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

96-42043 Switz

HFC-134
Assoc. Dir

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737
TELEPHONE: (301) 594-0093
FAX: (301) 594-2202

April 25, 1997

Novartis AG
CH-4002 Basel, Switzerland

Dear Mr.

This letter relates to the inspection of your sterile dosage form manufacturing manufacturing facility in Stein, Switzerland by Investigators Patricia Gupta and Paula Trost, and Chemist Azza Talaat, during the period of July 10 through 19, 1996. We have considered the written responses and discussions in meetings of October 19, 1996, March 18, 1997, and March 20, 1997 in our review of your facility's status. In addition, we are aware of the recent merger of the former Ciba-Geigy and Sandoz Ltd. organizations to form Novartis AG. We commend your firm for its commitment to reevaluate critical aspects of the plant's operation, most notably quality systems, facility design, and personnel training. Moreover, we acknowledge your firm's stated recognition of the importance of the role of a strong quality control unit in assuring corporate-wide compliance on an ongoing basis.

The July, 1996 inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of sterile pharmaceuticals. The deviations were presented to your attention on an FDA-483 List of Observations at the close of the inspection. These CGMP deviations cause your sterile pharmaceuticals to be unacceptable for use in the United States, since, under United States law, those CGMP deviations render your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Recent history of Ciba-Geigy, Switzerland includes a Warning Letter issued to Ciba-Geigy of Basel and Schweizerhalle on March 1, 1995. The letter noted deficiencies regarding cross-contamination and laboratory controls for non-sterile dosage forms. The cross-contamination deficiency was a facility-design related issue and the March, 1995 Warning Letter noted that the inspection could not identify all deficiencies at the facility, and consequently, we

recommended that you evaluate your facility for overall CGMP compliance.

Facility design issues as well as multiple additional significant deficiencies were noted during inspection of the sterile dosage form facility during May 15 - 23, 1995. CGMP deficiencies included areas such as maintenance, sterilization validation, insufficient monitoring, and poor practices by personnel. Following this inspection, a September 13, 1995 Warning Letter was issued to Ciba-Geigy's Pharma Division, which decided to voluntarily cease shipping processed products to the United States. Since the 1995 inspection, medically necessary products have been reviewed and cleared by our office on a lot-by-lot basis prior to distribution for use within the United States.

The July inspection demonstrates the continued existence of serious deficiencies relative to the facility's processing operations and quality control unit. Deficiencies include, but are not limited to:

FACILITY AND PROCESS DESIGN

1. Facility and process issues were noted again during the current inspection. For example:

- The was not performed

We acknowledge your reported global review of Please note this fundamental breach in post-sterilization method indicates the need to conduct a more comprehensive review of all processes employed by your corporation for any other serious deviation from well-accepted sterile manufacturing concepts.

- was done while an immediately adjacent door was open. This open door has been subsequently found by studies to cause While a sign has been placed on the door and an SOP prepared to prevent its being opened during operations, there is no indication whether training has taken place for all personnel associated with the operation. The new procedure represents a major change from past practices and the reasons for and specifics regarding the change should be formally reinforced with personnel.

- doors were permitted to remain open for approximately minutes in one case. This resulted in the potential for

-

QUALITY CONTROL UNIT

2. Several instances of contamination (e.g., were not investigated.

Further, investigations of out-of-specification results did not include review of trending data (e.g., a particular site or and trending systems in place at the time of inspection were not adequate.

3. plans were not always reviewed and approved by the Unit

Please indicate whether a broad response to this observation has been undertaken to assure that there is adequate Unit overview in all areas which may impact product quality, such as: written SOPs and policies; master batch records; product changes; or studies relating to processing or test methods.

4. There was no written SOP regarding notifying the of

During the October 19, 1996 meeting, a German version of the newly written SOP was provided. Please provide an English translation of this SOP. The written SOP should address type, duration, and documentation of a The response (e.g., should also be addressed.

