DEPARTMENT OF HEALTH & HOMAN SERVICES

Public Health Service

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Food and Drug Administration Rockville MD 20857

1996

!n response refer to File Numbe ___

This is in response to your request dated f/^o/. i n which you requested

'^r^l'equerfS^ received in the Center for Drug Evaluation and Reaeareh on Sa/y/# ¦ ‘

Enclosed is/are the dociment/documents you requested,

A search of the records of the Center for Drug Evaluation and Research did not locate any disposable documents responsive to your request.

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did not locate an approved Hew Drug Application mr an approved Abbreviated Heu^Drug Application for this/these product/products.

___did not locate a Completed copy of the inspection you requested.

___ did not locate a record an any such inspection by this Center.

___ found that final printed tableing is not yet available

Due to severe resource restrictions, this/these documents are only available on microfiche. Paper copy cannot be provided. You may wish to view the document at your local library or request a local eomoany provide paper copies from the fiche,

The minutes of the wo t i ng/mee t i ngs you requested f.re still in preparation and are not yet available

The document you requested is available from the national technical Information Service, 5205 Port Royal Road, Springfield, Virginia 22161, 7O3-A07-465C

The portion of your request regarding _____ as been referred to the

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In order to reduce processing time and costs, certain material may have been deleted from the record(s) furnished to you, because a preliminary review indicated that the deleted material is not required to be publicly disclosed. If, however, you wish to review any deleted material, identify the specific deletion and submit an additional request for this information.

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Iht following charges wilt be included in a monthly invoice: Reproduction _____ Search Review S_ //'J & Other

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If there are any problems with this response, please notify us in writing of your specific problem(s). Please reference the above file rxirbcr.

Requestor

hfd —205

Sincerely yours,

f Eulah H. Jones

Paralegal Specialist, FOl Center for Drug Evaluation

and Research, HfD-205

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FOt Sorvicatt, he.

11 Firsthakf Road Qahharsburg MD 20878-1703 USA

Phone: 301-97S-9400 Fax: 301-97S0702

ROCKVILLE, MD 20857

PURSUANT TO THE PROVISIONS OF THE FREEDOM OF INFORMATION ACT, PLEASE PROVIDE US WITH A PAPER COPY (PREFERABLY NOT MICROFICHE) OF THE FOLLOWING DOCUMENTS. IF THE COST OF PROVIDING THESE DOCUMENTS WILL EXCEED 100.00, PLEASE CALL US FIRST FOR AUTHORIZATION OF THE CHARGES, UNLESS INDICATED OTHERWISE BELOW.

PLEASE REFER TO OUR CONTROL NUMBER IN YOUR REPLY.

COPY OF THE EIRS AND 483S FOR THE 1/16-19/95 GMP INSPECTIONS OF PHARMACIA AB, RAPSGATAN 7, S- 751 -82, UPPSALA, SWEDEN AND PHARMACIA AB, BJORKGATAN 30, S.-751-82, UPPSALA, SWEDEN. THE INSPECTION WAS CONDUCTED BY THOMAS ARISTA.

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9/30/96

CONTROL NUMBER 143409

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SUMMARY OF FIHDIHGS

The inspection of this manufacturer was conducted: at the request from the office of Investigations & Compliance Evaluation Branch, HFD-324, concerning NDA #7-073 Supplement #097. The application provides fo,p this firm to perform microbiological testing for Azulfidine (Sulfasalazine Tablets 500 mg, USP) at the firm's Fyrislaund location.

The inspection also included a review of the firm's manufacturing operations at their Bolanderna location. During the inspection I was assisted by Mr. Gosta Sur6n - Senior Pharmaceutical Inspector, from Sweden's regulatory Medical Products Agency.

