January 28, 2011

U.S. Food and Drug Administration
Minneapolis District Office
Mr. Gerald Berg, District Director
250 Marquette Avenue, #600
Minneapolis, MN 55401

Re: Inspectional Observations Dated January 7, 2011

Dear Mr. Berg:

H&P Industries is writing with an initial response to the Inspectional Observations presented at the closeout meeting on January 7, 2011.

Due to the seriousness of the inspection and observations described, H&P Industries has implemented the following re-structuring and outsourcing plan to achieve compliance for all products manufactured.

For clarification, H&P Industries, Inc. is the manufacturer and Triad Group, Inc. is the distributor. HH&P, the New Jersey Operation, has been rolled into H&P Industries. As of January 11, 2011, the New Jersey facility has been completely vacated. All controlled documents will be changed over to the H&P Industries logo and incorporated into the current document control system as an on-going process.

Restructuring of the Quality Unit

The Quality Managers report to an independent third party group led by (b) (4) (Attachment 1A resume). (b) (4) has been appointed Quality Director and is responsible for overseeing the day-to-day operations of the Quality Control Laboratory, Quality Control, and Quality Assurance. In addition, she will also provide regulatory support. (b) (4) has been contracted for a minimum of six months and will physically be on site.

As a result of the inspection, H&P Industries has recognized that clear, defined roles and responsibilities have not been established for the Quality Unit. The immediate action taken to address this is to have all Quality Managers report to (b) (4) and responsibilities have since been defined within the organization. In addition, a training gap analysis has been performed for Quality Assurance, Quality Control Laboratory, and Quality Control. Additional training has been scheduled to introduce the new structure and close gaps with current systemic failures. Please see the attached Quality Organizational Chart for each respective department (Attachment 1) and Page 3 for a training plan schedule.

The following actions have taken place in the last 15 business days:

1. The following individuals have been hired:
    a. A Complaint Specialist
    b. A Validation Manager, Eric Wentorf (Attachment 1A resume)
2. A CAPA Coordinator/Complaint Specialist has transferred from New Jersey
3. A (b) (4) individual has been assigned as a batch record reviewer
4. The former laboratory manager and stability coordinator has been terminated
5. The Quality Manager overseeing the New Jersey facility has been terminated
6. A degreed microbiologist is sampling and reviewing all Environmental Monitoring results
7. Owner/COO is not involved in any quality decisions
8. Supplier qualifications continue to be scheduled and conducted for Over The Counter (OTC) liquid product actives, lubricating jelly and sterile alcohol
9. (b) (4)
10. Quality Unit has been restructured
11. An employee has been dedicated to past and current Phase I Out Of Specification (OOS) investigations
12. An employee has been dedicated to Phase II OOS investigations
13. An employee has been assigned responsibility for the coordination of the stability testing program.

1.0 Quality System Short and Long Term Plan

In addition to the 2010 internal Quality Assurance audit, a gap analysis was performed in 2010. H&P Industries has considered the results of the gap analysis and the 483 inspection observations in developing both short and long term plans to achieve compliance. The following systems and procedures will be revised and implemented by January 31, 2011:

A. Short Term Plan

1. Control of Original Records

All original lot histories and batch records have been moved (b) (4) (b) (4) room. (b) (6) is responsible for the controlled storage, filing system, and release of records for review purposes only. A limited list of authorized users has been implemented to control records needed for a variety of investigations. Furthermore, all 2011 lot histories and batch records will be scanned to a read only drive. The scanned version will serve as the back up to the original record.

(b) (4)
(b) (4) This document room contains, but is not limited to: Validation Documents,

Training Files, Master Batch Records, SOPs, Work Instructions, Laboratory Test Methods, and Regulatory Documents.

2. Training Program

The H&P Industries training program was in the process of being overhauled prior to the inspection. The revised SOP includes training modules and competency assessments for specific departments, a revised new employee orientation (including future temporary employees), and (b) (4) cGMP training. As department specific training is created, it will be added to the SOP. Refer to the attached Training SOP, and example Competency Assessments (Attachment 2).

As a result of the training gap analysis, the following training schedule has been established:

Department	(b) (4) cGMP	Completed Training Module	Refresher Training
Quality Assurance	March 15, 2011	January 28, 2011	(b) (4)
Validation	March 15, 2011	February 18, 2011	
QC Laboratory	March 15, 2011	January 28, 2011	
Quality Control	March 15, 2011	January 28, 2011	
Warehouse	March 15, 2011	February 18, 2011	
Batching	March 15, 2011	February 18, 2011	
Customer Service	March 15, 2011	April 15, 2011	
Engineering	March 15, 2011	April 15, 2011	
R&D	March 15, 2011	Not Applicable	
Front Office	March 15, 2011	Not Applicable	
Production	March 15, 2011	February 18, 2011	

3. Deviation Procedure

The Deviation SOP was revised to remove the QA Investigation SOP, which was redundant to the CAPA and OOS procedures. In addition, the form was revised to remove redundant information. Formal classroom training was conducted on January 14, 2011 and the revised SOP and Form were made effective on January 17, 2011. The training included a review of the changes, instructions on clearly documenting what transpired during the deviation, providing adequate justification and supporting documentation, and notification to QA. The competency assessment included a test case where the trainees completed a deviation on the new form. The Quality Systems Manager conducted the

training for QA, QC Lab, QC, Validation, Purchasing, and Operations. A copy of the revised SOP, Form and Training Roster is included (Attachment 3).

4. Notice of Destruction Procedure

During the inspection, it was clear the Notice of Destruction Work Instruction was not adhered to and the Form, in several cases, could not be located.

To further ensure traceability, a complete re-write of both the procedure and the form was performed. The SOP provides clear responsibility of which department is responsible for completing the notice of destruction. Quality Assurance will maintain a logbook and all original documentation. Formal classroom training was conducted by the Quality System Manager on January 21, 2011 and the new SOP, Form, and Logbook were made effective January 24, 2011. Training was conducted for QA, QC Lab, QC, Validation, Purchasing, and Operations. Training included a summary of the FDA inspection and examples of how the previous procedure and form were not followed, a review of the new SOP, Form, and Logbook, and completing a case study with the new form and SOP. A copy of the revised SOP, Form and Training Roster is included (Attachment 4).