5. There was no documented review of a

The December 16, 1996 written response states that the Ciba Standard Operating Procedure (SOP) for investigating a would be changed from Please note that any significant between processing facility rooms should be investigated. Significance is based upon comprehensive qualification studies which establishes When these specifications are not met, an investigation should be initiated. As an standard, it is necessary to investigate the origin and effect of any

6. The monitoring program was deficient.

Observation 22 of the FDA 483 notes deficiencies regarding sampling. Your written response states that certain do not have to be tested because sterilization of these product has been validated. In fact, each batch

As a result,

monitoring is a major element of the monitoring program.

Please indicate in your response whether such as the will be monitored at the of processing operations.

VALIDATION/DOCUMENTATION

7. Approximately vials were not accounted for in a validation run.

Written responses did not state that SOPs would be revised to reflect the need for documentation of these process validation runs.

8. An not supported by methods validation studies was used for determinations (Observation 52).

The written response to this observation lacked any commitment to undertake a global response to assure other products are not analyzed by unvalidated test methods. One global approach would be exploring whether your firm's change control procedures must be improved to prevent future similar deviations.

OUTSTANDING ISSUES

In addition to the documentation requested regarding the above deficiencies, please also address the following outstanding issues regarding submissions to our office following the July, 1996 inspection. Some of these issue have been discussed, at least in part, by phone conference or during meetings at our office:

1. Regarding Observation #4, please provide documentation of the studies performed to demonstrate acceptable Please include details such as

In addition, please inform us of any policy revisions instituted in response to to the study's findings.

2. readings have been noted in the area in which takes place. Please discuss provisions being discussed to prevent such when handling future batches. Include a discussion of the effect of

3. Regarding Observation #12, please provide your analysis of the results of monitoring at following the

4. Regarding Observation #20, a generally accepted

Please indicate the frequency with which you test for and the conditions used.

5. Please provide a copy (translation) of the study conducted to justify use of a rather than a for sampling (Observation 21).

6. Regarding Observation #27, do operators performing change their gloves after sampling?

7. Please briefly summarize the deviations which took place during the validation of systems used fro (Observation 43). In addition to the above issues, we acknowledge a March 26, 1997 facsimile communication from Mr. committing to address ten action items from the March 18, 1997 meeting.

We also note your commitment during the March 18, 1997 meeting to discontinue manufacturing Regitine in sterile room in of this year.

As discussed during the March 18, 1997 meeting, we encourage the transfer of products to the new modern facility, Building Mr. noted during this meeting that the transfer should take place by the end of 1998. During the previous November, 1996, meeting with representatives of the former Ciba-Geigy, a target of the end of 1997 for submitting NDA supplements was discussed. In order to confirm your firm's plans, please provide the current timelines within your response to this letter.

The CGMP deviations identified above 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.

We recommend that you evaluate your facility on an overall basis for CGMP compliance. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers.

Until FDA has reinspected your facility and it has been found in CGMP compliance, we will not recommend approval of any applications listing your firm as a supplier of produced drug products. Any produced products produced by your firm may be denied entry into the United States. Upon our confirmation during next inspection that significantly improved quality systems and CGMP practices are in place, we will eliminate the lot-by-lot oversight currently in place for medically necessary products.

Please contact Compliance Officer Richard L. Friedman [telephone: (301) 594-0095; fax: (301) 827-0145] of this division at the above address if you have any questions. Within your written response to this letter, detail corrective actions you plan to take or have taken to bring your operations into compliance. Please include a timetable of when each of the corrections will be completed and attach English translations of supporting documents.

Please reference **CFN# 9692043** within your written response.

To schedule a reinspection of your facility, after corrections have been completed and your firm has thoroughly evaluated overall compliance with CGMP requirements, send your request to: Director, International Drug Section, HFC-134, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5648 or by fax at (301) 443-6919.

Sincerely,

Mark A. Lynch,
Branch Chief