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SUMMARY OF FINDINGS

This inspection of a manufacturer of dietary supplements was requested by CFSAN/ OC/ Division of Field Programs & Guidance (HFS-615) under C.P. 7321.008(cGMPs for manufacturers of Dietary Supplements). The inspection was performed as a High Priority inspection under DFPG #08-22-ORA Concurrence #2008062501 and FACTS Assignment #951846.

The previous inspection was performed during March '08 pursuant to FACTS assignment #879747 to cover the manufacture of drug products and to follow-up a consumer complaint. The inspection disclosed Wyeth Ayerst/ Lederle ceased manufacturing all drug products at the location in Pearl River, NY with the exception of one product marketed as Mylotarg, an anti-cancer drug. The inspection also followed-up a possible product tampering situation related to Centrum and Centrum Silver dietary supplements. The inspection revealed a possible product tampering occurred at (b) (4) Officials at Wyeth reported a (b) (4)
(b) (4)

In addition Wyeth received 2 consumer complaints that reported a foreign product was contained in sealed bottles of Centrum and Centrum Silver tablets. As a follow-up to these complaints (to include FACTS Consumer Complaint #58106) several improvements were recommended to minimize the ability of (b) (4) The firm committed, in writing to improving their controls in the following ways: to re-implement a second slat fill operator; devise a system for ongoing camera surveillance and video storage of slat filler watch station; amend packaging written procedures to no longer allow operators to autonomously return rejects or remove bottles to the packaging line; replace clear plastic covers encasing the packaging line to extend to the level of the conveyors to minimize employee access to open product containers; and implement a tamper evident storage system for in-process, bulk Centrum products stored in the in-process warehouse. The inspection did not result in a FDA-483 and was classified as NAI. No refusals were encountered and no samples were collected.

The current inspection performed on 8/27/08 – 10/8/08 revealed Wyeth overseas 3 organizational units: Wyeth Biotech (a mfr. of vaccines), Wyeth Consumer Healthcare (a mfr. of dietary supplements), and Wyeth's clinical R&D division to oversee clinical research &development activities. The facility in Pearl River, NY is operated under parent company Wyeth Pharmaceutical Division of Wyeth Holdings Corp. and overseas an estimated (b) (4) employees. A majority of dietary supplements are manufactured (formulated, tested, labeled and packaged) for Wyeth Consumer Healthcare (WCH) in Madison, NJ. WCH has approximately (b) (4) employees. Wyeth manufactures multivitamin/ multimineral supplements and calcium tablets. One multivitamin marketed as Centrum Performance contains two herbal ingredients.

This inspection included a review of two products: Centrum Performance and Centrum Silver Film Coated tablets. Centrum Performance is a supplement that contains ginseng and gingko biloba extracts and Centrum Silver is marketed for people over the age of 55. No major issues were noted for Centrum Silver tablets. This product has been associated with complaints that report product mix-ups, and officials at Wyeth are continuing to investigate these complaints. The current inspection revealed that Centrum Performance tablets, on the other hand were associated with product quality issues related to two herbal ingredients used in the product. During April 2007 imported dietary ingredient ginseng extract manufactured by (b) (4) was tested by FDA's Seattle district and this dietary ingredient contained Tricyclazole (a pesticide). The raw ingredient was tested by the supplier to cover (b) (4) years of retained samples. All samples showed trace amount of Tricyclazole. (b) (4) (b) (4) The investigation revealed a processing tool used in the ginseng extraction process (rice chaff) introduce this pesticide in the ginseng. This material was subsequently removed from the process, and the supplier was allowed to ship ginseng to Wyeth. A review of batch records revealed Centrum Performance is the only product that uses this dietary ingredient. During April 2007, upon notifying officials at Wyeth about the tricyclazole issue, officials at Wyeth decided to destroy all inventory of Centrum Performance in stock, and returned ginseng to (b) (4) Any filled bottles of Centrum Performance tablets in stock and bulk tablets were destroyed. The estimated value of the destroyed items was (b) (4) No corrective action was

implemented for product already sold to customers. Wyeth's legal counsel contacted a person from CFSAN and based on the outcome of the conversation a decision was made not to take corrective action for products already distributed to customers. A Health Hazard Evaluation was conducted and found no safety concerns.

The inspection also revealed (b) (4) lots of Centrum Performance tablets (made with (b) (4) ginseng extract) were still within expiration. The last production batch will expire during January '09 (Control No. C05315). A DOC sample # 496576 was collected for this product to document I/s movement of imported ingredients as well as the finished product. A review of shipping records found this product was sold to a customer on 4/10/07 after Wyeth was notified by supplier (b) (4) on 4/5/07 concerning the tricyclazole/ginseng issue. All shipping records were sent to NYK-CBr for review. Five physical samples were also collected under sample No.s: 491225, 491238, 491240, 491241, and 491244

A review of Centrum Performance tablets also disclosed a second dietary ingredient Ginkgo Biloba extract (used to formulate Centrum Performance tablets) was associated with three batch failures due to the presence of pesticides. Officials at Wyeth decided to remove Gingko biloba as an ingredient from Centrum Performance tablets due to lack of confidence in the supplier's ability to test for pesticides using a validated method. Three recent batches of gingko biloba extract manufactured by supplier (b) (4) revealed the presence of pesticides (Acetamipride, Imidaclopride, and/ or Phomime). All 3 lots were rejected. The three lots were assigned (b) (4) . A review of shipping records revealed (b) (4) kgs of ginkgo biloba extract but only (b) (4) kgs were shipped to Wyeth's locations in Canada and Pearl River, NY. Approximately (b) (4) kgs of gingko biloba were not accounted for. Based on a review of shipping records the full amount ((b) (4) kgs) was originally shipped from (b) (4) to (b) (4) (a registered mfr/repacker under FEI # (b) (4)). Officials at Wyeth reported no business relationship with (b) (4) and were not sure why this ingredient was shipped to the above account. (b) (4) Based on shipping records the missing amount consists of (b) (4) kgs of Lot (b) (4) and (b) (4) kgs of Lot (b) (4) . On 9/26/08 all 3 lots at Wyeth's location in Pearl River, NY were loaded into a trailer and sent to a contractor (b) (4) to be destroyed. A copy of the destruction letter was provided. An estimated value of the destroyed gingko was $(b) (4) . A portion of this material sold to Wyeth Canada, a mfr of similar dietary supplements offered for the US market. Wyeth Canada quarantined the product and will destroy the material at a later date. None of the ginkgo was used in finished product.

On 10/ 8/08 a FDA-483 was issued and included the following observations: Laboratory exam and test methodologies do not appear to be appropriate for their intended use. Specifically, the test method using (b) (4) instruments (b) (4) produced negative trends that report equipment drifts, OOS CV standards and/or invalid results that required a re-test on several mineral lots but the test method continues to be used and has not been replaced with a more reliable

method. Failure to use an appropriate scientifically valid method to test the seal over plastic bottles. Specifically, the current method requires testing the integrity of the seal by applying pressure (using finger pressure) over the middle of the seal and visually inspecting the rim over the mouth of the bottle. No specifications were established for the amount of pressure and dwell time to apply or require the use of a calibrated tool to evaluate the integrity of the seal. Specifications for dietary ingredient(ginseng) are listed under Monograph [(b) (4)] code [(b) (4)] and require verification on the supplier's COA to test for pesticide (tricyclazole), but COAs for code [(b) (4)] did not include test results for this pesticide. In the packaging area, there was a failure to demonstrate that all requirements were met. Specifically, cap adjustment specs were not documented to support proper set-up of the packaging line. Also, when product changeovers occur there was no documentation of the removal of tablets inside metal detector bottles to avoid product mix-ups, and the men's restroom only furnished cold water. Officials at Wyeth will send a written response to the district office.

