DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 466 Fernandez Juncos Ave. San Juan Puerto Rico, 00901-3223 Tel. (787) 729-6948
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Francisco R. Rodriguez.	PERIOD OF INSPECTION 2/1-16/2000 / 2/21/01
TITLE OF INDIVIDUAL General Manager	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer
FIRM NAME Schering-Plough Products LLC	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same
STREET ADDRESS State Rd. 183 PRIDCO Industrial Park	STREET ADDRESS OF PREMISES INSPECTED Same
CITY AND STATE (Zip Code) Las Piedras PR 00771	CITY AND STATE (Zip Code) Same

C.F. NUMBER: FEI 100176708

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

Laboratory Controls:

1. Your laboratory failure investigations are inadequate in that you re-test without any scientific justification until passing results are obtained and/or fail to take corrective actions to prevent recurrence of the possible assigned cause:

   a. An Investigation # 00EXTR-211 dated 12/15/2000 for Theophylline pellets (final coat) lot [redacted] that obtained failing results of [redacted] NDA specifications [redacted] The first retest show results within specification but out of your internal guidelines (guidelines [redacted] with results of [redacted] Although a second retest showed results out of your guidelines [redacted] the original data was invalidated and the lot was released. The investigation indicates "that a possible error would be contamination, pipet or dilution of the samples and that "since an undetermined error could occur in the sample process"... There is no indication or evidence to support that a contamination may have ocurred.

   b. An Investigation # 00 EXTR-200 dated 12/13/2000 for Theophylline Pellets (final coat) lot [redacted] that obtained failing results of [redacted] The investigation again indicates "possible contamination, pipet or dilution of the samples that "since an undetermined error could occur in the sample process"... No evidence to support this conclusion is available and no corrective action was taken to prevent reoccurrence.

   In example a, the original results were below specifications and in the example b, the OOS values were above the limits. There is no scientific justification based on the data reviewed that would confirm that a possible contamination may have occurred.

   c. Investigations 00Rmat-73 (4/20/2000), 00Rmat-81 (5/15/2000), 00Rmat-85 (5/19/2000, and 00Rmat-89 (5/26/2000) related to OOS results obtained in lots [redacted] are inadequate in that your firm continued retesting samples until passing results were obtained. Ribavirin drug substance lot [redacted] initially showed failing

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results degradation products. Lots ##[redacted] also showed assay OOS results during this initial test. During the investigations different HPLC systems (which were not malfunctioning and for which the system suitability show no problems) and analysts were used until all lots showed passing results. All these lots were released for production and some were packaged and released, for example, lot[redacted] was used to manufacture final lot[redacted]

d. The potency OOS investigation 99-RMAT-23 of API Ribavirin USP lot[redacted] is inadequate. The assay failure was attributed to the use of a shaker instead of sonic during the sample preparation. However, the impact of this change was not considered in all the other lots in which a shaker was used. In addition, this issue, considered as the cause of a failure, was not addressed or included in the assay procedure to prevent a recurrence. Furthermore, a retest was not performed in duplicate by two analysts, as required in SOP KPR 02-007 revision 11.

e. The firm's incorrect practice to retest and/or report samples with better results can also be observed in the potency OOS investigation, lacking a traceability number, for Rivabirin 200mg capsules, lots#[redacted] The original results show a high variability among assay results in lots #0790048 and #0790053 and an OOS result (international specifications) for lot 0790048. The assignable cause for this variability was attributed to the inexperience of the original analyst with the product being tested. A retest was performed by the same analyst even though he was inexperienced and by an experience analyst with new samples and in a different HPLC equipment. Results again demonstrated a high variability among the samples tested. The same analysts performed a second retest obtaining results within specifications. These lots, exposed to continue retests, were the lots used for the certification of a new Ribavirin supplier from [redacted] submitted to the agency for approval.

f. Investigations 00-STAB-86 (6/30/00) and 00-STAB-87 (7/7/00) related to potency OOS results obtained during the 6-month stability interval for lots [redacted] and [redacted] are inadequate. A retest was conducted by the same analyst confirming the OOS result for lot [redacted] Your firm performed a second retest again with a second analyst using the same composite obtaining failing results. The original analyst performed another analysis from a new composite in triplicate,

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and one of the values was again out of specifications. At the end of the investigation two more runs were performed, with the original analyst and a third analyst, with results within specifications. The original data was invalidated. A total of 6 retest were performed. In addition, there is no evidence or justification to support the assignable cause of sample contamination.

