DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 466 Fernandez Juncos Avenue San Juan, Puerto Rico 00901-3223 Tel. (787) 729-6854	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Ricardo Zayas	PERIOD OF INSPECTION 5/1/01-6/13/01	C.F. NUMBER 2650149
TITLE OF INDIVIDUAL General Manager	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer	
FIRM NAME Schering-Plough Products, L.L.C.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS Road 686 Km 0.5	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Manati, Puerto Rico 00674-0486	CITY AND STATE (Zip Code) Same	

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Your firm's Quality Assurance unit lacks sufficient responsibility and authority to exercise the controls necessary to assure that consistent and reproducible manufacturing processes and controls are established and followed; that scientifically sound and appropriate product specifications are established; that scientifically sound and appropriate testing methods and procedures are established and followed; and that appropriate corrective actions are taken when process deviations or failures of product to meet established specifications occur for drug products manufactured by your firm. The Quality Assurance Unit also failed to assure that accurate and complete records of production and control activities were prepared and maintained appropriately and that timely, accurate and complete reports were submitted to FDA when appropriate. Some examples of the deficiencies which have not been adequately controlled by your Quality Assurance unit include the following

Data Accuracy and Integrity

1. Your firm does not have an adequate system for verifying the accuracy of production and control information to assure that oral and written information is consistent and correct. In addition, you do not have an adequate system to assure that relevant or required information is submitted to FDA in a complete, accurate and timely manner. The following are examples of incorrect, incomplete, inconsistent and untimely information obtained during this inspection and in your firm's communications with the Food & Drug Administration:

a) During this inspection, your personnel repeatedly informed FDA investigators that investigation into the source of benzophenone impurity found in Nasonex Nasal Spray included evaluation of stability samples for lots which were already distributed and within expiration date and also included testing of unlabeled bottles of the product. Your premise is that the benzophenone is leaching from the printed label, through the bottle into the product. Your personnel informed the investigators that test results for the stability samples and the unlabeled bottles found no benzophenone in these samples. When review of the test data was requested to determine the stability intervals tested and the methods used for testing, your personnel reported that the testing had never been performed.

b) Investigations into out-of-guideline (OOG) results for degradation products and impurities in Celestone Soluspan Suspension. Report that the guideline limit for [redacted] obtained at a RRT [redacted] is [redacted]%, and that for [redacted] e found at a RRT [redacted]%. However, an internal memo dated 3/5/99 indicates that the analytical [redacted] at a RRT of guidelines based on a review of a Product Quality Review (PQR) database for [redacted] has a [redacted] with a guideline specification of ≤ [redacted]. This memo also indicates th[redacted].

c) The investigation for Celestone Soluspan Suspension under MRB 20-010071 for lot # 1-AHU-2 indicates that the active ingredient with an OOS assay result was Betamethasone dipropionate. The formula for this product records that it consists of

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FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED — INSPECTIONAL OBSERVATIONS —

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the active ingredients of betamethasone acetate and betamethasone sodium phosphate.

d) Laboratory Investigation # 01-F2-03 for Celestone Soluspan Suspension batches 0-AHU-55 & 56 indicates that the day of the variance was 2/02/01. However, the investigation report was prepared and signed by two different persons on 2/05/00.

e) Laboratory investigation 01-F2-15 indicates on the front page that the investigation is related to batches 1-AHU-5 and 1-AHU-6. On this same page it discusses the out of guideline results for lots 1-AHU-3 and 1- AHU-4. The second page lists the results for lots 1-AHU-5 and 1-AHU-6.

f) You failed to maintain a photocopy/photo or any other suitable evidence that demonstrates that the TLC test for determination of impurity/degradants is being performed. Instead, a drawing of the alleged detected spots is made by the analyst and included in the record. There is no way to verify if the correct determination was made by the analyst. Examples are shown in the TLC test for:

(1) Celestone lots 0-AHU-52, 0-AHU-55, and 0-AHU-56
(2) Garamycin Cream lot 9-HB-1

g) You failed to have adequate security controls for your HPLC systems because your system, once accessed by one employee is left opened and available for other personnel to gain access to the original employee's analytical test reports. Analytical data generated by one employee can be reprocessed by another employee without the knowledge or consent of the original employee. For example, the analytical data generated for Celestone Soluspan Suspension, lots # 0-AHU-55 and 0-AHU-56 by one employee was invalidated and reprocessed by a second employee. The original employee denied knowledge of the reprocessing of the data. The computer record listed the original employee as sole owner of the record and did not indicate that any other individual entered or changed the record. There is no record to determine the identity of the individual who reprocessed the data.

h) Your failed to inform the FDA of a 4th impurity spot obtained in the ID test performed on Gentamycin Sulfate [redacted] lots # 990711431, 990912196, 990912197, 990912198 and #990912199 using the TLC method or that an additional 5th spot was also found in lot #990912199. Although these lots were rejected, lots #990410223, 990410225, 990410226 and 990610830 that also had the 4th spot were approved for use in manufacturing veterinary drug products. Even though you consistently found this 4th spot, you informed FDA of your intention to change your ID method from TLC to an HPLC method and did not notify the FDA about these additional spots. In addition, after making a commitment to FDA to identify and conduct toxicity testing on the substance found in the 4th spot, you selected batches 990610815, 990610902 and 990610904 which had less than 2% of the 4th spot for toxicity testing by an external laboratory and did not submit the batches with the 4th spot at 3% for toxicity testing. You still have not investigated the presence of the 5th spot.

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i) You failed to inform the FDA about a "fourth spot" found in the TLC ID test for Garamycin Cream, lot 9-HB-1, which is on the market and within expiration date (10/02). Laboratory investigation 99-F2-23 was listed in the previous FDA-483 (2/01) as being inadequate for lack of corroborating evidence that the fourth spot was characteristic of the product as stated in the conclusion of your investigation into this problem. You have not submitted a Field Alert Report notifying the FDA about this confirmed fourth spot in this marketed lot.

j) You failed to submit a NDA Field Alert (NDA 20-718) for lots 9-SBH-A-1, 9-SBH-A-2, 9-SBH-A-3, and 0-FWB-A-141 of *Integrilin Injections .75 mg/ml and 2 mg/ml* that failed the stability for the impurities A[redacted] and/or [redacted] at 6 or 18 months 25 °C or 30 °C interval.

In an initial Field Alert Report (FAR) to FDA, dated 5/10/01, you included an attachment of an internal memo dated 5/9/01, which stated that following replacement of a gasket in the filling machine for Celestone Soluspan Suspension, no further black specs were noted. This memo was the only information included in the FAR concerning excessive amounts of rejected vials of Celestone Soluspan Suspension due to visible particles. In an internal record of a telephone contact to FDA, dated 5/24/01, you record that you reported to CDER that, after replacement of the gasket on the filling machine, no additional lots of Celestone Soluspan Suspension had excessive reject rates for visible particulates. Our review of records during this inspection found that the gasket in question was replaced after the manufacture of lot 0-AHU-52 of the product. The following lots of this product manufactured after lot 0-AHU-52 had OOS reports due to excessive levels of visible particles, including black particles: lots # 0-AHU-54 and 0-AHU-56. Lots #1-AHU-7 and 1-AHU-8, manufactured in year 2001 also resulted with black specks and metallic particles. J 6/15/01

k) In the same FAR listed in ~~k~~ j above, you also stated that in an attachment entitled "Celestone Soluspan Suspension (AHU) Batch Segregation Protocol" that lot 1-AHU-8 passed the content uniformity test. You sent another copy of the same document, containing the same information, to FDA/San Juan District with a letter dated 5/17/01. Review of your OOS reports and investigations found that lot # 1-AHU-8 of this product also had OOS results for content uniformity. The original OOS results were invalidated without adequate justification and special test request was made to support disposition of the lot. In your record of the telephone conference with FDA/CDER mentioned in ~~k~~ j above, dated 5/24/01, you do not indicate that this information was reported to FDA/CDER. J 6/15/01

l) During the period from January 1999 to November 2000, your OOS results log book records over [redacted] OOS laboratory results for finished products and stability samples. During this same time period, only one FAR was submitted to FDA concerning the use of an incorrect pump on one product. Some examples of OOS results which should have resulted in FARs to FDA include the following: (1) Afrin Menthol Nasal Spray, lot 7-JBS-4 (36 months at 25°C) Benzyl alcohol assay below specification (Inv. 00-F1-31); (2) Diprolene Topical gel 0.05%, lot 6-RFH-503 (36 months at 25°C) Betamethasone Monopropionate assay above specification limits (Inv. 99-F2-24); and (3) Elocon ointment, lot 9-UHK-409 (6 months at 35°C) Mometasone furoate assay below specification (Inv.00-F4-017).

