DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

# Warning Letter

**Via FedEx**

**WL: 320-05-02**

August 16, 2005

Mr. Armin Späni
Member of the Board of Directors
Similasan AG
Chriesiweg 6
8916 Jonen, Switzerland

Dear Mr. Späni:

We have completed our review of the inspection of your pharmaceutical manufacturing facility in Jonen, Switzerland, during the period of April 4-8, 2005. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) Regulations (Title 21 Code of Federal Regulations (CFR), Parts 210 and 211) in the manufacture of drug products. These deviations were listed on an Inspectional Observations (FDA-483) form issued to you at the close of the inspection. These CGMP deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351(a)(2)(B)]. In addition, your products, as described below, are misbranded within the meaning of Section 503(b)(4)(A) of the Act [21 U.S.C. 353(b)(4)(A)].

Our review also included your May 3, 2005, and May 24, 2005 responses to the FDA-483 observations. The CGMP deficiencies need more comprehensive corrections than the actions you have proposed or taken.

## CGMP Issues

### FACILITIES AND EQUIPMENT SYSTEM

1. There was inadequate evidence that equipment used in the manufacture of sterile drugs is of appropriate design in that no heat penetration studies were conducted on the autoclave used for sterilizing filters. **21 CFR 211.63**

   Equipment cleaning and maintenance is inadequate to prevent microbiological contamination that would alter the safety, identity, strength, quality, or purity of the drug product. Specifically, there is not sufficient scientific data to justify the re-use of sterilizing filters. **21 CFR 211.67**

Your response indicates that you will conduct heat penetration studies which include load pattern and cycle for each piece of equipment. Your heat penetration studies should include worst case situations, including those variables related to the re-use of filters. We would like to see the design and data for your heat penetration studies.

According to the establishment inspection report you re-use sterilizing filters as long as they perform to the manufacturer's filter integrity standards of [ ] or for a maximum of your internal specification of 50 re-uses. We are concerned about the effectiveness of your filters after being re-used and autoclaved 50 times. We understand that you conduct a filter integrity test by the [ ] method before and after each batch. However, in order to justify 50 re-uses, we would like to see bacterial retention validation studies using product both upon the initial use of the filter and after the 50th re-use. Further, it is unclear to us whether you have conducted filter extractable and leachable testing with product. If you have this data, provide it to us. If not, let us know when you will be able to provide it to us.

2. There was insufficient evidence that ventilation and air filtration systems provided adequate control over microorganisms for the manufacture, processing, packing, or holding of a drug product. **21 CFR 211.46**

The following deviations were noted regarding ventilation and air filtration systems: There was no scientific justification for testing of [ ] filters in the Class A (ISO 5) area and sterile [ ] only once annually, the procedures did not include a specification for the required distance for taking [ ] test measurements, or for monitoring of pressure differentials between various operational areas. Your proposed corrections appear acceptable pending our receipt and review of supporting documentation.

**PRODUCTION SYSTEM**

3. Control procedures were inadequate to prevent microbiological contamination of sterile eye drops. **21 CFR 211.113 (b)**

There were several deviations in aseptic practices and technique. An operator was observed spraying [ ] near a [ ] intended for environmental monitoring, chairs positioned in front of three exhaust vents were obstructing air flow in the Class A/B (ISO 5) room, three individuals were observed in the Class A/B (ISO 5) room with exposed eye and partial forehead areas, there was no assurance that irradiated caps were exposed to [ ] for [ ] minutes as required by the batch production record and environmental monitoring did not include the area where duct tape surrounds the hole where bottles exit the Class A (ISO 5) filling area. We acknowledge that you have updated standard operating procedures and batch production records, re-trained personnel and provided face covering and eye protection to those working in the [ ] area. However, due to the limited amount of time the inspection team had available to

observe aseptic practices and the number and significance of the deviations, we have no assurance that all control procedures are adequate and suggest that a more comprehensive assessment of aseptic practices and techniques at your firm is needed to provide greater assurance of microbiological control.

4. Appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, were not established and followed. Specifically, written procedures were not established and followed to validate the [ ] filling process because of deficiencies in media fill studies. **21 CFR 211.113**

The media fill studies were inadequate in that: amber colored bottles which are not appropriate for viewing turbidity were used in media fill studies, the [ ] hour duration was not documented by recording the beginning and end of the process, preparation of the media was not documented, the media fill standard operating procedure (SOP) was not followed in that studies were performed annually rather than every six months, and the media fill SOP allowed a study to be classified as acceptable with three contaminated units. Your proposed corrections appear acceptable pending our receipt and review of supporting documentation.

5. Batch production records did not include complete information relating to production and control of each batch. **21 CFR 211.188**

The following information was not included on batch production records: reconciliation of yield for product solution; identification, checking and reconciliation of caps and bottles; the reason for and disposition of rejected bottles and caps; beginning and ending times of filling; in-process testing criteria; lot number of the sterilizing filter; filling speed; and a check by a second person of the weighing of components and in-process materials. Although you state in your response that you will update the batch production record with this information, we are unsure if you have also committed to updating the batch production records of all products marketed in the United States.

## QUALITY SYSTEM

6. Unexplained discrepancies were not adequately investigated by the quality control unit. **21 CFR 211.192**

Microbiological test results for personnel and environmental monitoring that exceed your firm's action level were not investigated and were inadequately investigated, respectively. We acknowledge your statement that you will conduct an internal review of your deviation reporting and to investigate all OOS results. However, we want to emphasize the importance of good documentation in relation to investigating deviations. For example, had your firm started documenting sterilizing filters in the batch production

records after the first time filters were mistakenly re-used for the wrong product, you would be able to retrospectively review records to see if any mix-ups have since occurred. Even though that product was not shipped to the United States, we take very seriously issues of cross-contamination and would like assurance that this has not happened since or on any routine basis. We encourage you to maintain the necessary documents and data to determine the root causes of failures.

