DISTRICT ADDRESS AND PHONE NUMBER

[redacted]

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 TO: Ileana Quinones	PERIOD OF INSPECTION 2/1-16/2001	C.F. NUMBER 2650149
TITLE OF INDIVIDUAL General Manager	TYPE ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer	
FIRM NAME Schering-Plough Products L.L.C.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS Route 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 I OBSERVED:

1. Your firm can not assure the processes used to manufacture finished pharmaceutical products can consistently produce product which meet their pre-determined specifications. For example,

a. The manufacturing process, including compounding and filling, for Gentocin Veterinary Solution 50mg/ml, 50 ml fill was validated using only one batch of [redacted] liters.

b. The manufacturing process, including compounding and filling, for Gentocin Veterinary Solution 50mg/ml, 10 ml fill was validated using only one batch of [redacted] liters.

c. The manufacturing process, including compounding and filling, for Gentocin Veterinary Solution 50mg/ml, 100 ml fill was validated using only one batch of [redacted] liters.

2.

d. The manufacturing processes for Afrin Severe Congestion, Afrin Sinus No-Drip Nasal Spray, and Afrin Extra Moisturizing No-Drip Nasal Spray were validated using one batch from each of the above products. Furthermore, the Afrin No-Drip Severe Congestion batch (0-SND-1) was rejected do to the a possible mix-up of units from lot 0-SND-1 and bottles filled with only water on the filling line when one of the units sampled for the validation revealed the bottle was filled with only water.

e. The manufacturing process for Nasonex Nasal Spray did not meet the acceptance criteria listed in the validation protocol when one of the samples taken from the compounding tank revealed a potency of 123%.

f. The process validated for Diprolene Cream is not the same as the process currently being used to manufacturer the product. Furthermore, the validation activity was conducted in June 1998 but the validation report was not approved until February 2001. The previous process validation for this product was conducted in 1997. Sample for both compounding and the finished product did not meet the firm's release guidelines. The firm changed their guidelines based on a review of previous batches. However, the batches still did not meet release guidelines, the firm then decided to evaluate and optimize the process.

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g. The process validation for Lotrimin Cream did not meet all the acceptance criteria listed in the validation protocol when one of the lots failed to meet in-process specifications. The firm deemed the process validated because the specification in question was not a "release specification." Furthermore, during the previous validation effort for Lotrimin Cream, the first batch did not meet specifications when an objectionable microbiological organism was found in the samples. The firm added a fourth batch to the protocol but only conducted the microbiological portion of the tested required by the protocol and not the chemical tests which are also required by the protocol.

h. The manufacturing process for Garamycin Injection has not been validated. Only two validation lots were manufactured and evaluated against validation protocol. P-SS-041 However, according to the firm approximately [redacted] additional lots have been manufactured and released since protocol was executed on 11/8/99. According to the current validation manager and the past validation manager, they do not know if the process was validated prior to 11/8/99 and could not locate any validation report prior to protocol P-SS-041.

2. 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 the firm has determined the effect the leaching may have on all other products, including AK Cide ophthalmic suspension and AK Sulf solution, which use the same container and label adhesive combination.

3. The firm detected a "fourth spot" in the TLC identity test for Garamycin Cream, lot 9-HB-1. The firm's tested one previous batch (5-HB-1) from its retain samples. The "fourth spot" was also present in this sample. The firm concluded "this extra spot observed could be characteristic in this product." However, there is no corroborating evidence to support this conclusion.

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4. The firm is not following their supplier qualification and audit procedures that require a audit of the supplier every two years . For example, the firm has not audited [redacted] which is a supplier of Oxymetazoline HCl; [redacted] which is a supplier of Clotrimazole USP nor [redacted] which is a supplier of Eptifibatide Diosynth BV. Out of the 42 suppliers of the list provided by the firm, 16 have never been audited and 4 have not been audited in the last two years.

5. Lot [redacted] of Diazoxide did not meet specifications for solubility in alkali. The laboratory investigation included generating an international change authorization to remove the solubility test from the specifications. The laboratory investigation then concluded the original out of specification result for solubility test was invalidated since it was not a requirement once the change authorization was approved.

6. The firm is not testing for impurities the following active pharmaceutical ingredients:

   a. Aurothioglucose Sterile Powder.
   b. Oxymetazoline Hydrochloride.
   c. Gentamycin Sulfate (Shanghai Fourth Pharmaceutical LDT, China).
   d. Eptifibatide Lyophilized Diosynth.
   e. Eptifibatide (Kromasil) Lyophilized Diosynth.

   For API Oxymetazoline Hydrochloride the Certificate of Analysis lacks impurity result nor Schering-Plough Manati perform impurity test.

7. The firm submission for Gentocin Solution, NADA # 38-292 dated December 18, 1996 included a Schering Plough's guideline for HPLC impurity limits for Gentamicin Sulfate study. A table dated 12/11/00 containing nine batches of Gentamicin Sulfate API received in 1999. This table shows that seven (7) of nine (9) batches failed one or more of the guideline impurity limits, but were released. The firm subsequently discontinued impurity testing and gathering impurity data.

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8. The firm does not perform identification of unknown degradation products and impurities for products that are listed under product quality review program. According to the USP impurities should be identified if they exceed 0.1% or greater. Examples of this practice are as follows:

a. Lotrimine Cream (Clotrimazole Cream USP) batch #9-KPE-405 unknown impurities result was 0.138%.

b. Diprolene Ointment (Betamethasone Dipropionate USP) batch #9-HYA-503/405 unknown impurities results were 0.420% / 0.372%.

c. Diprolene AF Cream (Betamethasone Dipropionate USP) batch #1-EEW-301/302 unknown impurities results were 0.32% / 0.64%.

According to the firm, the believe the impurities detected by the new impurity methods were always in the product at the same levels since the NDAs were approved. However, the firm has not provided corroborating evidence to support this "belief."

9. Batches of Gentocin Veterinary Solution were release even though they did not meet the release specifications for specific gravity test. Specific gravity specifications are [redacted] to [redacted] The firm's investigations concluded that the out of specification results are valid. In the investigation reports, the firm refers to a previous investigation in conducted 1998; however, the corrective actions from the 1998 investigation have not been completed. In the mean time, the firm has manufactured and released nine lots which do not meet the release specifications. Examples of this practice are as follows:

a. Batch No. 0-KMF-Comp.2 specific gravity result [redacted]
b. Batch No. 0-KMF-Comp.3 specific gravity result [redacted]
c. Batch No. 0-KMF-Comp.7 specific gravity result [redacted]

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10. Since 1998 the firm has been receiving consumer complaints concerning the spray delivery for Nasonex Nasal Spray. Consumer complaints have being increasing in the last three quarters of 2000 with a total of approximately 275 complaints in the year 2000 regarding the non-functioning of the drug delivery system . Despite this fact the firm still has not implemented a corrective action. The firm has not conducted an assessment concerning the safety and effectiveness of the product in that the problem with the spray delivery system can affect the dose release.

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