5. Quality Assurance Release and Rejection of Finished Goods

The responsibility of release of finished goods by QA was in the process of being overhauled prior to the inspection. As a result of the inspection, the SOP has been revised to include QA physically tagging finished goods as Released or Rejected. The QC Inspectors previously performed this function; In addition, QA will enter released finished goods electronically into inventory therefore, the entire process of releasing and rejecting finished goods into inventory is controlled by Quality Assurance.

Formal classroom training was conducted by the cGMP Trainer on January 27, 2011. The new SOP, Form, and labels will be effective January 31, 2011. Training included a summary of the FDA inspection and examples of how the previous procedure and form were not followed, a review of the new SOP and Form and completing an example release and rejection. Training was conducted for QA, QC Lab, QC, Warehouse, and Operations. A copy of the revised SOP, Form and Training Roster is included (Attachment 5).

6. General Rejection Procedure

The General Rejection procedure is in the process of a complete re-write. The SOP and Forms are routing for review. It is expected that the revised SOP and Forms be effective by February 20, 2011. Formal classroom training will be conducted.

7. Document Control

The Document Control System was in the process of being reviewed prior to the inspection. A review of all of the procedures for each department and manufacturing rooms is in process. H&P Industries will continue to review and assess and obsolete duplicate and redundant procedures. In addition some procedures may be combined for efficiency and to simplify all areas. Over the years, H&P Industries has been reactive to regulatory and customer inspections in creating documents rather than investigating root cause for correction.

This project is expected to take several months and may extend over a year for the entire facility. The status of the SOP/Procedure Master List will be included in future updates.

8. Environmental Monitoring

A formal Environmental Monitoring (EM) Program is being established at H&P Industries. An Environmental Monitoring SOP has been written (effective 01/28/2011) which includes a schedule of sampling for each area. To date, the following areas are being monitored: Blue Room Batching and Filling, Red Room Batching, and the Environmental Control Room. The EM Program will expand to all applicable areas of the facility over the next three to four months.(b) (4) has been qualified to perform all of the testing. In addition,(b) (4) performed on site training to H&P Industries employees ((b) (6)) to perform sampling. The training was conducted on January 12, 2011. The Environmental Monitoring Program Project Lead is(b) (6) is a microbiologist by degree and is responsible for sampling and reviewing results upon receipt. The EM Project Lead trained a back up for sampling on January 19, 2011. A copy of the new SOP and training records (Attachment 6).

9. Updated Supplier Qualification List

Prior to January 1, 2010, the following suppliers were paper audited by H&P Industries:

SUPPLIER'S NAME	CITY	ST	AUDIT TYPE	YEAR AUDITED
(b) (4)				

SUPPLIER'S NAME	CITY	ST	AUDIT TYPE	YEAR AUDITED
(b) (4)				

After September 1, 2010, the following on site audits have been completed or scheduled (up to February 24, 2011). These will be completed to comply with SOP-QA-010.

SUPPLIER'S NAME	CITY	ST	AUDIT TYPE	YEAR AUDITED
(b) (4)				

H&P Industries continues to actively contact and schedule supplier audits across the (b) (4) Updates will be provided as part of the on-going response.

B. Long Term Quality System Plan

Quality Assurance has identified the following systems for review as part of a long term quality improvement plan to achieve compliance.

System	Timeline to Implement
1. Housekeeping and Handling of Cleaned Equipment and Utensils	March 1, 2011
2. Complaint Investigations	April 1, 2011
3. Change Control	April 1, 2011
4. CAPA	April 1, 2011
5. Nonconforming Products	April 15, 2011
6. Handling of OOS Results	February 15, 2011
7. Incoming Inspection Procedures	May 1, 2011
8. Bioburden and Sterility Testing Methods	April 15, 2011
9. (b) (4) QA Metrics	April 15, 2011
10. Calibration Program	May 1, 2011
11. Preventive Maintenance Program (including Compressed Air System, Process Water System)	May 1, 2011
12. Annual Product Review	May 1, 2011
13. Monitoring of Process Water System	February 15, 2011
14. Validation Master Plan and Implementation of Department SOPs	March 1, 2011
15. Labeling Controls	April 1, 2011
16. Warehouse Controls	March 1,2011

These systems will be reviewed and revised over the next three to four months as necessary to improve effectiveness and clarity. Personnel will then be trained to understand the revised procedures and to properly document these activities. The CAPA Program will be implemented to investigate root causes and to develop corrective and preventive action plans to ensure effective action is taken; effectiveness checks will be performed.

Quality Control Laboratory Management

The Quality Control Laboratory has experienced systemic failures and has been inadequately staffed and managed. As a result of the most recent inspection and failures, effective December 2, 2010, microbiological testing of samples collected in process, stability samples, finished goods, and process water monitoring samples were outsourced to a qualified micro-lab (b) (4).

Each QC Lab employee will (b) (4) but they will report to the QC Lab Manager. The Lab Manager will be responsible to assign trained lab employees to conduct product testing, perform stability testing, evaluate OOS results, and to support method and process validation activities.

When corrective action is indicated to address confirmed OOS results, a CAPA will initiated and tracked to ensure closure and effectiveness.

Additional support with microbiology training will be added to oversee product bioburden testing, monitoring water quality, oversee dose auditing and trending. (b) (4) (b) (4)

(b) (4) analytical chemists have been recently added to the QC lab organization. These individuals will support method transfer activities related to products transferred from the NJ facility. These tasks include equipment validations (b) (4) method validation, and also include review and revision of all raw materials specifications (to meet USP requirements); and improvement and revision of lab SOPs and forms.

See Attachment 1 for the new QC Lab Organization Chart.

