DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER U.S. Food and Drug Administration CBER / OCBQ 1401 Rockville Pike, Suite 200N HFM-604 Rockville, MD 20852 (301) 827-6191	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Edwin H. Wegman	PERIOD OF INSPECTION See below	C.F. NUMBER 2424009
TITLE OF INDIVIDUAL President and Chief Executive Officer	TYPE ESTABLISHMENT INSPECTED Biological Drug Manufacturer	
FIRM NAME Advance Biofactures Corporation	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 35 Wilbur Street	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Lynbrook, NY 11563	CITY AND STATE (Zip Code) Same	

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. Out-of-specification lots of Santyl ointment have been released after it was determined the method of calculating potency based on a [redacted] relationship of standard to sample was in error. The Agency had been advised in July 1999 that the results of the study, "Demonstration of the Equivalence of Laboratory- [redacted] formulated Standard Collagenase Ointment and Actual Manufactured Standard Collagenase", approved 7/13-14/99 by Directors of Pharmaceutical Development and Quality Control, and the VP of Quality concluded that "there is no statistically significant difference in the results obtained from laboratory formulated and actual manufactured standard collagenase ointments". Later studies, conducted as early as January 2000, culminated with the reported conclusion in early June 2000 that historical potency data show that there is 70% recovery of the active in the ointment standard however, a 77% recovery in batches of final product ointment. Despite these findings, no modification to the existing method of determining potencies using the identified [redacted] conversion factor of [redacted] was made to SCP #102. Product continued to be released based on the earlier and erroneous [redacted] comparison of the results of these assays up to and including 7/25/00. From the beginning of June 2000 to July 25, 2000

   - Santyl Ointment Control No. 80254/ Packaging Batch 80255 (30.6 g tubes) was released for commercial distribution on 6/21/2000. Our review and recalculation of release potency data (using the recommended [redacted] conversion factor of [redacted] found the potency for each of the three tubes tested to be OOS with results of 68 (10^3) ABC units /200 gm; 69.9 (10^3) ABCunits/200 gm and 67.3 (10^3)ABC units/200 gm The specification for Santyl ointment is [redacted]

   - Santyl Ointment Control No. 3490-1017 (Exp 11/2002) (30.6 g tubes) was released for commercial distribution on 7/25/2000. This lot was a process validation lot. Our review and recalculation of potency data (using the recommended [redacted] conversion factor of [redacted] from samples collected throughout the filling operation found OOS results for six out of nine samples collected, ranging in potencies from 28.4 to 37(10^3) ABC units/200 gm The specification for Santyl ointment is [redacted]

   It was not until 7/26/2000 that a directive was issued to no longer use the current correction factor (which [redacted] with each assay) as the sole recovery factor in Ointment potency determination; a lot can only be released if it meets the potency specification using both [redacted] and [redacted] factor.

2. There is no established in-house master standard used to qualify the individual standards used in the potency testing of sterile Collagenase Santyl Ointment. Since August 1999, two ointment standards

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	Ann Marie Schofield	Ann Marie Schofield, CSO / Richard Thornton, CSO	8/11/00

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(0700A from Powder Lot P-99-02R and 0300 from powder Lot PK-99-01R) were qualified and approved by Quality Assurance on 7/12/2000 and 3/20/2000 respectively. This is a repeat Observation cited in the 1/28/99 FD483.

3. SOP 914, "Laboratory Investigation and Retest Procedure for Out-of-Specification (OOS) Test Results" dated 6/16/99, states that the QA Director can approve a second laboratory investigation (Phase II) of an OOS test result from a valid assay. The Phase II investigation allows for the retesting of the original sample (or new sample if original depleted) [redacted] additional times. The procedure states, [redacted] if all individual retest results, and their average, are within specifications. The procedure allows for the release of Santyl ointment lots with an initial OOS from valid assays, without extending the investigations into product history, production, or other lots effected.