## LABORATORY CONTROL SYSTEM

7. Laboratory controls did not include scientifically sound and appropriate test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity. **21 CFR 211.160**

Growth promotion testing was not performed on microbiological testing media, there was no assurance that yeast and mold will grow at the [ ] incubation temperature used to detect bacteria growth, microorganisms found during environmental testing were not identified, and the [ ] analytical method used on eye drops and nasal spray was not fully validated. Your proposed corrections appear acceptable pending our receipt and review of supporting documentation.

It is important to note that failure to conduct growth promotion testing is another example where you are missing a large body of data that is important for microbiological investigations where environmental results exceeded your firm's action level. We acknowledge you have now committed to conducting growth promotion testing, but we would like to emphasize that this is an important body of information that is missing for all investigations in the past. As mentioned above, we encourage you to maintain the necessary documents and data to determine the root causes of failures.

## PACKAGING AND LABELING SYSTEM

8. There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable. Specifically, the written procedures for the storage, examination, and issuance of labels were not adequate to assure labels that do not meet specifications are rejected and not used.. **21 CFR 211.122**

Quality assurance approved and released "Ear Wax Relief" labels misprinted with the words "Eye Drops." Although the investigator confirmed that these labels were not yet

used on marketed product, we are concerned that misprinted labels may have been used on marketed product in the past. An investigation should extend to the review of all labels of product remaining on the market.

In addition, the inspection team noted that labels were not stored separately and access is not restricted to authorized personnel, the number of labels issued to production was not recorded, and that line clearance instructions in the batch production record were not complete. These practices increase the likelihood that drug products will be mislabeled and are additional reasons why we believe it is necessary for you to review the labels of marketed product. Your proposed corrections to controlling labels in the future appear acceptable.

**General Comments**

The establishment inspection report identified another concern related to media fills that was not listed on the FDA 483 Inspectional Observations. That is the practice of using space heaters in the microbiology laboratory to increase the temperature to incubate the media fill tubes. For the purposes of accurately controlling the temperature we recommend the use of a qualified incubator.

Many of the observations cited on the FDA 483 Inspectional Observations can be traced back to the responsibilities of the Quality Control Unit. Specific areas include, but are not limited to, the Quality Control Unit's responsibilities in reviewing and approving batch production and control records including failure investigations, control procedures, and labeling. You state that you have hired two new employees in the Quality Control Unit and have hired consultants experienced in sterile manufacturing. We look forward to seeing how this has strengthened your Quality System.

**Labeling and New Drug Issues**

Because Similasan Pink Eye Relief eye drops are intended to relieve minor symptoms associated with viral and environmental conjunctivitis and Similasan Cataract Care eye drops are intended to relieve symptoms associated with diagnosed cataracts and aging eyes, they are articles intended for use in the mitigation and treatment of disease in man. Therefore, both of these products are drugs within the meaning of Section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(g)].

Similasan Pink Eye Relief eye drops and Similasan Cataract Care eye drops are misbranded within the meaning of Section 503(b)(1) of the Act [21 U.S.C. § 353(b)(1)] in that they are not dispensed pursuant to the prescription of a practitioner licensed by law to administer such drug. The conditions for which they are offered are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners. FDA

has found that OTC treatment is inappropriate for conjunctivitis because consumers cannot distinguish its symptoms from those of more serious disorders of the eye which are not amenable to OTC treatment (57 Fed. Reg. 60,417 (1992)). Likewise, FDA believes that OTC treatment is inappropriate for cataracts because consumers cannot distinguish its symptoms from those of more serious disorders of the eye which are not amenable to OTC treatment. Although the Cataract Care eye drops labeling notes that cataracts should be diagnosed by the user's doctor, some of the symptoms for which the product is intended to be used may be indicative of other serious disorders of the eye that are not amenable to self-diagnosis. The drugs are further misbranded within the meaning of Section 503(b)(4) of the Act [21 U.S.C. § 353(b)(4)] in that the product labels fail to bear the statement, "Rx only." The drugs are also misbranded within the meaning of 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)] in that their labeling fails to bear adequate directions for use as this term is defined in 21 C.F.R. § 201.5. Adequate directions for use cannot be written under which a layman can use these drugs safely and for the purposes for which they are intended.

Until FDA has confirmed correction of the deficiencies observed during the most recent inspection, and compliance with CGMPs, this office will recommend disapproval of any new applications listing your firm as the manufacturer of finished pharmaceutical drug products. In addition, failure to correct these deficiencies may result in FDA denying entry of articles manufactured by your firm into the United States. The articles could be subject to refusal of admission pursuant to Section 801(a)(3) of the Act [21 U.S.C. 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of Section 501(a)(2)(b) of the Act [21 U.S.C. 351(a)(2)(B)].

Please respond to this letter within 30 days of receipt. Your response should include data collected in your correction to the deficiencies cited as well as copies of procedures not already included. Ensure that your response to this warning letter addresses the deviations in a global manner and that documentation supporting corrective actions is submitted to this office in English. Please identify your response with FEI 1000110034. Please contact Karen K. Moksnes, Compliance Officer, at the address and telephone numbers shown below, if you would like to schedule a meeting, have any questions, a written response or concerns regarding these decisions.

U.S. Food & Drug Administration
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Rockville, MD 20852
Tel: (301) 827-9008; FAX (301) 827-8909

To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigations, HFC-130, 5600 Fishers Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

Joseph C. Famulare
Director
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research