ADMINISTRATIVE DATA

Inspected firm:	Wyeth Pharmaceutical Division of Wyeth Holding, Corp.
Location:	401 North Middletown Road Pearl River, NY 10965-1215
Phone:	845-602-5000
FAX:	845-602-5599
Mailing address:	401 North Middletown Road Pearl River, NY 10965-1215
Dates of inspection:	8/27/2008, 8/28/2008, 8/29/2008, 9/3/2008, 9/4/2008, 9/5/2008, 9/9/2008, 9/10/2008, 9/12/2008, 9/15/2008, 9/16/2008, 9/17/2008, 9/18/2008, 9/23/2008, 9/24/2008, 9/26/2008, 9/29/2008, 10/8/2008
Days in the facility:	18
Participants:	Jacqueline S. Warner, Investigator

I, Jacqueline S. Warner initiated a cGMP inspection on 8/27/08 at Wyeth, and upon arrival I showed my credentials to the following individuals: Ms. Ingrid Gibson, Director of QA Compliance Operations; Louis J. Ragne, Associate Director of Q. A. &Audits, and Mr. Robert LaBrecque, Principal Auditor of QA Audits(all assigned to Wyeth's Biotech unit). I informed these individuals that I planned to conduct an inspection to cover cGMPs issues for dietary supplements and would not review any vaccines or drug products. As such, these individuals advised me that

they would contact relevant persons assigned to Wyeth's Consumer Healthcare unit to assist me as Wyeth's Biotech area only handles vaccines. I was informed that individuals assigned to Wyeth Consumer Healthcare would arrive and assist me. I requested to issue a Notice of Inspection to the most responsible person overseeing the site, and was informed that Mr. Michael P. McDermott, V.P of Site Operations has ultimate responsible for overseeing all site operations. However, I was informed that he was not physically present, and I would need to issue the document to the second person in charge: Mr. Joseph T. Vitanza, Managing Director. Upon greeting Mr. Vitanza I showed him my credentials and issued him a Notice of Inspection. He mentioned he is responsible for overseeing the manufacture of multivitamin / multimineral supplements, as well as supplements intended for international sales. He overseas departments that handle production (to include final packaging) and provides support to the QA unit. The department managers who report to him are assigned to handle Product Strategy and Technical service related issues. During the opening meeting he provided me with a general overview of Wyeth's organizational structure, history of business, and products.

The persons who assisted me for the full duration of this inspection included: Mr. Farooq Moatter, Director of QA Compliance& Product Release and Mrs. Kristin Fassett, Audit Manager. Mr. Moatter answered several of my questions and provided me with a majority of documents included in this report. Ms Kristin Fassett, Audit Manager compiled a list of questions to forward via email to several employees to answer several of my questions. She also acted as note-taker, provided documents and coordinated teleconferences between NYK-DO staff and Wyeth officials. A third person was also present Mr. Josh Deutchman, Senior QA Auditor who did not actively participate. He acted strictly as a note-taker/ observer. Both Mr. Moatter and Ms Fassett accompanied me on a walk through of the facility where the dietary ingredients are stored, tested, blended, compressed into tablets, and coated. Other areas audited included Wyeth's warehouse and packaging & labeling areas. In addition, other persons who actively participated during this inspection included Mr. Paul Lucas, Senior Director QA(he answered several of my questions related to ginseng and gingko biloba issues,) and Ms. Yhomayra Cortegana, QA Manager who explained how dietary ingredients are tested.

On 10/8/08 a FDA-484(Receipt for Sample) and a FDA463a (Affidavit) were issued to Mr. Farooq Moatter, Director of QA Compliance & Product Release. He accepted the Receipt for Samples and mentioned it was OK but did not sign the document. On the document I wrote "REFUSED TO SIGN" in the block where Mr. Moatter was expected to sign. He mentioned he could not sign this document, as this was against the company's policy. He also refused to read, sign or acknowledge receipt of the FDA-463a (Affidavit) due to Wyeth's policy not to allow employees to read, listen, and sign this document.

On 10/8/08 a FDA 483(List of Inspectional Observations) was issued to Mr. Michael P. McDermott, V.P of Site Operations, and he read and accepted this document. He will respond to all observations in writing.

(b) (5)
(b) (5)

HISTORY OF BUSINESS

Dietary Supplements were originally formulated by Lederle Labs over 30 years ago. Lederle was founded by Dr. Ernest Lederle in 1906 and this business has been through several mergers. Lederle was purchased in 1994 by American Home Products and American Home Products was subsequently purchased Wyeth-Ayerst, and this site is currently registered as Wyeth Pharmaceutical Division of Wyeth Holdings Corp under FEI #2410662. Wyeth is a manufacturer of multivitamins, multiminerals, calcium tablets and vaccines. The location in Pearl River, NY includes several buildings where employees oversee clinical R&D projects. In the past Wyeth also manufactured drug products at this location but the previous inspection revealed only one partial manufacture of one anticancer drug. The facility has three organizational units: Wyeth Biotech, Wyeth Consumer Healthcare, and Wyeth clinical R&D. Mr. Vitanza mentioned all dietary supplements are manufactured under Wyeth Consumer Healthcare, and vaccines are manufactured under Wyeth Biotech area. (b) (5)
(b) (5)

Since the last inspection (March 2008)several improvements were implemented to monitor activities in the production area, to seal all bulk storage bins, to place cameras near areas where bulk tablets are stored, as well as to make improvements in the packaging area to prevent product mix-ups. I confirmed cameras were installed over slat fillers, clear plastic (Plexiglas) encased over packaging lines to extend to the level of conveyor system and Wyeth also implemented tamper-resistance mechanism (seals) that were placed on bulk containers.

This inspection included a review two multivitamin/ multimineral supplements marketed as Centrum Performance and Centrum Silver Film Coated tablets. Centrum Silver is intended for people over the age of 55, whereas Centrum Performance marketed for active people who want a boost of energy. The latter product contains ginseng and ginkgo biloba dry extracts. Centrum Performance is the only product that contains herbal ingredients. Most of the multivitamin/ multimineral supplements are formulated for adults but Wyeth also produces vitamins for kids. The chewable multivitamin tablets display cartoon characters on the unit box. All vitamins are sold in tablet form, and may be re-formulated to keep-up with the latest customer needs. None of the dietary supplements are sold as liquids or powders. Wyeth only produces tablet(Film Coated tablets, non coated tablets or chewable tablets). The chewable tablets are manufactured for kids and adults.

The firm's high selling products are Centrum Millennium, Centrum Silver, and Centrum Performance. All products are fully manufactured (blended, compressed into tablets, coated, tested

and placed into final packaging) at Wyeth's site in Pearl River, NY. On occasion, some batches may be sent to contractors for further processing or testing, as needed. I was provided with names of some contractors, listed below:

Name of Contractor	Function
(b) (4)	Package Centrum and Centrum Silver tablets
(b) (4)	Package Centrum and Centrum Silver tablets
(b) (4)	Rebulk and inspect dietary supplements
(4)	Perform micro test for raw materials/finished tablets

The firm's organizational structure consists of Michael P. McDermott, VP of Site Operations; Alex Eslava, AV.P. of Vaccines(Quality Operations); Joe Vitanza, Managing Director, and Paul Lucas, Senior Director of WCH. A list of top management overseeing the site was provided, see Exhibit 1 (Site Operations) along with organizational charts (Exhibit 2) that show persons assigned to Wyeth's consumer healthcare unit. The consumer healthcare unit includes finished product testing, incoming material sampling, QC lab operations, analytical method development, product stability, and quality audits. In addition, I was provided with a third organizational list(Exhibit 3) to show under Mr. Vitanza's group the PPU(Product Production Unit) which is headed by Mr. Manny Sanchez, Senior Director of PPU who overseas product blending, tableting, packaging, Manufacturing Support, and Compliance related issues.

