DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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Warning Letter

VIA FEDEX

WL: 320-01-08

JAN 1 1 2001

Dr. Thomas Åqvist
Plant Director Pharma Mälardalen
Pharmacia Corporation
Lindhagensgatan 133
S-112 87 Stockholm, Sweden

Dear Dr. Åqvist:

We have completed our review of the inspection of your Mälardalen sterile finished manufacturing operations which includes Swedish sites in Stockholm, Uppsala and Brunna by Investigator Thomas J. Arista and Chemist Robert D. Tollefsen during the period of June 26 – July 12, 2000. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice Regulations (Title 21 CFR, Parts 210 & 211) in the manufacture of sterile pharmaceutical products. The deviations were presented to you on an Inspectional Observations (FDA-483) form, at the close of the inspection. These CGMP deviations cause your pharmaceutical products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Specific areas of concern include, but are not limited to:

1. The Mälardalen operation uses both the [ ]System) and [ ]network computer software programs for materials and data management functions. The [ ]performs functions typical of a laboratory information management system. The quality control unit uses this program for disposition of materials, special studies, stability testing programs, and generation of summary test reports. Once material is dispositioned, [ ]communicates information to the [ ]network program used by warehouse and production personnel to control material in storage and production. Both the [ ]and [ ]network programs work in concert acting as the sole source of information which controls and maintains the status of raw materials and finished goods in the warehouse. Your operations use these programs in a similar manner to control in-process materials during manufacturing operations. These network program systems are deficient in that:

a. The[ ]network program lacked adequate validation and/or documentation controls. For example:
   - The system design documentation has not been maintained or updated throughout the life of the[ ]software dating back to 1985 despite significant changes and modification that have taken place. These include program code, functional/structural design, diagrams, specifications, and text description of other programs that interface with[ ]
   - The program was not controlled by revision numbers to discriminate one revision from the other.
   - Inadequate standard operating procedures to ensure that records are included with validation documentation, maintained and updated when changes were made.
   - Significant deficiencies regarding documentation controls were reported. Documents were either not dated, lacked a documentation control number, were missing, were reported in pencil on uncontrolled pages, or dates were crossed out without initials, dates, or explanation.
   - There was no assurance that complete functional testing had been preformed in the[ ]system. For example you failed to assess all historical testing and compare it with current functionality to ensure that all current[ ] functionality has been adequately evaluated.

b. The[ ]network program lacked adequate validation and/or documentation controls. For example:
   - The program uses a purchased custom configurable materials management software package. The software validation documentation failed to adequately define, update and control significant elements customized to configure the system for the specific needs of the operations. The following had not been maintained or updated from original release/design specification dating back to approximately 1985:
     - Revision control system.
     - Validation records did not address the order of libraries, which effect function.
     - Structural and functional diagrams and design descriptions.
     - Complete diagrams with text description identifying other network programs which interface with[ ]
   - Deficiencies regarding documentation controls such as maintenance of records, lack of review and approval of change control and other similar records.
   - Inadequate standard operating procedures to ensure that records are included with validation documentation, maintained and updated when changes are made.

c. The wide area network also identified as the[ ] is used to connect network applications to local area networks[ ] at Malardalen operational facilities. The[ ] and[ ] run both the[ ] and[ ] network application at each site by departments using these programs to perform their GMP function. Both the[ ] and[ ] documentation were not included in the[ ] and[ ] validation efforts and therefore lacked adequate documentation controls.

Your response for the[ ] acknowledges that the system has not been maintained throughout its life and there are gaps in the documentation. You indicate rather than expending resources on reviewing validation documentation that in some cases is 15 years old, you are looking forward to a replacement of the[ ] system with a new validated computer system in the near future. In the interim your validation effort was to review only the current system documentation with respect to the Investigator's computer concerns. You evaluated the functionality and reliability of[ ] by comparing the printout of 21 US batches against source documents and no errors were found. As a result you concluded that the[ ] system functions correctly and reliably and has been validated. Your response fails to trace back to source code, and the related software development cycle which establish evidence that all software requirements have been implemented correctly and completely and are traceable to system requirements. Software is validated in its controlled development and in control of ongoing maintenance of the software and its documentation throughout its life cycle. You make no commitment to retrospectively put the historical documentation together.

