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AUG 16 2004

WARNING LETTER

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

FEDERAL EXPRESS

Mr. Peter Luther  
President  
LifeScan/DDI  
1000 Gibraltar Drive  
Milpitas, CA 95035-6312

Dear Mr. Luther:

During an inspection of the Inverness Medical Limited (IML) facilities in Scotland, United Kingdom conducted between April 19 and 22, 2004, United States Food and Drug Administration (FDA) Investigator, Victor Spanioli determined that IML manufactures glucose test strip products for LifeScan, namely [REDACTED] and both companies jointly design the glucose test meters, namely [REDACTED]. These products are devices within the meaning of section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Although IML manufactures these devices for LifeScan, LifeScan is responsible for product design and actually imports the devices into the United States for distribution to consumers. As such, LifeScan has the responsibility to ensure that all LifeScan devices manufactured or contract manufactured by you or your facilities comply with the Quality System (QS) regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

The investigator documented violations of the Act causing the devices to be adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements for medical devices set forth in the QS regulation.

## Quality System Regulation

The investigator noted violations of the QS regulation during the April 2004 inspection of IML. Additional QS regulation violations were revealed upon review of materials related to the inspection. These violations, which render devices manufactured by IML adulterated within the meaning of section 501(h) of the Act, include, but are not limited to the following:

1. Failure to establish and maintain adequate procedures for identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100 (a)(3). For example:

- a) Twenty-four Corrective Maintenance Request (CMR) reports dated January 16, 2003 through December 22, 2003 documented broken vial rims at the [REDACTED] cutting and veiling operation. There was no quality management review of these reports, and corrective and preventive actions were not initiated. (FDA 483, Item #1).

IML's response dated May 12, 2004 and July 12, 2004 is inadequate. Although the IML response notes that a CMR task force has been formed, it provides no explanations regarding the procedures to be introduced to ensure defect awareness, no methodology to explain how the firm will determine the level/impact of the defects encountered, no procedures for when and how to apply CAPA procedures to identified defects, and no information regarding who has the responsibility to review and approve these activities.

- b) Corrective action was limited to the rework of specific nonconforming glucose test strip lots documented in seven Non-Conforming Material reports (NCMR) dated July 4, 2003, through Nov 12, 2003, related to broken rim vials. The firm failed to ensure that other lots manufactured under similar condition were not affected. (FDA 483, Item #1).

The IML response is inadequate. The firm promises a compliance evaluation and a revised SOP that will include a process for impact assessment and, *if appropriate or having potential to become appropriate*, subsequent elevation of NCMRs into the CAPA system. However, the procedure is vague, failing to define "if appropriate" or "having potential" and lacking detail regarding who would have responsibility to review and approve NCMR analysis and corrective action activities.

2. Failure to establish and maintain adequate procedures for corrective and preventive actions, as required by 21 CFR 820.100 (a). For example:

Corrective action implemented under CAPA#246 failed to be processed in a timely manner consistent with company policy. CAPA#246 opened on May 12, 2003 was intended to shorten the closure times for non-medical complaints. However, the April 18, 2004, update states that through June 2003 “over 60% of complaints were not getting closed within initial project timeliness. The mean service level was calculated at █%, far short of the company’s 2003 goal which targeted █%”. An “Innovative Improvement Phase” process to reduce the backlog was not implemented until April 2004. (FDA 483, Item #3).

The IML response is inadequate because the observation is not addressed except to state that correction has been completed without providing appropriate details on the applicable metrics used to prioritize problems and to establish timeliness.

3. Failure to implement and document the changes needed to correct and prevent identified quality problem, as required by 21 CFR 820.100(a)(5). For example:

IML/LifeScan acknowledged not knowing whether █ in █ had initiated corrective action for missing segments on the LCD (readout) screen display of █ meters (CAPA 54, June 20, 2003). The root cause was identified as LCD cable delamination traced to two common cable lots. Inspection review of the available records found that the incidence of LCD segment defects has not diminished.

