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Inspections, Compliance, Enforcement, and Criminal Investigations

Cayman Chemical Company 1/19/10



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL RETURN RECEIPT REQUESTED

JAN 19 2010

Ref: 10-HFD-45-01-01

Kirk M. Maxey, M.D.
President and CEO
Cayman Chemical Company
1180 East Ellsworth Road
Ann Arbor, MI 48108-2419

Dear Dr. Maxey:

Between May 12 and 18, 2009, Ms. Nancy Bellamy, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct as both sponsor and investigator of clinical investigations of the prostaglandin-containing investigational drugs Compound 1, Compound 2, and Compound 3, performed for Cayman Chemical Company/Maxey Cosmetics, LLC.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Bellamy presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

In the document entitled "Informed Consent," your company states, "Maxey Cosmetics (M-Cosmetics) will use volunteers to test an eyelash growth-enhancing product...." This statement regarding eyelash growth makes clear that this product is intended to affect the structure or function of the body of man or other animals¹ and therefore causes your product to be subject to regulation as a drug under Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(g)(1).

VIOLATIONS RELATED TO SPONSOR RESPONSIBILITIES [21 CFR 312.40, 312.8(a)(3), and 312.57(a)]

1. You failed to comply with the requirements for use of an investigational new drug in a clinical investigation by administering the investigational new drugs Compounds 1, 2, and 3 to subjects without an IND in effect [21 CFR 312.40].

FDA regulations (21 CFR part 312) contain procedures and requirements governing the use of investigational new drugs. 21 CFR 312.3(b) defines a clinical investigation as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice." Compounds 1, 2, and 3 are not approved for marketing in the U.S.A; therefore, any clinical investigation involving the use of these compounds must meet the general requirements for the use of an investigational new drug in a clinical investigation.

An investigational new drug may be used in a clinical investigation if the following conditions are met: (1) The sponsor submits an IND for the drug to FDA; (2) the IND is in effect under FDA regulations; (3) the sponsor complies with all applicable requirements of 21 CFR parts 50, 56, and 312; and (4) each participating investigator conducts his investigation in compliance with the requirements of 21 CFR parts 50, 56, and 312. [21 CFR 312.40(a)]

According to 21 CFR 312.40(b), an IND goes into effect thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold, or on earlier notification by FDA that the clinical investigations in the IND may begin. You did not submit an IND, yet you administered the new drugs to subjects. Therefore, you violated 21 CFR 312.40(a) by administering the investigational new drugs, Compounds 1, 2, and 3, to subjects without an IND in effect.

2. You failed to obtain prior written authorization from FDA prior to charging for an investigational drug [21 CFR 312.8(a)(3)].

FDA regulations state that a sponsor must obtain prior written authorization from FDA to charge for an investigational drug. You charged the study subjects an administration fee for the investigational new drugs, Compounds 1, 2, and 3 without obtaining prior written authorization from FDA.

3. You failed to maintain adequate records showing the receipt, shipment or other disposition of an investigational drug [21 CFR 312.57(a)].

The sponsor is required to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. You did not maintain adequate recordkeeping of the investigational drugs Compounds 1, 2, and 3 used in your studies. There was no documentation of the distribution, return of product from the study subjects, and final disposition of Compound 1 that was manufactured at your firm. Additionally, there was no documentation for disposition of Compounds 2 and 3 that was not distributed to study subjects.

VIOLATIONS RELATED TO INVESTIGATOR RESPONSIBILITIES [21 CFR 312.60, 312.66, and 312.62(a)]

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50, as required by 21 CFR 312.60.

Except as provided in 21 CFR 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative [21 CFR 50.20]. In seeking informed consent, the FDA regulations require that the following information must be provided to each subject [21 CFR 50.25]:

- a. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and

identification of any procedures which are experimental.

b. A description of any reasonably foreseeable risks or discomforts to the subject.

c. A description of any benefits to the subject or to others which may reasonably be expected from the research.

d. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

e. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

f. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

g. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

h. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

As an investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR part 50. Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form [21 CFR 50.27(a)].

You failed to obtain legally effective informed consent from subjects to whom you distributed the investigational new drugs, Compounds 1,2, and 3. You told the FDA investigator that you obtained informed consent from subjects to whom you distributed Compounds 1, 2, and 3. However, the documents that you provided as proof of informed consent to the FDA investigator did not contain the required elements described above, specific to the investigational drug product administered. We acknowledge that the informed consent document describes "possible risks" of the using the product. We also acknowledge that the informed consent states that, "The use of the results from the testing of the Product will not be confidential and can be used M-Cosmetics in any way deemed appropriate, including publication, clinical study, instruction of staff and/or marketing materials." This statement is not adequate to meet the requirements of 50.25(a)(5). The informed consent completely omits the remaining required elements of 50.25(a). We note that the informed consent documents you provided to subjects were not approved by an IRB.

Furthermore, FDA regulations governing informed consent [21 CFR 50.20] state that no informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. The informed consent document you submitted to the FDA inspector is not in compliance with this regulation because it specifically includes this statement:

I HEREBY RELEASE, discharge, and covenant not to sue Maxey Cosmetics, LLC, affiliates, directors, agents, officers, volunteers and employees (collectively, "M-Cosmetics"), from all liability, claims, demands losses [sic] or damages on my account caused or alleged to be caused in whole or in part by my use of the Product; and I further agree that if, despite this release and waiver of liability, assumption of risk, and indemnity agreement, I or anyone on my behalf, makes a claim against any, I WILL INDEMNIFY, SAVE AND HOLD HARMLESS M-Cosmetics, from any litigation's expenses, attorney fees, loss, liability, damage or cost which any may incur as a result of such claim.

5. You failed to ensure that an IRB complying with the requirements set forth in 21 clinical study [21 CFR 312.66].

FDA regulations require that clinical investigations not be initiated unless that investigation has been reviewed and approved by an IRB meeting the requirements of 21 CFR Part 56. Clinical investigators are responsible for assuring that an IRB conducts initial and continuing reviews of clinical investigations [21 CFR 312.66]. You violated these requirements by administering the investigational new drugs, Compounds 1,2, and 3, to subjects without obtaining IRB approval. You admitted to the FDA investigator that an IRB had not

approved the study. However, you initiated the investigation without IRB approval and proceeded to administer the investigational new drugs, Compounds 1,2, and 3, to subjects.

6. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

FDA regulations state that an investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. You did not maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, of Compounds 1, 2, and 3.

We acknowledge your response to the FDA Form 483, and note your statement that you will adhere to the required regulations. However, your response does not specify how you will ensure adherence to the regulations.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,

/S/

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

1 Products for which hair growth claims are made are drug products subject to FDA regulation. See *United States v. Belden*, 714 F. Supp. 42, 43-44 (N.D.N.Y. 1987).

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