Schering Plough Corporation

AUDIT OF SCHERING LABORATORIES MANUFACTURING FACILITY KENILWORTH, NJ AUDIT REPORT

Performed by:

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February 28, 2000—April 14, 2000

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CONSULTING GROUP

- High priority needs to be given to qualifying all operators and supervisors in critical task procedures and documenting the training, as well as developing and approving training procedures for all units.

- Upper management needs to demonstrate its long term commitment to product quality, such as through increased staffing/budget resource allocations and investments in new equipment, in order to supplant the traditional emphasis on production and firmly establish a company culture in which quality is, in fact, the number one priority.

David B. Barr
Director Pharmaceutical Consulting

Recommendations:

- Manufacturing management has tried to reduce the supervisory turnover rate by establishing an interim 18-month time in position requirement before the supervisor is eligible for promotion as well as hiring/training a slight surplus of supervisors. We endorse these initiatives and suggest that some permanent time in position/grade policy, e.g. 12 months, be established for all positions.

- Increased efforts should be made to locate and select supervisors and managers who have technical/pharmaceutical knowledge and experience, to assure proper oversight and troubleshooting of manufacturing operations in all product areas.

Quality Culture/Performance Management/Training

Sustained, top performance by all employees, excellent training/qualification programs and systems, and adequate resources are inextricably linked to creating a company culture in which product quality and cGMP compliance are of utmost importance.

- The performance appraisal and management system for the hourly workers does not adequately address unsatisfactory and reward outstanding performance. Operators feel no threat of adverse action for poor performance and this appears justified based on the very low numbers of adverse actions for performance at Kenilworth in 1998/9.

- Most units fail to have documentation demonstrating that operators are qualified in all required critical tasks. Some areas also lack approved training procedures.

- There has been a recent emphasis by upper management on quality that crosses all product lines. This has been demonstrated/supported by staffing increases, slower production lines, improved communications with staff, etc. However, there is staff concern that this commitment to quality may not be long term.

Recommendations:

- The employee management and evaluation system should be re-designed to establish sufficiently high performance standards and workers must be held accountable by management for meeting those standards. Supervisors should be trained and required to counsel employees, honestly evaluate worker performance, and take appropriate performance-based personnel actions.

- There must be provisions in the system to enable fair but timely discipline of workers for poor performance and reward them for outstanding work, including year-end bonuses and other cash and honorary award incentives based on appraisal ratings and exceptional service.

Observations and Recommendations

The very few cash awards given in the past 2 years indicate that this motivational tool is not being effectively used by supervisors and managers to reward Kenilworth employees for exceptional performance or service.

Recommendations:

a. The cash award system needs to be better publicized and utilized. A procedure should be written and disseminated describing it, so that managers, supervisors and operating employees are made aware of the process and the rewards available.

b. Strong consideration should be given to establishing Employee of the Month, Team of the Month and/or Employee/Team of the Year awards to recognize outstanding individual or group performance. This will help publicize, model and reward the type of work and employees the company highly values. The awards may be accompanied by cash, gift certificates, Schering-Plough caps/T-shirts, etc.

c. A formal suggestion program should be instituted to encourage employees to think of and submit ideas for improving quality, productivity, service, etc. and receive cash awards commensurate with the impact of the suggestion. The program should be publicized and a procedure written and disseminated describing it, so that employees, supervisors and managers are aware of the process and rewards available.

d. Managers and supervisors should be encouraged to express a genuine and timely "thank you" to employees for jobs well done. This can go a long way toward improving employee motivation and morale.

CULTURE CHANGE (COMMITMENT TO PRODUCT QUALITY)

Supervisors, managers, and operators were asked if they perceived a real change in the company's commitment to improving product quality since the aerosol recall/problems with FDA in late 1999.

Observations and Recommendations

1. Most managers/supervisors have adopted a wait and see attitude, to determine if upper management will "walk the talk" with respect to long term commitment to product quality. They state that for many years they have been under significant pressure to get production out and don't feel they have had enough time or people to do a quality job. They indicated that there has been in the past a continual push for increased production and decreased down time sometimes at the expense of high quality work and GMP compliance. They believe there has been an imbalance between quality and production, leaning considerably toward the side of production.

Recommendation:

It appears employee training and/or written instructions need to be reviewed to assure that dust collection equipment is used when needed.

2. Current procedures do not require that production lines are blocked off during the equipment set-up process when OOS units may be produced during determination of optimum settings. This was observed to be the case in the LOC packaging area.

Recommendation:

Revised procedures should be implemented as soon as possible.

3. Backup of sewage in the corridor adjacent to the room where albuterol solution for inhalation is manufactured has been occurring periodically over the last year or two without a plan for permanent correction and without any documentation of the problem or evaluation of product impact. During the early part of the audit, large pools of sewage were observed to form which were then tracked through the production facility. Ingredient containers and hoses came in contact with the floor and fecal organisms were observed to have a pathway into the product. Drugs produced in this area were not evaluated for exposure to fecal contamination.

Recommendation:

After this incident some investigational follow up was conducted. It is our belief that there needs to be an investigation into the reasons why this situation was not addressed earlier when it was known to have happened previously. Effective corrective and preventive action needs to be taken to prevent recurrence.

AEROSOLS

Observations and Recommendations

Evaluation of this manufacturing area disclosed significant changes in both procedures and record keeping practices. Overall, these were found to be positive, but some observations did reflect potential problem areas and perhaps even some degree of over-reaction to the recent aerosol product recalls.

1. While the new Pamasol filler downtime log is designed to capture all interruptions in the filling process, it is not being consistently documented as to its review by all shift supervisors. For example, the log for O-AMA-400, which was being filled on line 58, was being handled differently. Most of these log pages which were examined had each page signed and dated by the supervisor, along with the "Variance Required" block checked either yes or no. In the case of shift #1 (11:00

MANUFACTURING ORGANIZATION, PERSONNEL, POLICIES, PERFORMANCE

ORGANIZATIONAL STRUCTURE

Kenilworth manufacturing is currently organized into 2 major units, K-2 and K-10 Operations, each managed by a Plant Director, who reports to the Vice President, Pharmaceutical Operations, along with the Directors of Technical Operations Training and Technical Support. K-2 includes separate components with respective managers for Liquids/Ointments/Creams (LOC), Aerosols, and Packaging (3 shifts). K-10 components/managers are Solid Dosage Manufacturing, Tablet Coating, Central Weigh, Warehousing, Strategic Projects, and Packaging (3 shifts).

Observations and Recommendations

1. We believe the span of control is far too wide for the K-10 manager, to enable effective oversight of all the many and varied critical operations he is responsible for. The current structure makes it extremely difficult to assure uniform and consistent GMP controls in all of the respective K-10 manufacturing and packaging areas and support units.

2. The very small number of direct reports (4) to the VP Pharmaceutical Operations is not conducive to effective and efficient communication and management of problems, corrective actions, plans, and strategies pertaining to all production operations up and down the chain of command.

3. It is our understanding, based on interviews with supervisors and managers, that aerosol products are a major money maker for the company. In addition, significant manufacturing problems have been experienced with this product class, which is indicative of insufficient technical expertise and managerial oversight. This production area does not have the visibility and importance from an organizational standpoint that it needs in order to quickly and effectively recover from past problems, maintain satisfactory regulatory compliance, attract and retain necessary expertise, and grow in the future.

4. It is expected that a new line of products, i.e., dry powder inhalants (DPIs), will be brought on line at Kenilworth in the near future. There is no provision in the current organizational structure for this product class.

5. Strategic Projects/Planning and Manufacturing Support (Central Weigh, Warehousing) cut across all product classes as does Maintenance/Mechanics. These units need greater visibility and more direct access to the VP Pharmaceutical Operations than currently exists to improve their efficiency and effectiveness in servicing all manufacturing activities.

d. Such reports should be shared with Manufacturing and Packaging managers and the data used to respond to questions/allegations concerning analytical turnaround times for different product classes and components.

VENDOR AUDITS (COMPONENTS)

Tony Ferriera, Manager, Supplier QC was interviewed concerning the audit program for component suppliers. The following documents were examined: SOP 73.13.00; Supplier Quality Assessment for Packaging Components; SOP 73.18.00, Packaging Component Supplier Inspection Schedule; Supplier Audit Report "3M Neotechnic, Upbrooks, Clitheroe, United Kingdom", dated 12/2/98; spread sheet, showing vendor audit accomplishments/plans, which was provided by Mr. Ferriera on 3/13/00.

Observations and Recommendations

1. Mr. Ferriera identified vendor audits as an area of vulnerability, because some of the current vendor auditors are not fully trained/qualified and there is an insufficient number of auditors (Quality Engineers) to handle the vendor audit workload, including monitoring corrective actions associated with suppliers.

   Recommendations:

   a. The component vendor audit group will be incorporated into the new QA auditing unit being established in the QC Department under the QC re-organization plan. This will consolidate auditing functions and responsibilities, and enable increased resources to be devoted to vendor audits from the larger pool of auditors authorized for this new unit.

   b. A team approach in conducting vendor audits should be employed. This would include auditors who have special expertise in cGMPs and scientific/technical matters. In addition, a program should be undertaken to cross train auditors in all key GMP and technical audit elements.

   c. Auditor training should be improved by identifying critical vendor auditing tasks and having the trainer observe trainee performance in these areas.

   d. Auditor training should be improved by having auditors attend external courses on quality auditing. Arrangements can be made with the contractor to have these courses presented on-site, so that all or most auditors can attend.

2. Some components, such as aerosol valves from 3M Neotechnic, are received for testing already pre-sampled by the vendor. There is no assurance that the samples provided to Schering were collected by the vendor according to accepted sampling procedures and are representative of the entire lot.

3. Ms. Coan has taken the initiative on her own to update all test methods employed in her laboratory. She indicated that the test procedures used by the unit are up-to-date with the exception of aerosols. Some steps in the old aerosol procedures need to be better defined.

   Recommendation:

   Updating aerosol test procedures should be given the highest priority in light of past problems with this product class and the intense scrutiny Schering operations in this area is currently undergoing by FDA.

4. An in-process assay for the active ingredient in Proventil is not performed. Reportedly, R&D has been trying for several years without success to shorten the Proventil final release assay procedure, so that it is suitable for in-process testing.

   Recommendation:

   An in-process assay method for Proventil should be developed and validated as soon as possible so that the active ingredient is quantified in-process as is done for all other Schering aerosol products.

5. Assay results for aerosol concentrates are faxed by the in-process analyst to the manufacturing supervisor at the completion of initial testing. There is no second person check of the results before the data are sent to manufacturing.

   Recommendation:

   SOP 21.07 should be revised to insure that results are checked by the supervisor or a second analyst before they are faxed to Manufacturing.

6. There is no back-up generator for the in-process analytical testing laboratory. Reportedly, there have been electrical outages in the last 1 to 2 years that have lasted from 5 minutes to 1 hour before power was restored.

   Recommendation:

   All laboratory units should be provided with back-up generators, to insure that analyses are not delayed, instruments damaged, or sample storage compromised during electrical service interruptions.

7. There is no regular or centralized monitoring of temperature and humidity in the laboratory by Maintenance. Approximately 3 weeks ago, laboratory personnel took the initiative to install a temperature/humidity recorder to help monitor the lab environment. No procedure has been established to insure that recorder data is regularly assessed and appropriate actions taken when temperature/humidity excursions occur.

3. Content Uniformity specifications used is USP specifications. No heightened specifications were used, even though the process demonstrated control sufficient to justify tighter tolerances.

4. Summary reports for Claritin-D® 24 batches repeatedly correct a protocol specification for granulate LOD values. The protocol states a finished moisture range of between 0.5% to 1.5% LOD. The corrected value is stated to be 0.1% to 1.5%. No justification is given for the change. The batch records for several batches are inconsistent in that both ranges have been used. There is no "not to exceed" time/temperature specifications, and the effect of elevated time and temperature has not been investigated and validated. Yet the process is considered valid.

5. A deviation in the process occurred for all of the validation batches, in that the Fitzmill used for wet milling was run in reverse for the batches, thus not matching the impact forward milling condition. This was due to "reversed polarity" of an electrical outlet in an adjoining room where a portion of the milling was performed. All the validation batches were run this way, since it was discovered after five batches were completed. It was stated that the knives forward configuration was NDA acceptable, and that the data from other validation batches confirms this. Since all the validation batches were run this way, and since no data was presented to demonstrate that there was no difference, this contention is not supported.

6. The dry blending step in the Nauta blender failed protocol specifications for four out of five validation batches. While the subsequent sampling of the drying and the final blends demonstrated acceptable uniformity, these failures were discounted without explanation.

7. Compression validation did not demonstrate consistency of performance over the full range of tabletting machines in use in the compression area. Thus there is no justification for tabletting with machines other than the units used to conduct the validation study.

8. Previously filed validation reports for Claritin-D® (Once-a-Day), with the same product ID (GJKS), were performed in 1993. The protocols and final reports were reviewed and approved by production and quality in 1995. One of the batches manufactured failed final blend specifications, but this validation was approved by management nearly two years later. There was no statement as to the batch's disposition.

Recommendations:

a. Validation protocols should specify heightened acceptance criteria, reflecting the process capability. These should be determined before committing the process to validation. Criteria should be set according to preceding batches of

ANNUAL PRODUCT REVIEWS

Annual product review reports were evaluated for a number of LOC, tablet and aerosol products. They were generally good, but they may not be complete or accurate.

Observations and Recommendations

1. In the case of the Aclovate Ointment report it states that there were no MRB issues yet there were at least 3 MRB reports in the review period concerning assays that were outside the assay guidelines. In the Diprolene A/F Cream report there is a similar statement that there were no MRB issues but there were at least 10 MRB reports in the review period with the same type of assay situation.

   Recommendation:

   There may be valid explanations for the apparent discrepancies in the reports reviewed. However, there needs to be review and approval of these reports to be certain that they are accurate and complete.

2. Annual product reviews prepared in Union are not provided to Kenilworth. Discrepancies exist in the annual reviews, which would have been corrected by Kenilworth, such as overcharge amount of Albuterol active is actually 3%, but is stated to be 2.5% in the annual report.

   Recommendation:

   This situation seems to indicate a need for production staff to review the annual product review reports.

3. The annual product review and the annual product report are not done on the same cycle. In fact, it appears these operations are done independently.

   Recommendation:

   We recommend that there be better coordination between the annual product review activity and the annual product report. In most companies, the annual product review forms the basis of the annual report, and in fact with minor changes the annual review document can often be submitted as the annual report.

4. The annual product review for Claritin-D® 24 reflected 45 of 752 finished tablet batches were rejected. Of those there were 35 rejected for high moisture, 5 for variable loratadine content. This would seem to reflect that the process is not validated. There also were 44 batches that had low granulation yield based on product hang-up in the equipment. This same issue has been seen with other products and it is not apparent that there has been a for cause investigation done to determine why product is hanging up in the equipment. There also were 307

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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New Jersey District 10 Waterview Blvd. Parsippany, NJ 07054 (973)526-6000	See last page
	FEI NUMBER 2210048

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Steve Chellevold, Senior Vice President, Technical Operations

FIRM NAME	STREET ADDRESS
Schering-Plough Corporation	2000 Galloping Hill Road
CITY, STATE AND ZIP CODE Kenilworth, NJ 07033	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. The Quality Control Unit failed to assure that drug products were manufactured in compliance with cGMPs and therefore have the safety, quality, and purity that they purport, or are represented to possess. The Quality Control Unit failed to uphold their responsibilities to assure valid performance of manufacturing processes, suitability of equipment, support systems, and analytical methods for their intended use, and prevention of contamination through proper cleaning procedures.

2. The process validation for many products fails to support claims that manufacturing processes were capable of consistently producing products with the same quality, purity, and safety. The Validation Department and Quality Control Unit routinely generate and approve protocols and reports, which contain critical deficiencies, as listed below.

   a. Validation protocols were routinely written and approved after the validation batch had been manufactured. For example, Validation Protocols for Proventil Syrup, Etrafon Tablet Cores, Trilafon Tablet Cores, Chlor-Trimeton Repetab Tablet Cores, Afrin Extra Moisturizing Spray, Diprolene Gel 0.05%, Elocon Cream, and Lotrimin AF Solution were not approved by all required Validation and QC members before the validation batches were manufactured.

   b. Established acceptance criteria in validation protocols were not always met during manufacturing of the validation batch. Summary reports are signed and approved by Validation and QC Department Management which state that the process was considered validated, despite failure to meet acceptance criteria.

   For example:

Product	Validation No.	Acceptance Criteria Not Met
Lotrimin Lotion	VAL-5-102	Clotrimazole Assay
Estinyl Cores	3-GEN-166	Assay, Hardness
	5-GEN 136	Content Uniformity
	4-ERS-1	Assay
	4-ERS-3	Assay
	6-ERS-4	Content Uniformity

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	Daniel Grabicki for Erin McCaffery Joy Kozlowski-Klena Matthew Spataro	Daniel Grabicki, Joy Kozlowski-Klena, Erin McCaffery, Matthew Spataro, CSO	1/19/01

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Nasonex Nasal Spray	VAL-8-40	Mometasone Furoate Assay
Proventil Inhalation Solution	VAL-6-153 VAL-6-154	Assay Assay
Claritin Syrup	VAL-9-41	Assay (multiple)
Beclomethasone Dipropionate clathrate rework	VAL-2-43	Uniformity of Temperature

c. Multiple deficiencies were observed with Process Validation Packages, which included, but were not limited to the following:

Lack of Validation Protocol	Lack of Acceptance Criteria	Lack of Validated Methods for all Required Tests
Celestone 0.6mg 7-GEN-15,16,17	Claritin D-24 Hr. ER Cores VAL-0-61	Aclovate Ointment VAL-5-127
CTM Family (multiple batches)	Celestone 0.6mg 7-GEN-15,16,17	Elocon Lotion VAL-5-145
Estinyl Family VAL-9-124	CTM Family (multiple batches)	Proglycem Oral Suspension VAL-5-253
Trinalin Repetabs 5-PAA-101-115		

d. Validation of the Claritin D-24 hr. ER Tablet process, using a drug substance from a new source (Schering, Singapore) was not adequate in that only one batch was manufactured. Change Authorization #CA-99-248 allows for the use of this alternate source. The new drug substance was used to manufacture batch #'s 0-DCS-257 through 0-DCS-340, approximately 95 batches.

Daniel Grabicki Daniel Grabicki for Erin McCaffery

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EMPLOYEE(S) SIGNATURE
Joy Kozlowski-Klena
Matthew Spataro

EMPLOYEE(S) NAME AND TITLE (Print or Type)
Daniel Grabicki, Joy Kozlowski-Klena, Erin McCaffery, Matthew Spataro, CSO

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e. Validation Study #VAL-9-41 for the reformulation of Claritin Syrup (addition of Edetate disodium as a preservative) was inadequate in that only one batch was manufactured using the new formulation. In addition, validation acceptance criteria for active and preservative assays were not met during analyses of post filtration and bulk samples. This batch was approved as a supporting validation batch for the reformulation on 4/29/99 by five individuals, and the batch was subsequently released.

f. The current revalidation Protocol, #VAL-0-61, for Claritin D-24 hr. ER Tablet Cores contained incorrect acceptance criteria, but was signed and approved by Validation, QC, and Manufacturing Departments. Specifications for two finished product tablet tests were erroneously included as the acceptance criteria for the tablet cores.

g. Aerosol Manufacturing Line 76 with the online stress testing heating blocks was not validated in that the two validation attempts have failed to meet the validation protocol acceptance criteria.

i. Validation Summary Report #Val-9-184, (validation for the use of the heating blocks for on-line stress testing for Proventil/Albuterol) was inadequate in that 1 out of the 3 original Validation Batches, #9-BBS-640, was rejected for excessive downtime and rejected canisters (purged cans). An additional Validation Batch, #9-BBS-643, was also rejected due to out-of-specification leak test results.

ii. A second validation attempt of the heating blocks for on-line stress testing was executed under Validation Summary Report #VAL-00-48. This validation was inadequate in that Validation Batch #'s 0-BBS-572, 0-BBS-573 & 0-BBS-574 failed to meet the process validation acceptance criteria for total content of Albuterol. Additionally, the rinse method utilized by the laboratory to retest the total content of Albuterol per canister was never validated.

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10. Laboratory and Manufacturing deviations were not adequately investigated according to written procedures, and in a way that provides a timely and scientific conclusion on which to base the disposition of a batch. For example:

    a. Impurity evaluation of Drixoral Tablets, batch #9-NRR-18, produced an unknown impurity at a level of 0.26%. An unknown impurity at a level of 0.20% was observed during release testing of Claritin D-12 Repetabs, batch #SS8-JRP-534. Neither of these results was investigated.

    b. Materials for Batch #9-GEN-350, Claritin D-24 hr. ER Tablets were weighed in 2/99, granulated in 5/99, and tested in 5/99. Upon receipt of the samples in the laboratory, QC Tech Services was contacted regarding the dull finish of the tablets. This batch was not investigated or rejected until 3/00, ten months later.

    c. Although batch #9-DCS-586, Claritin D-24 hr. ER Tablets failed to meet USP criteria for Content Uniformity, an investigation was not conducted until 9/19/00, six months after the failing results were obtained.

    d. There was no documented investigation into a missing gasket on a filter screen located on the recirculation line for aerosol filling line #58. An operator observed the missing gasket after the manufacture of Vanceril Inhalation Aerosol batch #0-AMA-236. There also was no documentation to show the filter was installed correctly with the gasket during the manufacture of aerosol products on this line.

11. The Product Quality Review (PQR) methods for the Delivery of Albuterol through the Actuator and Particle Size for Proventil Aerosol Inhaler were inadequate in that the methods exhibit various unidentified extraneous peaks. PQR Methods for Total Content of Albuterol per Can Assay and Estimation of Degradation Products were also inadequate in that there was a lack of resolution between typical unknown peaks from neighboring active or placebo peaks. These methods were used to test and release product batches, as well as stability samples, from 10/11/99-12/7/00.

Dan John Drabicki for Erin McCaffery

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Clarinex® (Desloratadine 5mg Tablets NDA 21-165)

17. There was no assurance that the manufacturing process, parameters, equipment, or protocols and their acceptance criteria, conducted and generated at multiple sites for the production of Clarinex (Desloratadine Tablets, 5 mg) are equivalent, or capable of producing product of the same quality. Batch records, including process parameters, and validation protocols, were written separately at each individual site without a comparison or joint review to ensure equivalency. Differences include equipment sizes and models, processing parameters, acceptance criteria established in protocols, and acceptance criteria for analytical method transfers.

18. The test method transfer from Schering, Kenilworth to Schering, Union failed to demonstrate that accurate and reliable results could be obtained from the QC laboratory. Method Transfer Protocols did not contain acceptance criteria for individual tablets during content uniformity testing, nor were there acceptance criteria for estimation of degradation products, or moisture testing results. There was no documented evaluation, or established Inter-Lab Reproducibility acceptance criteria for dissolution results generated at the 30-minute time interval, the revised specification.

19. The test method transfer from Schering, Kenilworth to Schering, Puerto Rico failed to demonstrate that accurate and reliable results could be obtained from the QC laboratory. Method Transfer Protocols did not include acceptance criteria for the comparability with the Development Lab's results for dissolution, content uniformity, or estimation of degradation products.

20. There was insufficient comparability data for the drug substance, Desloratadine, manufactured at the firm's Ireland and Singapore sites to assure equivalence of the drug substance supply. For example:

    a. Ireland batch #IRQ-97-7M2, used for clinical studies and Singapore batch #'s SI-34117X2-99-03 and SI-34111 7X2-99-4, used for site specific finished product stability studies (NJ batch # 75882-072 and PR batch #0790082) were not manufactured using the current micronization process.

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