4. Failure to establish and maintain adequate complaint handling procedures to ensure all complaints are evaluated and investigated and processed in a uniform and timely manner, as required by 21 CFR 820.198(a)(1). For example:

- a) As of April 21, 2004, a total of 2,837 complaints have been opened for more than six months awaiting product closure, analysis or investigation. (FDA 483, Item #2).
- b) Approximately █ meters received during the fourth quarter of 2003 due to █ accuracy errors, including high control values, were not analyzed until March 2004. Some of the reported complaints were associated with clinical symptoms. Analysis primarily completed during the week of March 22, 2004, confirmed that the returned meters were defective as documented in █ (FDA 483, Item #2).
- c) Non-MDR inaccuracy complaints with unknown cause or no indication of user error are not evaluated and investigated until threshold numbers are reached. IML, however, did not provide adequate justification or data to support the use of these thresholds prior to initiating lot specific investigations. For example, inaccuracy complaints were not evaluated as a whole but only after specific threshold numbers (1-12) for each lot were surpassed. (Threshold numbers were set for those inaccuracy complaints where the test samples were blood vs. control solution and where the results were either erratic, low or high.) LifeScan provided

no rationale for either the segregation of different inaccuracy complaints or the selection of the threshold numbers. The use of a threshold number has the potential to cause delays in investigating potentially serious meter problems as described above (2b) and makes it difficult to distinguish when a non-MDR can become an MDR.

- d) Inaccuracy in results in lots with complaints was not followed up with field corrections even after these lots had failed both the 1st in-house Control Batch Performance testing and the 2<sup>nd</sup> Clinical Assessment for Complaints conducted by IML. [REDACTED] had failed the Control Batch performance Testing and Clinical Assessment using either Clarke Error Grid or the Parke Error Grid. However, because on assessment using the clinical performance goal of [REDACTED]% agreement within [REDACTED]% (or [REDACTED] mg/dL) of the reference method was met, no further action was taken. This failed to address the fact, for example, that for Lot 1023237 a potentially clinically significant number of outliers fell in zones associated with potential adverse outcomes including [REDACTED]% in the [REDACTED] using the [REDACTED] and [REDACTED]% in [REDACTED] using the [REDACTED].

The IML response regarding FDA 483, Item #2, is inadequate. Although IML stated that they have completed the review of backlogged, open complaints, IML has not described what and how procedure changes made can ensure that future complaints will be handled promptly and adequately.

5. Failure to investigate any complaints involving possible failure of a device to meet any of its specifications where necessary, as required by 21 CFR 820.198(c). There appears to be arbitrary exclusion of evaluation of some returned test strips, for example:

- a) A complaint about [REDACTED] test strips cracked vial lids ([REDACTED] received October 6, 2003) was not adequately analyzed and evaluated. No examination of the returned vial was conducted. Subsequent examination as part of CAPA 270 activities confirmed that this vial did have a damaged rim. (FDA 483, Item #4)
- b) A complaint about inaccurate control results for [REDACTED] test strips ([REDACTED] received on August 14, 2003) was not adequately analyzed and evaluated. Testing of the retention sample was conducted but the returned complaint vial was not inspected/analyzed. Later examination per CAPA 270 activities found a damaged vial rim. (FDA 483, Item #4).

The IML response is inadequate. Although IML stated that the procedure was revised to implement visual inspection of returned test strips for inaccuracy evaluation, the IML protocol does not include actual testing of the returned test strips when problems with inaccuracy are identified which cannot be attributed to user error. IML's Complaint Testing Technical Rational allows for possible testing on returned strips to capture special causes of failure, but the mechanism used to initiate such action is not described. IML has not put into place a system for assuring comprehensive evaluation of strips returned for performance failure. There is no assurance the company can identify in a well defined manner design or production problems that might be a cause of strip failure.

