

**VIA FEDERAL EXPRESS**Food and Drug Administration
555 Winderley Pl., Ste. 200
Maitland, FL 32751**WARNING LETTER**

FLA-01-15

November 17, 2000

Paul L. Guilbaud, President/CEO
Medix Pharmaceuticals Americas, Inc.
12505 Starkey Road, Suite M
Largo, Florida 33773

Dear Mr. Guilbaud:

During an inspection of your establishment located in Largo, Florida on September 15, 26 & 29, 2000, FDA Investigator Shari J. Hromyak determined that your establishment is a specification developer, manufacturer and distributor of Derma Freeze Ethyl Chloride USP, a medical device, as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Under the Federal Food, Drug, and Cosmetic Act (the Act), the product(s) that your firm manufactures are considered to be medical devices that are used to diagnose or treat medical conditions or to affect the structure or function of the body. The law requires that manufacturers conform to the Quality System (QS) regulation for medical devices, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

The above-stated inspection revealed that this device is adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Quality System regulation for medical devices, as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. Management with executive responsibility failed to establish its policy and objectives for, and commitment to quality to ensure that quality system requirements are established and maintained, that a quality plan is established, and that quality procedures are established and maintained as required by 21 CFR 820.20(b)(3)(i), (d), and (e). For example, your firm failed to establish a policy to ensure that all procedures, processes, and testing are established, maintained, and reviewed and documented. There is no evidence that this policy was implemented and maintained at all levels of your firm's organization.

2. Your firm failed to establish procedures for quality audits, to conduct audits of both your internal operations and of contractors and suppliers to assure compliance with the quality system requirements as required by 21 CFR 820.22. For example, there are no written specifications for all device components, no audits have been conducted at suppliers or contract manufacturers, and components and finished product were received and accepted without any verification to compliance with the certificates provided.
3. Your firm failed to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements as required by 21 CFR 820.50. For example, there is no documentation of supplier or contractor evaluations and no records that clearly describe or reference the specific requirements including quality requirements for each component of analytical test.
4. Your firm failed to validate all manufacturing and testing procedures as required by 21 CFR 820.75. For example, there is no record or documentation that the manufacturing operations and the finished product testing conducted by outside contractors were validated and that the analytical methodology is equivalent or better than the USP methodology (FDA 483, Item #s 1 & 3).
5. Your firm failed to establish and maintain procedures for implementing corrective and preventive actions as required by 21 CFR 820.100. For example, there are no procedures to analyze processes, work operations, quality audit reports, quality records, complaints, returned product or other sources of quality data to identify existing or potential problems.
6. Your firm failed to establish and maintain procedures for finished device acceptance to ensure each production run, lot or batch of finished devices meets acceptance criteria as required by 21 CFR 820.80(d) & (e). For example, there were no written finished product specifications and finished product testing was not conducted, documented, reviewed and signed off prior to release of the product to distribution. Certificates of Analysis confirming that lots complied with specifications were not provided until six months after manufacture. Also, it was noted that analytical methodology has not been validated (FDA 483, Item #s 1 & 2).
7. Your firm failed to develop, conduct, control, and monitor production processes to ensure that the device conforms to its specifications as required by 21 CFR 820.70. For example, a minimum 160 cans of Derma Freeze were shipped, identified as lot #992821B, prior to receipt and review of the analytical results (FDA 483, Item #2).

8. Your firm failed to establish and maintain procedures for control and distribution of finished devices to ensure that only those devices approved for release are distributed. Where a device's fitness for use or quality deteriorates over time, the procedures shall ensure that expired devices or devices deteriorated beyond acceptable fitness for use are not distributed as required by 21 CFR 820.160. For example, there is no established and maintained stability program (FDA 483, Item #5).
9. Your firm failed to maintain device master records (DMRs) that include device specifications, composition, component specifications, production and process specifications, quality assurance procedures, and packaging and labeling specifications as required by 21 CFR 820.181). For example, there are no records for the specifications for the container/closure system (FDA 483, Item #s 1, 3, 4, 5 & 6).
10. Your firm failed to establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit as required by 21 CFR 820.198 (FDA 483, Item #7).

