



SEP 7 1999  
VIA FEDERAL EXPRESS

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

WARNING LETTER

Dr. J. A. De Vries  
President  
European Medical Contract Manufacturing B.V.  
Middenkampweg 17  
6545 CH Nijmegen, The Netherlands

Dear Dr. De Vries:

We are writing to you because on March 15-18, 1999, an investigator from the Food and Drug Administration (FDA) collected information that revealed serious regulatory problems involving your Adcon-L device.

Under a United States Federal law, the Federal Food, Drug, and Cosmetic act (the Act), these products are considered medical devices because they are used to diagnose or treat a medical condition or to affect the structure or function of the body (Section 201(h) of the Act).

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

**1. Failure to employ appropriate statistical methodology where necessary to detect recurring quality problems, as required by 21 CFR 820.100(a)(1).** For example, there is [REDACTED]

[REDACTED] and the following [REDACTED] were not evaluated to determine if the [REDACTED] were [REDACTED]

(1a) One [REDACTED] and two [REDACTED] defects for Adcon-L lot [REDACTED] during [REDACTED]

(1b) [REDACTED] for Adcon-L lot [REDACTED]

(1c) [REDACTED] rejected in [REDACTED] of Adcon-L lot [REDACTED]

(1d) [REDACTED] Adcon-L samples from lot [REDACTED] had [REDACTED] results of [REDACTED] and there was no documentation that the [REDACTED] identified for [REDACTED] testing of the [REDACTED] were inadvertently [REDACTED]

- (1e) Result of [redacted] for [redacted] sample from lot [redacted] lot [redacted] had [redacted] sample [redacted] between [redacted] and,
- (1f) [redacted] rejected during [redacted] of Adcon-L lot [redacted] and [redacted] rejects [redacted] in lot [redacted]

Your firm's March 23, 1999, response appears to be inadequate because it does not demonstrate that in-process rejects were consistent with process validation baseline data. In addition, you did not submit documentation to support your other statements.

Your firm's April 23, 1999, response to 1 appears to be inadequate because it does not demonstrate that the following are consistent with process validation baseline data:

1. [redacted] and [redacted] defects for Adcon-L lot [redacted]
2. [redacted] defects for Adcon-L lot [redacted]
3. rejecting [redacted] that during [redacted] of Adcon-L lot;
4. [redacted] results of [redacted] and a proposed product [redacted] as high as [redacted]
5. not properly storing [redacted] used for [redacted] of lot [redacted] under [redacted]
6. results of [redacted] for [redacted] sample from lot [redacted] and [redacted] levels between [redacted] from lot [redacted] and,
7. rejecting [redacted] during [redacted] of Adcon-L lot [redacted] and rejecting [redacted] for lot [redacted]

In addition, your firm should submit data to support the acceptance of [redacted] of [redacted] to [redacted] during production, and data to demonstrate that these [redacted] levels do not raise the [redacted] levels above product specifications.

**2. Failure to investigate the cause of nonconformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(a)(2). For example,**

(2a) During manufacture of Adcon L lot [REDACTED]:

(2a-1) [REDACTED] results were in excess of [REDACTED] for [REDACTED] for [REDACTED] samples tested. Investigation did not identify the [REDACTED] and no additional testing was done to determine if other [REDACTED] might have been [REDACTED]

(2a-2) [REDACTED] found [REDACTED] of [REDACTED] samples [REDACTED] from each [REDACTED] sample size of [REDACTED] to be [REDACTED]. The [REDACTED] stated that the [REDACTED] used to [REDACTED] [REDACTED] was not [REDACTED] for at least [REDACTED] before [REDACTED] testing, but no analysis was done to determine if this was a sufficient explanation to [REDACTED]

(2b) No investigation was done to determine the root cause of the following [REDACTED]

(2b-1) Gliatech complaint [REDACTED] dated [REDACTED] relates to an [REDACTED] from Adcon-L lot [REDACTED]; investigation concluded that the complaint was valid and it was classified as a [REDACTED]

(2b-2) Gliatech complaint [REDACTED] dated [REDACTED] relates to an [REDACTED] from Adcon-L lot [REDACTED]. Investigation concluded that the complaint was valid and it was classified as a [REDACTED]

(2b-3) Gliatech report dated [REDACTED] states that Adcon-L lot [REDACTED] due to [REDACTED] [REDACTED] failure rate).

(2b-4) Gliatech report dated [REDACTED] states that Adcon-L lot [REDACTED] had [REDACTED] failures [REDACTED] samples tested).

Your firm's March 23 and April 23, 1999, responses to (2a-1) appear to be inadequate. Your firm should submit data to support the acceptance of theoretical [REDACTED] or rationale for your theoretical [REDACTED] and data to demonstrate that these [REDACTED] do not raise the final product [REDACTED] above product specifications.

Your firm's March 23 and April 23, 1999, responses to (2a-2) appear to be adequate.

Your firm's March 23, 1999, general response to (2b) appears to be inadequate because the [REDACTED] maintains the [REDACTED] of the Adcon-L [REDACTED] until it is [REDACTED]. There is [REDACTED] the health care provider does not identify the [REDACTED] before product use, even if the product labeling includes a precaution against such use.