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m) You failed to inform the FDA during a conference call held and documented via a contact record dated 5/24/01, that although you had replaced the black gasket to which you attributed the black particles and the metallic particles with a blue gasket, you continued finding the black and metallic particles. Furthermore, you did not inform FDA that an additional Celestone Soluspan Suspension lot 1-AHU-8 had also resulted with uniformity OOS that was attributed to an unsupported conclusion of a weighting error of the analyst and not that a normal volume fill variability may have occurred due to that you don't have a validated process for Celestone Soluspan Suspension using the MAR-50 filling machine.

Process Validation

2. There is insufficient evidence to assure that the current processes used for manufacture of the products listed below will consistently produce a product meeting its predetermined specifications. In addition, none of the products cited during the previous inspection that ended on 2/16/01 for inadequate or lack of validation have been revalidated. Additional examples are as follows:

a) Celestone Soluspan Suspension:

(1) ~~In February of 1995,~~ In February of 1995 you performed studies to determine the optimum number of vials which should be removed at critical time points (start-up and after stoppages of 30 minutes or more) during the filling operation to prevent solution homogeneity problems. These studies were performed using a [redacted] filling machine and concluded that the optimum number of vials to be removed at these critical time points was [redacted] vials. Although the studies were completed in ~~February~~ ~~1995~~, the filling procedure, # 645.91, was not prepared until ~~July~~ 1996. In July 1996, the [redacted] filling machine was replaced with a [redacted]-filling machine. As a result of an MRB # 97-000167 it was determined that the optimum number of vials to be removed at the critical time points for the new machine was [redacted] and although a validation protocol was prepared to validate this new equipment Project PS96-42), the results of the studies were never reported in a summary report and the validation protocol was never executed. Procedure # 645.91.01 was never changed to reflect the necessary changes required by the new filling machine, although the title of the document was changed to identify that it was a procedure for the [redacted] machine rather than for the [redacted] machine. Furthermore you fail to have a complete Validation with the current batch size of [redacted] and the actual process (current)

(2) Although the procedure mentioned above continued to instruct the removal of [redacted] vials at the critical time points in the filling operation, all batch production records reviewed during this inspection for lots manufactured between November 1996 and November 2000 showed that [redacted] vials were removed at the critical time points during the filling operation.

(3) In November 2000, you recognized that the written filling procedure was not being followed and began to follow the written procedure, including removing of only [redacted] vials at the critical time points during filling of new lots of the product. Of [redacted] lots manufactured after November 2000 using the written procedure, two had OOS results for suspension homogeneity. Your investigation into these failures determined that the unwritten and unvalidated procedure for the [redacted] filling machine from 1996 indicated that 200 vials, instead of 72 vials should be removed at the critical time points and you

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again began to remove [redacted] vials at critical time points in subsequent lots.

(4) In order to verify that [redacted] vials was the optimum number to be removed at the critical time points for the [redacted] machine, in April 2001, you conducted a "validation exercise" using one lot of product and concluded that [redacted] vials was the correct number to be removed.

(5) During the time period from November 1996 to November 2001, when [redacted] vials were removed during the filling operation with the [redacted] filling machine, sporadic OOS results for solution homogeneity were obtained for some lots of the product.

(6) Lot 0-AHU-13 failed to meet the Benzalkonium Chloride assay specification on 5/19/00 with results of 84.85%. A retest in triplicate confirmed the OOS results with values of 76.3%, 77.7 % and 76.4%. Additional samples were tested obtaining passing results and the batch was released.

(7) You have been unable to identify the source of black specks containing metal particles found during visual inspections performed to batches manufactured from 1999 through 2001. ~~#~~ lots manufactured during this period had increased rejection rates due to visible particles. Although investigation into the problem was conducted from December 1999 to December 2000, the corrective actions recommended and implemented as a result of the investigation were not sufficient t resolve the problem. Lots # 1-AHU-2, 1-AHU-7, 1-AHU-8, 1-AHU-11 and 1-AHU-12, manufactured after the corrections were implemented, also had excessive rejection levels for visible particles. No additional investigation has been initiated to determine the source of the particles in the five lots manufactured after the corrective actions were implemented.

(8) You fail to demonstrate that you have control of the impurities that appear in Celestone Soluspan Suspension (lots #0-AHU-52, 53, 54, 55 & 56; 1-AHU-1, 2 3, 4, 5 & 6) at a relative retention time (RRT) of [redacted] (identified as [redacted] and at a RRT of [redacted] (identified as [redacted] and for which you do not have clear and defined specifications. When higher than normal values of these impurities were found in the above mentioned lots, the corrective action was to discontinue monitoring for them in finished product samples with the explanation that they were process related impurities and would be monitored only during the drug substance testing. The information provided during the inspection to support this decision is inadequate for the following reasons:

- You fail to have data demonstrating that these impurities/degradants are currently being monitored as part of a bulk drug substance stability program.
- There is no explanation for the increase in the levels of these impurities in these lots of finished product.
- There is no data to support the conclusion that both impurities in the finished product are the same impurities found in the drug substance.
- The investigation also did not consider that in many of the finished product lots with out-of-guideline results for these impurities, the amount of the impurities detected in the finished product was higher than the amounts detected in the drug substance used to manufacture the finished product lots.

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- For example,
  Betamethasone acetate sterile powder batch 00I04-12 BE-Q-00-AFZA-12 had a result of "Not detected" for [redacted] (RRT [redacted]). This drug substance was used in lots 1-AHU-1 thru 1-AHU-5 which resulted with impurity values of:

  Lot 1-AHU-1 = 0.127% through 0.135%
  Lot 1-AHU-2 = 0.145% through 0.182%
  Lot 1-AHU-3 = 0.157% through 0.164%
  Lot 1-AHU-4= 0.155% through 0.158%
  Lot 1-AHU-5= 0.155% through 0.175%

  Betamethasone acetate sterile powder lot # 00118-14 - BE-Q-00-AZFA-14 also had a result of "Not Detected" for the impurity [redacted] However the following lots manufactured with this drug substance resulted with higher levels of the Impurity:

  Lot 1-AHU-5= 0.155% through 0.175%
  Lot 1-AHU-6= 0.167% through 0.17

- An internal memo dated 3/5/99 indicates that the analytical guidelines based on a review of a PQR database for Betamethasone acetate reports that [redacted] has a RRT of [redacted] and that [redacted] has a RRT [redacted].

- The environmental samples collected during the validation performed in 1995 with the previous filler show the presence of 1 CFU of Pseudomonas vesicular in the stopper hopper. In addition, 13 CFU of Staphylococcus sp. were obtained from the employee's glove.

b) Betasone Suspension 5/2 mg/ml

No validation for the current manufacturing process with the [redacted] filling machine has been performed.

c) Solganal Suspension 50 mg/ml

No validation for the current manufacturing process with the [redacted] filling machine has been performed.