In addition to location in Pearl River, NY Wyeth has other locations. For example, Wyeth has production sites in Guayama, PR; Aprilla, Italy; Montreal, Canada; and Suzhou, China; a corporate office overseeing dietary supplements(Wyeth Consumer Health care) in Madison, NJ and 4 Distribution Centers(DC's) located in Sparks, Nevada; Richmond, VA; Vonore, TN and San Juan, Puerto Rico. I was provided with a list of all addresses for sites under Wyeth's control, see Exhibit 4. A majority of dietary supplements are manufactured for Wyeth Consumer Healthcare (WCH) located at 5 Giralda Farms in Madison, NJ 07940. WCH is responsible for marketing all Centrum brand dietary supplements sold in the United States. However, other dietary supplements (for export) can be marketed by Wyeth Pharmaceutical Division of Wyeth Holding Corp, Lederle Labs Division of American Cyanamid Company in Pearl River, NY or Whitehall-Robbins Healthcare (Madison, NJ).

All regulatory issues are handled at Wyeth's corporate headquarters in Collegeville, PA according to Mr. Farooq Moatter, Director of QA who also mentioned this location also overseas drug manufacturing. On 9/25/08 Teri G. Hall, V.P of Quality& Compliance (office in Collegeville, PA) sat in as an observer.

The FMD145 copy and written correspondence should be sent to Michael P. McDermott, VP of Site Operations @401 North Middletown Road in Pearl River, NY 10965. He can be contacted @ mcdermm@wyeth.com or tel# 845-602-7100.

Wyeth's employee headcount in Pearl River, NY was estimated at (b) (4) f/t time employees, of which (b) (4) employees are assigned to manufacture dietary supplements under Wyeth Consumer Healthcare unit. The employee headcount for WCH was estimated at (b) (4) employees but only (b) (4) employees are located in the U.S.(to include the U.S. territory of Puerto Rico). A copy of the exact employee breakdown was provided, see Exhibit 5.

During '07 Wyeth's annual sales was an estimated (b) (4) dollars to cover different FDA regulated products, of which sales for dietary supplements accounted for $(b) (4) . On a yearly basis (b) (4) dietary supplement tablets are manufactured by Wyeth of which (b) (4) are sold to international market.

INTERSTATE COMMERCE

The dietary supplement manufactured in Pearl River, NY are transported to Wyeth's Distribution Centers in Sparks, Nevada; Richmond, Virginia; Vonore, TN; and San Juan, P.R. for further distribution to US customers. Dietary supplements are sold to (b) (4)
(b) (4)
(b) (4)

I/s records such as: Straight Bill of Lading, Delivery tickets, and Waybills were collected for Centrum Performance tablets sold under (b) (4) see Exhibit #s 6-8 and one Doc sample was collected for Centrum Performance tablets (b) (4) Exp Jan'09).

JURISDICTION

Wyeth manufactures the following dietary supplements:

Centrum Millennium
Centrum Silver
Centrum Performance
Centrum for Kids(chewable tablets with flavor ingredient)
Centrum Cardio (contains a natural corn derived ingredient marketed as CoroWise® to reduce cholesterol).
Centrum chewables for adults,
Centrum (for Export) marketed as Centrum Jr. w/ extra calcium
Centrum Performance (For Export)
Caltrate 600 calcium tablets
Stress Tabs

A product list was provided see Exhibit 9 along with product labels see Exhibit 10.
A Field Exam was conducted on labels as directed by the compliance program to assure labels bear contact information though which the person responsible for submitting reports of serious adverse events can receive all related complaints. My review revealed labels displayed telephone # 1-877-Centrum as well as email address: www.centrumperformance.com or www.centrum.com. Product labels for supplements sold to foreign accounts were not available; however drawings were provided (Exhibit 11) to show information printed on labels. The contact information included: name of business, city, state and zip code.

All dietary supplements are offered in different package configurations. For example: Centrum Performance tablets are sold in bottles of 45's, 45's +10, 75's, 120's, and 150's, whereas Centrum Silver tablets are sold in bottles of 15, 25's, 30's , 60's, 100's, 100+15, 150's, 220's, and 270's.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Several sign –in sheets (Exhibit #12) were collected to document persons interviewed during this inspection. As a general overview some responsibilities were further described, see below:

Michael P. McDermott, V.P of Site Operations. He is responsible for overseeing all site operations, overseeing the consumer healthcare division and all manufacturing. He has been with Wyeth for approximately 19 years and was present during the close out meeting held on 10/08/08.

Joseph T. Vitanza, R Ph Managing Director of WCH Manufacturing. He is responsible for overseeing the production of Centrum brand multivitamins (to include all multivitamins manufactured for international sales). He is also responsible for overseeing raw materials, final packaging, and provides support to the QA department. Department managers overseeing product Strategy and Technology departments report to him.

Farooq Moatter, Director of QA Compliance & Product Release. He is responsible for product release, validation, change control, auditing functions, and compliance issues. He reports to Mr. Paul Lucas, Sr. Director of QA.

Kristin Fassett, Manager of Audit Compliance, She is responsible for auditing and compliance issues and has been with Wyeth for 6 yrs.

Josh Deutchman, Senior Auditor of QA. He is responsible for conducting internal & supplier audits, and reports to Kristen Fassett. He has been with Wyeth for 6 years.

Paul Lucas, Senior Director Quality Assurance. He is responsible for all quality operations in Pearl River, NY that relate to dietary supplements and has been with Wyeth for 25 years. He reports to Teri Hall, V.P of Quality in Collegeville, PA.

Yhomayra Cortegana, QA Manager. She is responsible for QA release of batch records, reviews raw material test reports, and reports to Mr. Farooq Moatter, QA Director. She has been with Wyeth for 8 years.

Christopher Defeciani, Compliance Manager. He is responsible for overseeing investigations that impact product quality issues, and has been in his current job position for 1 ½ years. He has been with Wyeth for close to 20 years.

Alan Goldberg, Assoc Dir of Technology. He is responsible for Technology department (transfer of new products), validation of new products, process changes, overseeing Life Cycle Management (finding new suppliers), and all process related issues. He has been with Wyeth for 9 years but 2 years in his current position. He previously worked at Wyeth's R&D location in Richmond, VA.

Manny Sanchez, Sr Director of Centrum (PPU). He is responsible for manufacturing and packaging all Centrum products and has been with Wyeth for 6 years.

Don Benanti, Manager, Materials Compliance (Pharma Business Unit). He is responsible for overseeing procurement and shipping issues. He has been with Wyeth for 4 years. He explained warehouse alarm system and temperature control issues for building (b) (4)

Peter Sidoti, Associate Director of Site Operations. He is responsible for Contract Services, Goods Services, and aseptic cleaning for Wyeth Biotech and overseas all Pest Control issues.

Paulo Couto, Senior Process Engineer Performance PPU. He is responsible for maintenance of equipment in the processing area.

Ray Bartolucci, Senior Director of Technology. He is responsible for process validation, problem solving, handling raw material qualification issues and reports to Joe Vitanza. He has been with Wyeth for 24 yrs.

Corey Birmingham, Process Engineer. He was assigned to manufacturing area and is responsible for handling engineering issues, especially those related to tablet compression and coating. He has been with Wyeth for 2 ½ years.

David Quinones, Manager of Supply Chain System. He is responsible for (b) (4) Security and Project Management issues. He has been with Wyeth for 20 years.

Susan Liu, Principal Technology & Scientist. She is responsible for production support, process validation issues, and handles raw material problem solving. She reports to Al Goldberg, Associate Director of Technology and has been with Wyeth for 10 years.

Doreen Bologovasky, Training Coordinator She is responsible for overseeing Wyeth's central training and Shared Services.

Rick Garafalo, Logistics Process Improvement Manager of Supply Chain Management. He is responsible for receipt of incoming goods. Enters all information into (b) (4) database and has been with Wyeth for 16 years.

John Connor, Director Procurement. He is responsible for handling procurement issues.