   A. Since July of 1999, [redacted] lots with initial OOS results that were investigated and retested using this procedure have been released to distribution. Each of the investigations found no assignable cause and the lots were released with no investigations into the production of the lots or impact on other lots effected. For example:

      i. On 2/3/00, the middle and end sample tubes of lot 0000067144 failed to meet potency specifications [redacted] The phase I laboratory investigation determined the assay valid with no assignable cause for the OOS results (OOS 00-S002). The seven retests were initiated on 2/7, 2/14, 2/15 (2 retests), 2/23, and 2/29/00 (2 retests). Each of the seven retests for both the middle and end tubes were within specifications (middle tube range 49,000 - 58,600 ABC units / 200 g; end tube range 49,400 - 56,500 ABC units / 200 g). This lot was released for distribution on 5/2/00.

      ii. On 2/3/00, the beginning, middle and end sample tubes of lot 0000067143 failed to meet potency specifications (beginning tube 70,200 ABC units per 200 g; middle tube 76,000 ABC units / 200 g; end tube 67,200 ABC units per 200 g). The phase I laboratory investigation determined the assay valid with no assignable cause for the OOS results. Seven retests were conducted between 2/7 - 29/00. Each of the retests for the beginning, middle and end samples was within specifications (beginning tube range 49,400 - 61,100 ABC units / 200 g; middle tube range 52,800 - 60,700 ABC units / 200g; end tube range 45,100 - 60,200 ABC units / 200g). This lot was released for distribution on 5/2/00.

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iii. On 11/1/99, the end sample tube of lot 0000045979 failed to meet potency specifications with a result of 35,000 ABC units / 200 g. The phase I laboratory investigation failed to determine an assignable cause for the OOS and concluded the assay was valid. Seven retests of the original sample were initiated between 10/6/99 and 2/9/00. Each of the retests was within specifications (range 51,100 - 59,900 ABC units / 200 g). This lot was released for distribution on 3/17/00.

iv. On 12/21/98, the beginning sample tube of lot 34901148 failed to meet potency specifications with a result of 26,500 ABC units / 200g. The 6/30/99 Phase I laboratory investigation failed to determine an assignable cause for the OOS and concluded the assay was valid. Seven retests of the original sample were initiated between 6/18-29/99. Each of the retests was within specifications (range 42,200 - 63,300). This lot was released for distribution on 7/20/99. This lot has been associated with at least one adverse event report of lack of efficacy.

B. Protocol MSCP-003, Potency Evaluation for the Evaluation of In-Date Lots of Santyl Ointment, dated 7/29/99, was initiated to evaluate the product quality of all Santyl Ointment lots that were in-date. [redacted] lots were subjected to the previous retest/OOS procedure or were released based on the averaging of within specification results with OOS results. Retains of these lots were tested in accordance with the new procedure, SOP 914. Of the [redacted] lots tested [redacted] were determined to be acceptable based on the results of the 7 retests [redacted] in [redacted]

4. ~~SOP #916, Investigation and Retest Procedure for a Sterility Test Failure, is inadequate in that it does not require investigations to extend to other lots and production history.~~ REQUIRES Two of two investigations into sterility OOS results were incomplete:

A. On 8/12/99, turbidity was noted in the bulk sample of Collagenase ointment lot 35975. The sample was plated onto [redacted] and [redacted] plates and incubated. On 8/13/99, growth was observed on both plates, which was later identified as Bacillus pumilus. The investigation found no assignable cause and the lot was rejected. The investigation failed to extend to other lots effected in that a review of organisms isolated from the production area or the sterility test suite was not documented in the investigation. In addition, the bulk Collagenase powder lot, PK-98-01R was not investigated. This powder lot was sterility tested on 6/3/98 and released on 12/11/98. No additional sterility testing was conducted on this lot prior to incorporation into Santyl ointment lot 35975 on 6/29/99.

B. On 10/27/99, turbidity was noted in the bulk sample of Collagenase ointment lot 51234. The sample was plated onto [redacted] and [redacted] plates and incubated. On 11/2/99 growth was observed on the [redacted] plate and on 11/3/99 growth was observed on the [redacted] plate. The sample was identified as Bacillus

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pumilus. This organism was also isolated from the glove of a sterility test operator on the day of sterility testing. The investigation revealed that the operator reported difficulty obtaining a sample from the tube and concluded that the operator contaminated the sample and the OOS was invalidated. However, there is no evidence to support the conclusion that the organism originated in the sterility testing area. Additionally, the investigation failed to extend to other lots effected and the sterility of the bulk Collagenase powder lot, PK-98-02R, was not evaluated. The powder lot was sterility tested on 9/29/98 and released on 4/20/99. No additional sterility testing was conducted on this lot prior to incorporation into Santyl ointment lot 51234 on 9/30/99. Santyl ointment lot 51234 was retested for sterility on 1/5/00 and released for distribution on 2/10/00.

5. Concerning the "Supplemental Collagenase Santyl Ointment Blend Uniformity Study" approved by [redacted] and ABC on 8/12/99 to verify the uniformity of the mix in collagenase ointment:

   A. No assessment was made to demonstrate the relationship between the [redacted] used in the performance of the study (with its Formulated Theoretical Target value and acceptance ranges) and the ABC [redacted] assay and its established potency specifications. The ABC [redacted] method is used routinely to test for potency in samples collected over the filling operation.

   B. During the conduct of this study, low [redacted] values were obtained for the first three tubes filled plus a supplemental sample representing the sixth tube filled for Santyl validation batch 3490-0069. Values ranged between 0.56 to 0.63 [redacted] U/g (acceptance range was [redacted] Ointment samples began to be collected approximately [redacted] into the fill (at [redacted]) and tested by the ABC method with acceptable results (49.51, 51.74 and 48.32 ABC units x 10^{-3}/200 g [respectively]). The rate of the filling line was calculated to be approximately [redacted] The first passing [redacted] assay result was from a sample collected from the filling line at 9:15am

      i. No investigation was performed to address the appropriateness of the time when the routine initial sample is collected from the filling line to ensure it accurately represents the potencies of the first tubes filled, in light of the analytical data obtained from the [redacted] samples collected during the this study;

      ii. The investigation performed into the failing [redacted] method was limited to the review of records of equipment preparation, manufacturing, sampling and filling pertinent to this one lot. No assignable cause into the failures could be determined. [redacted] recommendation was to continue to monitor the first few tubes filled in the next several batches with the "purging of a

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specific amount of ointment from the system to ensure that the first tubes produced for the packaging meet the established criteria". The BPR does not require purging of the fill line prior to filling tubes of Santyl Ointment during routine production. The Disposition of this lot, approved by [redacted] on 7/9/99, was the discard of the first shipper of tubes ([redacted]30gm tubes) and the release of the remaining portion of the lot. The remaining portion ([redacted]1/30 gm tubes) was released by ABC[redacted] on 7/28/99.

Following the filling of Santyl Ointment Lot 3490-0069, Santyl Ointment lots 3490-0079, 3490-0089 and 33492 were filled and assessed per protocol requirements.

C. The lower acceptable collagenase powder potency of [redacted] ABC units per gram allowed for in SP #201, [redacted] Collagenase Powder, was not assessed in this study. Only the potency of [redacted] ABC units was assessed during this study. Since 1/99 to the present, the potency of powder used in the manufacture of Santyl Ointment fell within the range of 175,000-499,000 ABC units.

D. The study did not challenge the lower limits of the mixing temperature [redacted] and [redacted], only the temperatures between [redacted] and [redacted] were collected.

E. The study was not performed in a manner to demonstrate repeatability in that only [redacted] lots of 15 gram tube and [redacted] lots of 30 gram tubes with acceptable results were assessed. Batches of ointment filled into 30 gram tubes are mixed for shorter times than 15 gram tubes. The filling process for 15 gm tubes lots takes approximately [redacted] while the process for 30 gm tubes takes approximately [redacted]. During each of these filling processes, [redacted].

Homogeneity of the blending operation for Santyl Ointment was an issue cited on the 1/28/99 FD483. The letter issued to FDA on 5/8/00 stated the review and status of the protocol, sampling plans, test methods, studies and other aspects of the homogeneity study validation executed at [redacted] were complete.

6. Although a change in Santyl Ointment product appearance was observed, there have been no studies conducted to assure that this change has no adverse effect on product purity, potency, and stability. In February 2000, the Material Safety Data Sheet was revised to change the product appearance from opaque with off white to tan color to opaque, white to off white in color, with suspended dark enzyme particles. Black or brown specks have been observed in product complaint and retention samples.

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7. There are no documented training records for the visual description test conducted at regular stability testing intervals and during assessment of product appearance complaints. Additionally, there is no reference material that the employees can refer to during this test.