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d) Afrin Sinus Congestion No Drip, Afrin Severe Congestion No Drip and Afrin Extra Moisturizing No Drip Nasal Spray:

(1) The manufacturing processes for each the above products were validated using only one (1) lot per product. Furthermore, the Afrin No Drip Severe Congestion lot 0-SND-1, the single validation batch was rejected due to a possible mix-up of lot 0-SND-1 with bottles filled with only water on the filling line. Even though this observation was presented to you during the previous inspection you continue releasing products to the market without performing any re-validation of the filling process.

(2) You also failed to establish specifications for the degradants/impurities for the Afrin No Drip Nasal Spray and Afrin No Drip Extra Moisturizing. There is an increase in the degradant A and peak #6 levels in Oxymetazoline Hydrochloride assay in recent lots such as 0-TRJ-1 (12 mo. @ 25°C), 0-LKA-5 (9 mo. At @ 25°C), 1-LKA-3, and 1-LKA-4; however, there are no investigations related to the increase of this degradant.

(3) You fail to have a weight change specification for stability testing of Afrin No Drip Nasal Spray. During the stability testing of lot 0-LKA-6 (9 mo. @ 25°C), a difference of 8% in weight change was obtained for unit nine (9) and no investigation was performed.

e) Optimmune Ophthalmic Ointment

You changed the source of the active drug ingredient and validated this change with only one lot of the above product.

f) Integrilin Injection

Validations for Integrilin Injection process changes do not provide a high degree of assurance that these revised processes are capable of consistently produced products that meet pre-determined specifications and quality attributes for the following reasons:

(1) Only one lot was executed to perform the following change validations:

- P-SS-051 [Validation of Integrilin Injection, 0.75 mg/mL, [redacted] L Batch size, Using Active Ingredient [redacted] an alternate supplier, purified with the new [redacted]]
- P-SS-052 [Validation of Integrilin Injection, 2.0 mg/mL, [redacted] L Batch size, Using Active Ingredien[redacted] (an alternate supplier)]
- P-SS-046-P [Validation of Integrilin Injection, 0.75 mg/mL, [redacted] L Batch size, Using Active Ingredient [redacted] an alternate supplier], the validation consisted of an evaluation of one executed batch only.

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(2) For P-SS-053-P [Validation to establish 48-hours holding time period for Integrilin Injection 2.0 mg/mL, batch size [redacted] L], only 5 liters of the bulk solution were retained for the 48-hour period in the holding tank as opposed to the [redacted] L normal batch size.

g) Vancenase AQ Nasal Suspension:

You failed to conduct viscosity testing during the validation of Vancenase AQ Nasal Suspension 0.084% or provide written scientific justification for not conducting this testing.

6/15/01 ED 0.084%

Revalidation of Vancenase AQ Nasal Suspension ~~0.84%~~ compounding and filling process to eliminate an overcharge for both the active (Beclomethasone dipropionate) and the preservative (Phenylethyl Alcohol) was performed using only one lot of product. Numerous complaints ([redacted] during year 2000-2001) related to this product have been received.

h) Nasonex Nasal Spray:

(1) During the previous inspection, the process validation for Nasonex Suspension 0.5% was cited as being inadequate because samples of one validation lot collected from the compounding tank revealed a potency of 123% for Benzalkonium chloride. In addition, an addendum to the summary report of validation reports that assay results near the lower specifications were obtained in lot 9-KTL-104, and unknown and atypical impurity peaks were observed in the estimation of degradation product assay for this lot. You continue manufacturing and releasing the product for distribution without performing a re-validation.

(2) [redacted] complaints for Nasonex Nasal Spray were received during the period of 2000-2001. Most of the complaints are related to a problem with the pump delivery system. Additional indications of a delivery problem are reported in test results for the finished product prior to release. For example:

On 12/02/00 one of the units of Nasonex Nasal Spray lot #0-KTL-128 tested for Uniformity of Spray Content at label assay had an OOS result of [redacted] mcg weight per actuation. The investigation indicated that there is a high probability that agglomerate was present in the actuator. However, there is no indication that the manufacturing or delivery system was evaluated to assure that patients consistently receive the intended dose of the drug.

In a variance report dated 5/7/01, Nasonex Nasal Suspension lot 1-KTL-116 resulted with spray patterns rendering a non-conforming result. To correct delivery failures, your investigation summary recommends that the actuator be removed, cleaned with methanol and dried with a stream of nitrogen to correct delivery problems during testing. This modified procedure is not part of your validated delivery process. Furthermore, this modification is not feasible for patients using the product.

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Reprocess

3. You changed your manufacturing process for sterile products by including a re-filtration process of different products when the filters used in the aseptic filtration failed to meet the filter integrity test. A determination of the impact of the re-filtering of the products is not performed. Furthermore, this operation is not approved for the below products in their respective NDA applications. An investigation focused on a determination of the cause of the integrity failures is not performed. Examples are lots 0-AMK-Comp-6/Garamycin Injection, 0-AHU-Comp-2/Celestone Soluspan, 0-AHU-Comp-34/Celestone Soluspan Suspension, 0-RKP-Comp-20/Nuflor Injection, and 1-BEX Comp-4/Bacteriostatic WFI.

Microbiological Controls

4. You fail to have adequate microbiological controls in your sterile process operations as evidenced by the following:

a) You lack adequate validation of your cleaning and sanitation process for the different filling areas to assure compliance, adequate microbiological controls and a minimum risk of contamination of the products processed aseptically in sterile filling rooms 48, 49, 52, 55, 56 and 68. Indications that you lack environmental controls and therefore may be compromising the sterility of your products were observed. For example:

(1) During year 2000-2001 the presence of Penicillium sp. and other microorganisms have been detected in different sampling points locations of the above rooms such as: the middle of the room, near the empty vials, near and above the filling nozzles, area of the stoppers, near the filtration area and on the employees gloves and a revalidation has not been performed. In addition, no investigations were performed to determine the actual source of the organisms and eliminate the potential risk of contamination.

(2) Manipulative and environmental samples collected during 12/26-28/00 resulted in alert limits. Penicillin sp., and Staphylococcus sp., other than S. aureus, were isolated. Lots 0-SRB-C-44/final lot 0-SRB-46/ Bacteriostatic WFI, 0-KPR-118/Nuflor, and lot 0-ANG-9/Gentocin Durafilm Ophthalmic Solution were manufactured during this period. The investigation concluded that the possible cause for the contamination for the sample collected during 12/26-28/00 was that the media was contaminated. Testing of the plates found the organisms Cladosporium sp. And Acremonium sp. in the unused plate media. These organisms are different from the organisms isolated in the samples and no justification for the assumption that the plates were contaminated with the organisms found in the environmental samples was available.

(3) On 3/6/01, 5 CFU of Penicillium sp. were detected near the empty vials in room 49. On 3/6/01, 20 CFU of Penicillin sp. Were detected near the filling nozzles of room 48. On 3/6/01, 15 CFU of the same organism were also detected in the center of the filling room 48. On 3/6/01, 6 CFU of Penicillium sp. were also detected near the filling nozzles of room 56. On 3/10/ 01, 5 CFU were detected near the filling nozzles of the filler in room 49 and on 3/19/01, 62 CFU were reported in

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 466 Fernandez Juncos Avenue San Juan, Puerto Rico 00901-3223 Tel. (787) 729-6854	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Ricardo Zayas	PERIOD OF INSPECTION 5/1/01-6/13/01	C.F. NUMBER 2650149
TITLE OF INDIVIDUAL General Manager	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer	
FIRM NAME Schering-Plough Products, L.L.C.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
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room 68, above the filling nozzles. A result of 120 CFU of the same organism had also been reported in room 48 in a sample collected on 7/6/00.