The inspection found objectionable conditions concerning some of the manufacturing operations and microbiological testing capabilities that are used in support of the finished products. FDA-483's were issued to the firm on two separate occasions e.g., the first concerning microbiological testing and the second addressing the firm's manufacturing processes; The following observations list some of the deficiencies noted, however they are not limited to the following:

Microbiology Testing - Fyrislund

- biological indicators are not enumerated prior to or after use nor are there written procedure that describes positive control testing of BI1s.

- the analytical records do not document that a 2nd. review for accuracy, completeness & compliance to standard procedures have been performed.

summary sheet do not accurately reflect the initials of analyst who performed the work.

~ there is no record of the thermometer that was used to calibrate thermocouples for Validation runs

- there is no record of the temD. calibration or routine monitorina of refrigerator room

for BI storage.

Manufacturing Operations - Bolanderna

- there are cross-outs and obliterations of data throughout the manufacturing records and logbooks nor are there dates and initials of the person who crossed out or obliterated the data.

- logbooks have not been reviewed for accuracy, completeness or compliance to established procedures;

a) Tablet press for

b) c)

e) Complaint Records.

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- **there is no record that documents if the firm's current course of action is effective in reducing levels of microbial contamination in their manufacturing facility.**

- **training records do not accurately document employee training in SOPs and their current revisions.**

- **there is no record that documents whether all utensils used during sampling of raw in-coming components or in the tableting**

rooms have been cleaned and sanitized prior to or after use.

- **there is no set air pressure specifications for the designated**

manufacturing areas nor are the routinely

monitored.

- **the used to record and adjust the speed during the**

coating operations in the has not been calibrated nor

are their written specifications

At the conclusion of each inspection an FDA-483, Inspectional Observations, was issued to and discussed with management. Management agreed to make corrections and to respond in writing to HFC-134 within 30 days.

LOGISTICS

The town of Uppsala, Sweden is 35 km, approximately £ hour by taxi, from Arlanda Airport located just north of Stockholm. The lodging accommodations at the Hotel Linn6 were satisfactory and within established per diem rates. The hotel is located within easy walking distance to a variety of acceptable restaurants, shopping and the central train station.

Pharmacia has multiple manufacturing sites within the town of Uppsala. The microbiology testing laboratory is located in their Fyrislund facility, while the tableting operations are located at the firm's Bolanderna manufacturing site. Transportation to and from these locations was provided by the firm.

HISTORY OF BUSINESS

As described during the previous inspection the firm had changed their name to Kabi Pharmacia AB. This past year Kabi Pharmacia AB experienced a corporate restructure and

name change to Pharmacia. The restructuring has established seven business areas within the Pharmacia Group. These manufacturing areas, individual companies and list of responsible management individuals are described in attachment A.

The individual responsible for the Fyrislund and Bolanderna operations is Mr. Lars Wiberg, Vice President - Quality Management.

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Mr. Wiberg reports directly to Mr. Goran Pettersson, president of Pharmacia Pharmaceuticals in Uppsala.

The firm's corporate headquarters address, telephone and telefax numbers in Sweden;

Pharmacia Telephone: (46) 18 16 30 00

S-751 82 Uppsala Telefax : (46) 18 12 05 54

Sweden

Pharmacia's corporate headquarters address, telephone and telefax numbers in the U.S.;

Pharmacia Telephone: 614/764-8144

7001 Post Road Telefax : 614/764-8125

Dublin, Ohio 43017

The U.S. contact at the above address is Mr. Angel Luis Canales, Director - Regulatory Services, Generic Drugs & Compliance.

PERSONS INTERVIEWED

As previously mentioned I was accompanied by Mr. Gosta Suren -Senior Pharmaceutical Inspector who assisted with translations of various manufacturing and quality control documents. As Acting Director of Sweden's Medical Products Agency, and due to other regulatory responsibilities, Mr. Sur6n was unavailable for part of the inspection.