6. Failure to develop, conduct, control and monitor production process to ensure that the device conforms to its specifications, as required by 21 CFR 820.70(a). For example:

No in-process action limits have been established. The test strip manufacturing process in general consists of sequential [REDACTED] with subsequent [REDACTED] & [REDACTED] and [REDACTED] operations. Yields are at about [REDACTED] with losses primarily due to [REDACTED] operations (e.g. strips not aligned correctly or vial movement in the [REDACTED] of the system). The majority of these processes need validation and control. However, you stated that no process action limits have been established.

7. Failure of management with executive responsibility to ensure the suitability and effectiveness of the quality system, as required by 21 CFR 820.20(a). For example:

Management review and internal audits failed to address the significant number of [REDACTED] test strip vial rim defects recorded throughout 2003 as documented in the maintenance records, nonconformance reports, and complaints. Numerous opportunities during 2003 to comprehensively address the rim defects were missed and resulted in the distribution of defective [REDACTED] test strips that posed a health risk to customers, especially to those with hypoglycemia unawareness. Corrective action was not performed until early 2004. This reinforces the view that the firm has a weak linkage between its CAPA and Management Control subsystem. The firm failed to conduct adequate management review on relevant information on identified quality problems as required under 21 CFR 820.100 (a)(7).

Furthermore, the associated Report of Correction and Removal to FDA on March 4, 2004, would lead the FDA to believe that the only 3 lots were affected. IML's failure investigation report indicated ten lots were released with rim damage in the January production alone. Other lots manufactured in 2003 may have had similar or higher defect rates. FDA agrees with the firm's decision to notify all accounts because the vial rim defect could be present at unknown levels in virtually all commercially distributed lots.

8. Failure to establish adequate procedures to control products that do not conform to specifications, as required by 21 CFR 820.90 (a). For example:

The Strip Testing & Evaluation (Ex. 40) allows out-of-specification results (OOS) in slope, bias and precision after calibration to be handled without assignable causes or adequate scientific and statistical rationale in the following areas:

- Strip batches (typically [REDACTED] strips /batch) that originally failed calibration testing, were re-sampled, re-tested and released for distribution based on obtaining passing results with the re-test alone or with the combined original and retest results(i.e. averaging). This type of testing or averaging into conformance is not scientifically or statistically acceptable.
  - A batch release procedure based on passing by averaging together both original and retest results was addressed by introducing the requirement for contract clinic testing by an IML employee. This testing, however, was not performed on all the batch strip samples collected, but only on 5 vials after the batch has been put into vials. This limited or divergent sampling technique does not ensure product integrity because the method does not ensure that the batch strips failing batch testing originally or not tested at the batch stage are adequately represented in the finished device (product in vials) testing. In addition, the clinic testing procedure uses a wider acceptance criterion ([REDACTED]% or [REDACTED] mg/dL of reference) than the original design (all data to be within about [REDACTED]% of reference). The different criterion is introduced without justification and does not provide a sufficient safety margin for the product intended for lay users using capillary blood. Also, because the clinic testing procedure uses [REDACTED], it may not achieve the original designed acceptable quality level (AQL) and lot tolerance percent defective (LTPD) at critical glucose decision points.
  - The strip batches that failed clinical testing were given a second opportunity to pass release criteria by selecting a second [REDACTED] with combined calibration data if needed. Additional calibrations and data averaging could continue, until no further [REDACTED] is available. Only then was the batch scrapped. This technique of testing to conformance is without justification or explanation and does not provide for independent testing (after final calcode selected) to assure product integrity. While the use of clinical testing is a valid method to monitor design control outputs and product validation, it should not be used as a substitute for release criteria and/or to verify product performance.
9. Failure to establish and maintain procedures that define the responsibility for review and the authority for the disposition of nonconforming product, as required by 21 CFR 820.90(b). For example:
    - a) The disposition of the reject found during the rework for rim or container closure defect is unknown. No instructions or records are provided to indicate whether the rejected products are to be scrapped or not.