(4) A variance investigation report (No. 01-GIR-205) related to environmental samples of viable particles on gowning and non-critical surfaces collected during 2/23/01 through 4/30/01 is inadequate. This investigation attributes the OOS growth detected to possible contamination of the media plates through improper handling. The organisms found in the samples, Penicillin sp and Aspergillus predominated in all the environmental samples. Bacteria such as Micrococcus sp., Bacillus sp., Gram positive bacilli non-spore former. Pichia mexicana, and Candida parasilopsis were also isolated. The manipulative control plates for gowning also showed growth of Penicillium sp., and Micrococcus sp. These organisms have been found previously in the aseptic area samples. The investigation states that although contaminated plates were observed in the lots received during Nov. 2000 through April 2001 these were accepted with the exception of lot TSA 10173333A, because a [redacted]% of the plates received were contaminated. There is no justification recorded for the use of plates that were contaminated upon receipt in the laboratory. Attributing the contamination to the plates to improper handling cast doubts upon the adequacy of your inspection procedure for medium/plates received and used. The investigation is also inadequate (section 22.0) because it states that non-critical surface samples and gowning samples are not criteria necessary to accept a lot. Therefore, you approved batches 1-SRB-7, 1-CNX-202, 1-AHU-5, 1-AHU-7, 1-CJR-105 and 1-RKP-206 even though questionable results had been obtained. In addition, results at the alert or action limits for non-critical surface samples and gowning samples obtained for the following lots: 1-BEX-C , 1-RKP-C-4, 1RKP-208, 1-SRB-11, 1-SBHA-4, 1-RKP-9, 1-AEC-2, 1RKP-101 and 1-SRB-13, were also not considered as an acceptance or rejection criteria for these lots. Therefore you fail to demonstrate that you have total control of your environmental conditions and release products to the market even though you have environmental samples that demonstrate that the lots may have been at risk of becoming contaminated.

Furthermore, samples for viable particles collected during the filling of lots 1-SRB-7, a-CNX-202, a-AHU-7, 1-CJR-105, 1-AHU-5 and 1-RKP-206 were observed in the action limit. In addition, [redacted] of the [redacted] operators that participated in the filling of lot # 1-SRB-7 resulted in the action or alert limit for the gowning environmental sample. [redacted] of the [redacted] operators that participated in the filling of lot 1-CNX-202 resulted in the alert limit for the gowning environmental test.

In addition, you show lack of microbiological control by indicating that since Penicillin sp. And Aspergillus sp. were isolated in these dates (2/26/01, 03/08, 03/12/01, 03/22/01, 04/04/01, 04/20/01 and 04/23/01) it is expected that these fungi remain in the room environment and found in subsequent samples collected.

Your investigation is also inadequate and questions your justifications for release of lots 1-SRB-7, 1CNX-202, 1-AHU-5, 1-AHU-7, 1-CJR-105 and 1-RKP-206. The release of these lots was based on a passing sterility and LAL test. However, you fail to demonstrate that you had adequate

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environmental controls during the manufacture of lots 1-SRB-7, 1-CNX-202, 1-AHU-7, 1-CJR-105 and RKP-206 for which alert or action limits were obtained. Furthermore, you indicate that the results don't compare with the result historically found.

4. b) There is no assurance that your Water for *Injection* (WFI) *system* has been properly qualified in that continuous problems in maintaining the required temperature are encountered. For example:

(1) On 2/03/01 the WFI loop pump BP-216 was shut down (inconsistent pump performance) causing the temperature of the WFI loop to drop from the required 80°C to 48°C. The investigation indicates that this was an isolated case for year 2001. However, on 2/15/01 pump BP-217 was shut down due to a power failure causing the temperature in the WFI loop to drop from 80° C to 54°C. On 3/7/01, the temperature in the WFI loop dropped from 80°C to 55°C. The DW 80 loop dropped to 60°C and the DW 60 loop dropped to 33°C. Again, on 3/28/01 the water temperature in the WFI loop dropped from 80°C to 60°C. On 4/11/01 the WFI loop dropped from 80°C to 78°C.

(2) The WFI samples collected on 9/12/00 and 9/13/00 from the use points # FS-623 ([redacted]still that supplies water to 60°C and 80°C water loops) and BV-909 (supplies water to sterile compounding), respectively were not tested for LAL. The impact of the lack of test in any of the products manufactured during this period is unknown. Furthermore, this investigation has not been approved or closed.

4. c) The media fills performed during year 2000 and 2001 do not simulate the product's exposure time during your normal production. For example:

(1) Media fills 0-MF-22 & 1-MF-3 performed on 9/6/00 and 2/7/01 for line 2 do not represent or simulate your current manufacturing process and conditions. The media fills were performed within normal operational conditions. On 11/28/00 Integrilin Injection, lot #S0300A1 started its filling process at 2:35 p.m. At 5:00 p.m. the process was stopped because of a possible low fill problem. As a result of this situation the filling line was disassembled and assembled again on 11/29/00. After the assembly of the filling line the batch started to be filled again. Then to "assure" operational conditions the filling line equipment was disassembled cleaned, and sterilized. Then on 9:50pm of 11/29/00 the third portion of this lot started to be filled. The filling process ended at 12:20 am of 11/30/00. None of the media fills performed during year 2000 or 2001 simulate this extra handling and conditions. Furthermore, you have no study to support the holding time period to which the compounding # 0-SBH-C8, divided into lots #S0300A1, #S0300B1, #S0300C1, was exposed after it was aseptically filtered. The investigation report into

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this incident incorrectly states that the compounding exceeded the validated holding time of [redacted] hours. You have no validation of a [redacted]-hour holding time period for your Integrilin Injection compound. In addition, the [redacted] samples of the compounding sent to the laboratory for a sterility test were not tested.

(2) Media fill # 1-MF-4 for filling line # 1 had a filling time of 10 hours with 35 minutes. However, Integrilin Injection lot # TO334A1, filled on this line on 2/24/01, had a filling time of 13 hours and 50 minutes;

(3) Media fill # 1-MF-3 for filling line # 2 had a duration or media exposure time of 11 hours and 55 minutes. However, Bacteriostatic Water for Injection lot #1BEX101, filled on this line on 3/22/01 had a filling duration of 15 hours with 30 minutes;

(4) Media fills 1-MF-7 and 1-MF-8 for filling line # 6B, performed on 2/14/01 and 2/16/01, had a filling duration of 4 hours and 55 minutes, and 8 hours and 10 minutes, respectively. Optimmune Ophthalmic Ointment lots 1MBK1 and 1MBK2, filled on this line on 3/08/01 and 3/14/01, had a filling duration of 18 hours and 55 minutes and 15 hours and 45 minutes, respectively.

(5) Media fill 1-MF-8 also failed to meet the non-viable particulate test specifications ([redacted] particulates in 5/minutes/ft^3) for the sample collected from above the filling needles. The sample resulted with [redacted] particulate in 5 min./5 ft^3. Even though this media fill was executed on 2/14/01, you have failed to conduct an investigation to determine the cause.

4. d) Environmental samples are not collected as required. For example:

(1) During year 2000 no sampling of air or critical and non-critical surfaces in the controlled areas where sterile products are manufactured was performed. As of 6/5/01, an investigation has not been generated to determine why no samples were collected during this entire year.

(2) You failed to follow SOP 950.08.14, Surface Sampling in Aseptic Areas (translation), in that the microbiological environmental samples of the critical surfaces (filling needles) were not collected at the end of the filling process of Ocuclear Ophthalmic Solution lot 0-CJR-110 filled on 11/27/00.

(3) Investigation 00-GIR-138 states that the environmental samples for viable and non-viable particles were not collected at the end of the filling operation of Celestone lot 0-AHU-54. This same lot was also found out of limits for black specks during the visual inspection.

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(4) The Variance Report Logbook also indicates that Variance Investigation Report 01-GIR-120 is related to the failure to conduct environmental sampling in controlled areas. No investigation has been performed and no lots are identified as being affected. A Preliminary Variance Investigation Report also indicates that some air and critical surface samples were not collected during the period of February 1-15, 2001 as part of the environmental samples in controlled areas.

