DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
466 Fernandez Juncos Ave.
San Juan, PR 00901
(787) 729-6844

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED	PERIOD OF INSPECTION	C.F. NUMBER
TO: Ileana Quiñones	11/9-12/14/2000	2650149
TITLE OF INDIVIDUAL: General Manager	TYPE ESTABLISHMENT INSPECTED: Pharmaceutical Manufacturer	
FIRM NAME: Schering-Plough Products, LLC.	NAME OF FIRM, BRANCH OR UNIT INSPECTED: Same	
STREET ADDRESS: Ruta 686, Km 0.5	STREET ADDRESS OF PREMISES INSPECTED: Same	
CITY AND STATE (Zip Code): Manati, PR 00674	CITY AND STATE (Zip Code): Same	

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. Since February 1999 all stability testing of batches of Gentocin otic solution (Gentamicin Sulfate (3mg/ml) w/ Betamethasone Valerate (1mg/ml)) has revealed a contamination of the product in the form of an unknown peak in the Betamethasone Valerate assay. The investigation conducted by the firm concluded, in October 2000, that the product was contaminated with Dicyclohexyl Phthalate (DCHP) at a level of 5,800 ug/bottle (.77mg/ml). They also concluded that the DCHP was leaching from the adhesive used to adhere the label to the product container. There is no evidence that the firm has taken any action to ensure the safety and efficacy of the Gentocin otic solution and has continued to distribute the product with the label causing in the contamination. Furthermore, the firm has not determined the effect the leaching may have on other products, including Garamycin ophthalmic solution, which use labels with the same adhesive.

   The manufacturing process for Mometasone Furoate Active Pharmaceutical Ingredient (API) is not validated in that:

   a. There is no validation protocol for the specific process being validated.

   b. There were no predetermined specifications in that the procedures and specifications described in the validation report as being used during the validation effort are dated after the validation batches listed in the validation report were manufactured.

   c. Discrepancies between the in-process laboratory and the quality control laboratory regarding the observation recorded for the appearance specification for the Mometasone Furoate (MMF-E) were not investigated and resolved. The in-process laboratory recorded a result that fails the specification, and the quality control laboratory recorded a result that meets the specification.

   d. There is no scientific or statistical justification for the sampling plan used during the validation effort.

   e. The location and size of the analytical samples taken during the validation effort to support the validation are not described in the validation report.

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f. The sampling thief required by the sampling procedures was not used by the operators taking the in-process sample or even available to them. According to the operators, they used a small plastic spatula to sample from the top of the drum.

g. 30% of Mometasone Furoate lots manufactured in 2000 needed to be reprocessed in order to meet specifications.

3. The investigation conducted regarding the failure of five lots of Mometasone Furoate (MMF-E) API to meet specifications has not been completed. Lot O-MMF-E-6001 did not meet the specifications for appearance in March 2000 and was reprocessed. Since March 2000, four additional lots did not meet specifications and were reprocessed. The investigation as to why the process sporadically failed to produce Mometasone Furoate that meets its specifications has not been concluded.

Your firm's re-processing procedure for Mometasone Furoate (MMF-E) is not validated because:

a. there is no specific validation protocol for the process being validated

b. the general validation protocol used lists as the acceptance criteria "All reprocessed batches must comply with the Q.C. specifications for the product" even though the reprocess procedure is a duplication of a portion of the original process that yielded product that did not comply with the Q.C specifications for the product.

c. there is no justification for the sampling plan used to determine the re-processed product met specifications.

5. Antimicrobial Effectiveness (AE) Method Validation for Nasonex Nasal Spray (KTL) is not adequate, as follows:

a. there is no documentation showing the inclusion of negative controls and a gram stain of the test microorganisms as part of the validation.

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b. the test is performed using three media, Sabouraud Dextrose Agar, Potato Dextrose Agar and Trypticase Soy Agar. However, the confirmation of the inocula (positive controls) was performed by inoculating all the test organisms only in Trypticase Soy Agar

According to the firm, the AE method for the new product Nasonex Unscented Nasal Spray (MAA) is considered validated based on the AE method validation for KTL. This validation was completed on 3/96 according to protocol dated 12/85. On 12/98 the firm approved a new SOP (#947.71.00) for the AE method validation. Even when this new SOP includes the use of negative and positive controls as well as the gram stain of test organisms during the AE method validation, the firm has not revalidated the existing AE method for KTL.