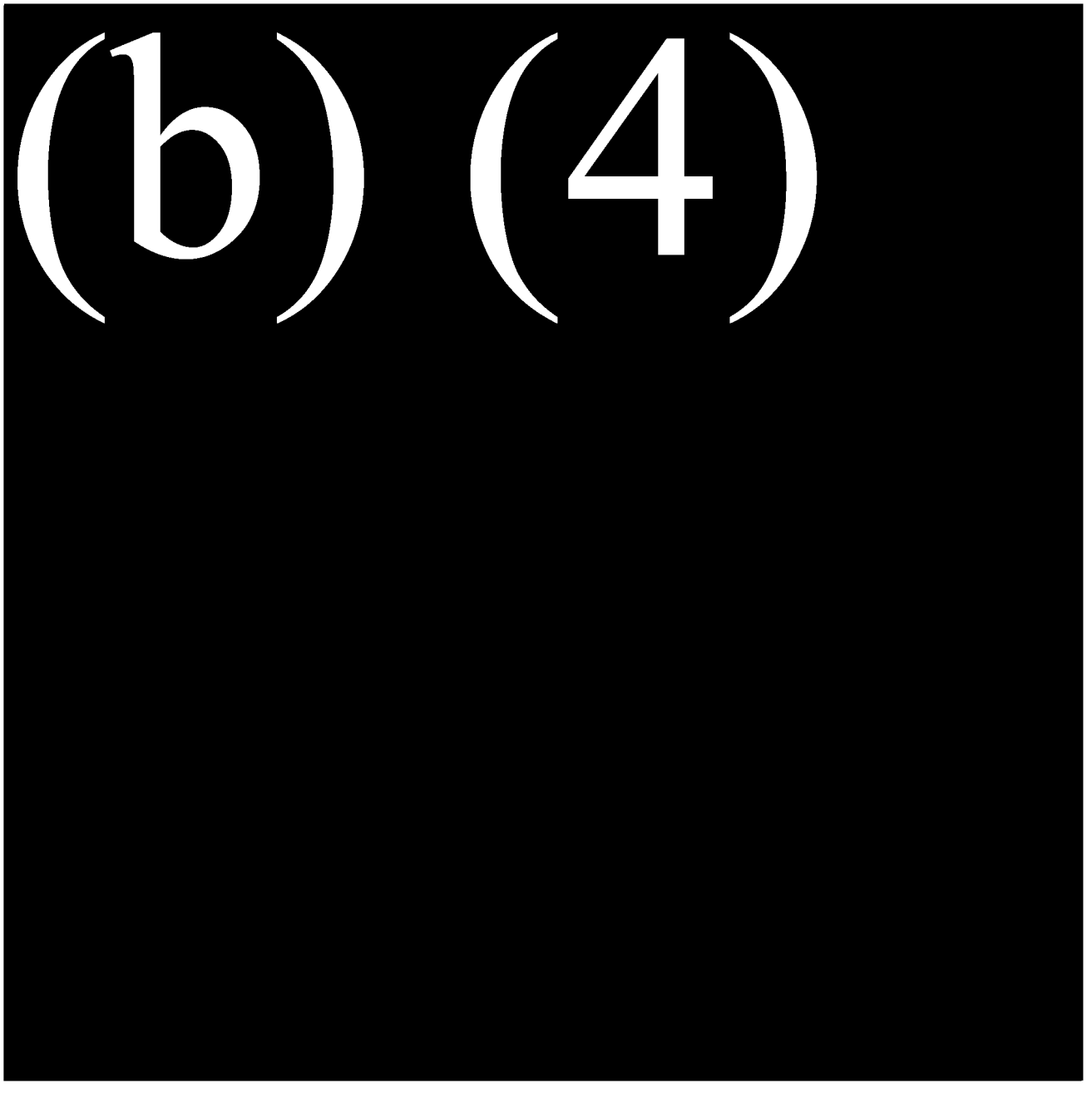
Restructuring of Operations / Manufacturing Units

Systemic failures have been noted in the latest Form 483. H&P Industries recognizes in addition to Quality Unit changes, changes are required in Operations / Manufacturing to meet the expectations necessary to comply with all regulatory thresholds.

Prior to the inspection, the Operations Group was lead by (b) (4) production managers, a quality control manager/supervisors, and floating maintenance and QC lab personnel. Each group assigned employees on a demand type basis, which provided the company versatility in managing its employees but negatively impacted performance due to the lack of accountability associated with random movement of employees.

(b) (4)

(b) (4)
(b) (4) H&P Industries has taken our best people (b) (4) to provide more control over our operations. The attached organizational charts (Attachment 1) demonstrate (b) (4) the before and after effects of our supervisory control.



As production demands increase, qualified staff and systems will be established to support these demands.

2.0 Additional Changes in the Last 15 Days

It is worth noting the following has already occurred in the past 15 business days since the closeout meeting:

1. (b) (4)
2.
3.
4. H&P Industries has ceased to make tablets for the foreseeable future
5. (b) (4)
6.
7.
8.

Risk Assessments

Liquid / Oral Products

As a result of the observations described on the Form 483, H&P Industries has performed a risk assessment on all liquid / oral products released to the market from the Hartland, Wisconsin facility. (b) (4) different formulations and/or packaging configurations have been produced at H&P Industries. We reviewed all batch records, OOS reports, process deviations, and the stability test records for all lots of these cough and cold products produced between May 2010 and January 2011 (since production was transferred to H&P from the NJ facility).

There are (b) (4) different product formulations/packaging configurations, each with a unique product number. (b) (4)

(b) (4)

To date (1-28-11) we have collected acceptable (b) (4) conditions testing results as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

There have been no OOS results for the (b) (4) lots that have been tested at the (b) (4) testing intervals. Based on this data, we believe that the risk of having products on the market that are not stable is very low. H&P Industries recognizes that the absence of stability data is a serious issue and therefore as soon as additional lots of products are produced, we will place them on stability testing, such that at least (b) (4) lots of each product are evaluated for stability to support an expiration dating period of (b) (4) years.

The validation records for these products were reviewed and they indicate that during process validation, some process controls parameters were revised or "tweaked" during production, such that additional validation lots should have been produced and assessed. However the processes were accepted as validated based on results from only one or two lots that were produced using the same processes. Since the validation lots were produced, several lots of each product type have been produced that have met established specifications, so we do not believe that the acceptance of validation status based on fewer than three consecutive lots poses a safety or efficacy risk to users for products that have already been distributed.

A review of the OOS reports and process Deviation reports on the cough and cold products revealed a significant processing error on lots produced between May 2010 and November 2010. During that time frame, the production process did not include a requirement to flush the piping from the mix tanks through the fill machine with an adequate amount of product to remove the residual final rinse water (b) (4) from the equipment and transfer lines. This (b) (4) water used for final rinse is the

same water quality /source that is used for product formulation. Prior to November 2010, some lots (and/or portions of lots) were rejected due to dilution of the product, resulting in out of specification concentrations of active ingredients (too low). All lots that were released met the active ingredient specifications; however, H&P was testing a(b) (4) (b) (4) (b) (4) test results for the beginning of the lot were not collected. There is some risk that some of the lots that were released may have included some bottles filled at the beginning of the lot that were diluted with the residual rinse water.