Michael Iurato, Q.C. Manager. He is responsible for overseeing the Finished Product Lab and has been with Wyeth for 6 years.

John Moynihan, Manufacturing Systems Specialist. He is responsible for troubleshooting issues in the packaging department and has been with Wyeth for 31 years.

Kelly Stuart, Associate Director of QC. She is responsible for QC labs and product sampling of raw materials and finished products, and has been with Wyeth for aproximatley10yrs.

Roger Fuchs, Sr. Project Engineer. He is responsible for engineering projects, validation and qualification of equipment and handles issues related to production. He has been with Wyeth for 29 years.

Margaret O'Toole, Dir of Engineering and Maintenance. She is responsible for equipment maintenance issues.

Robert Kressler, Packaging Engineer. He is responsible for maintenance of equipment (to include packaging equipment) and problem solving, and has been with Wyeth for 26 years.

Jerry Keaney, Assoc. Director of QA and Validation. He is responsible for overseeing QA issues, process validation, equipment cleaning, and computer validation. He has been with Wyeth for approximately 17 years.

Derek Burt, Sr. Technology Scientist II. He is responsible for the technology, overseeing packaging validation, validation of raw materials, and study plan execution. Mr. Burt has been with Wyeth for 9 years.

Jacqueline Hibbert, Sr Investigator. She is responsible for performing investigations for the manufacturing area and handles process deviations. She has been with Wyeth for 6 years.

Michael Aboyoun, Maintenance Manager. He is responsible for maintenance department for WCH and has been with Wyeth for over 5 years.

Laura Ziegler, Manager of QC/AD (Analytical Development). She is responsible for validating new test methods.

Frank DePierro, Systems Analyst IV. He is responsible for (b) (4) maintenance and has been with Wyeth for 2 ½ years.

PRODUCTION OF CENRTUM SILVER & CENTRUM PERFOMANCE TABLETS

Wyeth Consumer Healthcare is a manufacturer multivitamin/multimineral supplements of which an estimated (b) (4) tablets were manufacture in 2007. A small portion of these products were manufactured at Wyeth's facility in Pearl River, NY. The exact amount of dietary supplements manufactured at Wyeth's location in Pearl River, NY was disclosed see Exhibit #13 (Production Volumes for 2006 and 2007). All dietary supplements are manufactured inside one building (b) (4). This building has (b) (4) floors. On the (b) (4) floor is a Shipping& Receiving area where all dietary ingredients are stored. All dietary ingredients must be held inside a sealed container and transported to a weighing station to weigh in drums or skid/pallets or weighed in a light or heavy weigh room. The heavy weigh room is designed to weigh materials that are over (b) (4) kilograms, whereas the light room is intended to weigh all materials that are less than (b) (4) kilograms. Wyeth's (b) (4) database keeps track of all materials that were weighed and removed from the stock. All ingredients are transported to the (b) (4) floor and weights checked by (b) (4) individuals and a supervisor. Once all ingredients are weighed, the materials are transported to the (b) (4) floor inside a blend room. The type of blender to select would depend on the batch size. The (b) (4) blender is used to manufacture powder blends for Centrum Performance tablets and the (b) (4) blender is used to manufacture powder blends for Centrum Silver tablets. No liquids are used in the blending room. Wyeth uses only dry ingredients. Small batches that consist of chewable tablets are formulated in smaller (b) (4) blenders. Most batches are transported by a gravity-feed process to a (b) (4) floor ((b) (4) floor) to be feed into tablet compressors. Again, depending on the batch size, different machines are selected. For example, the (b) (4) Tablet Compressor is used to manufacture Centrum Performance, Centrum Export, and Centrum Cardio tablets and Centrum silver tablets are manufactured using an (b) (4) Tablet Compressor and automated Continuous Tablet Coater (CTC). After the blended powder is compressed into tablets and coated the tablets are dispensed on the (b) (4) floor via (b) (4) to the (b) (4) floor where the packaging line is set-up. Wyeth has (b) (4) packaging lines. After packaging, all filled bottles are transferred to the (b) (4) floor to be shipped to one of four Distribution Centers. The Distribution Centers are responsible for selling the finished product to customers.

Production of Centrum Silver tablets

Centrum Silver tablets (code (b) (4)) are manufactured using (b) (4) blenders. All ingredients are filtered through (b) (4) and/ or (b) (4) and poured into the blender. Prior to blending all ingredients are weighed. (b) (4) individuals and a supervisor will verify all weights. The product containers are read with a bar code scanner to verify correct ingredients are loaded into the blender.

All ingredients are blended according to charging order described in the Master Batch Record for (b) (4) minutes for the first set of ingredients, and (b) (4) for additional materials. Next, the (b) (4) (b) (4) is transported to a storage bin to weigh. The theoretical yield and actual yield documented on the batch record.

Next, the product is transferred to the tablet compression room using an automated (b) (4) tablet press or a (b) (4) compressor. The speed for the (b) (4) tablet press is set at (b) (4) rpm(speed range (b) (4) rpm) whereas the (b) (4) is set at (b) (4) rpm(speed range (b) (4) rpm). All machine set-ups are performed according to written Job Aids(work instructions). The tablets compressor is installed with metal punches, metal detectors, and de-buster. Each tablet engraved with word "Silver" and "A" on the left side and "f" on the right side. Specifications for tablet hardness, thickness and weight were established. The tablet's weight range (b) (4) g. The hardness range (b) (4) KP(target@ (b) (4) KP) and the thickness range was set (b) (4) inches to (b) (4) inches. During the tablet compression process samples are taken every (b) (4) to verify the tablet weight, thickness, and hardness.

In the tablet coating room, Centrum Silver tablets are coated with Film Coating Solution((b) (4) contents) prepared using a (b) (4) and purified water. The solution is allowed to mix for (b) (4) minutes. This inspection included an evaluation of the purified water and did not find any adverse findings. The water conforms to USP standards. The minimum holding time for the solution is set (b) (4) hours to (b) (4) developed during the mixing process. There is also a maximum hold time set for (b) (4) hrs to avoid the solid contents in the solution from separating.

All tablets are coated using an automated Continuous Tablet Coating (CTC) machine set with the following process parameters:

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

All samples are visually inspected for defects to verify tablets were evenly coated and not over sprayed. The tablets are placed inside plastic bins and transferred to the packaging area.

Prior to packaging, all new shipments of labels are inspected using an (b) (4) inspection or by using a software (b) (4). The (b) (4) is an automated

system that checks all printed information on the label. The system maintains a scanned image of the master label and the master label is compared to one label received as part of the new shipment. The program actually overlaps the two labels and checks that the information on the label is correct. All master labels are approved by QA prior to use. I asked if the [redacted] was qualified, and according to Mr. Moatter this automated system has been reviewed during prior FDA audits and was qualified. A small amount of labels may also be inspected using an [redacted] process implemented by the supplier. The supplier qualifies the label and provides certification that it meets Wyeth's specifications. A label that has gone through [redacted] inspection will be provided to Wyeth rolled outside-in to distinguish from other labels that have not been inspected.

In the packaging area tablets are filled in plastic bottles, sealed and affixed with a label. Every [redacted] samples are pulled to inspect for correct tablet count, tablet defects, check cap torque, check the quality of the seal, and to review the label (check Control No. and Expiration date).

Production of Centrum Performance tablets

The manufacture of Centrum Performance tablets begins with a screening process where ingredients, such as [redacted] drums. The drums are labeled [redacted]. Next, other ingredients [redacted] and a portion of [redacted] are screened into a polyethylene-lined drum labeled [redacted]' will be loaded into a [redacted] slanted blender and allowed to blend for [redacted] minutes then [redacted] is added to the blender along with [redacted]. The [redacted] blend is allowed to blend for [redacted] minutes. Afterwards, more [redacted] along with [redacted] are added to the blender along with [redacted]. Additional ingredients are added to the [redacted] blend, such as [redacted] and blended for [redacted] minutes using an [redacted] speed. After [redacted] minutes, all ingredients blended for an additional [redacted] minutes without the [redacted]. Next, [redacted] is discharged and blended for [redacted] minutes and [redacted] is screened and feed into the blender. The ingredients are allowed to blend for [redacted] with the [redacted] set at [redacted] followed by [redacted] additional minutes with out the [redacted]. Once the ingredients are blended the [redacted] is discharged and placed into polyethylene-lined drums and weighed.

The second major operation is to convert the powder into tablets using [redacted] compression machine. Each tablet is engraved with "Centrum" on one side. The left side engraved with "P" and the right side engraved with "F". Inside the tablet processing area the tablet press is set-up and [redacted] samples are collected every [redacted] Each tablet is inspected for thickness, hardness, weight, and friability. The friability spec is not more than [redacted]% loss. The tablet is tested for disintegration. Each

tablet must disintegrate within [redacted] minutes. Every [redacted] tablets are inspected for weight, hardness and thickness. The weight set at [redacted] g per tablet (weight range [redacted] g; the hardness set at [redacted] Kp(tablet's hardness range [redacted] KP), and the tablet's thickness should be within [redacted] inches to [redacted] inches.

After the tablet compression is completed tablets are transported to a film coating process using a [redacted] Coaters. The sprayers are fixed at a specific angle to maintain coating consistency. The sprayers must be set at a specific distance to avoid over coating. After the coating is completed, the tablets are evaluated for COD (classification of defects) and transferred to the packaging area.

In the packaging area, the tablets are filled in a plastic bottle, capped, bottle's rim is sealed and affixed with a label. Samples are pulled every [redacted] to review label, seal, tablet count, cap's torque, and overall appearance of tablets.

A review of packaging and labeling requirements confirmed requirements for packaging and labeling were established. The packaging line consists of the following hardware: [redacted] unscrambler ([redacted]), [redacted] Loader and tablet filler ([redacted]), [redacted] Metal Detector([redacted]), [redacted] Capper([redacted]), [redacted] Crooked Detector([redacted]), [redacted] Sealer([redacted]), [redacted] ([redacted]), [redacted] [redacted] Labeler([redacted]), and [redacted] Heat Tunnel([redacted]).

Three validation reports were reviewed and showed changes in settings on the packaging line for the tablet filler, metal detector, [redacted] labeler from 2004 to 2005 for package line# [redacted]

In the packaging area there is a line clearance required whenever a new product is placed on the line. A product changeover is when there is a switch from one product to a different product (for example a switch from Centrum silver tablets to Centrum performance tablets). As part of line clearance all installed tools([redacted] Loader and Tablet Filler) must be dismantled, cleaned, and visually inspected to ensure no tablets are present. Two operators in the packaging area and a supervisor must examine the packaging line and verify line clearance was performed. In the packaging area, individuals assigned to this area include a Floor Leader, a Supervisor, a mechanic and several operators. The line clearance is verified by two operators and a Supervisor. The process includes the removal of bulk materials from the packaging line(to include partial rolls, rejected materials, and samples). I was informed that only full product rolls can be returned to the stock room. The Master Packaging Record will keep count of all labels affixed on bottles and the number of labels returned or destroyed. All inspections and equipment set-ups are documented on the Master Packaging Record. If no product changeover occurs the same product (different lot#s) can be allowed to be filled on the same packaging line without performing line clearance. On the Master Package Record the first order of the string of same product is recorded on the batch record to support why no line clearance was needed. Areas on the Master Packaging Record specific to line clearance will be

crossed out and initialed by the operator. If the operator is setting up a new bottle size, additional adjustments are required to be recorded on the Master Package Record to reflect a new tablet count and bottle size.

Every (b) (4) samples are removed and tested to verify correct tablet count, the correct labels on bottles, tablet defects (broken tablets, chipped tablets), verification that the cap is tightened, and cap does not appear to be crooked. The inspection also includes verification that the seal over the mouth of the bottle is intact. Each plastic cap is purchased with a foil placed inside the cap. There are specifications established for the foil type. The specifications for the cap were defined. After the cap is affixed to the bottle, a (b) (4) Sealer applies electrical energy to the surface of the cap, and the inner foil is heated and sealed over the bottle. The seal is visually inspected for wrinkles and any scorching. The seal test is a finger press on to middle of the seal to attempt to break the seal. Next, the seal is peeled off and a visually inspected to verify uniform adhesion around the mouth of the bottle.

The following FDA-483 issues were cited for the packaging process:

Failure to use an appropriate scientifically valid method to test the seal over plastic bottles to ensure uniformity of the sealing process across all plastic bottles. The current method requires testing the integrity of the seal by applying pressure (using finger pressure) over the middle of the seal and visually inspecting the rim over the mouth of the bottle. No specifications were established for the amount of pressure and dwell time to apply or use of measurable tool to evaluate the integrity of the seal.

In the packaging area, failure to demonstrate all requirements were met. Specifically, as part of Master Packaging Record, specifications for cap adjustments (distance from cap to bottom of sealing head) were established to show proper alignment to the sealer; however adjustments were not documented to support proper set-up. Also, when product changeovers occur bulk materials (to include tablets stored in metal detector challenge bottles) must be removed from the packaging line and destroyed; however there is no evidence that tablets inside metal detector bottles were emptied and removed from the packaging line.

As part of my review of Packaging and labeling requirements, I confirmed all suppliers of components were audited and SOPs were established for inspecting, storing, and disposal of bottles and labels.

MANUFACTURING CODES

Most bulk tablets are assigned an internal lot # recorded on the batch production record, and once all tablets are placed into final packaging, the bulk lot is re-assigned a Control No. displayed on the bottle. The Control # begins with a letter followed by a5-digit#. For example: C46001, (b) (4) likely would be (b) (4) In 2008, some of the Control #s will begin with "D" followed by a5-digit number.

INVESTIGATION RE: GINSENG EXTRACT FROM SUPPLIER (b) (4)

On 4/5/07 officials at Wyeth was informed that one lot of ginseng (Lot (b) (4) assigned product code (b) (4) manufactured by supplier (b) (4) was shipped to the US and detained by customs because FDA's office in Seattle tested this product and found it contained a pesticide (Tricyclazole). The ginseng was assigned batch (b) (4) product code (b) (4). This pesticide was detected at (b) (4) ppm and is not approved for use in herbal ingredients imported into the US. On 3/30/07 (b) (4) (Supplier of ingredient) received a 'Notice of FDA Action' for batch (b) (4) The ginseng supplied by (b) (4) is used to manufacture Centrum® Performance Millennium Film Coated tablets (Product Code (b) (4). No other dietary supplement uses this ingredient. Upon notification of analytical report, all ginseng batches in stock (manufactured by (b) (4) were placed on hold while the supplier conducted an investigation to determine the root cause. The two batches received from (b) (4) were quarantined at Wyeth. Since the root cause was not yet known Wyeth placed all ginseng batches on hold including ginseng received from a second supplier (b) (4) under Lot (b) (4) (product code (b) (4)). The investigation revealed the actual root cause was attributed to rice chaff, a processing aid used during the ginseng extraction process. The supplier (b) (4) eliminates the use of rice chaff and committed to further testing batches of ginseng provided to Wyeth within the last 2 years. The supplier found all samples contained trace amounts of tricyclazole. A copy of the analytical report was provided see Exhibit 14. (b) (4) Further testing was extended to ginseng supplied by (b) (4) supplier). The test report for (b) (4) did not detect this pesticide, and (b) (4) confirmed they did not use rice or rice chaff in the Ginseng manufacturing process. As such, all blocked (b) (4) lots were unblocked and made available for production. The investigation focused only on ginseng supplied by (b) (4)

The investigation revealed (b) (4) is a manufacturer of dietary ingredients to include (b) (4) Ginseng Dry Extract. (b) (4) has a corporate headquarters and shipping warehouse at (b) (4) (b) (4) however the ginseng extract is actually manufactured at (b) (4) production site (b) (4). To manufacture this dietary ingredient (b) (4) uses a (b) (4) and filters it through an (b) (4) to produce (b) (4) (b) (4). The (b) (4) are mixed with (b) (4) to produce the final product (ginseng extract). This dietary ingredient is sold to Wyeth to manufacture Centrum Performance tablets.