Uniformity of Spray Content assay is not always representative of the lot being tested. For example,

a. The actuator of one of the units of lot 7-KTL-6 being tested for stability testing at the room temperature 18 month stability interval was replaced with a "control" actuator when the original actuator supplied with the unit did not yield results within specifications.

b. One of the units of lot 0-KTL-110 being tested for release testing was replaced with another unit when the analyst noticed that the "crimp closure" was not sealed properly causing the actuator to have a "slight inclination." An adequate investigation was not conducted to determine if the improperly sealed container/closure system extended to the rest of the lot and what corrective and preventive actions should be implemented.

c. One of the units of lot 0-KTL-124 being tested for release testing was replaced with another unit when the analyst noticed a defect in the crimp closure system. The unit was replaced with another unit from the same lot. An investigation was not conducted and corrective actions implemented to ensure other units in the same lot did not have the defect.

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. The analytical laboratory is instructed in Doc. No. 145.188.01, in the event of an Out-of-Specification (OOS) test result for the Uniformity of Spray Content for Nasonex that is attributed to a "possible" clogged actuator, to clean actuator with methanol and water. However, the product insert provided with the product instructs the consumer to clean the actuator with "cold water." For example, the uniformity of spray content at the labeled number of actuations test for lot 7-KTL-6 of Nasonex resulted in an OOS at the 24 month 25°C stability interval. The analyst was instructed to "remove he actuator tip, clean the tip with methanol and water and dry it with a stream of nitrogen. The result of the retest after the cleaning was within specification and was reported as the final result.

. The firm's retest procedure for Uniformity of Spray Content/Uniformity of Spray Content at Labeled number of Actuations, Doc. No. 145.188.01, allows the firm to retest units that generate OOS results without supporting information that reveals an assignable cause, or strong possible cause, for the initial OOS result.

. Your firm did not submit NDA Field Alert Report to the San Juan District Office within three working days, as follows:

. after being aware that Nasonex Nasal Suspension (KTL), batch No. 9-KTL-104 rendered above specification result for the osmolality test during the 15-month stability test interval, and;

. after being aware that lot 8-GMP-N-6002 of Gentamicin Sulfate API , which was used to manufacture Garamycin Ophthalmic Solution, did not meet impurity specifications at the 24 month stability interval.

0. The firm detected an unknown "spot" during the TLC identity testing of eighteen lots of Gentamicin Sulfate received from [redacted]. The firm's first corrective action was to change the TLC specifications from "Sample chromatogram agrees with reference standard chromatogram." to " The intensities and R_f values of the three principle spots obtained from the test solution correspond to those obtained from the Standard solution." Therefore, after this change, the firm could ignore a potential quality problem with the Gentamicin Sulfate even after the firm concluded that the fourth "spot" being detected "...is indicative of manufacturing process inconstancy and/or inadequacy of controls during processing."

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The firm's second corrective action to the detection of the fourth "spot" was to eliminate the TLC test which was detecting the impurity with the only justification being "elimination of a non-compendial tests"

The firm fails to follow procedure No. 145.144, Handling of Stability Samples, in that the initial testing of stability samples is not being completed within the month scheduled and within two weeks of receipt for accelerated stability samples. For example,

accelerated stability samples for batch No. 9-KTL-5, Nasonex Nasal Spray (15 months, 25°C) were submitted to the laboratory for weight loss determination on 6-7-00. The samples were weighed on 7-10-00 and final calculations and verifications of the results were conducted on 7-13-00. This lot expiration date was 5/00. Therefore, the weight loss test corresponding to the product's expiration date (15-month time interval) was performed and verified approximately two months after the batch expired.

accelerated stability samples for batch No. 0-WCA-301, Mometamax Ointment (3 months, 40°C), were submitted to the laboratory for weight loss determination on 6-19-00. The samples were weighed on 7-3-00 but calculations and final verifications were performed on 8-25-00.

stability samples for batch No. 0-FWBA-141, Integrilin Injection (3 months, 25°C), were submitted to the laboratory for stability testing on 10-19-00. Final verification of the results was conducted on 11-29-00.

addition, a delay form was not completed for batch No. 9-KTL-5, Nasonex Nasal Spray (15 months, 25°C) id batch No. 0-WCA-301, Mometamax Ointment (3 months, 40°C) as required in procedure 145.144 revision 1 ffective on 6-19-00). According to the procedure, every time the stability lead-time is not met, a delay form is to be completed.

OBSERVATIONS 1, 6, 7, 10 ; UNDER CONSIDERATION
OBSERVATIONS 3, 9 : CORRECTED BUT NOT VERIFIED
OBSERVATIONS 2, 4, 11: CORRECTIONS PROMISED
OBSERVATIONS 5, 8 : CORRECTIONS PROMISED BY 12-22-00

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