Being aware that this dilution could result in product that does not meet label claims, we have reviewed the analytical data for all lots manufactured prior to implementing a flush of the transfer lines. We compared the active ingredient and(b) (4) results of the batch sample (pre-filling) to the results of the finished goods to identify lot numbers that had a decrease in active ingredient concentration and/or a(b) (4) . Of the (b) (4) lots produced prior to the process improvement, only six (6) lots have been identified with a slight decrease in an active ingredient that exceeds what would be expected due to assay variability (b) (4). To define what a significant decrease was, we reviewed the test results for the products for which beginning middle, and end samples were tested off the line, that were known to be diluted with residual rinse water, and these results showed active ingredient for beginning bottles to be in the(b) (4)% range. (Note: The cases of product with known low actives were discarded and are not the subject of this investigation). Since (previous OOS) products with known low actives were in the(b) (4)% range, we believe that retesting products currently in the field that are showing a decrease of (b) (4)% uses a conservative approach which errors on the side of caution.

(b) (4)

However, to assure that no products have been adversely affected, retesting has been initiated on the retain samples for these six lots. Both the batch and finished goods samples are being retested. The data will be reviewed and if the results show that the initial bottles filled may be diluted below the active ingredient specification, these lots will be recalled. Testing of these lots will be completed on or before February 4, 2011.

To determine if there was a safety risk (due to potential contamination of the products with(b) (4)), all batch records were reviewed to verify that the final rinse water samples

met the specification for residual (b) (4). A sample of the final rinse water is routinely collected as it passes through the fill nozzles (prior to filling) and is tested to verify that the rinse step is effective at removing the cleaning agent (b) (4). The (b) (4) residual test results were acceptable on all lots that were cleaned using (b) (4) (b) (4); therefore there is no risk that the residual rinse water that may have diluted product was contaminated with (b) (4).

The retest data will be reviewed as soon as it is collected and if the results show that the initial bottles filled may be diluted below the active ingredient specification, these lots will be recalled. Testing of these lots will be completed on or before February 4, 2011. H&P Industries, Inc. has notified the distributor and the distributor has placed any inventory of the six (6) lots on HOLD.

Stability Studies with Failures

As a result of the observations described on the Form 483, an internal review of all stability test records is being performed. All stability test reports for all products will be reviewed to determine if additional lots need to be placed on stability test (due to missed test points or missed (b) (4) lot testing requirements). There are several hundreds of reports to review. Those products with a reported OOS result or a missed testing time point will be prioritized for review.

A risk assessment will be performed on any stability study with a time point failure to determine if there is a risk that product in the field that may be deteriorated. This determination will be made by March 1, 2011.

The stability testing reports for the cough and cold products have been reviewed as of the date of this report, and there have been no stability test OOS results reported for the cough and cold products that have been placed on stability testing.

Introductory Closing

The owner's roles and responsibilities as H&P Industries move forward are as follows:

(b) (4) will continue to manage finances for both H&P Industries and Triad Group. In order to make room for new H&P Industries COO, Dave Haertle will vacate the President's position and continue to manage Triad Group (distributor) as previously stated. Eric Haertle will remove himself from the position of COO and assume the position of H&P Industries company President. Eric will no longer be involved in the day to day production operations. All product quality related activities will be managed by (b) (4)

Finally, H&P Industries is committed to adding additional managers to upgrade the organization. (b) (4)

(b) (4)

Responses to Inspectional Observations

Observations 1-6 for Sterile Lubricating Jelly

During the November 29, 2010 inspection, H&P Industries voluntarily shut down all manufacturing and distribution of Sterile Lubricating Jelly on December 3, 2010. In addition, all Sterile Lubricating Jelly in the field was recalled. The recall was initiated internally on December 17, 2010; recall letters were mailed certified return receipt on December 24, 2010. Furthermore, all Sterile Lubricating Jelly in inventory was tagged HOLD per NCRs G10122804 and Y10122801. All Sterile Lubricating Jelly and Alcohol inventory is in the process of being destroyed. Upon completion, all paperwork will be forwarded to the District Recall Coordinator.

H&P Industries has contracted (b) (4) (Attachment 1A (b) (4) to project manage the new sterilization validation for Sterile Lubricating Jelly. In addition, the batching, cleaning and filling processes will be validated. The (b) (4) specification will be defined per feedback on the usability of customer evaluation of samples. Furthermore, qualified (b) (4) will perform all bioburden testing and environmental monitoring for the pre-validation studies and validation protocols.

The primary packaging suppliers will be qualified prior to distributing product. Any critical raw material suppliers will be qualified as well.

The incoming inspection paperwork for Observation #6 will be corrected to document a visual inspection of the peelable seal.

A QC Laboratory employee will be assigned the responsibility of collecting samples for quarterly dose audits, sending samples, receiving and reviewing results, initiating any required investigations, placing lots on HOLD, if applicable, ensuring SOP is current and accurate, ensuring (b) (4) has the validated specifications on file, communicating any failures to the QC Laboratory Manager, Quality Systems Manager, and Quality Director. This QC Laboratory employee will report to the QC Laboratory Manager and a job description will be created. The review of the sterility results has been added to the QA batch record and lot history review SOP-QA-005 and Form FRM-QA-007. Stability studies will be initiated for all validation lots.

It is expected that the lubricating jelly process validations will be completed in April 2011.

Observations 7, 8, 9, 15, 16 for Quality Unit, Training, Headcount, Practice versus Procedure

H&P Industries has, in several instances, been unsuccessful in adhering to internal procedures. The number of qualified personnel has been inadequate for the number of finished goods manufactured. Since the inspection closeout, a number of actions have taken place to correct the observations described.

As described in the introduction, clear defined roles and responsibilities have been written and implemented for the Quality Unit. Refer to the attached organizational chart (Attachment 1).

In addition, the Training Work Instruction was updated to a SOP with training modules and competency assessments. The current training schedule is described on Page 3 of this response. A copy of the new SOP and an example training module is attached (Attachment 2). Training in GMPs and specific job tasks and procedures will be required for both temporary and permanent employees.

Additional staffing has been added in the Quality Unit in addition to the third party individuals. (b) (4) (b) (4) Refer to the attached organizational chart (Attachment 1).

Improvements will be made in implementation of CAPA and handling of OOS results and nonconforming products and/or processes. Records of these activities and product disposition, including records of destruction, will be completed.

QA release of finished goods SOP has been revised to include QA physically tagging finished goods as Released or Rejected. In addition, QA will enter released finished goods into inventory; therefore the entire process of releasing and rejecting finished goods into inventory is controlled by Quality Assurance. QA personnel have been trained and assigned to review the batch records and QA is now responsible for releasing or rejecting products. All discrepancies are recorded and investigated, and decisions regarding product disposition are made solely by QA. Products that do not meet in-process or release specification will be carefully evaluated and only released for distribution if there is sound rationale, based on a risk analysis of the affect of the nonconformity on product safety and efficacy, to support that decision. A copy of the revised SOP, Form, and Training Roster is included (Attachment 5).

Refer to Section 1.0.A. and B. of this response for actions and completion dates.

Observations 10 and 11 – Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of the in-process material of the drug product.

Control procedures fail to include adequacy of mixing to assure uniformity and homogeneity.

As a result of the validation observations, a risk assessment has been completed to address all cough and cold products on the market. Refer to Page 10.

A risk analysis will be conducted on each product line, and where indicated, process validations will be implemented or repeated, including mixing validation. Statistically based sample plans will be developed to collect data that will support conclusions made. Appropriate test methods will be used (USP methods, and/or validated methods, if indicated) to assess product uniformity and homogeneity. The risk assessments for all product types are expected to be completed by March 1, 2011.

Process validations are now being managed by a new Validation Manager, who is preparing validation protocol development procedures, templates and practices to ensure that the process validations are conducted in a planned, controlled manner that is approved by Quality Assurance prior to implementation. Validation protocols will include worst case conditions, and it will be required to assess changes to validated processes for the need to revalidate.

The new validation protocol development procedures, templates, practices, and master validation plan are currently being implemented, and will be formalized by March 1, 2011.

It should be noted that during the inspection, H&P Industries implemented a (b) (4) (b) (4) for all batching and filling validations as a result of the inspectors' comments. The implementation of the (b) (4) to validation batches/lots. One of the inspectors observed the (b) (4) protocol on the floor during the inspection. A copy of an example (b) (4) protocol is included (Attachment 7).

Observation 12 – Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

(b)(4) & (b)(6) s revising the OOS procedure to comply with the FDA OOS Guidance (Investigating OOS Test Results for Pharmaceutical Production) and will require that confirmed OOS results and product nonconformities are investigated to determine whether other batches of similar products or products associated with the same processes or materials may have been affected. If other products may have been affected, CAPA will be initiated to investigate the effects and to develop a corrective action plan.

It is expected that the OOS SOP will be revised and implemented by February 15, 2011. Formal classroom training will be conducted and documented.

During the 2010 Management Review on December 22, 2010, per SOP-QA-014-002, Quality Assurance made the ultimate decision to no longer release or reject partial batches and/or lots. All batches and lots will not be released until all results, including microbiological, are obtained from (b) (4) samples. A copy of the management review attendance record is included (Attachment 8).

As demonstrated during the inspection, (b) (4) (b) (4) and revise the master batch records. As discussed previously, QA will perform the final QA review and release of all products which prevents any inadvertent release of products by the QC Lab or QC Inspectors.

Observation 13 – Individuals responsible for supervising the processing and holding of a drug product lack the education to perform their assigned functions in such a manner as to assure the drug product has the safety, identity, strength, quality and purity that it purports or is represented to possess.

As of December 2, 2010 all microbiological testing for finished goods, in-process, stability, and water has been outsourced to a qualified contract laboratory.

Observation 14 – Employees engaged in the processing and holding of a drug product lack the education required to perform assigned functions.

As of December 2, 2010 all microbiological testing for finished goods, in-process, stability, and water has been outsourced to a qualified contract laboratory. A trained microbiologist (HP employee) has been assigned responsibility to oversee all environmental monitoring results; responsibility for oversight of all product bioburdens (in process, finished product and validations samples, dose audits, and water samples) will be assigned to a qualified individual (microbiologist). The latter tasks are currently being filled by (b) (4) consultant with microbiological training (b)(4) & (b)(6) . (b) (4) (b) (4) the Lab Organizational Chart (Attachment 1).

A validation Manager has been placed to oversee development, execution of validation protocols, and evaluate results. New and modified production and laboratory equipment will be validated (b) (4) prior to release to production.

Although there are no degreed engineers on staff at H&P Industries, the current staff has several years of experience working in the pharmaceutical industry, with responsibilities at previous employers for engineering related activities. We believe that the issues related to equipment design and maintenance stemmed not from a lack of experience, but from lack of attention. Therefore, the maintenance department is developing a plan to assess the equipment and utilities throughout the facility to identify opportunities to improve, repair, or replace current equipment. Each production area will be carefully reviewed, and a plan implemented for corrective action, where indicated. A calibration and preventive maintenance program will be developed to ensure

equipment and utilities (water system, compressed air system, air handling systems) are properly maintained. Individuals within maintenance, quality and validation will be assigned responsibilities for supporting the maintenance and calibration programs.

Observations 15 and 16
See responses provided under **Observations 7, 8, 9, 15, 16**

Observation 17 – Written procedures are not followed for evaluations done at least annually and including provisions for a review of complaints, recalls, returned or salvaged drug products and investigations conducted for each drug product.

H&P Industries annual product review work instruction has been in place as of September 23, 2009. However, as a result of poor execution, the Annual Product Review procedure will be reviewed and revised as necessary. (b) (4) several products or product families will be reviewed, such that all products are reviewed annually, to identify the need for changes in drug product specifications or manufacturing or control procedures. The records reviewed will include:

- A representative number of batch records and associated documents
- Complaints and recalls
- Returned or salvaged product
- OOS Investigations and NCRs
- CAPAs associated with production processes
- Change Requests.

It is expected that this revised program be in place by May 1, 2011.

Observation 18 – Drug products are not quarantined before being released by the quality control unit.

All products will be quarantined either by labeling or designated locations in the warehouse until released by QA effective January 28, 2011. Released products will be labeled as such.