Your response for[ ] indicates upgrading[ ] version[ ] installed during 1997 to version[ ] on or about December 2001 and inclusion of corrective actions in version[ ] Also you will continue to use, and complete a retrospective evaluation of [ ] on or about December 2000. The inspection reports that the documents reviewed did not define the system as being validated but was a qualification document for the[ ] version upgrade. The records did not describe the custom configuration of the[ ] system as it is in place. Your response did not evaluate requirements or trace changes to determine side effects. Further, your response failed to address the issue of what sites are approved to use the[ ] application nor does it address defining what restrictions will be in place for each site with respect to defining what functions in MOVEX are approved for use at each site. In order to consider a computer system to be validated, all elements which make up the system must be clearly defined. Appropriate systems definition documentation, properly updated when necessary throughout the life cycle of the software, is part of the control and ongoing maintenance of a computer program. Your response fails to discuss extending the retrospective evaluation to other elements of the system needing to be defined and controlled as part of the overall configuration management.

It could be difficult to retrospectively validate a computer system if there were changes and revisions that were not documented and the cumulative affects of many revisions had not been assessed. Lack of sufficient system documentation would make it impossible to

perform meaningful retrospective validation. FDA concludes that the [ ] and [ ] systems lack adequate validation and therefore are unacceptable for use in the production of the drug products. Please indicate whether you can perform a retrospective validation of the [ ] and [ ] systems or rely in the interim on manual operations that use source documentation until the new validated computer systems are functional.

2. The Mälardalen local computer systems lacked adequate validation and/or documentation controls. For example:

   a. The [ ] computer control alarm system that monitors the air handling units temperature, humidity, and airflow/pressure, the [ ] water system, and temperature of various freezers and refrigerators, lacked the following:
      - Documentation demonstrating an adequately validated system, for example:
        - System description.
        - Functional tests of systems capability of simultaneously monitoring normal operations and/or assessing alarm conditions.
        - Description and definition of utility and equipment alarm settings.
        - Exact number of monitoring and/or controlling devices and equipment monitored.
        - Evaluation demonstrating accurate printed information.
      - Adequate handling of records generated with inaccurate time frames dating back sixteen years for mainframe computer clock and three years for the local workstation computer clock due to Y2K compliance related issues.
      - Appropriate procedures to ensure that records are included with validation documentation, maintained, and updated when changes were made.

   b. The [ ] alarm system that communicates, records, and controls alarms related to air balance and temperatures for production, warehouse and testing areas, storage rooms, and coolers, lacked the following:
      - Change control documentation approving change in the software. In addition, there was no qualification [ ] documentation for this change.
      - Validation documentation failed to include complete and updated system design documentation, and complete wiring/network diagrams to identify all computers and devices connected to the [ ] system.

   c. The [ ] equipment's computer used for [ ] filling operations which retains equipment errors that occur during filling operations, lacked the capacity to retain electronic data. After every 15th filling operation, the information was overwritten due to the storage capacity of the equipment's hard drive.

3. Inadequate oversight by the Quality Control Unit (QCU) to ensure that controls which impact the quality of sterile products are implemented for manufacturing operations. For example:

a. The QCU failed to ensure that adequate procedures were put into place to define and control computerized production operations, equipment qualifications, documentation review and laboratory operations.

b. The inspection reported numerous deficiencies regarding the lack of approved procedures, failure to follow procedures, and inadequate laboratory controls for documentation, storage and handling of samples pertaining to the stability and environmental monitoring programs.

4. Inadequate[ ]operating procedures. For example:

a. Inadequate simulation (media fill) of[ ]filling operations:
   - Failure to demonstrate that planned manual interventions during media filling operations do not contaminate (negatively impact) the media filled containers. Following these manual interventions an unspecified number of units containing media near the intervention areas are discarded and not incubated, which could result in a bias of the media fill results.
   - Discarding of unspecified numbers of media filled units indicates that the media fill qualification would not be able to substantiate that the contamination rate was not exceeded in order to obtain the confidence level described in the validation protocol[ ]

b. Routes of contamination:
   - Partially stoppered[ ]filled cartridges, were not kept under class 100 conditions during the transfer process to the[ ]or following [ ]for phase[ ]filling operations.
   - Non-viable particulate monitoring was not performed in the class 100 area immediately adjacent to the[ ]where partially stoppered filled vials are exposed.
   - Cleaning and disinfection of[ ]panels positioned over the [ ]filling zone and class 100 areas were not documented. The panels are removed semi-annually and there were no records demonstrating sanitization.
   - Unnecessary materials which lacked any records of disinfection were observed in the[ ]filling zone (e.g., printer paper).