MEDICAL DEVICE REPORTING

Your devices are misbranded within the meaning of section 502(t)(2) in that there was a failure to furnish material or information required by or under section 519 respecting the devices. These violations include, but are not limited to the following:

11. Your firm failed to develop, maintain, and implement written MDR procedures as required by 21 CFR 803.17.

The specific violations noted in this letter and in the List of Observations (FDA 483) issued to you at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for Class III devices to which QS regulation deficiencies are reasonably related will be cleared until the violations have

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been corrected. Also, no requests for Certificates for Products for Export will be approved until the violations related to the subject devices have been corrected.

In addition, please provide copies of all documentation covering the importation of the finished product shipped from the contract manufacturer located in Canada. Documentation should identify or include the port and date of entry, copy of the consumption entry and invoice filed with U.S. Customs, and all shipping records (freight bill). If this documentation cannot be provided, please provide the name, address and telephone number of the carrier and any other information that describes this entry.

Your letter dated October 27, 2000 responding to the Inspectional Observations (FDA 483) is inadequate for the following reasons:

- You now claim the product is USP grade. Your firm replaced the USP titration method with a GC method for purity without verifying that the new method is equal to or greater than the USP test method, which also was not validated, as noted above. There is no assurance that this product meets USP specifications and you failed to address how the product is distributed with or without the USP designation on the product label and in the package insert. Further, you failed to provide analytical test records showing that the product passes USP specifications for each batch.
- Your response to FDA 483, Item #2 is inadequate because you provided the same three COAs that were collected by the investigator during the inspection. You failed to discuss the out of range notation on the chromatogram report for lot C. There is no assurance that the testing is representative of each lot and accurate since there is no description of the method of sampling in accordance with a valid statistical methodology. There is no description provided of how the sample was handled, prepared for analysis, the conduct of the analysis and a copy of the finished report. A COA is only acceptable when the laboratory has been audited and all processes have been verified/validated. There is no assurance that the stability program that you have proposed will support a two-year expiration date. Until you have documented analytical evidence that the product is stable for that period, you may not claim a two year expiration. Please describe how you plan to relabel each container to comply with the required labeling regulations.

- As noted above, no methodology for the GC has been provided. A letter from your laboratory does not provide assurance that their methodology is complete and accurate and that their handling of the sample, sample preparation, analytical methodologies and testing, and recording is acceptable.
- Your firm's response to FDA 483, Item #4 is inadequate because it fails to address product specifications at any given station, e.g., weight loss too high, low purity, etc. The procedure fails to address retests or reporting out-of-specification results and how they will be handled. There is no assurance that the contract manufacturer's processes have been evaluated and validated. There is no description of the sampling method of products used during production and no valid statistical methodology for sampling is described.
- As noted above, the stability records provided during the inspection and those included in your response fail to support a two-year expiration date for the product. The current six month testing was of released inventory and fails to address product (e.g., not inverted or product stored on its side or other environmental conditions that may impact the quality of the product). The memo from Fort Lauderdale Laboratories refers only to testing already collected during the inspection. Full USP testing was not conducted. The purity method was not provided and there is no record showing that it supports a two-year expiration. Your contract manufacturer did not process the pilot batches submitted and no batch records have been provided. There is no assurance that the same or similar conditions were employed at the separate manufacturers to substantiate the manufacturing operations, that their operations are comparable and support the two-year expiration.

There is no documentation to show the suitability of the container/closure system. You need to conduct the compatibility study referenced in paragraph two of your letter under item #6. It was determined during the inspection that this product has never been packaged and distributed in this container/closure system. There is no assurance that this system and the components of the system are appropriate for use with this product. All of these items must be addressed and validated before distribution and sale.

Your response will be made part of the Florida District file.

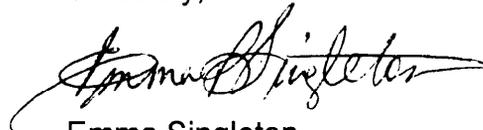
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You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties. Any further distribution of this product, is made on your own responsibility.

Please notify this office in writing within fifteen (15) working days of receipt of this letter, of any steps you may have taken to correct the noted violations, including (1) the time frames within which the corrections will be completed if different from those annotated on the FDA 483, (2) any documentation indicating the corrections have been achieved, and (3) an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. You should also tell us your intention to either continue or cease distribution of the product in writing, until your firm's level of compliance with the Quality System regulation can be verified by the FDA.

Your response should be sent to Timothy J. Couzins, Compliance Officer, Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, Florida 32751, (407) 475-4728.

Sincerely,

A handwritten signature in black ink, appearing to read "Emma Singleton", with a long horizontal flourish extending to the right.

Emma Singleton
Director, Florida District