Observation 19 – Each batch of drug product purporting to be sterile is not laboratory tested to determine conformance to such requirements.

H&P Industries will sterility test each lot of sterile alcohol pads and swab sticks products purported to be sterile. The sampling plan and sterility testing will comply with USP <71>. Implementation will be prior to releasing any product to the market (currently being revalidated).

The sterile lubricating jelly medical device products are sterilized in accordance with (b) (4) and therefore do not require sterility testing. Product will be released based on use of validated sterilization methods and quarterly dose audits.

Observation 20 – Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Sterile Alcohol and non-sterile alcohol pads and swabs will be tested for the presence of micro-organisms, using valid microbiological techniques. These tests will be performed by (b) (4) They are currently validating the bioburden test method (b) (4) (b) (4) Since B. cereus has been isolated from samples of non-sterile alcohol pads, we will (b) (4)

(b) (4) will complete the suitability testing of the bioburden test method used to assess the alcohol pads and swabs by mid- February, 2011. When the alcohol pads production processes are revalidated (see response to Observation 30) and development and validation products are produced, product bioburden testing will also be completed, and all isolates will be characterized. If objectionable organisms such as *Bacillus cereus* are isolated in the post-sterilization samples or in non-sterile alcohol products, additional controls will be implemented to prevent contamination of these products.

We have developed and implemented an environmental monitoring (EM) plan for collection, identification and monitoring the viable organisms present in the air and on surfaces (equipment, floors, walls) in (b) (4) production areas: red room batching (nasal sprays and cough and cold), (b) (4) (filling of nasal products), and the powdered products blending and filling room. This EM program will also be implemented in other areas where product such as towelettes, suppositories, alcohol pads and swabs, and ointments/creams are produced. Once we have identified the types of organisms present in the production areas, we will determine which finished products need to be tested for the presence of specific objectionable organisms, and this will be implemented.

Environmental monitoring and product testing will be implemented by April 1, 2011 in all production areas where products that are required to be free of objectionable organisms are produced.

Observation 21 – Deviations from written specifications and sampling plans are not followed.

The Deviation SOP and Form were recently revised. Refer to Page 3 of this response. Formal classroom training was conducted specifically to communicate when deviations are required, who is responsible for initiating the deviation, Supervisor and Manager roles in the deviation and review process, and Quality Assurance notification and involvement.

The implementation of the Quality Assurance release and rejection also serves as an additional measure to ensure deviations are documented when reviewing batch records and lot histories.

(b) (4)

All confirmed OOS results and process deviations will be reviewed by QA during batch record review. Products with confirmed OOS results and process deviations will not be released without documented justification from QA.

Observation 22 – Established sampling plans are not followed.

An employee with microbiology training will be assigned to oversee and manage the quarterly dose audit program to ensure sampling plans and schedules meet specifications.

Observation 23 – There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

An Analyst has been identified as responsible for Phase 1 of OOS investigations.

All confirmed OOS results and process deviations will be reviewed by QA during batch record review. Products with confirmed OOS results and process deviations will not be released without documented justification from QA.

Observation 24 – Written records of investigations into unexplained discrepancies do not always include conclusions and follow-up.

In the past, it is has been the sole responsibility of the Lab Manager, to complete the Phase 1 investigation within the allotted (b) (4) period. This process has been found to be ineffective. As of 01/02/11, an Analyst has been identified as responsible for this procedure so there is no delay in completing the Phase 1 investigations. The Lab Manager will work with Analysts to complete the Phase 1 investigation and review once it has been completed. The Phase II portion of the investigation has been removed as a responsibility of the Engineering department. Responsibility for Phase II has been assigned to the R&D Manager to focus on completing them more efficiently and further reduce the overall amount of time the process takes, and ensure that root causes are being identified by persons knowledgeable about the processed being investigated.

Observation 25 – Laboratory controls do not include establishment of scientifically sound and appropriate test procedures designed to assure that components and drug products conform to appropriate standards of identity, strength, quality and purity.

The "Validation of Microbiological Testing" VAL-R-0011 has been noted to not be robust. At this time all microbiological testing of finished products, stability samples, batches (where applicable), and water samples are being outsourced to an approved contract microbiology laboratory.

The Lab is currently in the process of completing the validation reports for the specified methods. Additionally, a plan is being developed to verify that the stability test methods are stability indicating. H&P Industries is considering (b) (4) (b) (4) A more complete timeline will be provided in the February 2011 update.

Method transfers have been completed for (b) (4) % of the test methods used to released oral adult and children's drug products. The balance of the New Jersey method transfers will be completed by April 15, 2011.

Observation 26 – Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release.

After the validation of the Alcohol products is complete, the current Batch record for the Alcohol solution is being revised to include a finished good testing sheet. Going forward samples from (b) (4) of each lot of alcohol products will be tested and the results compared with established specifications to determine if products meet release specifications.

During the 2010 Management Review on December 22, 2010, per SOP-QA-014-002, Quality Assurance made the ultimate decision to no longer release or reject partial batches and/or lots. All batches and lots will not be released until all results, including microbiological, are obtained from (b) (4) samples. A copy of the management review attendance record is included (Attachment 8).

The Production Work Orders for the oral products will be revised to remove any parameter on the finished goods inspection that is not applicable. QA will review all change requests to ensure required parameters are not deleted. In addition, the entire work order will be reviewed and revised to ensure that all of the appropriate instructions are included in the paperwork for the employee. It is expected that this project be completed by June 2011.

Observation 27 – The written stability testing program is not followed.

The previous Stability Coordinator has been relieved of her duties and the organization has identified one person who is dedicated to organize samples, maintain and monitor the test schedule, and notify the laboratory, in advance, when testing is due. She will also ensure that new products and (b) (4) samples are placed on stability testing.

The QC Laboratory employee (s) assigned to each (b) (4) is responsible for testing the stability samples for that group of products.

Product families will be described and justified in a report that summarizes the results of the review and corrective actions to be taken to better manage the stability program. It is expected that this report be completed by March 2011.

Observation 28 – Results of stability testing are not used in determining expiration dates.

All stability test results are being reviewed to determine if additional lots need to be placed on stability to collect data to support current expiration dates. If indicated, expiration dating periods will be reduced.

Observation 29 – Laboratory records do not include the lot number or other distinctive code for sampling.