I asked why ginseng was not tested in the past for tricyclazole, and was informed Wyeth's existing specification was to test this ingredient using USP Test Method and USP Test Method does not require a test for tricyclazole. I was informed that this chemical is typically sprayed on rice and no requirement was established to identify this pesticide. Since finding tricyclazole in ginseng, all batches currently require a test for tricyclazole. (b) (4) worked with an external lab to improve the method using HPLC Mass Spec(MS) and a specification was established (No More Than (b) (4) mg/kg). (b) (4) is using external lab (b) (4) located at (b) (4) to test for this pesticide. As part of (b) (4) corrective action, the test method was improved and validated.

According to Mr. Paul Lucas, Senior Director QA at Wyeth' s Consumer Healthcare division there was no known tolerance or exemption granted to (b) (4) by the EPA to allow this pesticide in herbal supplements. He mentioned that (b) (4) did not submit any paperwork to EPA to establish a maximum tolerance for tricyclazole or any other pesticide for ginseng extract. As such, the tolerance level should be set at zero; however, the analytical instrument normally can't detect to zero, and can only read <0.01mg/kg. As such <0.01mg/kg was the specification established for this test. He also mentioned the test for this pesticide also has to be validated, and he mentioned that he did not believe FDA's test method was validated. Officials at (b) (4) were asked to test several samples in stock and confirmed the presence of tricyclazole. A copy of the test report showing all samples contained tricyclazole was provided, see Exhibit #14.

Some actions that had been implemented by Wyeth in lieu of analytical findings were mentioned as follows: to visit (b) (4) manufacturing facility in (b) (4) to gather information on the ginseng extract process, conduct a legal assessment to determine all applicable federal and/or state pesticide regulations, ask (b) (4) to investigate the issue, as well as to implement corrective action; determine any health risk to the consumer; determine the amount of product and raw materials in stock, and to contact an official at CFSAN to discuss all findings in order to determine if a market removal was needed. A copy of Wyeth's Recall procedure was provided, see Exhibit #15.

The outcome of the investigation resulted in several corrective actions. First, the supplier determined the root cause was indeed rice chaff, a processing tool used in the extraction process that introduced tricyclazole into the ginseng. As a corrective action the rice chaff was removed and (b) (4) improved the extraction process. Also, (b) (4) worked with the external lab (b) (4) to improve the test method. Mr. Moatter, Director of QA Compliance& Product Release mentioned the ginseng (starter material) was fine. There was never an issue with this material containing pesticides upon receipt at (b) (4) I was informed that (b) (4) selects this material from a reliable source and officials at Wyeth audited (b) (4) in the past and found this supplier was acceptable. Mr. Moatter was willing to voluntarily share information about the audits so that I could see details about the audit questions and outcome. No adverse issues were noted. (b) (4) was listed as an approved supplier. Information concerning the business agreement established between (b) (4) and Wyeth was collected see Quality Agreement Contract (Exhibit 16). I also collected a copy of the approved supplier's list established at Wyeth see Exhibit 17. All suppliers of dietary ingredients

must be audited every (b) (4) years. As a result of the incident regarding the ginseng, a third audit was performed. In addition to the audit performed at (b) (4), another corrective action was to update the monograph for ginseng (maintained at Wyeth's plant in Pearl River, NY) to require testing for tricyclazole. Another corrective action was to reject all batches of raw materials (ginseng from (b) (4)) and finished product (Centrum Performance tablets) affected by the ginseng/ tricyclazole issue. The following products were rejected, as listed below:

Centrum Performance Tablets(manufactured with (b) (4)
Lot#s: (b) (4)
(b) (4)
(b) (4)
(b) (4) were rejected.

Ginseng Extract code (b) (4)
Lot#s: (b) (4)
(b) (4)
(b) (4)

During a review of MIR #270291(Exhibit 18) Wyeth became aware by the supplier (b) (4) on 4/5/07 that ginseng was tested by the FDA and contained Tricyclazole and Wyeth decided on 4/09/07 to block material (ginseng) and all lots of Centrum Performance tablets; however a review of shipping records found one batch of Centrum Performance tablets (b) (4) was shipped to a customer on 4/10/07, despite the notice to block product on 4/9/08, according to MIR (b) (4) Copies of all shipping records for related shipment under Control No. (b) (4) were collected under DOC sample #496576.

MIR [redacted] contains documents, such as: summary of investigation, safety assessments/ health hazard evaluations, test reports for rice chaff (found tricyclazole), analytical report for starter ginseng material(no tricyclazole detected) , Change Control Form issued by (b) (4) a letter issued by [redacted] to report no tricyclazole found in their product), copies of Wyeth's PQRMC Minutes, Management Notification of GMP- Critical Events dated 4/9/07 (to document notification to Wyeth's sites affected by ginseng/ tricyclazole issue), an email dated 4/5/07, a copy of analytical recovery data, a copy of lab report issued by [redacted] to show dry ginseng extract contained tricyclazole, and a copy of an addendum to validation report for analytical method.

Note: A copy of Wyeth's Incident Management SOP was collected to describe how to notify other Wyeth sites when there is an incident that may impact other locations see Exhibit 19: Incident Management SOP PPG-0044410.

During this inspection I asked F. Moatter to furnish the following information to me: the amount of (b) (4) ginseng and finished product (using (b) (4) ginseng affected by the rice chaff/ tricyclazole issue) currently in stock, the material disposition for the finished product (evidence product was destroyed or returned to vendor); the amount of lots in the market that were still within expiration and the amount of retains in stock. Mr. Moatter responded that all finished product affected by the tricyclazole issue had been destroyed and the ginseng batches returned to the vendor. No bottles of C.Performance tablets or ginseng were in stock. The distribution center also did not have any product on hand. The units within expiration consist of 4 batches ((b) (4) (b) (4)) and I collected information on the 4 batches (amount released, rejected and shipped), see Exhibit #20. The last batch shipped was on 4/10/08 from Wyeth's distribution center in TN. An updated list (Exhibit 21) was provided due to a change in the number of bottles for Control No. (b) (4) actually destroyed. The original amount reported was (b) (4) bottles and was changed to (b) (4) bottles. In addition, I was provided the amount of retains in stock, see Exhibit 22 along with copies of Material Rejection Reports(Exhibits 23 & 24) to show items destroyed (finished product and raw materials). The following records were provided: Material Rejection Report for Centrum Performance tablets dated 5/30/07 and Material Rejection Report dated 5/31/07 for ginseng Lot (b) (4) .

Incorrect query:>> An incorrect query was conducted and resulted incorrect information provided. The information provided for the 4 batches of Centrum Performance was incorrect in terms of the amount of product within expiration. On 9/25/08 I was informed that the prior information was not correct. The original information provided on 9/4/08 showed 4 batches within expiration, but as of 9/25/08 the correct information was reported as (b) (4) lots see updated list (Exhibit 25A). During a conference call between Wyeth and FDA's district office held on 9/18/08 Wyeth's QA department wanted to review the information already provided to me because they thought the amount was close to batches; however on 9/25/08 it was noted as (b) (4) lots. I was also provided with a list of retains on stock for the lots (Exhibit 26). A verbal explanation was provided for the original query basically reporting a human error was made when reporting the original information. The query was not performed correctly and had to be manually performed to get the correct numbers. Further information on this mistake was provided in writing, see Exhibit 27.

