DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 466 Fernandez Juncos Ave. San Juan, PR 00901 (787) 729-6844	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Fransicso R. Rodriguez	PERIOD OF INSPECTION 5/1-6/5-2001	C.F. NUMBER FEI 100176708
TITLE OF INDIVIDUAL General Manager	TYPE ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer	
FIRM NAME Schering-Plough Products L.L.C.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 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	

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

1. You are not following the process described in the "Change Being Effected 30-Day notice" submitted on October 4, 2000 and approved February 21, 2001 for K-Dur (Potassium Chloride) Extended Release Tablets. The CBE submitted calls for the manufacturing of [redacted] batches of Extended Release coated pellets, testing a composite of samples taken from each of the [redacted] batches, and then blending the [redacted] batches to manufacturer one batch of blend. The blend lot is then used to manufacture one lot of finished tablets. However, 13 batches of K-Dur 20 meq ER tablets were manufactured by using only a fraction of the sub batches tested as a composite of the sub batches. The left-over portion of the sub batch is available for and has sometimes been used in the manufacture of other lots. There is no analytical testing to ensure the individual sub batch used meets the NDA requirements for dissolution. On 5/22/01, It was necessary to issue a FAR because "A subpart of potassium chloride ER coat was used without being tested."

2. You have not developed validation/qualification master plans encompassing process, cleaning, computer and analytical method validation as directed by the Corporate Quality Assurance Guideline titled Master Plans for Validation/ Qualification issued 10/12/1999.

3. Corrective actions you commited to in your response dated October 12, 1999 to the FDA-483 issued on September 21, 1999 concerning data maintance and security in laboratory instruments have not been completed. For example, you commited to "the assessment of the approach for other critical instrumentation, besides HPLC and GC units, will be documented and individual actions plans will be developed as appropriate. However, your laboratory does not maintain the raw data obtained from your laboratory equipment, such as, HP UV-Vis Spectrophotometer Chemstation Dissolution System, Atomic Absorption Spectrophotometer, Zymate XP SPL-21 Dissolution System and others. These systems have not been assessed and you have not developed the individual action plans necessary to bring these systems into compliance.

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	Steven B. Barber Arlene M. Badillo	Steven B. Barber, Investigator Arlene M. Badillo, Investigator	June 5, 2001

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4. Your Out of Specifications (OOS) laboratory investigations system is inadequate in that:

a. After your laboratory obtained an OOS value, they performed the re-testing without a justification documented.

b. Your laboratory investigations fail to support the conclusion and/or assignable cause, which invalidated the original analytical data and validated the data obtained during re-testing.

c. Your laboratory investigations fail to have adequate corrective actions to prevent the recurrence of OOS results.

For example,

On May 4, 2001, I requested the laboratory investigation # 01-ETR-148 for the KDur ER Coat, lot #0210307, which was in- progress at that time. During my review, I found that on April 29, 2001 your laboratory obtained a high atypical value in the dissolution testing, and on May 1, 2001 they generated the Investigation Tracking Checklist required by the SOP KPR02-007 "Analytical Laboratory Investigations Including Out-Of-Specification Results". Your laboratory did not report any problem with the equipment or the sample preparation, and approved the re-test without an explanation. I requested the justification for the re-testing and your laboratory personnel explained me that this is an aberrant or atypical value that was previously observed in other lots from the same product. In the previous investigations, your laboratory performed the re-test and invalidated the original aberrant value using the same assignable cause related to the interference caused by the [redacted] in the dissolution vessel. These investigations do not have analytical data to demonstrate the validity of this assignable cause. During the inspection, your laboratory performed a study to prove this assignable cause and they found that this assignable cause previously used to invalidate data is not valid.

The laboratory investigation #01-EXTR-121 for KDur ER Coat, lot #0210072 is an example of a previous investigation that was closed, in which analytical data was invalidated using the same assignable cause. I found 21 laboratory investigations from years 2000 and 2001, in which the same assignable cause was used to invalidate original data. None of these investigations have an adequate corrective action to address the problem.

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Your laboratory is releasing KDur ER Tablets lots using the dissolution data obtained by a laboratory equipment [redacted]), which fails to function adequately. Your laboratory assigned to this equipment the cause of the multiple OOS results obtained from June 2000 to May 2001. Nevertheless, during this period of re-current OOS results, your laboratory did not challenge the performance and accuracy of this equipment to correct the problem that supposedly was causing the multiple OOS results. During the period of this inspection, your laboratory initiated the investigation and performed various experiments, which disclosed on May 8, 2001 that the high atypical values were related to the outpouring of the dissolution vessels. Your laboratory made modifications to the system to avoid that the washing solution remains in the vessel during the washing cycle and causes the outpouring. On May 18, 2001, they approved a new performance qualification to test the adequacy of the modifications. After that, your laboratory continued the use of the instrument to perform the dissolution testing of eight KDur ER Tablets stability samples, but during these runs the problem was observed again. On May 24, 2001, your laboratory found another problem with the equipment balance, which was causing outpouring of dissolution media during the delivering of it. It was not after this finding that your laboratory discontinued the use of the equipment to perform official release testing of KDur ER Tablets.

5. The content uniformity testing performed during blend uniformity validation does not ensure a uniform blend of the Extended Release coated Potassium Chloride crystals used to manufacture K-Dur 10 and 20 mEq tablets.

