TRIAD GROUP

August 17, 2009

Ms. Marie Fadden, Consumer Safety Officer
Food and Drug Administration
250 Marquette Ave., Ste. 600
Minneapolis MN 55401

Dear Ms. Fadden:

Please refer to your records of the inspection of our facilities which you, Lt. Hustedt, and Ms. Hughes conducted during the period of July 15 through 17, 2009. Please also refer to the Inspectional Observations you presented at the conclusion of that inspection on July 17. We appreciate the verbal observations and recommendations you offered during the inspection. The purpose of this letter is to provide our formal responses to the Inspectional Observations presented on Form FDA 483 dated July 17, 2009.

Quality System
OBSERVATION 1: The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

RESPONSE: A draft copy of the new Triad Procedure Responsibilities of the Triad Group Quality Unit is provided as **Attachment 1.** This procedure will be implemented with appropriate employee training by August 30, 2009. We will provide documentation of this implementation and training no later than September 18, 2009.

OBSERVATION 2: GMP training is not conducted with sufficient frequency that employees remain familiar with the cGMP requirements applicable to them.

RESPONSE: The cGMP intranet-based training modules are currently being conducted every 12-18 months. Training Guidelines, WI-TRN-0007 will be revised to include an outline and schedule for initial cGMP training and refresher training. The intranet-based training modules designed for specific job functions will be administered to new employees as their job function dictates. cGMP refresher training modules are being developed and will be administered to manufacturing departments on a quarterly training schedule starting November 30, 2009. Employees with administrative job functions will continue to receive the intranet-based training module every 12-14 months. The objective of these refresher modules will be to give the trainee a more applicable and hands-on interpretation of the cGMP regulations as they relate their job functions. In an effort to build and demonstrate GMP leadership, this training will be developed and administered by management of the manufacturing departments. The refresher program will be administered quarterly to all manufacturing departments and will be dynamic in format, such that current manufacturing issues relating to cGMP will be the training topics.

OBSERVATION 3: Investigations of 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. Specifically, multiple Out of Specification investigations into Hemorrhoidal Suppositories with Phenylephrine were not extended to other products containing Phenylephrine, *i.e.* Hemorrhoidal Cream and Ointment and Phenylephrine.

RESPONSE: During the inspection, documentation of Triad Group CAPA H-09-005 was reviewed. This CAPA, initiated in April 2009, extended the investigation of one OOS for a specific product, hemorrhoidal ointment, to all products that are emulsions/suspensions. CAPA H-09-005 demonstrates that Triad has, in fact, extended investigations of batch failure into other batches of the same/similar drug product. An additional copy of the CAPA is provided as **ATTACHMENT 2.**

OBSERVATION 4: Reprocessing was performed without the approval of the quality control unit. Specifically, the Infant and/or Adult Glycerin Suppositories, formula # 04-154, are manufactured using (b) (4) . The quality unit does not approve the reprocessing of the batches prior to production.

RESPONSE: Batch record 04-154 for glycerin suppositories is specific for batches manufactured from (b) (4) and requires testing and release by the Quality Lab prior to molding. After reviewing this process, Triad Group has (b) (4) See the attached batch record 04-144 (**ATTACHMENT 3**) which details the revised handling of (b) (4) The (b) (4) The Quality Control approval of the scrapings prior to their use is documented on page 4 at step number 200. Training and implementation of this revised batch record will be completed by August 31, 2009.

OBSERVATION 5: Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacturing or processing operations for which they are unsuitable. Specifically, Glycerin Suppository lot #9C150B was observed in the Glycerin Suppository room with a "QA Accepted Material" tag on it. The material was in a corner of the room with items around it. The material was dispositioned on 7/16/09 after we observed it stored in the corner.

RESPONSE: Triad Group acknowledges that the Glycerin Suppository room did not have a properly identified, specific Quarantined area. We have assigned a designated area and labeled this area which is located outside of this room. This area will be specific for all rejected materials.