Correction to amount destroyed. There was another correction reported for previous information provided for the amount of Centrum Performance tablets destroyed. I was informed all lots of Centrum Performance that had been in stock at production sites and at Wyeth's Distribution Centers were destroyed but actually there was one batch (Control No. (b) (4)) that was not destroyed and held in Wyeth's warehouse in TN. This information was disclosed on 9/25/08 and the above Control # consisted of Centrum Performance tablets in bottles of (b) (4) tablets.) This batch will be destroyed on 10/8/08, and consist of the full amount manufactured. No product was sold to customers. A copy of the destruction list was provided, see Exhibit 25B(I.D.'s Distribution Centers, Material Description, Batch, Quantity, Ship Date, Ship To, Destruction Date, Method of Destruction and Notes).

On 9/26/08 I collected five physical samples of Centrum Performance tablets in different package configurations (retains only). All samples displayed an expiration date of Jan 09 and were randomly collected from Wyeth's stockroom. The original cardboard box holding all retained samples had been ID'ed as "Samples FDA 9/26/08 JW"(initials). Mr. Lucas was advised that a FDA-484(Receipt for Samples) would be issued for the samples at the close of the inspection. This document was issued on 10/8/08. Mr. Paul Lucas requested 3 to 6 bottles remain in stock for regulatory reasons, as such the full amount of samples available could not be collected. I was provided with a document (Exhibit 101)signed by Mr. Lucas to show what samples were provided.

As part of the investigation into the ginseng/tricyclazole issue there was Material Review Board (MRB) meeting held on 4/9/07 to discuss product safety and medical assessment issues in light of the presence of tricyclazole in ginseng. Using the highest detectable level found ([redacted]ppm) a Health Hazard Evaluation was completed by Jay Goldring, PhD of Global Scientific Affairs on 4/09/07. The investigation found that although Tricyclazole was not approved in the US, a maximum permissible level of [redacted]ppm in rice brand, rice hulls, and rice polishings was found. This maximum level does not cover other food or food additives. An assessment was determined that using the maximum daily dose of Ginseng in Centrum Performance [redacted]mg a day and taking into consideration the amount of pesticide in the ginseng, there was no safety risk. The amount of pesticide that would be seen in the finished product would be so little there was no health risk to the customer. The amount would be far less than the maximum limit allowed in rice. The investigation also disclosed that based on data collected as part of a [redacted]year pre-clinical study using tricyclazole in rats, the rats were administered up to [redacted]mg/kg/day and revealed no adverse effects, including cancer. This information translates to a human dose of over [redacted]grams of tricyclazole per day. The investigation revealed that Centrum Performance tablets may contain a maximum of [redacted]ng of tricyclazole per tablet based on a theoretical calculation using [redacted]mg of Ginseng/ tablet. The serving for Centrum Performance is one tablet daily. This translates into [redacted]safety factor, and was concluded that there was no safety issue to consumer.

In addition to the above information Wyeth's investigation also revealed that on 4/27/07 Wyeth's outside counsel [redacted]contacted Joseph Baca, Director of the Office of Compliance in CFSAN regarding the ginseng issue. Wyeth's outside counsel informed Mr. Baca that certain lots of Ginseng contained trace amounts of pesticide (tricyclazole) and Mr. Baca did not disagree with Wyeth's plans not to remove product on the market. As such Wyeth's PQRMC team decided no action was required for product already sold to customers. The only agreement was not to further distribute any lots of Centrum Performance (with [redacted]ginseng) to customers once they were aware that tricyclazole was in the product. The PQRMC team agreed not to distribute the end product in the U.S. or to any other markets.

All relevant information concerning the investigation was included as part of MIR[redacted]
Additional records were provided, see below:

- Documents titled "Ginseng Pesticide Issue" created by Paul Lucas, Sr. Director Quality Operations, see Exhibit#s28 & 29(revised copy dated Sep 16, 2008 and the original copy dated Aug29, 2008).

- (b) (4) Product Description for Ginseng Dry Extract/HF (Exhibit 30) w/ attached lab report issued by Lab Analysis(report (b) (4) to show ginseng is now tested for tricyclazole.

- A copy of (b) (4) COA(Exhibit 31) showing no test for tricyclazole required back in 2006 This document attached to Wyeth's Final Disposition Report (b) (4) dated 2/16/07

- Visit to (b) (4) Plant(Exhibit 32) on April 27, 2007

- Change Control Request Record ((b) (4)) to add specification to monograph for ginseng to test for tricyclazole), see Exhibit 33

- Wyeth's Internal Correspondence (Exhibit 34) dated September 12, 2008

- Letter dated 9/5/08(Exhibit 35) signed by P. Lucas related to conversation with Wyeth's outside counsel and Mr. Joseph Baca, Director of the Office of Compliance/ CFSAN)

- Estimated value of goods destroyed (Exhibit 36) for Centrum Performance tablets) affected by ginseng/tricyclazole issue

- A list of rejected Ginseng from (b) (4) (Exhibit 37) from 2006 to 2008)

- Customer Distribution List(Exhibit 38) for Centrum Performance

INVESTIGATION OF GINKGO BILOBA FROM (b) (4)

Ginkgo Biloba extract is the second herbal ingredient used to manufacture Centrum Performance tablets and was associated with three recent batch failures due to the presence of pesticides. A review of test requirements revealed that this ingredient is tested by supplie(b) (4) for pesticides using the USP method and sent to an external lat(b) (4) to test for tricyclazole. Mr. Farooq Moatter, Director of QA Compliance/ Product Release reported Gingko Biloba is an old leaf typically self preserving and does not need to be sprayed with pesticides; however, Wyeth does request that each supplier of this material test for different pesticides using the USP method. A

review of the history of rejects for this material did not find any major product quality issues. I was advised that three batches were recently tested and found trace amounts of different pesticides. These batches were tested by an external lab (b) (4) and were still in stock. Officials at Wyeth planned to return all batches to (b) (4) however I explained that this action was not allowed. Wyeth was not allowed to ship FDA regulated products via interstate commerce that knowingly contain a pesticide. The firm's management was informed of this and made plans to have this material destroyed. Copies of all test reports (Exhibit # 39) for the 3 lots were provided. The test reports showed the presence of the following pesticides: Acetamipride, Imidaclopride and/ or Phoxime. I asked for all names of supplier and was provided with two suppliers of ginkgo biloba((b) (4) (b) (4). The ginkgo powder from (b) (4) was assigned code (b) (4) and the gingko from (b) (4) was assigned code (b) (4) The full name of (b) (4) (b) (4) has a second location in (b) (4) (b) (4) and one (b) (4) operating as (b) (4) (b) (4) For the investigation into this issue no root cause has been disclosed. The investigation is ongoing. No issues were reported for gingko received from 2nd supplier (b) (4) under code (b) (4) ginkgo does not have any pesticides. As such, this investigation only focused on (b) (4) ginkgo. Based on communications with the supplier (b) (4) I was advised that there was no confidence in the supplier's ability to test this material using a validated method and officials at Wyeth decided not to use ginkgo to manufacture Centrum Performance tablets. This herbal ingredient was removed from the formula. A new product formula was created and the manufacturing process was re-validated to show removal of this ingredient during the blending process. I was informed that this was a difficult decision to make. All three batches that contained pesticides were received from (b) (4) and had been rejected and placed inside a locked cage.

