DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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VIA FEDERAL EXPRESS

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

WARNING LETTER

Mr. John Huang
Manager, Regulatory Affairs
IND Diagnostic, Inc.
1629 Fosters Way
Delta, B. C., V3M 6S7
Canada

DEC 23 2003

Dear Mr. Huang:

This letter is in response to your June 27, 2003 and July 2, 2003, correspondence in which you addressed the violations cited in the inspection report (FDA 483 FEI 3003148151) which resulted from the Food and Drug Administration's (FDA's) June 2 - 5, 2003, inspection of your firm. The [redacted] is a device within the meaning of section 201 (h) of the Federal, Food, Drug and Cosmetic Act (the Act).

An FDA investigator collected information regarding your manufacturing processes for the [redacted] Damian Kakwaya, Medical Device Specialist, Health Canada, Health Products and Food Branch, participated in the inspection as an observer representing the British Columbia government agency.

The inspection revealed that the device is adulterated within the meaning of section 501 (h) of the Act, in that the methods used in, the facilities or controls used for, its manufacture, packaging, storage, or installation are not in conformance with the Current Good Manufacturing practice (CGMP) requirements of the Quality System regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

The significant deviations found during the inspection include, but are not limited to the following items:

1. **Failure to validate processes and document the validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, as required by 21 CFR 820.75 (a).**

For example:

a) There is no documentation of the process validation activities and production processes for the [redacted] According to Ms. Carrie

Li, the firm's Quality Assurance Manager, the firm developed the specifications and began the manufacture of the [redacted] 1992. No documentation of the validation activities was performed during the development stages of the device.

The [redacted] is manufactured in various stages that begin with the cutting and measuring of the membrane material. After the membrane dimensional attributes have been obtained, the resultant membrane materials are washed and dried. The purified membrane is coated with antibody. The treated membrane with the antibody is incubated for a specified time. After incubation the treated membrane is blocked to properly disperse the coating materials. The blocked membrane is tested to ensure proper uniformity of the coating materials. The colloidal gold conjugate is added to the coated membrane with the buffers. The finished coated membrane is cut to its desirable size and packaged in its package board. The package board is cut into strips and tested against proper controls. The finished products are packaged in cassettes or sold as strips. There is no documentation indicating that any of the processes described above have been validated.

b) There is no documentation that demonstrates that the Barnestead Reverse Osmosis water system used in the production reagents, buffers, conjugate, and controls used in the manufacture of the [redacted] has been validated.

<u>Your firm's June 27, 2003, response to (a) is not adequate.</u>

The corrective action plan is to document all in-process quality inspection regularly and provide a library of specific quality testing data for review. The Corrective Action Request dated June 10, 2003, under Item 1 did not provide documentation to FDA that this plan is completed.

<u>Your firm's June 27 and July 2, 2003, responses to (b) are not adequate:</u>

The Correction Action Request dated June 10, 2003, under item 2 is to contact the supplier of the Barnstead Reverse Osmosis water system or a laboratory water system specialist and set up an appointment to validate the installation and perform all necessary testing on the system. The firm's response also states that it will set up a routine water quality testing program to ensure consistent quality of the deionized water for production use. The firm has not provided to FDA documentation to show that these activities are completed.

2. **Failure to document the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used as required by 21CFR 820.75 (b) (2).**

For example:

There is no documented evidence describing the monitoring and control methods and data, the dates performed, individuals performing the process, the major equipment used in determining the effectiveness and reproducibility for the production process used in the manufacture of the buffers and conjugates, for the [redacted]

Your firm's June 27, 2003, response is not adequate:

The Corrective Action Request dated June 10, 2003, item 1, states that for the S4 colloidal gold preparation process identified in the inspection, the firm will setup a retrospective validation procedure to analyze routine in-process quality inspection data collected for each batch product during the past year for verification of the reproducibility of the process used in the manufacture of these buffers and conjugates. For the S1 coating identified in the inspection the firm will set up a prospective validation procedure to be performed annually to verify the reproducibility of the process. The firm has not provided to FDA documentation to show that these corrective action have been completed.

3. **Failure to establish and maintain procedures to ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results as required by 21CFR 820.72 (a).**

For example:

Certain measuring equipment is not suitable for its intended purposes or capable of producing valid results. Specifically, the laboratory Mettler scale was observed bearing a calibration date indicating repeat calibration should have been performed 4 months prior to this inspection. Mr. Huang, the firm's Manager, Regulatory Affairs, stated this due to an oversight, this calibration had not been done.

Your firm's June 27, 2003, response is not adequate:

The firm has not provided to FDA documentation for a calibration procedure and the status of calibration schedule.

4. **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).**

There is no calibration sticker on the pH meter used to conduct pH readings for reagents, conjugate, buffers, and controls, and no documented records for calibration were available for review.

Your firm's June 27, 2003, response is not adequate:

The firm's response stated that it will set a monthly calibration procedure for the SP20 pH meter. The firm has not provided to FDA documentation to show that it is been done.

5. **Failure to provide means by which the user may be assured that the product meets appropriate standards or identity, strength, quality and or the time of use as requested by 21 CFR 809.10 (6) (i).**

For example:

There is no documentation that demonstrates the shelf life for production reagents, controls, or conjugates. Specifically, buffers, reagents, including testing reagents used in the production of the [redacted] o not have a pre-determined shelf life. Some buffers in active production inventories had been prepared 6 months prior to inspection, but there was no data to support use of that buffer for that length of time.

Firm's response:

Shelf-life for all solutions used for production purposes and their acceptance criteria will be documented in a procedure describing the method for routine testing. The preparation of solutions will be validated according to documented acceptance criteria. Training will be provided to employees to reinforce the practice.

Your firm has not provided to FDA documents to show that a system for stability testing has been put in to place.

This letter is not intended to be an all-inclusive list of deficiencies at IND Diagnostic Inc. 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 Form FDA 483 issued at the conclusion 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.

Given the serious nature of these violations of the Act, all products manufactured by IND Diagnostic Inc., Delta, B. C., Canada may be detained without physical examination upon entry into the United States until these violations are corrected.

In order to remove the devices from this Detention Without Physical Examination, 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 you have submitted an adequate response, it will be your responsibility to schedule an inspection of your facility. As soon as the

inspection has taken place, and the implementation of your corrections has been verified, your products may resume entry into this country.

Please notify this office in writing within fifteen (15) working days of the specific steps you have taken to correct the noted violations, including 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. Please include in your response any and all documentation showing plans for correction. If documentation is not in English, please provide an English translation to facilitate our review. Please address your response and any questions 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, to the attention of Mr. James Woods.

Should you require any assistance in understanding the contents of this letter, do not hesitate to contact Ms. Claudette D. Ellis at the letterhead address or at 301-594-3084 or Fax 301-594-5940.

Sincerely yours,

S. Gutman

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