c. Inadequate personnel monitoring:
   - Production personnel perform personal monitoring (fingers on agar plate) on each other. An operator was observed spraying 70% ethanol on gloved hands just before sampling and on two separate occasions, operators were observed sampling with wet gloves.

d. Inadequate laminarity (smoke) studies:

- Laminarity of air flow was not adequately demonstrated during dynamic conditions within class 100[ ]filling zones.

e. Inadequate documentation of temperature distribution studies on processing equipment:
   - There was no documentary evidence to support the validity of the [ ]placement and most difficult to sterilize locations for the [ ]chamber, and the partially stoppered container transfer carts.

Regarding your response to 4.a, we acknowledge your commitment to corrective actions. However, some questions still remain. Your response failed to demonstrate that a predetermined number of units are removed during routine production and that each of the specific circumstances under which these units are removed have been clearly defined by written procedures. Please demonstrate that the planned interventions during media fills were reflective of actual production practices, procedural requirements, and worst case conditions regarding the number of units discarded. Each production intervention should be defined in detail within written, approved procedures. Details relating to the intervention should include the specific type, duration, extent, and number of units removed. These details should be recorded in batch production records. The activities defined by procedures and documented by production records may then be simulated during media fills in a manner that justifies the worst case production conditions permitted in actual operations.

5. Inadequate maintenance of equipment and utilities. For example:

a. Inadequate diagrammatic representation of utility systems:
   - The air handling system's diagrams did not accurately describe or reflect the air system such as the EU rated filters and air ductwork.
   - The drawings that illustrate particulate classifications of production areas were not accurate. An area used to handle[ ]filled containers into transfer carts was erroneously classified 10,000 instead of 100.
   - There were no Isometric drawings for[ ]water system that supplies[ ]water to the[ ]system.
   - An outdated schematic (revision 2) of the[ ]water system hanging on a wall appeared to be in use by the engineering maintenance staff. The current schematic at that time was revision 4.

b. Plumbing system defects:
   - There was no assurance that a pressure relief security valve positioned above the[ ]storage tank was sealed closed to prevent ingress of microbial contamination into the[ ]storage tank.
   - The plumbing system contained two manually operated by-pass valves, positioned above[ ]micron filters which can permit unfiltered

water to the [ ] feed tank. System qualification did not address use of [ ] water to the [ ] system.

Our review also included your company's response letters to the FDA-483 observations dated July 20, 2000, August 17, 2000, September 4, 2000, October 1, 2000, November 17 and 28, 2000, and December 11, 2000. We acknowledge that many corrections have been made, or are in progress. Your response to observation 1 addressing the [ ] and [ ] computer validation and observation 4.a, addressing media filled units was inadequate as discussed above. Except for observations 1 and 4, the corrections when fully implemented appear to satisfactorily address the deficiencies listed on the FDA-483. The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practices.

Please respond to this letter within 30 days of receipt. Your response should include copies of procedures generated as well as data collected in your correction to the deficiencies cited. Please identify your response with CFN 9691013. Until FDA can confirm compliance with CGMP's and correction to the most recent inspection deficiencies, this office will recommend disapproval of any new applications listing your firm as the manufacturere of active pharmaceutical ingredients.

Please contact Edwin Melendez, Compliance Officer, at the address and telephone numbers shown above, if you have any questions, written response or concerns regarding these decisions.

To schedule a reinspection of your facility after corrections have been completed, and your firm is in compliance with CGMP requirements, send your request to: Director, International and Technical Operations Branch, HFC-134, Division of Field Investigations, 5600 Fisher's Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 443-1855 or by fax at (301) 443-6919.

Sincerely,

Joseph C. Famulare
Director
Division of Manufacturing and Product Quality

CC: Gary Harbour, Ph.D
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