ADVANCE BIOFACTURES CORPORATION

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September 01, 2000

Mr. Steven Masiello
Director, Office of Compliance and Biologics Quality, HFM-604
Center for Biologics Evaluation and Research
US Food and Drug Administration
1400 Rockville Pike, Suite 400 South
Rockville, MD 20852

Dear Mr. Masiello:

The attachment to this letter responds to the observations in the FDA 483, issued on August 11, 2000, covering an inspection conducted by Ms. Ann Marie Schofield and Mr. Richard Thornton at our facility on July 20, 2000 through August 4, 2000. We would like to acknowledge the thoroughness and the professionalism of Investigators Schofield and Thornton during this inspection and our appreciation of their helpful suggestions.

This submission is intended to demonstrate Advance Biofactures Corporation's continued commitment to be in substantial compliance with current Good Manufacturing Practices and other FDA regulations as they apply to the manufacture of our product, Collagenase Santyl® Ointment. The response is formatted such that each of the FDA 483 observations is reiterated in a tabbed section corresponding to the observation number, followed by our response to each observation. Documentation referred to in each response will be included as numbered attachments appended to each response.

We look forward to resolving the issues identified in the recent FDA 483 in a responsible, timely and cooperative manner. We will be contacting you within ten days from the date of this submission to CBER, to schedule a meeting if necessary and address any issues that may still be of concern to CBER.

It is respectfully requested that copies of our response to the FDA 483 be included with any request for the FDA 483, with the exception of attachments in the response that are considered "Confidential" in accordance with the Freedom of Information regulations.

If you should have any questions regarding this response, please do not hesitate to contact the undersigned at (516) 593-7000.

Sincerely yours,

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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 - 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 there is a 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) ABC units/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.

We acknowledge the concerns of the investigators regarding the delay in adopting the new universal extraction correction factor and we have taken immediate measures as discussed below to address these concerns. It should be noted, however, that we were adhering to a written, step-wise, plan for implementing the new [redacted] extraction correction factor which allowed implementation after certain defined steps had been achieved (Attachment 1), and adequate documented studies completed to support this action.

The change from a [redacted] correction factor [redacted] to a universal extraction correction factor [redacted] is a direct result of the progress of our efforts to comply with our Corrective Action Plan (CAP), specifically CAP items Q1 through Q5, originally submitted to CBER in June 1999. These CAP items were intended

to address all of the observations regarding the ointment potency assay that were mentioned in the January 28, 1999 FDA 483. The change from a [redacted] correction factor to a [redacted] correction factor provides an important step forward to improving the quality control of our product. However, it needs to be recognized that this neither alters the test methodology nor changes the existing release specifications. This change provides for important lot-to-lot linkage, enhanced accuracy in the potency value, and product reliability. (See further explanation in Attachment 2). Our response to observation 2 from the August 11, 2000 FDA 483 contained in this response provides a complete discussion on the concept and advantages of a [redacted] correction factor.

Following the completion of the comprehensive method validation studies conducted from May 1999 to January 2000, an attempt was made to establish a [redacted] correction factor, which was initially determined to be [redacted] We subsequently realized that this was not an accurate number. Several weeks before the July 2000 inspection, Advance Biofactures identified a possible explanation for the inaccuracy of the [redacted] figure, based upon a partial review of historical data (approximately 6 years). At the same time, on the basis of a different approach and a review of a much larger data base, we realized that the conclusions reached in a July 1999 study ("Demonstration of the Equivalence of Laboratory-Formulated Standard Collagenase Ointment and Actual Manufactured Standard Collagenase") needed revision. Prior to the July 2000 inspection, we finalized an implementation plan for CAP item Q5 (Attachment 1) to define the next steps necessary to implement a [redacted] correction factor. At that point, we began to analyze a larger data set to arrive at a more accurate correction factor. In order to summarize the approach to all of the issues involved with the potency assay, to provide an answer to CAP item Q2 and to explain the inaccuracy of the [redacted] correction factor, we provided the FDA Investigators with a draft addendum to our method validation report (CAP item Q5), titled "Preliminary [redacted] For Santyl Ointment Potency Determination - Systematic Comparison of Laboratory-Formulated Standard Collagenase Ointment and Actual Manufactured Standard Collagenase Ointment". This draft addendum projected a [redacted] correction factor of [redacted] based on approximately 8 years of data. The draft addendum, which contained incomplete data at the time of the inspection, was scheduled for completion, finalization and approval by August 1, 2000, in accordance with our implementation plan. Because of the inspection, the completion of this addendum was delayed and was not finalized and approved until August 18, 2000. The completed addendum, now based on 10 years of data, confirmed the preliminary [redacted] correction factor of [redacted] This addendum completed the second part of the Method Validation Report: The Potency Assay for Collagenase Ointment (SCP 102). A copy of the addendum is provided in Appendix 2 of Attachment 2.