Your firm's March 23 and April 23, 1999, responses to (2b-1), (2b-2), (2b-3), and (2b-4) appear to be inadequate because you have not identified the root cause of the [redacted]. In addition, you have not provided the results of the [redacted] and [redacted] from lots [redacted].

**3. Failure to identify the actions needed to correct and prevent recurrence of non-conformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(a)(3). For example:**

- (3a) Corrective action for previously distributed product (i.e., same lots or lots processed under conditions causing the failures) was not initiated for the following:
- (3a)(1) Gliatech complaint [redacted] dated [redacted] relates to an [redacted] from Adcon-L lot [redacted] investigation concluded that the complaint was valid and it was classified as a [redacted].
  - (3a)(2) Gliatech complaint [redacted] dated [redacted] relates to a [redacted] from Adcon-L lot [redacted] investigation concluded that the complaint was valid and it was classified as a [redacted].
  - (3a)(3) Gliatech report dated [redacted] states that Adcon-L lot [redacted] due to [redacted] failure rate).
  - (3a)(4) Gliatech report dated [redacted] states that Adcon-L lot [redacted] had [redacted] samples tested).
- (3b) [redacted] for Adcon-L [redacted] requires that the [redacted] in which Adcon-L is manufactured be tested for [redacted] no more than [redacted] before starting [redacted] results for lot [redacted] show that test results were within specified limits. However, review of [redacted] records found that the [redacted] results obtained before production for this lot included an out of limit quantity of [redacted] (limit is [redacted]). There is no documentation that corrective action was initiated in response to this out of limit result.
- (3c) No corrective action is initiated unless [redacted] test results relate to samples [redacted] collected in the [redacted] of [redacted] and there is no documented justification for [redacted] when [redacted] results are obtained for samples collected during [redacted].

Your firm's March 23 and April 23, 1999, responses to (3a)(1) and 3(a)(2) appear to be adequate.

Your firm's March 23 and April 23, 1999, responses to (3a)(3) and (3a)(4) are incomplete because you have not provided the [REDACTED] of the [REDACTED] for lots [REDACTED] and you have not indicated what [REDACTED] you will take.

Your firm's March 23 and April 23, 1999, responses to (3b) appear to be inadequate because you have not indicated what the [REDACTED] are to product safety, and you have not demonstrated that lack of [REDACTED] data has no adverse effect on product safety.

Your firm's March 23 and April 23, 1999, responses to (3c) appear to be adequate.

**4. Failure to establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained; and failure to document these activities, as required by 820.72(a). For example:**

- (4a) The [REDACTED] is not calibrated periodically, and there is no documentation justifying the lack of a calibration requirement.
- (4b) Investigation of [REDACTED] for Adcon-L [REDACTED] for lot [REDACTED] concluded that the [REDACTED] were caused by a [REDACTED]. An [REDACTED] after [REDACTED] and before [REDACTED] found no discrepancies. No evaluation was done or documented concerning whether [REDACTED] may have been adversely affected by this [REDACTED] problem.

Your firm's March 23 and April 23, 1999, responses to (4a) appear to be adequate.

Your firm's March 23 and April 23, 1999, responses to (4b) are inadequate because you have not demonstrated that [REDACTED] and [REDACTED] were within specification for [REDACTED] prior to the installation of the [REDACTED] and that [REDACTED] met [REDACTED] specifications. In addition, you have not provided English translations of SOPs [REDACTED] and [REDACTED].

**5. Failure to provide for remedial action to reestablish calibration limits and to evaluate whether there was any adverse effect on a device's quality, when accuracy and precision limits are not met, as required by 21 CFR 820.72(b). For example:**

- (5a) Contractor-provided [REDACTED] results are not reviewed to determine if [REDACTED] was completed according to [REDACTED] requirements, and to determine if [REDACTED] for any [REDACTED] product is necessary (a record of a [REDACTED] done by [REDACTED] the manufacturer of the [REDACTED] does not include information as to the [REDACTED] and whether any [REDACTED] were necessary).

(5b) Investigation of [redacted] deviations for Adcon-L [redacted] and [redacted] for lot [redacted] concluded that the [redacted] were caused by a [redacted]. An [redacted] after [redacted] and before [redacted] found no discrepancies. No evaluation was done or documented concerning whether [redacted] may have been adversely affected by this [redacted] problem.

Your firm's March 23 and April 23, 1999, responses to (5a) are incomplete because you have not submitted the [redacted] and [redacted] data.

Your firm's March 23 and April 23, 1999, responses to (5b) are inadequate because you have not demonstrated that [redacted] were within specification for [redacted] prior to the installation of the [redacted] and that [redacted] met [redacted] specifications. In addition, you have not provided English translations of SOPs [redacted] and [redacted].

**6. Failure of the DMR (device master record) to include device specifications including appropriate drawings, composition, formulation, component specifications and software specifications, as required by 21 CFR 820.181(a). For example:**

(6a) No [redacted] specification has been established for Adcon-L [redacted] or [redacted].