At the onset of our inspection, I identified myself to the key responsible individuals at the Fyrislund facility. They were:

- **Mr. Lars Wiberg**
- **Ms. Inger Persson**
- **Ms. Inger Lindell**
- **Ms. Lory Wikstrom**
- **Ms. Anita Enqvist**

Vice President - Quality Management Quality Management - Director QA Quality Management - Manager QA Manager of Quality Assurance QA/QC Manager Quality Control Microbiology

- **Mr.**
- **Mr.**
- **Mr.**
- **Mr.**
- **Ms.**

Hans Elg Ingvar Asplund Anders Askaner Mikael Vikstrom

Plant Manager - Bolanderna Regulatory Affairs Chemical Production Manager Pharmaceutical Production Manager

Anna Gasste-Folkesson

Quality

Analysis

Control

Chemical

The U.S. representative present during the inspection was Mr. Angel Luis Canales, Director -- Regulatory Services, Generic Drugs & Compliance.

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These individuals provided the majority of the inspection information, not otherwise observed. I was accompanied at all times during the inspection by a number of these individuals.

The firm agreed to an end of the day meeting to discuss and clarify any misunderstanding concerning the information listed in the firm's documentation.

FACILITIES

The firm's microbiological testing is performed in their Fyrislund facility. Within the past year the microbiology laboratories moved from an older building and quarters to new laboratories within Fyrislund. The analytical laboratories appeared to be suitable for their various functions.

Pharmacia is currently renovating, expanding and building new multi-store structures at their Fyrislund location. However, these new developments do not effect the production of sulfasalazine.

The Sulfasalazine tablets are produced at the firm's Bolanderna manufacturing site. The buildings appeared to be of adequate size and constructed for their intended use.

OPERATIONS

Alternate microbiology test methods for finished product analysis for sulfasalazine USP tablets for NDA 7-073 Supplement #085 is listed in attachment B. Currently the firm performs total spread

The firm has yet to manufacture sulfasalazine at the Bolanderna facility for the U.S. market, as such, they have not performed all of the analysis listed in the NDA Supplement. During the inspection a review of the laboratory's proposed methods of analysis, standard operating procedures, as well as, their current

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methods and capabilities was performed. Issues concerning their current laboratory capabilities and practices are noted in a list of FDA-483 observations. ;

This is a brief overview of some of the production operations with respect to the manufacture of the sulfasalazine tablets fh® f-i™

The firm described a number of established procedures, normal operations and controls that are in place. Their material handling system appears to be in good order. The firm maintains finished product at a commercial distribution and warehouse center located in Brunna, approximately 20 km south of Stockholm. The time allotted did not provide for an inspection visit or review of this separate location.

The bulk drug substance is manufactured by Pharmacia at their Bolanderna manufacturing site. The bulk manufacturing operations was not reviewed during this inspection. A brief description of the various methods of manufacturing are listed in attachment C. Included is a list of ingredients, manufacturing scheme and some of the key pieces of equipment that are used. The following list some of the manufacturing processes performed at this location;

Sulfasalazine is manufactured A formulation comparison of raw components between the Virgin Islands facility and proposed Uppsala tablet manufacturing are listed in attachment D.

OBJECTIONABLE CONDITIONS

During the inspection there were deficiencies noted in the firm's manufacturing operations and quality control testing. At the conclusion of reviewing the microbiology testing capabilities and inspection of the manufacturing operations a list of observations were issued to the firm's management. The inspection's observations are listed below and a narrative is provided.

Microbiology Testing - Fyrislund

Biological indicators are not enumerated prior to or after use.

1.

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d) Complaint Records.

Ms. Wikstrom explained the logbooks documents product name, batch number, the number of units involved the complaints, reason for the complaint and if the complaint file is closed. Similar to Mr. Vikstrom concern, the logbooks are used to document a description of a complaint in the aforementioned summary format, exhibit #2B.

These are a few examples, and not an all inclusive list, of the logbooks that are commonly used throughout the firm's manufacturing operations. Many of these logbooks maintain manufacturing data

that is transcribed from a batch production record, in-process checks or taken during normal production.