Process Validation Issues:

7. Your validation process for several of your products reviewed is inadequate in that it fails to provide documented evidence that you are capable of producing a product with a high degree of assurance that the specific processes will consistently produce a product meeting it's predetermined specifications and quality attributes, for example:

a. Your process validation for Theo-Dur tablets 100, 200, 300, 450 mg is inadequate in that it fails to demonstrate that you have control of your manufacturing process and that you are capable of consistently producing a product that meets predetermined specifications. In addition, your firm has not been able to determine the causes of the dissolution or potency failures obtained for in-process active or final coating pellets and Theophylline tablets that has lead you to reject in-process and finished product batches or to submit Field Alert Reports to the FDA. Your validation is inadequate in the following:

b. The validation of the active pellets process, wax coat process and final coat process can not be related to the completion of a manufacturing process of lubrication/blend and subsequently the compression of the material into Theophylline tablets. The revalidation exercise included in the report PP-109A with a completion date of 5/5/99, only covers up to the final coating operation of the three final coat lots [redacted]. Your current process requires that 6 or 7 batches of Theophylline pellets Final Coat be blended to produce one lot of finished tablets of Theophylline. Your validation report conclusion that your process is validated is incorrect because it does not represent the current manufacturing process. Furthermore, these 3 lots of Theophylline final coating were not continued to the lubrication/blend step and then to the compression of the tablets and evaluated as a complete process.

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c. Your validation of the lubrication and compression process which produces the Theophylline tablets 200 mg, 300 mg and 450 mg is inadequate in that it fails to consider or evaluate as part of the validation exercise the manufacture of the theophylline active pellets, wax coating and final coating batches that were used to manufacture the finished tablets lots of Theophylline 200 mg (lots [redacted]

d. The portion of your validation related to the manufacture of Theophylline base solvent, active, wax and final coating of the pellets fails to identify all the critical factors that may impact the dissolution of the product. It fails to include predetermined specifications for particle size and bulk density. Your report indicates that the particle size and bulk density values were collected for information only.

e. The validation of the active, wax and final coating of the Theophylline pellets is also inadequate in that neither the report or the protocol specifies how and from what location in the drums were the particle size and bulk density samples collected. The protocol only states that 80 grams of active pellets, waxed coat pellets and the final coating be collected from each drum.

f. You fail to establish dissolution specifications for the final coating validation lots and to include a particle size, and bulk density evaluation for your Theophylline Pellets final coat. It is also inadequate in that it fails to include an evaluation of the fluidization air flow, outlet air temperature and the drying process. These factors were part of the reason for which a decision to revalidate the process.

g. It is also inadequate in that no specifications or acceptance criteria for the average weight, tablet hardness, nor thickness was predetermined for the validation of the Theophylline compression process. No friability or disintegration determination was evaluated.

h. Your validation of the lubrication stage failed to established predetermine specifications for particle size. Instead your report indicates that the results were for information only.

i. The Re-validation of the compression process is also inadequate in that although the tablet lots

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[redacted]

(Theophylline 300 mg) were divided in 10 intervals only 3 tablets per each interval were collected to determine content uniformity. Furthermore, only the averages obtained in each interval were included in the final report.

In addition, the compression force and a moisture determination was not evaluated. A determination of the optimum conditions of the process was addressed or included in the report.

3. Your validation process executed for Labetqlol reviewed is inadequate in the following: there is no scientific justification for collecting only 5 blend samples of a 50 ft blender and composite samples from the blend product inside the drums, failure to have particle size specifications, failure to justify the collection of only 3 tablets per each interval (10 intervals) for content uniformity for a total sample of 30 tablets for the entire batch.

4. Your validation process for Claritin is inadequate in the following: failure to have predetermined specifications for particle size, ~~thickness, hardness, friability and disintegration~~. There is no scientific justification for the collection of only 3 tablets per each of the 10 intervals to demonstrate the uniformity of an entire lot.

Cleaning Procedures:

5. Your equipment cleaning SOP for the Ribavirin production line is inadequate in that it fails to require that a mayor cleaning be executed between lots of Rivavirin obtained from an approved drug substance supplier and a non-approved supplier. Batches of Rivavirin blend were manufactured with drug substance received from a China or France supplier (not included in the NDA), followed by Ribavirin drug substance received from Orgamol (Switzerland plant), the approved supplier without performing a cleaning to prevent a cross-contamination of impurities that may be present in the different drug sources.

Analytical Methods

6. Failure to implement, in a timely manner, the new HPLC methods for assay and Chromatographic impurities of Theophylline API and finished product. Both methods were transferred

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from New Jersey on 1998. The API method was finally implemented on December 2000 but for the finished product you are still using the UV method for assay determination. The finished product is not currently been tested for impurities.

7. During the performance of the content uniformity for UNI-DUR 600 mg ER tablets lot [redacted]ou failed to follow the USP XXIV requirements for the content uniformity test. During this test tablets 3 and 10 obtained results 116.4 % and 122.2%, respectively. Instead of testing 20 additional tablets (S-2) as required by the USP XXIV, you stopped the test to investigate without any justification and as in other investigations mentioned in this FD-483, you attribute the OOS to a possible contamination that only affected the OOS vials. Then, you reanalyzed the lot obtaining passing results to release the lot.