Triad Work Instruction WI-QC-0094, General Rejection Procedure (copy provided as **ATTACHMENT 4**), addresses the proper handling of rejected materials. Production and Quality Control personnel will be retrained in the requirements of this procedure by September 18, 2009. Documentation of this training will be provided no later than September 30, 2009. The

Quality Assurance Lab staff were formally trained, with documentation, on WI-QC-0094 on July 27, 2009. A copy of this documentation is provided as **ATTACHMENT 5**

All production areas have established HOLD areas outside of the rooms which include floor markings and wall signs. We are exploring the best means of providing additional physical barriers surrounding these areas to further assure segregation of materials. We will summarize and report these efforts and final actions no later than September 30, 2009.

OBSERVATION 6: Drug products failing to meet established specifications are not rejected. Hemorrhoidal Suppository with Phenylephrine has a phenylephrine specification of (b) (4) (b) (4) , multiple batches of this product were released outside of the specification range as follows: [table of 8 lots and test results].

RESPONSE: Concurrent with the restructuring of the Triad Group Quality Unit on July 20, 2009 the Quality Assurance Lab will not approve out of specification batches for further processing. Only IN SPEC, fully tested product will be released for further processing, packaging, and distribution to our customers. Quality Assurance Lab personal have all been trained on this commitment by Triad Group executive management and have been instructed to send any managers/employees from other departments to Quality Unit management if there is any question. If appropriate, any in-process batch or finished product failing to meet specifications will be retested and the record will be reviewed by Quality Unit management prior to disposition.

OBSERVATION 7: Deviations from written specifications are not justified.
a) No out of Specification investigation was documented for Out of Specification finished product assay for Hemorrhoidal Suppositories with Phenylephrine lots 8K100 and 8K151.
b) The procedure "Laboratory Out of Specification (OOS) Investigations" #WI-LAB-0040 effective 6/17/09 section 3.3.10 requires approval by Quality Unit Managers. Nine out of eleven OOS investigations did not have Director of QA/QC/RA and Technical Services signature. According to the Lab Manager this should have been signed.

RESPONSE: While the investigational reports cited were not signed by the "Director of QA/QC/RA and Technical Services," this position was eliminated prior to any of these investigations. The reports were reviewed and signed-off by appropriate Quality Unit staff with authority to do so, on signature lines representing their positions. The Procedure should have been revised at the time staffing was changed and responsibilities were reassigned.

Procedure WI-LAB-0040 was reviewed and revised to specifically incorporate recommendations from the *Agency Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production – October, 2006*. A copy of the revised and approved Work Instruction is provided as **ATTACHMENT 6**.

OOS investigations were contemporaneously conducted and documented for lots 8K100 and 8K151. The investigations are attached to the deviations, H1008.001 and H1008.002 respectively, and are provided as **ATTACHMENTS 7 & 8**. Although the OOS form was not completed, all the elements of an OOS investigation are captured in the summaries.

OBSERVATION 8: 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.

RESPONSE: Triad Group recognizes the need to verify the reliability of suppliers' analysis for chemical components and not to rely solely upon certificates of analysis received with each shipment. A thorough review of all chemical component specifications will be conducted, identifying the critical parameters of each component, and a plan will be written to independently verify each parameter. The plan will be completed by October 31, 2009. A copy of the plan will be provided no later than November 13, 2009. In addition, our supplier qualification procedure will be used to qualify any new chemical suppliers.

OBSERVATION 9: Procedures describing the warehousing of drug products are not followed. Specifically, the finished product reject storage are described in the procedure "General Rejection Procedure" 3WI-QC-0094 effective 5/06/09 section 3.2.7.3 is not indicated by signs or other designation and is not spatially separated from acceptable material.

RESPONSE: Please see our response to Observation 5, above, which also addresses the Observation and summarizes our plan to determine the best means of providing additional physical barriers surrounding product/material-hold areas to further assure segregation of these materials. As noted, we will summarize and report these efforts and final actions no later than September 30, 2009.

.

Facilities and Equipment

OBSERVATION 10: Equipment used in the manufacture, processing , packing or holding of drug products is not of appropriate design for its intended use and cleaning and maintenance.
a) The Starch Hemorrhoid Suppositories operators utilize a plastic five gallon bucket to transfer product from the mixing vessel to the suppository forming and packaging machine.
- the plastic bucket is not easily cleaned and sanitized and it is nor documented
- the plastic bucket has not been evaluated for cross contamination with the product
b) the Infant and Adult Glycerin Suppository filling line is not appropriate for the manufacture of OTC drug products in that:
- the scraper used to remove material from the molds is (b) (4) a plastic like material, with notable chips and scratches. It is not inspected periodically to ensure that it is safe for use.
- the pins used to force the suppositories out of the molds are (b) (4) It is not easily cleanable and is a direct product contact surface. Several pins were observed to be missing. The pins are not inspected periodically to ensure that it is safe for use.
- the ejector bin in which the suppositories are placed to ensure they are cool is plastic with clear plastic tape holding a piece of what appeared to be heavy paper inside of it. This is not easily cleanable and is a direct product contact surface.

RESPONSE: Triad Group acknowledges that the use of plastic buckets for transfer of product is not optimal. A stainless steel bucket has been purchased and is dedicated to the S12 hemorrhoid

suppository line. The bucket is cleaned and sanitized prior to each use. Work Instruction WI-PM-0101 Cleaning and Sanitizing of Product Contact Buckets, Fittings and Utensils is being revised to include detailed instructions for each category. The operator control chart for the S12 hemorrhoid suppository Line, FM-MFG-0004, is being modified to include the documentation of the cleaning and sanitizing. These document changes and training on their application will be completed by September 30, 2009. Documentation of these actions will be provided no later than October 16, 2009.

Triad Group acknowledges that the glycerin suppository filling line can be improved. We are

(b) (4)

(b) (4)

OBSERVATION 11: Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.
a) in the suppository mixing room the spatula, with product residue on it, that is used to scrape in process product off the sides of tank 51 was observed during the manufacture of lot #9G115B to be sitting on the portable metal steps that the operator steps on to access the tank.
b) the fans used in the Infant and Adult Glycerin Suppository room to cool the suppository molds were observed on 7/16/09 to have accumulations of debris.

RESPONSE:. All plant employees are being re-trained in cGMP procedures during the week of August 10, 2009. Due to the significance of this observation that written procedures that were not being followed, two employees received disciplinary action. Daily housekeeping logs are being written that are specific to this room and will include weekly cleaning of the entire room and all fans. These activities will be completed by November 15, 2009. Training documentation as well as a copy of the new cleaning log will be provided no later than November 30, 2009.

OBSERVATION 12: Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product. Specifically, during a tour of the facility on 7/15/09 the following deviations from the procedure "Cleaning and Sanitizing Batching Equipment, Tanks and Totes" #WI-PM-0056 effective 4/06/09 were observed:

a) mixing tank #50 had a "ready for use" sign affixed to it, the "in use" tag was not completed, the tank was observed to have product in it. According to management the next suppository batch had been started, lot #9G123B was in the melting phase of production.
b) the "Tote or Tank Activity Record" for tanks 50 and 51 did not have any entries for the use of those tanks after 7/2/09.
c) mixing tank #40 was observed to have a "ready for use" sign affixed to it, the "in use" tag was not completed. We were informed by the operator that Hemorrhoid Cream, lot #9G109B was in the mixing tank.
d) the "Tote or Tank Activity Record" for tank #41 was observed with the entry "7/15/09 Hem Oint 9F109B" – as mentioned above that product was observed in tank #40
e) the "Tote or Tank Activity Record" for tank #40 did not have any entries after 6/29/09.

RESPONSE: Procedures "Cleaning and Sanitization Batching Equipment Tanks and Totes WI-PM-0056 , "Assigning Status Tags to Batch Tanks" WI-PM- 0090 and "Tank and Tote Activity Records" WI-PM-0090 were not properly followed at the time of this inspection and those activities were not recorded. Batching employees were re-trained during the week of August 10 2009 on procedures WI-PM-0056 and WI-PM-0090. Lab personal training has already been conducted in reference to WI-PM-0090 during the week of August 3, 2009. Documentation of this training will be provided not later than August 30, 2009.

OBSERVATION 13: Written procedures for cleaning and maintenance fail to include description in sufficient detail of methods, equipment and materials used and description in sufficient detail of the methods of disassembling equipment as necessary to assure proper cleaning and maintenance. Specifically, the procedure "Cleaning and Sanitizing Batching Equipment, Tanks and Totes" #WI-PM-0056 effective 4/06/09 does not include instructions to differently designed pieces of equipment i.e. Infant and Adult Glycerin suppository filling line, (b) (4) suppository filling line, alcohol prep pad filling line and tube filling line.

RESPONSE: To date Triad Group has used general cleaning instructions that address how to clean and sanitize equipment and materials based on the previous solution processed in a production system. Although it may not be appropriate to judge the adequacy of procedures to detail cleaning and maintenance of equipment and processes not inspected, Triad Group is committed to developing more detailed instructions for overall cleaning, maintenance and sanitizing performance. We have reviewed all processes and have laid out a plan to complete the additions to and/or upgrades of cleaning, maintenance and sanitizing procedures to be completed by June 1, 2010. Triad Group will provide bi-monthly updates detailing the progress made on this project.

OBSERVATION 14: Records of inspections of automatic, mechanical or electronic equipment, including computers or related systems, are not maintained. Specifically, the infant and Adult Glycerin Suppository Molding Press Machine and the (b) (4) Scale Automatic Weighing Machine (used for packaging the Glycerin Suppositories) have no records of qualification.

RESPONSE: The present inspection was limited to (b) (4) processes which have run on the same machines for many years. Triad Group understands the value and necessity of having formally

documented equipment qualifications. We have gathered retrospective data from all of our equipment in order to create formal IQ, OQ, PQ documents. We will continue our machine qualification program with a planned completion date of June 15, 2010. Triad Group will provide bi-monthly updates documenting our progress toward completion of this program.

Laboratory

OBSERVATION 15: The number of containers to be sampled is not based upon appropriate criteria. Specifically, the procedure "Sampling, Testing, Approval and Release of Incoming Chemical Materials #WI-QC-0203 effective 7/14/08 does not specify the number of containers within a lot of raw material to sample.

RESPONSE: A statistically based sampling plan has been identified for incoming chemical testing. This equation ((b) (4)) was incorporated into work instruction WI-QC-0203 "Sampling, Testing, Approval and Release of Incoming Chemical Materials". The effective date of this work instruction is August 21, 2009. A copy of the revised Work Instruction is provided as **ATTACHMENT 9**.

OBSERVATION 16: The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established and documented.
a) AS the method "HPLC Analysis – Phenylephrine HCl Content for Gel, Suppositories, Ointment #WI-LAB-0117 effective 5/28/08 is currently being run it is not validated.
b) The method HPLC Analysis – Phenylephrine and Pramoxine HCl Content #WI-LAB-0120 effective 6/15/07 has not been validated.

RESPONSE: A method validation matrix has been created to ensure that non-compendial instrument methods are validated by 31 December 2009.
a. Method WI-LAB-0117 (b) (4)
(b) (4)
b. Method WI-LAB-0120 (b) (4) method for the analysis of phenylephrine and pramoxine. This method will be validated by September 30, 2009. A copy of this revised method will be provided no later than October 12, 2009.

OBSERVATION 17: The use of instruments not meeting established specifications was observed. Specifically, the (b) (4) HPLC was used for assay of several OTC finished products prior to the PM/OQ/PV being completed.

RESPONSE: All active analytical instrumentation has been re-qualified to ensure that all current analytical testing is performed with properly qualified instrumentation. Work instruction WI-LAB-0141 will be amended to include a statement that new analytical equipment is not approved/released for use with OTC drug finished products until all equipment qualification is completed and approved. The revision will be completed by September 15, 2009. Documentation of the requalification and a copy of the revised Work Instruction will be provided no later than October 16, 2009.

OBSERVATION 18: All major equipment used during production of a batch of drug product is not properly identified at all times to indicate contents.
a) tank #50 was observed with a "Ready for Use" tag on it. The tank contained the product Hemorrhoidal Suppository with Phenylephrine, lot #9G123B
b) mixing tank #40 was observed to have a "ready for use" tag affixed to it. We were informed by the operator that Hemorrhoid Cream, lot #9G109B was in the mixing tank.

RESPONSE: Quality Laboratory personnel, who are responsible for proper placement of these tags, were re-trained on usage of the tank status signs. This retraining was completed on July 27, 2009.

OBSERVATION 19: Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically, this firm has not validated any of their manufacturing processes for OTC drug products. Examples of OTC drug products currently manufactured under contract and/or their own label include Infant Hemorrhoidal Suppositories, Adult Phenylephrine and other active ingredient Hemorrhoidal Suppositories, Mouthrinse products, Antibacterial Towelette, Sterile Lubricating Jelly, Sterile Alcohol Wipes, Cold Sore medication, Acne Pads, and Lice Kits.

RESPONSE: Triad Group has completed (b) (4) validations of (b) (4) systems; we will continue these efforts to insure all systems are validated in a timely manner. In addition, we have established a validation master plan to address the prospective validation of all OTC product processes. The engineering group has developed a timeline to complete all process validations by June 15, 2010. Triad Group will provide bi-monthly updates detailing progress toward completion of this program.

OBSERVATION 20: Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile are not established.
a) operators were observed carrying Infant and Adult Glycerin Suppository (b) (4) from the suppository mold machine over to the mixing vessel. The operators touched (b) (4) after touching the movable metal steps, (b) (4) touched their clothes and were exposed to the air
b) (b) (4) were observed in the Glycerin Suppository room. (b) (4) have been sitting there for up to four weeks. Some are covered by a thin bag, some are not covered at all and some of the bags have holes in them.

RESPONSE:
a) All plant employees were re-trained in cGMP procedures during the week of August 10, 2009. Documentation of this retraining will be provided no later than August 31, 2009. As noted in RESPONSE 11, disciplinary actions have been administered.
b) As noted in RESPONSE #4, we will be modifying all Glycerin batch records to (b) (4) (b) (4) (b) (4). In addition all batchers will be trained in these new procedures by

September 14, 2009. Documentation of this training will be provided, along with a new Production Work Instructions no later than September 30, 2009.

OBSERVATION 21: Strict control is not maintained over labeling issued for use in drug product labeling operations. Specifically, labels were observed unattended in the staging area. According to management this is standard procedure for all products and the labels can be left unattended inn the area for 1 hour up to 2 days.

RESPONSE: A new Procedure, "Production Work Order Component Picking and Staging" is in final draft. This Procedure requires, among other activities, that properly identified and selected labels and labeling be placed into appropriate containers, the labeling be verified by a QC Inspector, the container be sealed by the Order Picker, and the label part number, lot number, and label quantity be recorded on the sealing tape. Both the order picker and QC will initial and date the tape sealing the shipper. This Procedure will be finalized no later than September 14, 2009 and training on the Procedure will be completed no later than September 21, 2009. A copy of the draft procedure is provided as **ATTACHMENT 10**. A copy of the final procedure and documentation of the training will be provided no later than September 28, 2009.

As noted in the response to Observation 6, the Triad Group Quality Unit was restructured on July 20. Quality Control and the Quality Assurance Lab now report to Jack Waterman, formerly Triad Group's Regulatory Affairs Manager. A copy of Mr. Waterman's résumé is provided as **ATTACHMENT 11**, for your information. Quality Assurance and Document Control continue to report to Mr. Waterman.(b) (4)

(b) (4)

In closing, I assure you that Triad Group recognizes our responsibility for full compliance with the Agency's Regulations applicable to our operations and that I have delegated the authority necessary to achieve this ongoing compliance to our Quality Unit.

Yours truly,

Eric Haertle /dj

Eric C. Haertle
Chief Operating Officer