undergoes monthly calibration. The [ ] used for incoming raw materials is due for calibration biannually, but was out of calibration for five months. The [ ] was continually out of calibration/standardization since the change of the specification to a [ ] allowance was initiated. These incidences were specifically noted on the FDA-483, but not specifically addressed in your response. Also, the retraining of your employees is not an adequate corrective action since there are documented problems with your training program. The main issue of employees not following work instructions or understanding the importance of maintaining equipment was not addressed.

3. Laboratory facilities and equipment used for testing and approval or rejection of components and drug products were found to be inadequate.
21 CFR 211.160

Two of the FDA-483 observations indicated laboratory equipment was used in a different manner than that for which it was qualified. Specifically, two [ ] could not maintain uniform temperature. In one case, an ice pack was used to lower the temperature in a hot spot, and in another, two shelves were marked do not use because of the high temperature. This indicates a lack of adequate qualification of your equipment. If the equipment were adequately qualified and maintained, then these measures would not be needed for the equipment to function properly. There were also several incidences of the failure to calibrate equipment in a timely manner. The accuracy of your equipment is necessary to provide true and accurate data for your processes. Failure to maintain the accuracy of this equipment calls into question the validity of your data.

Observation #9 cited a lack of control in your microbiology laboratory. Your corrective actions do not address the issue of personnel readjusting instrumentation to control the environment without initiating an investigation or assessment when an out-of-range observation was found. This issue was seen for multiple pieces of equipment.

4. The written stability testing program[ ]is inadequate.
21 CFR 211.166

Several observations on the FDA-483 documented problems with your stability testing program. For example, reworked lots were not placed on stability, stability samples were not tested at predetermined intervals, tests used for the stability program were not stability indicating, and stability samples were not stored under adequate conditions. The specific issues documented on the FDA-483 were not addressed adequately. We acknowledge that you have hired a qualified person to maintain your stability program and have purchased new stability chambers. However, hiring new people and purchasing equipment does not correct the deficiencies noted in respect to maintenance and use of the equipment. The failure to follow work instructions relating to the stability program, and the inadequate stability testing methods, were not addressed.

Labeling and New Drug Issues

We have reviewed labeling collected during the inspection for various products marketed by your firm. We have found the labeling to be seriously deficient for marketing the products in the United States and consider these products to be misbranded, and in some cases unapproved new drugs, as described below.

The fluoride level in your fluoride products exceeds limits for over-the-counter (OTC) marketing, as described in 21 CFR 355.10, and therefore, these products must be marketed as prescription drugs. These products are misbranded because their labeling fails to bear a prescription legend, as required by Section 503(b)(4)(A) of the Act [21 U.S.C. 353(b)(4)(A)].

Regarding your Denti-Care oral rinse product, chlorhexidine gluconate 0.12%, oral rinse products are not generally recognized as safe or effective for the treatment of gingivitis or to reduce redness, swelling, or bleeding of the gums. Therefore, the Denti-Care product is a new drug, as defined by Section 201(p) [21 U.S.C. 321(p)]. This product is not the subject of an approved application, and its marketing in the United States violates Section 505(a) [21 U.S.C. 355(a)]. In addition, the product is misbranded because its labeling fails to bear a prescription legend, as required by Section 503 (b)(4)(A) [21 U.S.C. 353(b)(4)(A)].

Topical oral health care preparations containing tetracaine are not generally recognized as safe and effective for OTC use (see 21 CFR 310.545(a)(14)). Therefore, your OTC oral health care products that contain tetracaine in combination with benzocaine are new drugs, as defined by Section 201(p) [21 U.S.C. 321(p)]. These products are not the

subject of approved applications, and their marketing in the United States violates Section 505(a) [21 U.S.C. 355(a)].

General Comments

1. Additional Quality Assurance Issues

Your organizational chart indicates that there is only one person in your quality assurance group. This person is responsible for overseeing the quality assurance not only for the [ ] pharmaceutical products exported to the U.S.A., but also the medical devices for the U.S.A. and Canada and the infection control products, prophy powders, skin cleansers, disposable items, and pharmaceuticals for the Canadian markets. There are multiple batches of multiple products produced at your facility, and yet, only one person responsible for ensuring that each batch of each of these products is of the appropriate quality, strength, and purity. Many observations related to training and not following procedures are directly related to inadequate staffing of your Quality Unit. More resources are needed to assure that procedures are in place and are followed, as well as that documentation is being reviewed. An adequate Quality Unit is necessary to ensure that all documentation is issued, completed, and reviewed in accordance with CGMPs.

2. Your Responses to the Inspectional Observations

We received your November 8, 2004 response to FDA-483 observations. A copy was also faxed for the investigator's reference. Both documents were not exact copies of each other. The first page, the signatures of approval, is identical, but the rest of the pages are not. First, there are different timelines for completion of action items. Second, your response to observation #4 states that a technician recalibrated the [ ] used to weigh raw materials on November 1, 2004. The other copy of the response has this date as November 4, 2004. Also, in the faxed copy of your December 23, 2004 response, the 60 second APF Topical Fluoride Gel Lot [ ] was said to be placed on stability in December of 2004, when in your previous response, you had said that this was done in October of 2004. Lastly, the original documentation submitted in the November 8 response revealed several instances where data was either crossed out or written over without explanation. These examples of poor preparation of your response and poor documentation practices show a lack of understanding and concern for CGMP, and call into question the validity of data at your firm.

Overall, your responses did not commit to adequate changes or improvements. Your responses committed to several corrective actions, but did not provide supporting data. A global approach was not taken, corrective actions did not extend to a wider range of batches and processes. It is important that your firm and employees understand the specific CGMPs as well as the general concept of CGMP. Also, it was noted that many of your employees were new. A high turnover rate makes training as well as maintaining continuity of quality difficult.

Until FDA has confirmed correction of the deficiencies observed during the most recent inspection, and compliance with CGMPs, this office will recommend disapproval of any new applications listing your firm as the manufacturer of finished pharmaceutical drug products. In addition, failure to correct these deficiencies may result in FDA denying entry of articles manufactured by your firm into the United States. The articles could be subject to refusal of admission pursuant to Section 801(a)(3) of the Act [21 U.S.C. 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practices within the meaning of Section 501(a)(2)(b) of the Act [21 U.S.C. 351(a)(2)(B)].

We also note that most of the labels collected during the inspection include a DIN number indicating that these products were intended for marketing in Canada, and not in the United States. Because drug products marketed in the United States generally are identified with an NDC number, you may wish to follow this convention.

Please respond to this letter within 30 days of receipt. Your response should include data collected in your correction to the deficiencies cited as well as copies of procedures not already included. Please identify your response with FEI 300166001. Please contact Carole Jones, Compliance Officer, at the address and telephone numbers shown below, if you have any questions, written response or concerns regarding these decisions.

U.S. Food & Drug Administration
CDER HFD-325
11919 Rockville Pike
Rockville, MD 20852
Tel: (301) 827-9054; FAX (301) 827-8909

To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigations, HFC-130, 5600 Fishers Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

Joseph C. Famulare
Director
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research