Stability Issues:

8. You fail to test your stability samples at the scheduled intervals. Stability lots are packaged and started in the stability program up to up more than 6 months after the products have been manufactured.

   a. Uni-Dur 400 ER lot [redacted] was manufactured on 2/99, but started under the stability program on 8/17/99.

   b. Uni-Dur 600mg ER manufactured on 9/99, packaged on 5/30/00 and placed under stability on 9/14/00.

   c. Claritin tabs. lot [redacted] manufactured on 1/99, packaged 5/99 but placed in stability on 7/99.

   d. Normodyne/Labetalol Tablets 300 mg lot [redacted] was manufactured on 9/1999 and initially tested on 1/2000.

9. You fail to have stability studies to justify extensive holding times of your products stored in bulk containers until packaged for release to distribution. For example:

   a. Normodyne 300 mg tabs. bulk lot [redacted] was manufactured on 6/18/99 and packaged (packaging lot [redacted] on 5/25/2000. No data supporting this amount of time was available.

   b. Normodyne 200 mg tabs. bulk lot [redacted] was manufactured on 9/01/99 and packaged

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(finished lot # [redacted] on 8/18/2000. No data supporting this amount of time was available.

c. K-Dur 20 mg ER tabs bulk lot [redacted] was manufactured on 8/31/99 and packaged (finished packaged lot [redacted]) on 4/5/00. No data supporting this amount of time was available.

d. The Theophylline ER tabs. 200 mg was manufactured on 9/25/98 (active ingredient was added) and packaged on 1/20/00 (finished package lot # 9PHN793).

e. Claritin tabs. bulk lot [redacted] was manufactured on 5/25/99. This lot was packaged on 7/19/00 into finish package lot # [redacted] No data supporting this amount of time was available.

f. Rebetol lot [redacted] was manufactured on 12/15/99 and packaged on 10/9/2000. The firm fails to have stability data that would justify approximately 10 months of bulk storage prior to being packaged.

Furthermore, an internal memo dated 10/17/00 suggest the following holding times based on the acceptable results obtained:

Maximum holding time of 90 days for Claritin;
Maximum holding time of 90 days for Theo Dur and Theophilline tablets

Maximum holding time of 90 days for Normodyne.

General GMP Issues:

10. During the review of a Variance Report No. 0511-24 for a Yield OOS investigation for Ribavirin (Rebetol 200 mg.) we observed that the Variance Report Memo, dated 9/22/00 indicates that as of 9/22/00 the personnel involved was stressed (trained) on proper documentation of all waste. However, the training document collected indicates that the training took place on 11/10/00, several months after

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the memo was written and not as of 9/22/00.

11. Your Analytical Laboratory Investigation SOP for Out of Specification Results is inadequate in that it fails to include that the FDA be notified through a Field Alert Report within 3 working days of becoming aware of a stability out of specification result. In addition, your Stability Program SOP No. KPR 02-009 is inadequate in that it indicates that once the OOS is confirmed they must notify the FDA. There is no requirement to notify the FDA if the OOS is not confirmed within 3 working days.

12. The tracking system for investigations into OOS results is not adequate because not all investigations are included, for ex. Ribavirin 200 mg lot # [redacted] and [redacted] was unnumbered and not included in the firm's tracking system.

Import/API Issues

13. There is no documentation to account for the disposition of 140 kilograms (100 kg. Manufacturer Lot [redacted] Schering-Plough lot # [redacted] and 40 kg. Manufacturer Lot [redacted] Schering-Plough lot # [redacted] of active pharmaceutical ingredient IMPORT for EXPORT "RIBAVIRIN". This material was used during the manufacture of blend Lot [redacted] that was rejected due to blend contamination. This active pharmaceutical ingredient was manufactured by [redacted]

14. The Transaction History Report System does not provide accurate data. For example:

    a. Transaction History for lot number [redacted] active pharmaceutical ingredient IMPORT for EXPORT "RIBAVIRIN" accounts for the use of 80 kilograms in blend lot [redacted] However the batch record for blend lot [redacted] accounts for the use of 100 kilograms of lot [redacted] Therefore the Transaction History Report shows a discrepancy of 20 kilograms.

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11. Your Analytical Laboratory Investigation for Out of Specification Results is SOP Inadequate in that it fails to include that if assignable cause is not determined within 3 working days of obtaining a failing result with the an FAR should be submitted to the FDA. In addition, your Stability Program SOP No. KPR 02-009 is inadequate in that it indicates that once the OOS is confirmed they must notify the FDA. There is no requirement to notify the FDA if the OOS is not confirmed within 3 working days.

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b. Transaction History for lot number [redacted] also accounts for the use of 20 kilograms in blend lot [redacted] However the receiving records accounts for the receipt of 100 kilograms. Batch record for blend lot [redacted] accounts for the use of all 100 kilograms of lot [redacted] Therefore the Transaction History Report shows a discrepancy of 20 kilograms.

c. Transaction History for lot number [redacted] active pharmaceutical ingredient IMPORT for EXPORT "RIBAVIRIN" accounts for the use of 60 kilograms in blend lot # [redacted] However the batch record for blend lot # [redacted] accounts for the use of 40 kilograms of lot [redacted] Therefore the Transaction History Report shows a discrepancy of 20 kilograms.

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