8. Investigations into product complaints were incomplete, and the data was not evaluated for adverse trends. Specifically:

   A. [redacted] of the [redacted] product complaints received from 1/99 to 7/00 reported brown and/or black particles in Santyl ointment. Although the presence of black/brown specs were confirmed in returned and retain samples, the particles were not isolated, identified or evaluated for particle size. For example:

      i. Complaint investigations 99-001, 00-003, and 00-004 reported that the particles noted in returned samples and retains of lots 34900838, 34900458, 67147 and 70751 broke apart when pressed with finger.

      ii. The visual inspections of the returned/retain samples confirmed the presence of brown/black specks in several lots, and the investigations stated that the particles were believed to be Collagenase powder suspended in petrolatum. For example, complaint #99-001 reported "rusty specks" in Santyl ointment lots 34900458 and 334900838. The investigation confirmed "brown specks" in both the returned samples and retains samples of the lots, and concluded that the "ointment is similar to other bulk samples and retention tubes." The response to the complainant concluded "although it is not possible to determine the nature of the brown particles, we strongly believe that the brown particles are collagenase powder particles suspended in the petrolatum." However, there are no finished product specifications for visual appearance and the visual inspection specifications listed in the Santyl ointment stability protocol does not include brown or black specks in the product description. The specification states that the ointment should be "off-white to light straw colored" showing homogeneous dispersion of collagenase powder.

      iii. Complaint investigation #00-003 documented that several complaints of this nature have been received since Collagenase powder lot PK-96-05R was manufactured. However, there was no investigation into the manufacturing process of the [redacted] bulk.

      iv. Complaint investigations 00-007, 00-006 and 00-003 concluded that "the only way to explain the observation (brown/black specks) is the recent change in the manufacturing procedure. The previous [redacted] sterilization process, which yielded a darker and yellow ointment, has been

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replaced by a new procedure of [redacted] sterilization, which yields a lighter, more clear ointment base. The lighter, clear base provides an enhanced base to observe the dark enzyme particles." However, since 4/28/99 [redacted] of the [redacted] lots implicated in complaints of brown/black specks were produced with the old sterilization process.

v. Complaint investigations 99-001, 99-002, 00-003 and 00-004 reported that retain and returned samples were compared to other ointment lots manufactured by the same bulk lots. However, there is no documentation of this visual inspection. For example, Complaint 00-003 documents that the ointment removed from returned sample of Santyl ointment lot 67147 is similar in nature to retain samples of other lots manufactured from Collagenase powder lot PK-98-03R. However, there is no documented visual inspection of retain samples of other lots.

vi. Complaint #00-006, requested the examination of retain sample of lot 44236 for brown/black particles. The sample examination section of the complaint investigation ~~documents that there was no examination~~ ("Sample Examination: None"). Response letter to the complainant, dated 7/20/00, reports that retain samples of this lot were examined and revealed no anomalies.

vii. Complaint #00-003 included potency testing of the returned sample of lot 67147. This testing was initiated on 7/5/00 and reported an uncorrected potency value of 52,490 ABC units / 200 g and a corrected potency value of 59,800 ABC units / 200 grams. However, use of the firm's 6/99 proposed correction factor ([redacted]) would result in an OOS result, 68,237 ABC units / 200 grams (specification [redacted] ABC units. No further investigation was conducted.

viii. Complaint #99-001 reported brown flecks Santyl lots 34900838 and 34900458. The complainant stated lot 34900838 had more specks that lot 34900458. Visual inspections of the returned samples and retains of both lots confirmed the presence of brown particles. However, the investigation did not address the report of a difference in the amount of particles observed.

B. There is no system in place for evaluating adverse drug events to determine if a complaint investigation is warranted. Review of the Adverse Reaction files revealed that from 1/99 to the 7/00, [redacted] complaints of lack of effect and [redacted] complaints of burning/pain at the application site were received. For example, MedWatch report #S00074-99 dated 10/11/99 and #S00071-99 dated 8/16/99 reported that Santyl ointment lot 34901148 did not exhibit the normal color and smell and was ineffective. The investigation into this complaint (Complaint #99-004) only investigated the appearance and odor of the lot, and failed to address the lack of effect complaint.

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9. There is no assurance that the [redacted] Collagenase powder remains stable throughout its unspecified shelf life. Specifically:

   A. The integrity of the container / closure system (hermetically sealed flexible plastic bags) of the sterile Collagenase powder has not been evaluated.

   B. There is no stability data demonstrating the [redacted] powder meets sterility and moisture specifications at time of finished product manufacture.

10. There is no assurance that the [redacted] and [redacted] process achieves the desired particle size and a uniform blend.

   A. Processed Collagenase powder is not tested for particle size.

   B. Post-[redacted] and post-[redacted] samples of the processed Collagenase powder, which are tested for moisture, potency and Collagenase activity, are not representative of the lot in that the Master Formula does not define the method for collecting the post-blended samples. Additionally post-[redacted] samples are obtained in the following manner: As the [redacted] of the [redacted] powder is poured into a plastic bag, [redacted] samples are obtained and labeled as [redacted] samples labeled as [redacted] are collected as the [redacted] of the [redacted] powder is poured into the plastic bag. The [redacted] samples labeled [redacted] are collected as the [redacted] of the [redacted] powder is poured into the plastic bag.

   Additionally, there is no assurance that the collagenase bulk API powder used in the preparation of the ointment testing standard ~~is collected in a manner which assures it~~ is representative of the lot. This is a repeat Observation cited in the 1/28/99 FD483. Ares 8/11/00

11. Evaluation and Interpretation of potency data are not consistently performed. Specifically, SOP #915, [redacted] for the Potency Assay of Collagenase Ointment, requires that a [redacted] test be conducted on potency assays. This test is conducted to ensure at least a [redacted] confidence that the lot under test falls within the specified product limits for potency ([redacted] ABC units / 200 g). The confidence interval is calculated from the potency values obtained from the [redacted] lot test samples. However, this test is not applied to potency assays that produce an initial OOS value, as the OOS procedure only requires the retesting of the individual tube(s) producing the OOS, and does not require the testing of all three tubes.

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12. Reports of problems encountered during sterility testing are not assessed for deviations requiring investigations and corrective actions. These reports are documented on paper towels and are attached to the sterility test record with a paperclip. The records are not signed or dated.

    A. Review of these reports from July 1999 to the present revealed 4 instances where the sterility testing was not conducted in accordance with validated procedures. The paper towels attached to the sterility test records dated 2/1/00 and 1/4/00 documented that [redacted] media was mixed in the [redacted] canisters. The paper towels attached to sterility test records dated 10/26/99 and 10/19/99 documented that during the testing [redacted] media was mixed in [redacted] canisters. No deviation reports were initiated. There was no documented evaluation of the integrity of the product samples.

    B. The paper towel attached to the sterility test record for lot 35982 dated 8/3/99 documented that dirt was observed "under the cap" of the bulk sample. Bulk samples consist of the [redacted] tubes off of the fill line. There was no deviation initiated to investigate this occurrence.

13. The ABC Quality Assurance responsibilities of operations at the contract manufacture are not defined. For example:

    A. There is no procedure in place for conducting audits of the [redacted]

    B. There is no oversight of the stability program. The [redacted] is responsible for determination of which Santyl ointment lots are placed on stability, and storage of stability samples. ABC does not know which lots have been placed on stability until receipt of the six-month stability samples.

    C. There is no system in place for tracking and trending of process deviations. Deviation reports are filed in individual batch records.

    D. There is no assurance that reports of Adverse Events are being handled in a manner to obtain all required information when available. Of the [redacted] adverse event reports received since January 1999, only one report included a lot number. Receipt of adverse event reports has been subcontracted out to a third party.

    E. A Validation study for ABC's licensed product has been conducted without the review and ~~oversight~~ Approval of the ABC Quality Assurance unit. In addition, sampling plans used did not ensure an accurate assessment of normal production processes, and complete investigations into study failures were not

Subsequent

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performed. Notably, during the period 7/1/99-12/17/99 a Collagenase Santyl Ointment Blend Uniformity Verification Study, approved as completed on 6/13/00, was performed to verify the blend uniformity for Santyl Ointment batches manufactured in the approved manufacturing facility [redacted]. During this study, [redacted] batches were tested by [redacted] of [redacted] by the combination of [redacted] formed with the [redacted]

i. The protocol was generated, the study was conducted and final report summary with conclusions was generated outside of ABC's approval ~~and/or oversight~~ AMS 8/11/00

ii. No assessment was made to demonstrate the relationship between the [redacted] used in the performance of the study (with its Formulated Theoretical Target value and acceptance ranges) and the ABC [redacted] assay and its established potency specifications. The ABC [redacted] method is used routinely to test for potency in samples collected over the filling operation