Ms. Wikstrdm and Mr. Vilstrom could not offer or provide some degree of assurance if these or other logbooks have been independently checked or routinely reviewed by a second person.

3. There is no record that documents if the firm's current course of action is effective in reducing levels of microbial contamination in their manufacturing facility.

Document _ list the firm's

Microbiological Environmental control of their production facilities, exhibit #3B. Table #2 list the number of contaminants recovered during manufacturing periods from 1992 to 1994. The firm has subsequently set up microbial alert and action limits.

We asked Ms. Enqvist if any of the contaminants recovered during this environmental control study were identified to the genus or species level. Ms. Enqvist stated the majority of the contaminants recovered were Bacillus or Staphylococcus microorganisms. When asked for the supporting analytical documentation, Ms. Enqvist explained that a gram-stain and visual identification of the colony morphology was performed. However, the firm did not have nor

could they provide the supporting analytical documentation to support their environmental monitoring control study.

SOP # CI-174-016/4 is the firm's Microbiological Control procedure that would be used is response to microbial contamination that exceeded the firm's action levels, exhibit #3B.l. Ms. Enqvist confirmed that this SOP describes the cleaning procedure that would be used in the manufacturing area that was contaminated. The firm prepared a translation that is taken from page 3 of the SOP (exhibit #3B.l) and describes the following corrective actions to be taken:

1. Repeat the cleaning according to current SOP.

2. Perform a follow-up investigation.

3. If the value still are high shall Quality Control Microbiology be present when the cleaning operation is performed in order to evaluate possible improvements.

4. Implement improvements after discussion with involved personnel and supervisors.

It should be noted that the firm uses

distillation equipment to clean manufacturing equipment and some of the production areas. The firm does not use cleaning agents or sanitizing solutions in this facility or manufacturing operation.

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The four points noted above were discussed and further clarification was requested from Ms. Enqvist. Specifically, item #1 and how would repeating a cleaning step, that was initially ineffective, demonstrate that it is adequate to reduce contamination of unknown microorganisms. Ms. Enqvist stated that she would not avn«ct to find many microorganisms that would be able to withstand Mr. Arista explained that without first identifying the normal r of the manufacturing operations the firm could not ascertain if the was effective or.adequate. Ms. Enqvist reiterated that the majority of the contaminants recovered during the environmental monitoring study identified Bacillus and Staphylococcus organisms and they could easily be destroyed. Mr. Arista pointed out there is no analytical data or documents to support Ms. Enqvist claim. In addition, the firm does not have analytical data

or supporting documentation to confirm the absence of organisms that could be resistant to temperature levels.

The SOP list in item # 2 that a follow-up investigation will be performed. However, when asked the firm could not offer an explanation of what the follow-up investigation will include.

4. Training records do not accurately document employee training in SOPs and their current revisions i.e.:

a) Current revision of the Cleaning SOP;

Exhibit # 4 documents a typical employee training record that is maintained by the firm. The cleaning procedure is described in SOP #S-218 and the record document the employee received training on May 30, 1994. Ms. Wikstrom confirmed the current cleaning

procedure is revision #2.

b) SOP TUP-1 215-1 for Chemical & Production personnel;

Ms. Wikstrom stated training was required for all personnel in both Chemical & Production operations. You will note in exhibit # 4B the training records do not document that the employee received the necessary training. Previously noted in observation #1 are notable documentation discrepancies observed to be common place throughout the firm's manufacturing areas.

c) SOPs 614 & 617 noted in the preparation of the coating solution.

Mr. Vikstom stated these procedures are required during the initial preparation of the

Concerning these observations, the firm could not provide

supporting documentation to demonstrate that employees receive the appropriate training concerning new revisions of the existing SOPs.

5) There is no record that documents whether the following utensils have been cleaned and sanitized prior to or after use:

a) used to sample various in-coming raw components;

b) used in the tableting rooms.