b) Review on batches with out of specification (OOS) or out of trend results was not adequate. 1) Batch [REDACTED] did not meet the [REDACTED] month stability test point of [REDACTED] mg/dL (results of testing showed a [REDACTED]% deviation compared to established tolerance limits of +/- [REDACTED]%, at [REDACTED]°C/[REDACTED]% RH.) 2) Batches [REDACTED] showed out of trend results at four weeks at all of the study temperatures ([REDACTED]°C, room temperature, and [REDACTED]°C/[REDACTED]%RH) and at all [REDACTED] glucose levels used in the test [REDACTED] and [REDACTED] mg/dL). For example, the four week trend for strip performance stored at [REDACTED]°C shows a [REDACTED] to [REDACTED]% shift in mean bias. Typically, negligible bias would be expected at [REDACTED] weeks. (FDA 483, Item #6).

The IML response is inadequate. The response asserts that the OOS problem is due to incorrect results observed on Day 0 baseline. If this is the case, corrective action should have been taken when these incorrect results were first observed. IML plans to replace the specified stability testing with augmented evaluation of shelf-life observed during regular clinic testing. This is not an acceptable replacement for use of established release criteria for product. Monitoring use of product at clinical sites can be an important part of a manufacturer's quality system but should not be used as a substitute for proper stability evaluation.

10. Failure to retest and reevaluate the rework of nonconforming product to ensure that the reworked product meets the current approved specification, as required by 21 CFR 820.90 (b) (2). For example, post inspection audit sampling and examination was not done for [REDACTED] lots that had been 100% visually inspected for vial rim defects. (FDA 483, item #5)

These reworked products were not audited to make sure that the rework operator did not make any errors in inspection or closure sealing. These reworked products were also not evaluated to ensure that they met current approved specifications.

The IML response is inadequate. Although IML has stated that it will revise its procedures to include an appropriate sample size for post-rework examination, IML provided no information regarding the products release without post-rework examination. Rework could result in moisture intrusion, which could cause inaccurate results or premature product degradation. IML relies on customer identification/notification of the missed defect. Although the company assumes visual inspection is [REDACTED]% effective, there is no evidence to support this claim.

## IML Response

The Agency has reviewed the IML response to the FDA 483 issued following FDA's April 2004 inspection. Although IML has made general commitments to implement corrective actions, these actions do not describe in sufficient detail the specific revisions made to IML procedures or processes. Additionally, it does not appear that the cause(s) of the CGMP deficiencies have been identified so that needed corrective actions can be implemented. As a result, even if the proposed corrective actions are implemented, violations are likely to recur.

## Responding to this Warning Letter

This letter is not intended to be an all-inclusive list of deficiencies at the IML facility. It is the responsibility of both LifeScan and IML to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious underlying problems in IML's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

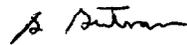
You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions may include seizure, injunction, civil penalties and/or the refused entry of your affected products until the corrections are completed.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter, of the specific steps you have taken to correct the noted violations, including (1) the time frames within which the corrections will be completed, (2) any documentation indicating the correction have been achieved, and (3) an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to ensure that similar violations will not recur. If you plan to make any corrections in the future, include those plans with your response to this letter as well. If the documentation is not in English, please provide a translation to facilitate our review.

Your response should be sent to the Food and Drug Administration, Center for Devices and Radiological Health, Office of *In vitro* Diagnostic Device Evaluation and Safety, HFZ-440, 2098 Gaither Road, Rockville, Maryland 20850, USA to the attention of Mr. James Woods.

If you need help in understanding the contents of this letter, please contact Tena T. Wei at the above address or at (301) 594-3084 or FAX (301) 594-5941

Sincerely yours,



Steven I. Gutman, M.D., M.B.A.  
Director  
Office of *In vitro* Diagnostic Device  
Evaluation and Safety  
Center for Devices and  
Radiological Health