iii. In this study, two lots failed due either to non-detectable [redacted] units/gm (Batch 53653) or low [redacted] units/gram potencies from the samples collected from the beginning of the fill (Batch 9279). Batch 59279 consistently had passing [redacted] results from samples collected from the beginning, middle and end of the filling operations, while Batch 53653 had OOS (low) results. Although the investigation report into these failures noted the relationship of the [redacted] to the [redacted] Assay is not known, the reason for rejection was based on the "presence of water in the filling line, and the uncertainty of the effect of water on the product". No investigation into the adequacy or capabilities of the [redacted] assay was performed subsequent to these failures

iv. Memoranda filed in Batch records for at least [redacted] of the lots subject of this study directed that in each lot, [redacted] tubes be filled [redacted] of the [redacted] tubes for the [redacted] The normal production/filling of Santyl ointment outside of this study does not require the [redacted] of [redacted] units from the filling line [redacted] to the first commercial unit. For example,

a. The BPR for lot Santyl Ointment 30gm lot 65030 filled on 12/20/99 can only account for [redacted]30 gram tubes pulled from the filling line for weight check and [redacted]/30gm tubes collected for "residue", both prior to first unit generated for commercial distribution;

b. BPR for lot Santyl Ointment 30gm lot 65031 filled on 12/22/99 can only account for [redacted]30 gram tubes pulled from the filling line for weight check and [redacted]30gm tubes collected for bulk sterility, both prior to first unit generated for commercial distribution

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ann Marie Schofield	Ann Marie Schofield, CSO / Richard Thornton, CSO	8/11/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER U.S. Food and Drug Administration CBER / OCBQ 1401 Rockville Pike, Suite 200N HFM-604 Rockville, MD 20852 (301) 827-6191
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Edwin H. Wegman	PERIOD OF INSPECTION See below C.F. NUMBER 2424009
TITLE OF INDIVIDUAL President and Chief Executive Officer	TYPE ESTABLISHMENT INSPECTED Biological Drug Manufacturer
FIRM NAME Advance Biofactures Corporation	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same
STREET ADDRESS 35 Wilbur Street	STREET ADDRESS OF PREMISES INSPECTED Same
CITY AND STATE (Zip Code) Lynbrook, NY 11563	CITY AND STATE (Zip Code) Same

c. BPR for lot Santyl Ointment 30gm lot 65033 filled on 12/28/99 can only account for [redacted] 30 gram tubes pulled from the filling line for weight check and [redacted] 30gm tubes collected for bulk sterility, both prior to first unit generated for commercial distribution.

14. Stability testing was not conducted as required by the Collagenase Santyl Ointment Stability Study Protocol. Specifically, the protocol requires performance of the physical description and potency test at [redacted] and [redacted]-month intervals. The general safety test and sterility testing is required at the [redacted] month interval. However, review of the stability data revealed that testing was not always conducted in accordance with these intervals. For example:

A. Santyl ointment lot 34900015 was placed on stability on 2/22/95. Although the [redacted]-month stability samples were received from [redacted] on 10/1/99, the potency testing was not conducted until 6/28/00.

B. Santyl ointment lot 34900756 was placed on stability on 8/14/96. Although the [redacted] month stability samples were received from [redacted] on 8/2/99, the visual description and potency testing was not conducted until 6/19/00 and 6/28/00 respectively.

C. Santyl ointment lots 3401007, 3401017, 3401027, 3401037, 3401047 & 3401057 were manufactured in 12/97. The [redacted]-month stability testing was conducted on [redacted] and the [redacted]-month stability testing was conducted on 1/5/00.

15. Validation Protocol MVP-002, Equivalency Study of the Moisture Content Determination, dated 6/18/99, was designed to determine the equivalence of the ABC moisture assay with the "USP 23, Fifth Supplement <731>" method used be a contract laboratory. There is no justification for the acceptance criteria of [redacted] variability between the two methods. In addition, the executed protocol dated 8/9/99 fails to provide documented rationale as to why the results obtained during the study (9.60%, 12.86%, 6.27% and 11.29% variability between the laboratories) are considered equivalent.

OBSERVATIONS 1-15: UNDER CONSIDERATION

13A. CORRECTED + UNVERIFIED

ADDENDUM: DATES OF INSPECTION - 7/20-21, ~~28~~ 24-28, 31/00, 8/1-4, 11/00 AMS 8/15/00

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ann Marie Schofield	Ann Marie Schofield, CSO / Richard Thornton, CSO	8/11/00

On 8/15/00, I advised Mr. Wegman of the [illegible] AMS