4. e) Your determination of your filter laminarity and air flow in your filling rooms is inadequate in that the determination is not a dynamic exercise. None of the employees normally present during routine operations were present during the evaluations to determine if the laminarity and air flow is affected by the presence of the [redacted] employees that are normally present in the room during a production. In addition, you fail to have evidence (e.g. video) to demonstrate that the smoke test was adequately executed.

4. f) You fail to have validated holding times for your sterile products after the products are filtered. Examples of the above are as follows:

(1) On 11/28/00 *Integrilin Injection*, lot #S0300A1 started its filling process at 2:35 p.m.. At 5:00 p.m. the process was stopped because of a possible low fill problem. As a result of this situation the filling line was disassembled and assembled again on 11/29/00. After the assembly of the filling line the batch started to be filled again. Then to "assure" operational conditions the filling line equipment was disassembled cleaned, and sterilized.. Then at 9:50pm on 11/29/00 the third portion of this lot started to be filled. The filling process ended at 12:20 am on 11/30/00. Investigation into this incident incorrectly states that the compounding exceeded the validated holding time of [redacted] hours. You have no validation of a [redacted]-hour holding time period for Integrilin Injection compound. In addition, the four samples of the compounding sent to the laboratory for a sterility test were not tested.

(2) A holding time study for Integrilin Injection documented under report P-SS-053-R with a final Approval date of 5/8/01 is inadequate because it was performed with only 5 L of portions of Integrilin compound. The actual batch size of an Integrilin compound is [redacted] L.

(3) Garamycin 0-AMS-101 was aseptically filtered on 12/15/2000 and filled on 12/19/2000. No Holding time validation for this amount of time (4 days) is available.

(4) Gentocin Durafilm Ophthalmic Solution lot 0-ANG-9 was aseptically filtered on 12/22/00 and filled on 12/26/00. No holding time validation for this amount of time (4 days) is available.

(5) Ocuclear Ophthalmic Solution lots 0-CJR-110 and 0-CJR-111, filled from the compounding lot #0-CJR-C-8, were aseptically filtered on 11/22/2000 and not filled until 11/27/2000 and

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11/28/2000. No validation for this holding time of 5 and 6 days is available. In addition, the environmental swab sample of the critical surface in direct contact with the product (filling needles) were not collected at the end of the filling operation as required by SOP GMP. PR 950.08.14, Sampling of Surface in Aseptic Pharmaceutical Area (translation).

4. g) You fail to test for sterility and LAL at the 24-month and other stability intervals as required. Examples are as follows:

(1) Variance Investigation Report #01-GIR-224, dated 5/4/01 (unsigned), indicates that Nuflor Injection, lot #9-RKP-301 was not tested for Sterility and Pyrogens (LAL) at the 24-month interval because the samples were misplaced and discarded by error.

(2) Variance Investigation Report #01-GIR-225, dated 4/2/01 indicates that Azium Solution lot #8-AGJ-1 was not tested for sterility at the 24-month interval. Furthermore, even though the test was scheduled for 2/10/01 and you noticed that a test had not been performed on 3/01, you still decided not to conduct a sterility test to assure that the product had remained sterile.

(3) Variance Investigation Report # 01-GIR-227, dated 4/17/01 indicates that on 2/8/01, Celestone Phosphate Injection, lot #7-AKP-1 was sent to the lab. (42 months from date of manufacture) because no sample was delivered to the laboratory for analysis at the 36-month expiration period.

(4) Your Variance Report Logbook also indicates that Variance Investigation Report # 01-GIR-106, dated 2/13/01, is related to another LAL test that was not performed to a WFI point. No investigation has been performed.

4. h) When samples are not available, assumptions are made that results are within specifications even though there is no evidence to support this assumption. Examples are as follows:

(1) Assumption that a swab test that was supposed to be collected on 8/13/00 from a critical surface (#48-5) after the filling of lot 0-KPR-109 resulted with 0 CFU was made even though there is no documentation to confirm the results. You conclude that because the sample was not sent to the ID lab the result was 0 CFU (Variance Report 00-GIR-012).

(2) Variance Report # 01-GIR-027 (dated 01-16-01) indicates that although you have no evidence to demonstrate that the positive controls resulted in positive results, these were positive because the analyst certifies that they were positive.

(3) Variance Report # 01-GIR-040 indicates that a sample collected on 12/18/00 from Room 56, point # F-8 (next to the filling machine) during the filling of lot 0-SRB-43 (Bacteriostatic Water for Injection) was lost. One (1) CFU was

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obtained but the organism could not be identified because the sample was lost. The investigation indicates that although one (1) CFU was obtained it was within the normal limit established. There is no indication if the organism found was a Gram negative or positive bacterium.

4. i) On 11/16/00 you used stoppers with expired sterility dates to fill 6,299 units of the vials for batch 0-RKP-117 (Nuflor Injection). A Variance Investigation Report has not been finalized. A preliminary investigation was prepared a month after the incident, dated 12/29/00.

j) You actions taken after obtaining water samples above your action limit of ≥ [redacted] CFU are inadequate. On 5/13/00 a water sample collected from point BV-709 (sterile compounding area) resulted with 82 CFU. Although you acknowledge that the cause of the contamination was not determined, lots 0-KMF-201, 0-CNX-104, SO244A1, 0-ANG-3, 0-AHU-16 manufactured with the contaminated water were released. Furthermore, other points (BV-310 and BV-707 corresponding to DW 80°C loop also resulted with the same organism. Furthermore, the conclusion indicates that the QC inspector who took the samples is relatively new to this task and has no aseptic techniques training. None of the samples collected by the same QC analyst which resulted in compliance were questioned.

k) Your microbiology laboratory Observation Report 00-BIM0027 dated 5/24/00 is inadequate. The bioburden test for Gentocin Solution (Veterinary (100mg/ml) lot 0-BNP-Compound 12 resulted in 81 CFU (action level [redacted] CFU/100 ml). Two samples were collected on 4/6/00 (Mixer tank BT-151) and 4/7/00 (sample taken from approximately 24 hours after pre-filtration through a 0.22 µm filter after compound). No intergrity test was done to the filter. The sample collected from the mixer tank tested by SDA resulted with 81 CFU/100 ml (Candida parapsilosis). The sample collected from after the pre-filtration resulted by method MCTA with 168 CFU/100 ml and by SDA and estimate of 250 cfu/100 ml (Gram positive bacilli non-spore former). The investigation is inadequate because it shows no evidence as to why you conclude that the source of the contamination originated in the laboratory.

Failure Investigations/Corrective Actions:

5. Your laboratory investigations are inadequate in that atypical and unexpected analytical results are invalidated without adequate investigations which include examination of possible causes for the problem, determination of the root cause of the problem, possible involvement of other lots of the product or other products, and appropriate corrective actions to prevent recurrence of the problem. For example:

a) On 4/16/01 Celestone Soluspan lot 1-AHU-8 failed to meet assay (suspension uniformity) specifications for both active drug ingredients (Betamethasone Acetate and Betamethasone Sodium Phosphate) with results of 123.6% and 127.3, respectively (specs. [redacted]). Investigation #01-F2-18 attributes the OOS to a possible error in recording the entry weight of the sample by writing it as 21.0435g instead of 22.0435g. No reason was given for the assumption that the sample weight was recorded incorrectly. Similar variability in sample weight was observed in other vials which had analytical results which were within

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specifications. The analytical results for these samples were not questioned or invalidated.

b) MRB #20000287, dated on 9/01/00 and related to a sample of Celestone Soluspan Suspension 0-AHU-32 showed OOG results for Betamethasone Acetate and did not meet the RSD criteria for stage II suspension uniformity assay for Betamethasone Acetate. A re-preparation was tested and resulted with values of 89.9 % (3/5th), 88.69 and 86.40 %. The investigation indicates "Although the re-preparation results confirmed the initial results, it were not considered for the stage II evaluation. No justification was recorded for invalidation of the original results.

c) Investigation into unknown peaks found in several lots of Nasonex Nasal Spray concluded that the unknown peak was benzophenone, and that the source of the peak was the leaching of benzophenone from the printed label, through the bottle into the product. A summary of the investigation and your conclusions was submitted to the FDA via a letter dated 5/3/01. The information obtained from your investigation was inadequate to prove the conclusion for the following reasons:

- You failed to test unlabeled filled bottles to determine whether the impurity was present when there was no label on the bottle.
- You also failed to test any retain or stability samples of the lots which were within expiration and already distributed to determine if the impurity was present in other lots of product on the market.
- You failed to test all the lots of Nasonex distributed with the label which was the alleged source of the benzophenone impurity.
- You failed to determine the actual times in relation to the age of the product when the impurity was being found.
- You failed to evaluate your process and bulk drug synthesis.
- This same impurity was also found in two other products (Lotrimine and Gyne-Lotrimin Cream) manufactured at your facility. These products are packaged in metal tubes and do not use the same type of label as the Nasonex Nasal Spray. You failed to evaluate if there was any relation between the Benzophenone found in Nasonex and the Lotrimin and Gyne-Lotrimin Creams (Clotrimazole Cream 1%). Furthermore, you are aware of the presence of Benzophenone in your products containing Clotrimazole since prior to 1/28/98, when internal guidelines were established for Lotrimin Cream 1%. However, the stability records for Lotrimin Cream/Gyne Lotrimin & Femcare Vaginal Cream shows that there are no established specifications for this impurities and that it is being monitored for information only.
- Only one (1) lot with the new replaced was entered in the stability program.

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- An internal communication dated March 01, 2001 in which your firm states that the benzophenone responds poorly when tested by LC/MS and that your firm was unable to confirm the presence of Benzophenone in batch 0-KTL-112 by LC/MS although the impurity was found in this lot when it was tested by HPLC/DAD. LC/MS was used to perform the study determining the presence of benzophenone to verify that it was leaching from the product labels.

- Only six (6) lots were tested as part of the investigation.

- Unspecified impurity peaks have been found in complaint samples received since 1999. Furthermore, a complaint investigation related to the ineffectiveness of lot 0-KTL-102 (mfg. 2/4/2000) received on 8/21/00 indicates that the product had shown a result of 0.14% of the impurity. There is no indication of what may have caused the increase of the impurity.

- The label used on the Nasonex Nasal Spray has not been changed since 1997, however your firm has not notified FDA of any findings of this impurity in previous lots of product.

5. d) In an investigation into a "fourth spot" found in the TLC ID test for Garamycin Cream, lot 9-HB-1, which was re-opened after the FDA-483 for the inspection of February 2001 listed it t as being inadequate for lack of corroborating evidence that the fourth spot was characteristic of the product as stated in your conclusion. You conducted a subsequent laboratory study on 2/28/01 that shows that the fourth spot possibly comes from the excipient [redacted] and not from the active ingredient. However, you have not conducted the "placebo test" as committed in your response to the FDA-483 to confirm that the fourth Spot comes from this excipient.

5. e) You failed to determine the cause of the increase of impurity M in Gentamycin Sulfate. Even though the cause of the increase is unknown you are proposing to change the specifications from [redacted]% to [redacted]%. This new specification does not assure that your lots of Gentamycin Sulfate will be in compliance. For example, lot 9-GMF-N-6017 resulted with a 2.20% and re-test results of 2.26%, 2.25% and 2.25% (MRB 20-000075/ Lab Inv. 00-BU-005).

f) Your Laboratory Investigation for Celestone Soluspan Suspension lot 1-AHU-2 and MRB #20-010071 show a discrepancy in the active drug ingredient that failed to meet the uniformity specifications. The above MRB indicates that the active ingredient is Betamethasone Dipropionate. However, Laboratory Investigation #01-F2-11 for the same product indicates that the active ingredient that failed uniformity is Betamethasone Acetate.

g) You invalidated an assay OOS result of 113.66% (re-injection 113.48%) for Elocon Ointment lot 1-UHK-303 in Lab. Inv. # 01-F4-012, even though you had no conclusive evidence to demonstrate that an inadequate sample preparation had occurred.

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h) You invalidated the initial atypical analytical data for Betamethasone Acetate and reported the data obtained from a new sample preparation for the stability testing at 12 month 25 °C interval for Celestone Soluspan Suspension, batch 0-AHU-1, on the basis of an unconfirmed assumption that the atypical results were due to a problem with the original sample composite (Lab Inv. # 01-F2-12). There was no information available in the investigation report that supported the premise that the composite sample was prepared incorrectly.

i) *In Lab. Inv. # 01-F3-013, you invalidated the initial and confirmation uniformity of spray content assay results of* Vancenase AQ Nasal Spray lot 9-TEH-326, tested as a result of a consumer complaint. The first actuation tested on 3/14/01 resulted in a value of 126.6%. A re-injection of the same vials tested on 3/16/01 confirmed the initial result with a value of 133.7%. A triplicate retest was then performed showing satisfactory results. Your investigation stated that the cause for the OOS could not be confirmed. However, you discarded the OOS test results on the basis that the most probable assignable cause was agglomeration of suspended active ingredient in the tip of the bottle or sample or that it was improperly agitated prior to filtration during the sample preparation, or that the bottle sample was improperly shaken prior to pump priming. There was no information in the investigation report to support any of these conclusions.

j) The conclusion of Lab. Inv. # 00-F2-15/MRB 2000-0205 for atypical results for Benzalkonium Chloride (BAC) assay, a preservative used in Celestone Soluspan Suspension, in stability batch 0-AHU-6A at 3 months 25 °C interval was incomplete. According to the investigation report, batch 0-AHU-6A consisted of [redacted] units and was a portion of commercial batch 0-AHU-6 of [redacted] units of Celestone Soluspan Suspension. Sub-batch 0-AHU-6A was fitted with stoppers from a new supplier and was placed in stability as part of a study (protocol 00-FP-004) to qualify the new stopper supplier. The study was cancelled *for reasons not related to the atypical results for BAC and the stability samples were removed from the stability program.* According to the conclusion of the MRB 2000-0205, no further action was required since the batch 0-AHU-6A was removed from the stability program. However, you failed to test the retain samples of commercial batch 0-AHU-6 for BAC to determine if the atypical values were also present in this batch or were caused by the new stoppers.

5. k) In the following three recent laboratory investigations, you concluded that extraneous peaks in sample chromatography were the result of contaminated glassware. Notably, the glassware used for the testing of both Vancenase and Nasonex products involved in these investigations is dedicated for testing of the individual products.

(1) Lab Inv. 01-F3-009, dated 2/21/01, for Vancenase AQ Nasal Spray, 0.84 mg/g, lots 9-TEH-313 and 9-TEH-314 (18 months @ 25°C) reported that an extra peak was detected at about [redacted] minutes in the sample chromatography of all units tested in the original run of Uniformity of Spray Content at Labeled number of actuations ([redacted]) assay. This peak showed up in all ten product samples and not in the standard preparations. Your conclusion was that the extra peaks could be attributed to glassware contamination introduced by the 50-ml volumetric flasks. However, you failed to conduct glassware testing, i.e. rinse solutions, to confirm that the peak was definitely originating from contamination in the 50-ml volumetric flasks and not from other sources. You also failed to indicate why the glassware for all 10 samples was

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presumed to be contaminated while the glassware for the standard preparations was not.

(2) *Lab Inv. 01-F3-027, dated 5/08/01, for Vancenase AQ Nasal Spray, 0.84 mg/g, lots 9-TEH-321 (18 months @ 25°C) and* 1-TEH-305 reported that an extra peak was detected at about [redacted] minutes ([redacted] RRT) in sample chromatography of unit # 4 of stability batch 9-TEH-321, and unit # 2 of batch 1-TEH-305, tested in the original run of Uniformity of Spray Content at Labeled number of actuation ([redacted]) assay. Your conclusion was that the presence of the extra peak was due to glassware contamination introduced by "new" 50-ml volumetric flasks, even though you conducted a special testing of new glassware [redacted]) that resulted in chromatography results without any extraneous peaks.