Mr. Vikstom stated these pieces of equipment are routinely used. In addition, he confirmed they do not routinely record the cleaning of these utensils.

6) The firm requires to be maintained

throughout their desianated manufacturina "blue" areas. However, there is i

the routinely monitored.

The firm uses

possibility of cross contamination from occurring between the various manufacturing areas. are located in many

of these areas. When asked, the firm stated they did not have

iifferentials set nor have they established set parameters for the various manufacturing areas. Management confirmed they have not nor do they routinely monitor the

7) used to record and adjust the speed during the

coating operations i has not been calibrated.

Mr. Vikstrom explained that J adjustments are an important

parameter to be considered during the coating operations. He c visually adjusted with the use of When

asked, Mr. Vikstrom stated ; has not been calibrated.

8) There is no written specification for the

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a written specification that is used to prepare this cleaning solution.

9) There is no record to document calibration has been

performed on the dissolution apparatus.

Laboratory personnel described a variety of events that occur when calibration of

However, the firm could not provide records to document that of the dissolution

apparatus are routinely calibrated.

10) The operating instructions for

have not been formalized into an otticial document.

Exhibit # 10B describes a number of important manual procedures that guide the analyst on how toWhen

asked if this was part of the formal established procedure, Ms. GAsste-FoIkesson stated this was a quick summary and not part of the firm's SOP.

11) The firm does not follow their SOP for calibration of the pH meter.

During the inspection we observed handwritten instructions that describe calibration of in the analytical laboratory.

This is a similar issue noted in observation #10. Ms. Persson kindly disposed of the handwritten notation.

DISCUSSION WITH MANAGEMENT

At the conclusion of each day of the inspection, there was an informal discussion with management to relate the findings and to clear up any potential misunderstandings that may have occurred.

At the conclusion of the inspection a list of observations were noted on an FDA-483 and issued to Mr. Lars Wiberg, Vice-President, Quality Management. In addition to Mr. Wiberg the following individual were present during the preceding discussion of the deficiencies listed:

- **Mr. Lars Wiberg**

- **Ms. Inger Persson**

- **Ms. Inger Lindell**

- **Ms. Lory Wi^strom**

- **Ms. Anita Enqvist**

- **Mr. Hans Elg**

Vice President - Quality Management Quality Management - Director QA Quality Management - Manager QA Manager of Quality Assurance QA/QC Manager Quality Control Microbiology Plant Manager - Bolanderna

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- **Mr. Ingvar Asplund Regulatory Affairs**

- **Mr. Anders Askaner Chemical Production Manager**

- **Mr. Mikael Vikstrom Pharmaceutical Production Manager**

- Ms. Anna Gasste-Folkesson QC Chemical Analysis

A copy of the FDA-483 was made for each of the participants. Prior to reading each of the listed observations aloud, I invited management to feel free to ask any questions or make any comments during the reading. Management was informed that the listed observations were in my opinion deviations from Current Good Manufacturing Practices.

As a closing statement, Mr. Wiberg stated they would move to act on and respond to all observations in a timely manner. He added that the correction would be implemented within approximately 6 weeks.

Attached with this report are the following documents and copies of the FDA-483:

#4F -#5F -

#7F - Training record for SOP # Cl 173-091. Bolanderna Site

#1B - SOP # TUP 1-215-1 Documentation requirements; #2B - Complaint Logbook records;

#3B - Microbiological environmental control document

#3B.l- Microbiological control SOP # Cl 174-016/4; #4B - Typical employee training records;

EXHIBITS

Attachments

Description

A

B

C

D

Pharmacia organization chart;

Microbiological methods;

Methods of manufacture;

Formulation comparison between the Virgin Island & Uppsala tablet.

Exhibits

Description

Fyrislund Site

#IF - BI manufacturer's insert:

#2F - Validation of the

#3F - Typical microbiological records;

#10B~

Thomas J. Arista

Consumer Safety Offict

National Expert -'Biotechnology