6. After obtaining an Out-of-Specification assay result during the validation the K-Dur extended release coating process, you reanalyzed the same sample preparation. When a second OOS result was obtained, you retested the sample using two analysts, this time obtaining two OOS results. These preparations where then further agitated and reanalyzed in duplicate by each analyst obtaining four OOS results for a total of eight out-of-specification results. You then resample the batch, tested the sample and obtained passing results; this result was used as the official result to release the batch for further processing and for validation purposes. The investigation states "In a conversation with Technical Services [Personnel], an error in the original sampling process was made. The original results will be voided and resample results will be used as official for this test." You could not provide a description of the sampling error, the specific procedure that was not followed, or any corrective action to prevent a reoccurrence. Furthermore, the undocumented error in the original sampling

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process was decided after the second sample which came from an undocumented source, passed. In addition, other results, which met specifications and were obtain from the same original sample, were not invalidated.

7. Preliminary variance report 20010219 was initiated to document a low net yield and a interruption during processing of K-Dur ER coated pellets lot 0210071-D in the Glatt. As part of the investigation, special request KPR 01-0599 was issued for analytical testing. However, the preliminary report does not list the results but instead states "Pending analytical test results". However, the Recommendation For Material Disposition states "Based on the investigation and special request results, approval of lot is recommended" even though the person writing the report did not have the results of the testing yet.

8. Analysis performed in order to accept Potassium Chloride active pharmaceutical ingredient are performed on a sample your receive from your supplier and not the actual Potassium Chloride, USP received.

9. Your performance qualification of the manufacturing process of Potassium Chloride ER Coat in the [redacted] is inadequate, in that, it does not reflected your actual manufacturing process procedure. Your actual process includes the manufacturing of [redacted] ER Coats lots, but the performance qualification was performed using [redacted] ER Coats lots only.

10. Variance investigation 20000482 conducted during the qualification of Potassium Chloride manufactured by [redacted] is not adequate. An dissolution test of the ER coated potassium crystals resulted in an average value of 48%, which is outside your guidelines of [redacted]%. The investigation states "since no assignable cause manufacturing or testing related and dissolution results are within NDA specifications, no additional testing was performed. This investigation leads to conclude that bulk lot 0700298 complies with NDA specifications for product." However, the investigation does not mention any investigation of the manufacturing process and does not mention the fact that four out of the six dissolution results used to determine the average of 48% were outside the NDA specification of [redacted]%.

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11. The process for 200mg, 300mg and 450 mg theophyline tablets is not validated in that the observations cited on the FDA-483, Inspectional Observations, issued to your firm on February 16, 2001 have not been corrected. In addition, according to Schering-Plough Products LLC management, there are no plans to validated this process. However, your firm has continued to distribute theophyline tablets manufactured using the unvalidated process after February 16, 2001.

12. Your analytical method no. 632 "Determination of assay, identification and estimation of chromatographic impurities of theophyline drug substance" is inadequate, in that, it does not assure the detection and quantitation of the possible impurities [redacted] and [redacted]

13. The Rebetol 200mg Capsules manufactured in rooms 258A and 258B is not validated because the validation lots manufactured did not meet the predetermined specifications listed in the protocol.

14. The current process for Eulexin is different form the process that was originally validated in 1990, for example:

a. The current process calls for the [redacted] prior to the batch blending, the original validation batches did not include this pre-mixing. Furthermore, the change authorization does not offer any explanation as to why the process was changed.

b. The batch record used during the original validation called for blending the active dilution for "[redacted] minutes" cause the active dilution to be blended for [redacted] minutes. However, the current batch record calls for the active dilution to be blended "for [redacted] minutes" cause the active dilution to be blended only for 10 minutes.

15. The process for Normadyne tablets is not validated in that the observations cited on the FDA-483, Inspectional Observations, issued to your firm on February 16, 2001 have not been corrected. However, your firm has continued to distribute Normadyne (Labetalol) tablets manufactured using the unvalidated process after February 16, 2001.

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16. After obtaining an Out of Specification test result of 121.6% for blend uniformity during the performance qualification of the [redacted]r and [redacted] for the Claritin 10 mg tablet process, your firm re-analyzed the same sample preparation. The retest result of 121.9% confirmed the original result. A second sample, with undocumented origins, reportedly from the same lot and blender location was tested obtaining a result of 122.0%. However, this value was invalidated due to chromatography problems. The second analysis of the second sample obtained a value of 100%, this value was ~~excepted~~ accepted without questioned and reported in the validation report.

17. The laboratory analytical balances used for the testing of your products do not comply with the USP 24 Chapter <41> Weights and Balances.

18. During the course of the inspection, the following records were not available for review:

a. The justification for establishment of the dissolution guidelines of K-Dur tablets during release testing has been destroyed

b. The justification for the establishment of a particle size specification for accepting Potassium Chloride from your suppliers has been destroyed. Furthermore, you do not know the purpose of the specifications.

c. Laboratory investigation 01-EXTR-123 for K-Dur ER coat lot 0202240 is missing.

d. Laboratory investigation 01-EXTR-150 for Theo-Dur ER tablets lot 0KHP613 is missing.

e. The raw data that supports the K-Dur dissolution method transfer for the method currently being used for in-process testing as well as release testing of K-Dur was destroyed.

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