(3) *Lab Inv. 00-F1-11, dated 4/12/00, for Nasonex Nasal Spray, lot 0-KTL-105 reported that an unspecified impurity peak* that eluted at [redacted] minutes exceeded the specification limits ([redacted] in Mometasone Furoate and Degradation Products Assay. Your conclusion was glassware contamination of the volumetric, the volumetric stopper or the centrifuge tube even though this glassware is dedicated and pre-treated prior to testing. There was no information in the investigation report (# 00-F1-11) that supported the premise that the glassware was contaminated. The unspecified peak was not characterized. A new sample from lot 0-KTL-105 was prepared and tested and passing results were obtained. You reported the new results and invalidated the original ones based on this conclusion.

5. l) Laboratory investigation 01-BU-002/MRB # 20010021 of an atypical result of assay and related substances test for Betamethasone Acetate bulk lot 0-DOH-JJNN-6551 is inadequate in that the original and confirmed results were discarded and the re-test in triplicate results were reported. No justification for the invalidation of the original results was recorded.

6. Corrective actions when atypical results are obtained during stability testing sometimes involve the removal of the failing samples from the stability program. Examples are as follows:

a) On 6/15/98, a Lab. Inv. # 98-BU-0034 was prepared because the initial stability results (30°C) for Betamethasone Alcohol batch # 8-DOH-HH-6004 (converted into 8-DOH-X-6007) failed to meet the specifications for ordinary impurities (NMT [redacted]%) with results of [redacted]% and duplicate retests of [redacted]%. An additional testing request for laboratory investigation (Lab. Inv. # 00-BU-011) was generated on 2/8/00, but no test was performed. A memo dated 8/16/2000 (approx. two years later) indicates that the batch was restricted for the Japanese market. It also indicates that "Since no international batches are included in the stability program the batch will be discontinued from the stability program. No further testing will be performed for the subject batch."

b) Celestone Soluspan Suspension batches 0-AHU-7 (main portion), 0-AHU-7a and 0-AHU-7b were filled from the same compound 0-AHU-C-7. Portions 0-AHU-7a and 0-AHU-7b were placed on stability as part of the qualification/stability study of an alternate supplier for the stoppers. These portions failed the uniformity test with results of 86.86% (lot 0-AHU-7a), 86.43% and 84.15% (lot 0-AHU-7b). In this case the main portion O-AHU-7 was released to the market, but was not placed on stability. The investigation into the OOS results for lots 0-AHU-7a and 0-AHU-7b indicates that the OOS is due to a suspicion

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that the operator may have failed to reactivate the recirculation system after lot 0-AHU-7 was completed, since the two sub-batches were filled after the main batch. There is no evidence to support this suspicion. Furthermore, since these two lots were filled within approx. 15-20 minutes of each other, there is no documentation to support the assumption that a stop requiring rejection of the first portion occurred. [redacted]d units were discarded before filling batch 0-AHU-7a. Lots 0-AHU-7a and 0-AHU-7b were removed from the stability program for reasons not related to the uniformity test failures. No investigation was made to determine if the OOS uniformity results were also present in lot 0-AHU-7. There was no indication in the records that the new stoppers were the cause of the OOS results.

c) Celestone Soluspan Suspension lot 0-AHU-6A produced atypical results for the Benzalkonium chloride assay results. The lot was removed from the stability program and the product was shipped internationally.

7. Laboratory Controls/Analytical Methods:

a) You altered the HPLC (high performance liquid chromatography) analytical method 032088-220B-022-01.02, for the assay of Nasonex (Mometasone Furoate), degradation products, and leachables analysis of lot 0-KTL-112 to decrease the sample injection volume from 200 uL to 100 uL. Your firm justified this change of sample injection volume as a constraint of sample loop of the HPLC despite this method has been used 200-uL-sample injection since 6/07/00.

b) You did not investigate the high difference in weight change test for stability samples at 9 and 12 months @ 25°C interval of lots 0-LKA-6 and 0-TRJ-1, respectively. The weight change showed a difference up to 1.5 % for lot O-TRJ-1 tested on 4/17/01 and 8.03% for Lot O-LKA-6, 9 month @ 25°C tested on 4/10/01.

c) You failed to provide the rationale on why Procedure 990.81.00 (HPLC, GC and System Suitability Criteria) allows variability of [redacted]% potency or label strength between sequential injections of the same or different samples.

d) In addition, you prepare composite samples for Integrilin injection for assay/uniformity by HPLC, as part of the on-going stability program, which is contrary to the official method submitted to the FDA. In the official method 944.112.02 [Integrilin Injection (Finished) SBH (2 mg/mL); FWB (0.75 mg/mL)] single injections of two vials each should be run. However, you have been using a general procedure 990.113.01 (Testing of packaged Solutions, Creams, Ointments and Suspensions). A normal batch of Integrilin is [redacted]s during filling operation. According to this general procedure, a composite sample is to be prepared with all representative [redacted] and then two aliquots injected. Some examples are lots 9-SBH-A-1, 9-SBH-A-2, 9-SBH-A-3, and 0-FWB-A-141.

e) You failed to have stability indicating analytical methods for the following products:

Garamycin Injection (AMK)
Garacin Injection (DFX)
Gentocin Injection (BNP)
Garasol Injection (EJR)

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Gentocin Veterinary Solution (KMF)	*Garasol Chick (RCK)*
Garamycin Ointment (HF)	Otobiotic Otic Solution (BEN)
Sodium Sualmid Ophthalmic Ointment (JG)	Banamine Solution (CNX)
Gentocin Ophthalmic Solution (AMS)	Garamycin Ophthalmic Solution (AMS)
Metymid Ophthalmic Ointment (AH)	Gentocin Pinkeye Spray (PKY)
Azium Solution (AGJ)	Diprosone Ointment
Afrin Menthol Nasal Spray (JBS)	*Afrin Duration Nasal Spray (CFC)*
Occuclear Ophthalmic Solution (CIR)	Afrin Sinus Nasal Spray (GAD)
Afrin 4 hrs Decongestant (PBW)	Afrin Extra Moisturizing Nasal Spray (SBE)
Netromycin Injection (UWH)	Metimyd Ophthalmic Suspension (ACY)
Gentocin Durafilm Solution Ophthalmic (ANG)	Gentocin Otic Solution (ANW)
Betasone Aqueous Suspension (BBK)	Ethamoline Injection
Garamycin Cream (HB)	Gentocin Phtalmic Ointment (HJ)
Garamycin Ophthalmic Ointment (HJ)	*Solganal Suspension (WS)*
Afrin Menthol Moisturizing Saline Mist (KDH)	Banamine Paste

f) You failed to identify/characterize unknown impurities/degradation peaks [redacted]% as per your commitment made in the response to the previous FDA-483. You have recognized in your document titled "PQR Methods-Unknown Peaks [redacted]%" that you have six (6) drug substances and 18 drug products that have impurities >[redacted]; however, up to this date, you have not initiated the ID/characterization of these impurities. The following drug substances and drug products identified by you as typically having unknown impurities >[redacted] are: a) *Drug Substances- Betamethasone Acetate DS, Alclomethasone* Dipropionate DS, Betamethasone Sodium Phosphate DS, Dexamethasone DS, Betamethasone Valerate DS, Gentamicin Sulfate DS; b) Drug Products- Celestone Phosphate Injection, Gentocin Otic Solution, Betasone Aqueous Suspension, Trilafon Injection, Hyperstat IV Injection, Azium IV Solution, Gentocin Durafilm Solution, Diprosone Ointment 0.05%, Diprolene Ointment 0.05%, Diprolene AF Cream 0.05%, Lotrimin Cream 1%, Elocon Cream, Elocon Ointment, Celestone Soluspan Suspension, Trilafon Injection, Diprolene Gel 0.05%, Lotrisone Cream, Normodyne Injection.