It needs to be recognized that it was Advance Biofactures who had, prior to the FDA inspection, identified this issue and had already initiated actions aimed at incorporating the findings into our implementation plan for improving the assay. A draft document titled "Action Plan To Follow the Implementation of the Universal Correction Factor", which was signed off by the Director QC on

July 21, 2000, prior to the discussion of this issue with the FDA Investigators, provided a contingency plan to address the potential impact of the [redacted] correction factor on product in the field. Specifically, the document described a plan for re-calculating the lots within expiry based on the new [redacted] correction factor, subjecting them to an investigation procedure if OOS results are obtained and, if appropriate, recalling the lots in question. A copy of the draft action plan was provided to the FDA Investigators during the inspection. A copy of the finalized action plan is provided in Attachment 3.

In addition to the above, based on the concerns of the FDA Investigators on this issue, we:

1. Sent a facsimile, from our Director QA, to the Senior Director QA at [redacted] on [redacted] informing [redacted] to put a hold on the last [redacted] ointment lots released (Attachment 4). It should be noted that the [redacted] lots cited in the August 11, 2000 FDA 483 (i.e., 80254 and 3490-1017) were among the [redacted] lots placed on hold.

2. Issued a memorandum (Attachment 5), from the Director QA on July 26, 2000, stipulating that, prior to the official implementation of the new [redacted] correction factor, a lot can only be released if it meets the potency specification as determined by using both the new universal and the variable extraction correction factors.

As noted by the FDA Investigators, the potency of ointment lots 80254 (packaging lot 80255)and 34901017, when re-calculated using the new [redacted] correction factor of [redacted] was out-of-specifications (OOS). Advance Biofactures Corporation has re-calculated the potency of the following:

1. All ointment lots released by Advanced Biofactures Corporation and/or submitted to CBER after June 1, 2000.
2. All ointment lots tested for release after June 1, 2000.

When re-calculated using the new [redacted] correction factor, the potencies of ointment lots 67145 and 80262 were also found to be OOS. Lots 67145, 80255, 80262 and 34901017 had been released for distribution based on their potencies being within specifications when calculated according to the approved license procedure, which required the use of a variable [redacted] factor. On July 26, 2000, our [redacted], was requested in writing to put ointment lots 80255, 80262 and 34901017 on hold. On August 21, 2000, our distributor, [redacted], was requested in writing to put ointment lot 67145 on hold. It should be noted that none of the aforementioned batches were on the market. As noted above, these batches will be subjected to further investigation before any decisions regarding their disposition are made.

As explained to the FDA Investigators during the inspection and as discussed above, the report establishing the new [redacted] factor was not completed, finalized and approved at the time the ointment lots cited (i.e., 81255

and 34901017) in this FDA 483 observation were released by Advance Biofactures Corporation. Based on the concern expressed by the FDA Investigators regarding the release of these lots, Advance Biofactures Corporation immediately issued a policy statement (Attachment 5) on July 26, 2000 indicating that, during the transition period prior to finalizing the new [redacted], no ointment lots could be released unless the potency specification was met, as calculated by both the variable and the new [redacted].

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 (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.***

Advance Biofactures Corporation (ABC) took this observation seriously when it was first cited in the January 28, 1999 FDA 483 and had taken steps to address it. The activities required to address this observation were incorporated into our Corrective Action Plan (CAP), which was submitted to the FDA in June 1999. As progress was made in addressing this observation, the CAP was updated and these updates were periodically submitted to the FDA.

As described in this observation, the potency of the ointment is tested against an individual ointment standard. This was based on the following reasoning:

1. Individual ointment standard was assumed to be Collagenase Powder lot-specific and could, therefore, not be used for any ointment lot made from a different Collagenase Powder lot. (As noted below, it was subsequently learned that the Collagenase extraction from ointment was not Collagenase Powder lot-specific.)

2. Individual ointment standard therefore could not be calibrated against any master standard.

It should be noted that, if item 1 is true, then it is very difficult to establish a master standard. This is why ABC could not simply and immediately designate any single ointment lot as a master standard. This further explains why we could not treat this FDA 483 observation concerning a master standard as an isolated issue. We incorporated this master standard issue into the CAP and used a systematic approach to address it. After re-characterization of the potency method, it was concluded that the extraction of Collagenase from ointment was not Collagenase Powder lot-dependent. This finding made it possible to have a master ointment standard or to establish a [redacted] as was noted in observation 5 in the January 28, 1999 FDA 483.

As of August 2000, ABC implemented the use of a [redacted] in lieu of a master standard for the potency testing of Collagenase Santyl® Ointment. In this response, we will discuss the validity of the [redacted] and demonstrate why the [redacted] is preferable to a master standard. The rationale for this follows.