A sample identification number is assigned to each sample submitted to the laboratory. The sample identification number is recorded in the sample submission log. An Environmental Monitoring Project Lead has been identified and this person is responsible for recording all sample identification numbers and results.

A QC Laboratory employee has been identified to collect (b) (4) DI Water samples and to review and record the results whereas previously this activity was not assigned.

Observation 30 – Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

During the November 29, 2010 inspection, H&P Industries voluntarily shut down all manufacturing and distribution of Sterile and Non-Sterile Alcohol on December 2, 2010. Manufacturing and distribution of Sterile Alcohol was resumed on December 10, 2010 and shut down on December 22, 2010. The recall was initiated internally on December 21, 2010; recall letters were mailed certified return receipt on January 3, 2011, 2010. Furthermore, all Sterile and Non-Sterile Alcohol in inventory was tagged HOLD per NCRs G10122804 and Y10122801.

H&P Industries has contracted (b) (4) to support the new sterilization validation for Sterile Alcohol. Prior to implementing revalidation, (b) (4) sterilization processes, the batching, cleaning and filling processes will be validated. Furthermore, qualified (b) (4) will perform all of the bioburden testing and environmental monitoring for the pre-validation studies and validation protocols. They will use test methods that have been validated for (b) (4) method will be used.

The primary packaging suppliers will be qualified prior to distributing product. Any critical raw material suppliers will be qualified as well.

A QC Laboratory microbiologist will be assigned the responsibility of collecting samples for quarterly dose audits, sending samples, receiving and reviewing results, initiating any required investigations, placing lots on HOLD, if applicable, ensuring SOP is current and accurate, ensuring (b) (4) has the validated specifications on file, communicating any failures to the QC

Laboratory Manager, Quality Systems Manager, and Quality Director. This QC Laboratory employee will report to the QC Laboratory Manager and a job description will be created. The review of the sterilization results has been added to the QA batch record and lot history review SOP-QA-005 and Form FRM-QA-007. Stability studies will be initiated for all validation lots.

It is expected that the Sterile Alcohol process validations be completed in April 2011.

Observation 31 – Deviations from written production and process control procedures are not recorded and justified.

The Deviation SOP and Form were recently revised on January 17, 2011 and formal classroom training was conducted on January 14, 2011 specifically to communicate when deviations are required, who is responsible for initiating the deviation, Supervisor and Manager roles in the deviation and review process, and Quality Assurance notification and involvement. The Quality Systems Manager conducted the training for QA, QC Lab, QC, Validation, Purchasing, and Operations.

The implementation of the Quality Assurance review of batch records and lot histories prior to release and rejection also serves as an additional measure to ensure deviations are documented and justified. This action is completed.

CAPA-10-002 is in process to address the disposal of the last (b) (4) of phenylephrine.

The lot history paperwork for alcohol prep pads with benzocaine will be updated to include instructions to record the second inspection.

Observation 32 – The master production and control records for each batch size of drug product are not prepared, dated, and signed by one person with a full handwritten signature and independently checked, dated, and signed by a second person.

On December 10, 2010, Quality Assurance instructed assigned Document Control to convert all master batch records and production work orders from Word Documents to PDFs. Document Control converted all of the files over the weekend of December 11-12, 2010. On December 14, 2010, Quality Assurance and IT presented the changes and explained security access to the FDA lead auditor. To date, all master batch records and production work orders cannot be changed on the company intranet as they are in PDF form (read only).

Observation 33 – Written production and process control procedures are not documented at the time of performance.

All employees will be trained on the job and in GMP training to complete quality records as they complete the associated tasks. The employee that admitted he did not follow procedure was re-

trained on January 25, 2011 to complete the batch record as each step is completed, and to obtain verification by a second operator at the time of addition of ingredients to the batch (Attachment 9). A GMP training course will be provided on February 18 and March 15, 2011 (Refer to Page 3).

Observation 34 – Examination of testing of samples is not done to assure that in-process materials conform to specifications.

As part of a global initiative, all product family batch records and production work orders will be reviewed and revised to require recording of critical process data. Sample plans and records of samples collected, accept/reject quantities and reasons will be required to be recorded in the batch records. This project is expected to extend over several months and is expected to be completed by September 2011. Updates will be provided as part of the on-going response.

The procedures for (b) (4) testing of tubes, swabs, pads, and large pouches will be reviewed and revised to define the products to be tested, the responsibility for testing, and to require recording of quantitative results. The production work orders will be updated to reflect changes to sampling and testing plans. This will be completed as part of the review and revision of batch records and production work orders described above.

Observation 35 – The batch records do not record the distinctive identification number to identify major equipment to show the specific equipment used in the manufacture of a batch of a drug product.

A SOP will be written to describe the process for writing and approving master batch records. All new batch records will be written following the SOP. As current batch records are revised, major equipment identification at each step will be added. It is expected that the SOP will be written and implemented by March 1, 2011. Revision of all batch records is expected to be completed in April 2011.

Observation 36 – Actual yield and percentages of theoretical yield are not determined at the conclusion of each appropriate phase of manufacturing of the drug product.

As batch records are being reviewed and improved to include other required changes, they will also be revised to include calculation and recording of actual yields at appropriate steps, such as production, filling and/or packaging steps. This is expected to be completed by September 2011.

Observation 37 – Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its cleaning and maintenance.

Production equipment and supplies are being examined to identify opportunities to improve cleanability, and to revise procedures to require periodic cleaning of all product contact surfaces.

Rusty equipment is being repaired or removed and replaced. Equipment maintenance and cleaning schedules will be created or revised, as needed, to assure an acceptable state of repair and cleanliness of the production equipment and work areas.

The floors in the production rooms will be cleaned and sanitized at least (b) (4) to reduce viable and non-viable counts in the air and on surfaces. The walls will be cleaned at least (b) (4); and personnel will be required to wear lab coats over their street clothes (while in the production rooms only - not to be worn while outside the production rooms). These steps will be implemented by March 1, 2011.

The air quality in the production rooms is being evaluated through environmental monitoring for viables and non viables in the air and on surfaces. The air handlers will be inspected and cleaned and repaired as needed to improve air quality, including installation of clean, new filters. After making these and other improvement to control the air quality, environmental monitoring and product bioburden results will be reviewed to determine if additional controls are necessary. Up to (b) (4) of environmental monitoring data and product bioburden data will be collected in each production room and evaluated prior to deciding if additional air quality controls are needed.

Environmental conditions will be monitored and FDA will be updated as to the affect of these actions on the environment and on product bioburdens.

Observation 38 – Written procedures for sanitation are not followed.

Room and equipment cleaning procedures and forms are being revised to require more frequent and more thorough cleaning and sanitization, and to record these activities. Trash will be removed from each production room daily or at the end of each production run, if necessary. These steps will be implemented as soon as possible and formalized by March 1, 2011.

Observation 39 – Equipment and utensils are not cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

All production equipment and utensils are being reviewed to identify the need for improving cleaning, storage, and use procedures. The (b)(4) water system maintenance and monitoring procedures are being revised to ensure adequate monitoring and maintenance schedules. A QC Laboratory employee has been assigned responsibility to collect and track (b)(4) Water System Monitoring results. The Maintenance Department will be responsible for ensuring appropriate maintenance of the compressed air and (b)(4) Water System. These tasks are expected to be completed March - May 2011.

Observation 40 – The plumbing system contains defects that could contribute to the contamination of drug products.

The isolated incident was immediately corrected. Refer to the attached Damage Report and Corrective Action dated December 22, 2010 (Attachment 10).

Observation 41 – Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile are not established.

We have developed and implemented an environmental monitoring (EM) plan for collection, identification and monitoring the viable organisms present in the air and on surfaces (equipment, floors, walls (b) (4) production areas: red room batching (nasal sprays and cough and cold), (b) (4) (filling of nasal products), and the powdered products blending and filling room. This EM program will also be implemented in other areas where product such as towelettes, suppositories, alcohol pads and swabs, and ointments/creams are produced. Once we have identified the types of organisms present in the production areas, we will determine which finished products need to be tested for the presence of specific objectionable organisms, and this will be implemented.

Environmental monitoring and product testing will be implemented by April 1, 2011 in all production areas where products that are required to be free of objectionable organisms are produced.

Observation 42 – Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

A new Supplier Management SOP was effective on September 30, 2010. QA first focused on contract service providers and has made significant progress completed supplier audits compared to the past. Refer to Page 6 for a current list.

Each supplier will be qualified to provide components, raw materials and active ingredients. (b) (4) lots of chemicals from each supplier will be inspected and tested for conformance with USP requirements (or other established specifications). Product contact packaging components from each supplier will be evaluated for microbial content to qualify the supplier. Suppliers whose components contain objectionable microorganisms will not be approved. After qualification, the materials will be accepted based upon receipt of the CoA, with at least an identity test (if a USP chemical), and for conformance with critical dimensional specifications. Some suppliers may be qualified based upon a retrospective analysis of historical evidence of compliance to specifications. This plan will be completed May 2011; implementation will be an on-going process until (b) (4) lots have been received and tested.

Observation 43 – The production air supply lacks an appropriate air filtration system.

The air quality in the production rooms is being evaluated through environmental monitoring for viables and non viables in the air and on surfaces. Initial monitoring will be performed to assess the current air quality. Then, the air handlers will be inspected and cleaned and repaired as needed to improve air quality, including installation of clean, new filters.

Room and equipment cleaning procedures will be improved, and personnel will be required to wear lab coats over their street clothes while in the production rooms. After making these and other improvement to control the air quality, environmental monitoring and product bioburden results will be reviewed to determine if additional air handler controls are necessary. Up to (b) (4) (b) (4) of environmental monitoring data and product bioburden data will be collected in each production room and evaluated prior to deciding if additional air quality controls are needed.

Observation 44 – Each lot of a component, drug product container, and closure that is liable to microbiological contamination that is objectionable in view of its intended use is not subjected to microbiological tests before use.

Packaging components or production materials that could introduce microbial contamination in microbial controlled products will be evaluated for microbial content through the supplier qualification program. Incoming materials specifications will be reviewed to determine which materials and components need to be microbially tested. These will include, but not be limited to, the foil materials needed to package the alcohol prep pads and swab sticks, the prep pad and cotton swab materials, adhesive and sticks.

Product contact packaging components from each supplier will be evaluated for microbial content to qualify the supplier. Suppliers whose components contain objectionable microorganisms will not be approved. After qualification, the materials will be accepted based upon receipt of the CoA and microbial testing will be repeated, at least (b) (4) for each component. Responsibility to assure (b) (4) testing will be assigned to the in-house microbiologist. This plan will be completed May 2011; implementation will be an on-going process until (b) (4) lots have been received and tested.

Observation 45 – Procedures describing the warehousing of drug products are not established and followed.

General Warehousing procedures will be developed and implemented. These will include instructions for labeling and storage of materials in designated areas, packing and storing products and components to prevent damage to maintain cleanliness, and to respond to spills and leaks. This procedure will be established and implemented by March 2011.

Observation 46 – The drug product is not identified with a lot or control number that permits the determination of the history of the manufacture and control of the batch.

A lot number will be added to the individual packages of alcohol prep pads. This requires a modification to the equipment, and validation. This will be implemented in April 2011, during re-validation of the alcohol prep pads production and sterilization processes.

In closing, H&P Industries would like to express appreciation for the advice provided and discussions during the inspection. H&P Industries will provide monthly updates documenting the progress of the Short and Long Term Objectives in addition to any open observations. Monthly updates will be provided on:

February 28, 2011
March 31, 2011
April 29, 2011
May 31, 2011.

Please contact me immediately if any part of this response is inadequate.

Sincerely,

Eric Haertle
President
H&P Industries, Inc.
262-538-2908
ehaertle@triad-group.net

Attachments

Attachment 1 – Past and Current Organizational Charts
Attachment 1A – Resumes for (b)(4) & (b)(6)
Attachment 2 – Training SOP, Example Training Modules
Attachment 3 – Deviation SOP, Form and Training Roster
Attachment 4 – Notice of Destruction SOP Form and Training Roster
Attachment 5 – QA Release and Reject SOP, Form and Training Roster
Attachment 6 – Environmental Monitoring SOP and Training Roster
Attachment 7 – Example (b) (4) protocol
Attachment 8 – Attendance Roster for December 22, 2010 Management Review
Attachment 9 – Re-training for batching employee
Attachment 10 – Damage Report and Corrective Action