Stability:

8. a) The explanation recorded for removing Gyne-Lotrimin Cream 2% validation batch No. 8-BPW-1 from the stability program was because this product was exposed to a high temperature in the stability chamber. However, another validation lot (8-BPW-2) remained in the same chamber until completion of study. No documentation to confirm that a chamber problem had occurred was available and no other product or lots in the same chamber were questioned.

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b) Samples were removed from the stability program or placed into the stability program and the dates on which these events occurred were not documented in the chamber logbook. For example:

(1) At the time of implementing a new system on 5/99 you failed to determine when the samples were entered into the program.

(2) All samples in stability chamber #2 were removed on 12/29/00 due to a shutdown of the chamber. A handwritten note in the stability records indicates that the samples were transferred from stability chamber #2 to a refrigerated van on 12/29/00 and returned on 1/15/01. However, there is no record in the chamber logbook of this transfer. Furthermore, there is no record in the refrigerated van's logbook that these samples were stored there during that time period.

8. c) There is no assurance your firm has control over the stability samples stored in chambers # 2, 3, 4, 6, 10 & 11. For example:

(1) A sample of lot 0-GFL-3 was removed from chamber # 1, but the date and the reason for the removal was not documented in the logbook or in any other document.

(2) There is no date of entrance for the stability samples that were placed on stability in chambers #3, 4, 7, 10 & 11prior to 5/24/99. In addition, some samples were taken out of chambers #3 and 6, but the date was not documented.

(3) Some lots were entered into the chambers up to 7 months after they were received in the stability area. For example, Lot 0-DOH-HHN-6304, according to the Material Transfer Sheet, was received on 4/17/00 and entered to chamber # 10 on 11/3/00. Similarly, Lot 0-PKY-1 received on 6/6/00 was entered in chamber # 6 on 8/30/00.

Consumer Complaints:

9. a) You failed to investigate consumer complaints in a timely manner. For a total of [redacted] consumer complaints received during years 2000 and 2001 for all your products, only 276 have been investigated. These are some of the more recent consumer complaints that are still pending or were not investigated in a timely manner:

(1) #2001-010586B Vancenase AQ, lot 9-TEH-313, Adverse Event, dated 3/27/01, classified as "Urgent" was still incomplete
(2) #2001-001793, Vancenase AQ, Unit will not spray, dated 1/17/01, not investigated;
(3) #2001-002486, Vancenase AQ, Unit will not spray, dated 1/24/01, not investigated;

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(4) 2001-002179, Vancenase AQ, Unit will not spray, dated 2/6/01, not investigated;
(5) 2001-000739 Vancenase AQ, Unit Leaked not sprayed, dated 1/10/01, completed on 5/2/01, 4 months after receipt at Manati;
(6) #2001-000850, Nasonex Nasal Spray, Unit will not spray, dated 1/10/01, completed on 5/3/01, 4 months after receipt at Manati.

g) The timetable specified in SOP 149.07.05, Handling/Investigation of Domestic Complaints and Veterinary Products used to handle complaint investigations is not adequate, in that:

(1) For complaints classified as "Urgent", the SOP allows 30 days for an investigation. This is in addition to the 60 days that New Jersey allows to receive the product from the consumer. (New Jersey centrally receives all consumer complaints and then forwards them to the Manati facility). This could amount to 90 days before an "urgent" investigation is completed.

(2) For complaints classified as "Routine" the SOP allows for up to 60 days to investigate complaints accompanied with the product. This is in addition to the 60 days allowed by New Jersey to receive the product from the consumer. This could amount to 120 days to complete an investigation.

10. Raw Materials

a) You have not executed the new Audit Qualification Plan 2001 to audit suppliers of active ingredients and raw materials as committed in your response to the previous FDA-483. For example, audits of [redacted] and [redacted] were scheduled to be performed in April and May 2001, respectively, and have not been conducted yet.

b) When a problem with excessive rejection of vials due to visible particles was encountered for several lots of Celestone Soluspan Suspension, you contacted the contract sterilizer of the API Betamethasone Acetate, [redacted] to determine whether the particles were present in the sterilized API. (This API is manufactured in your facility and then sent to the contract sterilizer to be sterilized) In three separate investigation reports, you state that the supplier denied that there were particles in the sterilized API, however, in the fourth report, you state that the supplier stated that particles were present in the Betamethasone Acetate API and that they were "intrinsic to the process". These investigations span a period from 12/99 to 5/31/01. Review of your OOS reports for 1999/2000 shows several instances when lots of Betamethasone Acetate API (sterile and non-sterile) were found to be OOS for visible particles, black particles or foreign matter. No steps were taken to audit and perform a complete evaluation of the contract's sterilizer process or to increase sampling and

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monitoring of this API after finished lots were reported as above limits for particle rejects.

Training:

11. There is no assurance that the training provided during year 2000 and 2001 to your analysts is adequate as evidenced in the following laboratory events:

a) During Laboratory Investigation # 99-BU-079 initiated on 9/13/99 to investigate an OOS result in the assay of Beclomethasone Dipropionate, you concluded that the OOS result was caused by a pipetting error by the analyst. There is no record to indicate that the analyst received training in this technique. A year later, on 10/12/00, this same analyst was reported as providing training to other analysts and supervisors about correct glassware handling and pipetting as a corrective action after additional OOS results were attributed to pipetting errors.

b) Several OOS results (Lab. Invs. 01-BU-003, 00-BU-006, and 00-BU-105) were identified as errors made by the analysts during sample preparations, pipetting of samples (Lab Inv. 00-BU-022), error in filling the vials in the HPLC, and errors verifying the analytical results against the product specifications (Lab Inv. 01-BU-010).

c) During Laboratory Investigation # 99-BU-082, it was concluded that the Specific Rotation OOS result for Beclomethasone Dipropionate lot 8-BLO-CC-6017 (6 Mo. @ 30°C) was due to improper cleaning of the polarimeter cell; however, there is no record that the analysts were re-trained on proper cell cleaning.

d) The efficiency and adequacy of the training program is questionable in that numerous training sessions are performed during the same day. For example, on 9/7/00 all of the following training sessions were given to the same employee.

- Procedure for spill control and disposition of chemical reagents in the QC Lab (translation)
- Standardization of the volumetric solutions
- Preparation and documentation of acidic solutions in sterile mixtures (translation)
- Analytical test for release of bulk compounding
- Operational procedure for pH determination in cream samples
- Analytical laboratory documentation policy
- Analytical laboratory investigations
- Rounding and reporting data

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In addition, the date the following training sessions were conducted is questionable as the training date is recorded as 9/7/00; however, there are additional annotations in the training record that these training sessions were actually given on 9/8/00, 10/2/00 and 10/6/00.

- Syringeability test for suspensions (10/6/00)
- Usage of pre-numbered analytical notebooks (10/2/00)
- Usage of QC low humidity room (9/8/00)
- Testing of package solutions, creams, ointments, and suspensions (10/6/00)
- Handling of stability samples (10/6/00)

e) There is no assurance that adequate training was given to all analysts on how to use the HPLC Millennium system software. This software has been used for the calculation of degradant products. Although the training was given on 4/20/99, an analyst was thoroughly re-trained on 3/5/00 (Lab. Inv. # 00-F1-11).

Additional Microbial Control/GMP issues

12. You fail to demonstrate the effectiveness of your media to promote the slow-growth microorganisms that may be found in your environment. Furthermore, the only criteria considered to challenge your media is by using the more frequently found microorganisms.

13. The documentation reported related to the collection of water samples from several points in your facility is questioned in that these samples, collected aseptically from different sampling points, are collected by the same individual within a period of 5 minutes between samples. For ex. Samples collected from the point BDB-202 (BV-916) located after BHE-202 was collected on 1/8/01 at 5:40 am and the sample from the point BDB-300 (BV-909) to BT-303 was collected by the same individual at 5:45 am.

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