(6b) No release specifications have been established for [redacted] used to [redacted] Adcon-L gel before [redacted] used for [redacted] and [redacted] used for [redacted].

Your firm's March 23 and April 23, 1999, responses to (6a) appear to be inadequate because your firm has not submitted data to support a [redacted] and has not submitted data to demonstrate that a [redacted] would not raise the [redacted] above product specifications. In addition, there is no indication that the [redacted] testing done on each [redacted] is done [redacted] of the [redacted] or that the [redacted] are [redacted] they are [redacted] Adcon-L.

Your firm's March 23 and April 23, 1999, responses to (6b) are incomplete because there is [redacted] of the [redacted] for the [redacted] used for [redacted].

**7. Failure to establish and maintain procedures to adequately control environmental conditions where those conditions could reasonably be expected to have an adverse effect on product quality; and failure to document those activities, as required by 21 CFR 820.70(c). For example,**

- (7a) There is no documentation that [redacted] used in the [redacted] of the [redacted] [redacted] were [redacted] prior to use.
- (7b) [redacted] requires [redacted] at [redacted] between [redacted] but is being [redacted] where the [redacted] has varied from [redacted]
- (7c) Analytical Control Record for Adcon-L lot [redacted] includes an [redacted] using [redacted] no results are provided, and there is no documentation verifying that Gliatech eliminated this requirement.

Your firm's March 23 and April 23, 1999, responses to (7a) are incomplete because you have not provided documentation that the [redacted] used in the [redacted] [redacted] were [redacted] at [redacted] prior to use.

Your firm's March 23 and April 23, 1999, responses to (7b) are incomplete because you have not provided documentation that you are [redacted] at [redacted] as defined by [redacted]

Your firm's March and April 23, 1999, responses to (7c) appear to be adequate.

**8. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications, as required by 21 CFR 820.70(a). For example, there is no documentation:**

- (8a) confirming that the [redacted] procedure [redacted], issued [redacted] has been [redacted]
- (8b) confirming the [redacted] and [redacted] specified in the [redacted] procedure were used during manufacturing;
- (8c) confirming the [redacted] of Adcon-L [redacted]
- (8d) confirming [redacted] of the Adcon-L solution [redacted]
- (8e) confirming the [redacted] of the Adcon-L gel [redacted] for [redacted] before [redacted] and,
- (8f) confirming that the [redacted] Adcon-L [redacted] test samples are [redacted] from [redacted]

Your firm's March 23 and April 23, 1999, responses to (8a) are incomplete because they do not include documentation that the [redacted] issued [redacted] has been [redacted]

Your firm's March 23 and April 23, 1999, responses to (8b), (8c), (8d), (8e), and (8f) appear to be adequate.

**9. Failure to validate a process with a high degree of assurance and to approve it according to established parameters, where the results of a process cannot be verified by subsequent inspection and test, as required by 21 CFR 820.75(a).** For example, the [REDACTED] procedure has not been validated.

Your firm's March 23 and April 23, 1999, responses appear to be incomplete because you have not included [REDACTED] and [REDACTED] to support [REDACTED] the [REDACTED] with [REDACTED] and [REDACTED].

**10. Failure to document training, as required by 21 CFR 820.25(b).** For example, there are no training records showing that individuals responsible for the operation of the [REDACTED] have been appropriately trained for the procedure.

Your firm's March 23 and April 23, 1999, responses appear to be adequate.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued 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.

We acknowledge that you submitted to this office two responses, dated March 23, 1999, and April 23, 1999, concerning our investigator's observations noted on the form FDA 483. We have reviewed your response and concluded that it is partially inadequate. An evaluation of specific responses is entered after each one of the deviations listed above.

Given the serious nature of these violations of the Act, the Adcon-L manufactured by European Medical Contract Manufacturing may be detained without physical examination upon entry into the United States (U.S.) until these violations are corrected.

In order to remove the devices from this detention, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review. After we notify you that the response is adequate, it will be your responsibility to schedule an inspection of your facility. As soon as the inspection has taken place, the implementation of your corrections have been verified, and you are notified that your corrections are adequate, your devices may resume entry into this country.

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.

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

It is necessary for you to take action on this matter now. Please let this office know in writing within (15) working days from the date you received this letter the steps you are taking to correct the problem. We also ask that you explain how you plan to prevent this from happening again. If you need more time, let us know why and when you expect to complete your correction. If the documentation is not in English, please provide a translation to facilitate our review. Please address your response to:

Carol Arras  
Office of Compliance  
Division of Enforcement III (HFZ-343)  
Center for Devices and Radiological Health  
2094 Gaither Road  
Rockville, MD 20850

If you have any questions about the contents of this letter, please contact Ms. Arras at the above address or at (301) 594-4659, or fax (301) 594-4672. You may obtain general information about all of FDA's requirements for manufacturers of medical devices by contacting our Division of Small Manufacturers Assistance at (301) 443-6597, or through the Internet at <http://www.fda.gov>.

Sincerely yours,



Lillian J. Gill  
Director  
Office of Compliance  
Center for Devices and  
Radiological Health

Cc:

