DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 466 Fernández Juncos Avenue San Juan, Puerto Rico 00901 (787) 729-6801	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED To: Ms. Ileana Quiñones	PERIOD OF INSPECTION see last page	C.F. NUMBER 2650149
TITLE OF INDIVIDUAL General Manager	TYPE ESTABLISHMENT INSPECTED Human and Veterinary Drug Manufacturer	
FIRM NAME Schering Plough Products, L.L.C.	NAME OF FIRM, BRANCH OR UNIT INSPECTED same	
STREET ADDRESS Road No. 686 Km 0.5	STREET ADDRESS OF PREMISES INSPECTED same	
CITY AND STATE (Zip Code) Manati, Puerto Rico 00674	CITY AND STATE (Zip Code) same	

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. Failure to have adequate laboratory controls as follows:

a) the validation of analytical methods is not always established and documented. For example, there i no documentation showing that the Perphenazine Assay Stability method used for Trilafon injection ha been validated.

b) the Benzalkonium Chloride stability assay described in procedure 938.56.03 "Garamycin Ophthalmi solution stability procedure (AMS)" does not reflect the current practice as describe by laborator management. According to the procedure (part IV section D.2) the sample will be tested "as is' However, laboratory personnel described the sample to be tested as a composite of portions of sampl collected from the first, middle and last stages of the filling process. Nowhere in the cited procedure i described that the sample will be prepared and tested as a composite. Moreover, there is no documente evidence that the sample for Benzalkonium Chloride assay has been prepared and tested as a composit sample.

c) the procedure GMP 145.143.00 "Retest/Resample for out-of-specifications (OOS) or out-of guidelines (OOG) Results"and GMP 145.142.01 "Analytical Laboratories Investigations" do not defin the step that the analysts should perform when the re-injection of samples do not confirm the origina results. As explained by laboratory management the decision on what to do in these cases is made o the case to case basis and according to the supervisor and analyst judgment.

d) the firm does not maintain a backup file for the laboratory UV Spectrophotometers. As described i observation report 99-BIM-026 the UV absorption chromatogram for the re-preparation analysis o batches 9-CNX-123 & 9-CNX-218 (Banamine Solution) were lost. Due to the lack of a back up system these results could not be recovered. Additional preparations of the sample were necessary in order t give the batches a final disposition.

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e) there are instances where the firm laboratory practice to calculate Uniformity of Spray Content and Uniformity of Spray Content at Labeled Assay for Vancenase AQ Nasal Suspension and Nasonex is not adequate. At least in four (OOS) laboratory investigations the laboratory practice was to retest only the individual (OOS) results, at least in duplicate, in a run different from the original one. The results obtained are averaged and added to the original results as individual values.

rp: item #1 - UNDER CONSIDERATION

2. Failure to submit NDA Field Alert Reports within three working days, as follows:

a) after being aware that Trilafone Injection batch no. 8-AEC-3 failed the Perphenazine assay for the 12-month stability test interval.

b) after being aware that the following batches had failed the Benzalkonium Chloride assay at different stability test intervals:

Garamycin Ophthalmic solution batch 6-AMS-1.
Garamycin Ophthalmic solution batch 5-AMS-5.
Garamycin Ophthalmic solution batch 6-AMS-4.
~~Gentocin Ophthalmic solution batch 6-AMS-101.~~ rp: f.c.h 4-7-00

~~c) after being aware that reserve sample for Gentocyn Ophthalmic solution batch 5-AMS-107 tested as part of a complaint investigation, failed the Benzalkonium Chloride Assay.~~ rp: f.c.h 4-7-00

rp: item #2 - REPORTED corrected (by SOP implementation to address this issue) but not verified. f.c.h 4-7-00

3. Failure to adequately identify and control the length of time between the end of processing and each cleaning step during the cleaning validation of equipment used in the manufacture and filling of creams and ointments. In all but one of the cleaning validation processes approved the firm has used the first contact approach to establish the holding time of the dirty equipment.

rp: ITEM #3 - REPORTED CORRECTED BUT NOT VERIFIED

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4. Failure to always perform adequate analytical laboratory investigations into the causes of product out- of - specification (OOS) and atypical results as follows:

a) initial (OOS) and atypical results, obtained upon testing stability batches of Gentocyn and Garamycin ophthalmic solutions for Benzalkonium Chloride Assay (Investigations # 98-000241 and #98-000246), were invalidated based on the conclusion that an inefficient HPLC column was used to perform the test. However, there is no data to support this conclusion.

b) Investigation 99-f2-19 for Trilafone Injection stability batches #7-AEC-1 and 8-AEC-3 documented out-of -specification results for Perphenazine Assay. The results were invalidated "based on high variability due to considerable sample handling". In this investigation the firm did not consider the fact that the absorbance values obtained were outside the calibration range of the UV Spectrophotometer used to perform the test. Moreover, the firm failed to conduct a linearity test in order to demonstrate that the equipment was suitable at the specific range of the absorbances obtained.

item #4 - under consideration

5. Your firm release for distribution one lot of Banamine Solution (8-CNX-223) after demonstrating throughout investigation that the sterility of this lot is questionable. The product is a sterile parenteral used for veterinary purposes.

According to Observation Report 99-F-001, during the filling in-process inspection of Banamine solution lot 8-CNX-223 the "spot check" acceptance criteria was exceeded due to presence of particulate, mainly "green fibers". The same "green fibers" were observed in the micrometallic filters, a component of the filling equipment, when inspected at the end of the filling process. The investigation on this event showed that the source of the green particulate were green sponges used for the cleaning of the micrometallic filters. The use of these sponges is not part of the validated cleaning process for this equipment. This lot was placed on distribution except for that portion where "green particulate" was visually detected.

item #5 - under consideration

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f. the firm is using

6. ~~Failure to use~~ non-stability indicating methods to test products for which a stability indicating method has been developed and approved by the firm. For example: Diprolene Gel and Celestone Phosphate Injection.

¶ item #6 - under consideration

7. The firm release for distribution Vancenase AQ lots 9-~~THE~~-309, 9-~~THE~~-310 and 9-~~THE~~-311 which included pump assemblies that did not meet the Hexane extractable specifications for Irgaphos 168 of [redacted] mcg/g of pump. ¶ item #7 - under consideration

TGA ¶ TEH ¶ TEH ¶

to ¶

With respect IND #39250/000:

8. Failure to provide with documentation to support the use of TOC method as the most adequate method to detect cleaning residues (active ingredient) during cleaning validation of Ampligen product.

¶ item #8 - under consideration

With respect to NDA 20010/000:

9. The release specifications (946.85.10) for Betamethasone Dipropionate, USP do not comply with USP 23 Supplement 9 for other impurities. In addition, the firm failed to complete, in a timely manner, the change authorization proposal to add PQR HPLC methodology for chromatographic impurities and USP requirements for other impurities in test procedures and specifications.

¶ item #9 under consideration ¶

10. Failure to follow procedure EMP-PR 145.95.04, "Procedimiento Para Generar Perfil Anual de los Productos" (Annual Product Review) in that the firm does not always perform a review and evaluation of manufacturing data and other relevant information related to its drug substances. The annual product review for the following bulk substances ~~have~~ has ¶ not been discussed since 1996:

- Alclomethasone Dipropionate Micronized
- Betamethasone Dipropionate USP micro
- Betamethasone Sodium Phosphate

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- Dexamethasone
- Bethamethasone Micronized
- Bethamethasone Acetate
- Momethasone Furoate
- Betamethasone Valerate

wp. item #10 – under consideration

Dates of Inspection: 11/30-12/1,2,6,7,9,15,16/99, 1/24-27, 2/2-4,8,9,11,14-17,22-24, 3/1-3,6,8-10,24,28/00

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