During this inspection I reviewed shipping records to account for materials received by Wyeth versus the amount imported to the U.S. and found a discrepancy. There was a larger amount of dietary ingredients imported than sold to Wyeth. (b) (4) The 3 batches imported into US were assigned codes Lot #s (b) (4) was re-assigned Wyeth's Lot # (b) (4) when sold to Wyeth Canada and re-assigned Lot# when received at Wyeth's 2nd location in Pearl River, NY. The firm's management was asked to provide information on the amount of goods ordered versus the exact amount received. The following information was provided:

imported kgs of Ginkgo Biloba Extract during Oct 2007 that represented Lot#s (b) (4) kgs); kgs) and kgs) Approximately (b) (4) kg received at Wyeth's production sites in Quebec(Montreal) Canada and Pearl River, NY. The amount not received by Wyeth was kgs kgs of LOT# (b) (4) kgs of LOT# (b) (4)). The full amount kgs was shipped to (a registered mfr/repacker under FEI #). I asked officials at Wyeth it they were familiar with (b) (4) The company officials reported is not an approved vendor, and they did not have a business relationship with this company and did not know why the product was shipped to

(b) (4) As a general discussion on food security measures, I reminded the staff about reviewing all paperwork to ensure all products were properly received from the correct vendor. I had been advised that the shipping record I reviewed did not go to Wyeth's NY warehouse. The Goods Receiving area received other paperwork such as shipping records from Wyeth Canada that had (b) (4) reference only. The NY site reviews all paperwork, and the paperwork maintained did not have any references to (b) (4). All shipping records had been requested via (b) (4) management by Wyeth to account for ginkgo lots imported into the U.S. (b) (4)
(b) (4)
(b) (4)

Based on a review of actual shipping records, Wyeth (Pearl River, NY) received the following ginkgo lots:
(b) (4) kgs of Ginkgo extract under Lot (b) (4)
(b) (4) kgs of Ginkgo extract under Lot (b) (4)
(b) (4) kgs of Ginkgo extract under Lot (b) (4)

The last item (Lot (b) (4) was actually sold to Wyeth Canada and the full amount was reported as (b) (4) kgs. Approximately (b) (4) kgs had been transferred from Wyeth Canada to Wyeth (Pearl River, NY) leaving (b) (4) kgs at Wyeth Canada. This amount was assigned Lot# (b) (4). Wyeth Canada destroyed an estimated (b) (4) kgs) of this material due to damage, and currently has (b) (4) kgs in stock. They plan to destroy this material and will contact M. Caride R&E Coordinator in NYK-DO after the product is destroyed.

Wyeth(Pearl River, NY) request (b) (4) kgs of ginkgo under (b) (4) Lot # (b) (4) from Wyeth Canada and assigned the material Lot# (b) (4) upon receipt at location in Pearl River, NY.

In Wyeth's database a total of three lots of ginkgo was received from (b) (4)
(b) (4)

Supporting documentation to show the amount received by Wyeth was provided see Material Document List(Exhibit 40). NOTE: Approximately (b) (4) kgs of this material used as a sample and this list was updated, see Material Document List Exhibit 41((b) (4) kgs). The amount in stock @ Wyeth (Pearl River, NY) was noted as (b) (4) kg of Gingko Biloba Extract representing (b) (4) Lots(w/ detectable levels of pesticides)

On 9/26/08 the full amount (kgs) was marked " NON –HAZARDOUS WASTE" loaded into a trailer operated by and transported to (b) (4)
(b) (4) to destroy by incineration. The following documents were collected: a copy of the Disposal Request For Hazardous/ Problem Waste Document #

[redacted](Exhibit 42); a copy of [redacted] Shipping Document under Tracking [redacted](Exhibit #43), two waste removal labels (Exhibit #44) and a copy of the letter of destruction see Exhibit 45.

A review of I/s shipping records revealed Ginkgo Biloba Extract(made in [redacted]) was shipped from [redacted] and sold to [redacted]. A portion of this material went to Wyeth Canada [redacted] and [redacted] were sold to Wyeth(Pearl River, NY). The [redacted] sold to Wyeth Canada was transferred to Wyeth (Pearl River, NY) and the location in Pearl River, NY has a total of [redacted] lots in stock.

I also collected the following documents:

-Bill of Lading No. [redacted](see B/L # on bottom of document) issued by [redacted] dated Oct 17 2007 that shows [redacted] drums of Ginkgo Biloba placed on [redacted] pallets [redacted]kgs wit [redacted] under consignee(importer on file) ID'ed as [redacted] see Exhibit 46

- Packing List [redacted] dated Oct 17, 2007 for ginkgo three items([redacted]kgs of Lot# [redacted] kgs of Lot# [redacted] kgs of Lot [redacted]) dated Oct 17, 2007. This product made in [redacted] as declared on the document. The material is manufactured by [redacted] see Exhibit 47

- [redacted] Straight B/L Shipper's No. [redacted] shows product under Lot #s [redacted] stored in [redacted]. Total amount [redacted] drums [redacted] see Exhibit 48

- [redacted] Memorandum Shipper's No. [redacted] kgs of Ginkgo Biloba Extract shipped to [redacted] under Lot#s [redacted].(Exhibit 49)

- Bill of lading issued by [redacted] dated 12/10/07 for Ginkgo Biloba 2 Lot No.s: [redacted] drums or [redacted] kgs) and [redacted] drums or [redacted] kgs) shipped to Wyeth Pharmaceuticals in Pearl River, NY (Exhibit 50)

- Wyeth's Inbound Delivery Ticket [redacted] shows Wyeth in NY received Ginkgo biloba extract from Vendor: [redacted] and Lot# [redacted] see Exhibit 51

-Purchase Order issued by Wyeth Canada for [redacted] kGS of Gingko Biloba received from [redacted] see Exhibit 52

-Packing Order [redacted] issued by Wyeth Canada for Ginkgo Biloba Extract [redacted] to Wyeth Pearl River, NY Lot [redacted] Exhibit 53

-Bill of Lading issued by [redacted] under Shipper's No. [redacted] for [redacted] drums [redacted] of Ginkgo biloba(total amt. [redacted] under Lot # [redacted] see Exhibit 54

A company decision was made to discontinue using Gingko Biloba and reformulate Centrum Performance tablets due to inability of supplier to test ingredient using a validated method. As a result of this action the product code for Centrum Performance was changed from [redacted] Copies of the validation report [redacted] for code [redacted] was collected (Exhibit 55) to show the removal of ginkgo and the substitution of microcrystalline cellulose. Microcrystalline cellulose was an existing ingredient used in the finished product. The amount was increased to maintain the total weight of the tablet. A copy of the original validation protocol/ report [redacted] for code [redacted] was provided (Exhibit 56) to show ingredients and equipments had been approved for use to manufacture Centrum Performance. I was also informed that several documents were updated to remove ginkgo.

NOTE: The supplier's overall status was still noted as "approved" on the supplier list. This issue was verbally discussed with the firm's management. Specifically to discuss what issues prompted disqualification. To my knowledge, this material was not used in any other products, only Centrum Performance. I indicated that supplier SOP could be improved to organize all instructions in the order each step was performed. Since this material was no longer used in Centrum performance, as a corrective action the supplier and material were both disqualified. I was provided with documents to show the supplier's original status (Exhibit 57) versus the disqualification status as of 9/26/08.

Other records collected are listed below:

- Copy of labels for ginkgo destroyed on 9/26/08(Exhibit 59)
- Cost of Ginkgo lots sent for destruction on 9/26/08 (Exhibit 60)
- Copy of [redacted] COA Ginkgo Extract(Lot [redacted] shows no test for Tricyclazole) dated 7/25/06, see Exhibit 61
- Copy of [redacted] COA dated Jan 14, 2008 (Lot [redacted] w/ test report issued by Lab Analysis([redacted] for all pesticides to include tricyclazole (pg 3 of 8), Exhibit 62
- Quality Agreement between [redacted] and Wyeth, acting by and through its Wyeth Pharmaceuticals Division and its affiliate Wyeth Canada (Exhibit 63)

DIETARY SUPPLEMENTS CGMP's/ FACTS ASSIGNMENT #951846

The following is a summary of cGMP issues reviewed for Centrum Performance and Centrum Silver tablets:

Personnel

Wyeth maintains written procedures that describe the training program for employees under SOP# 00002306(Employee training) and a review of actual training records for different areas found employees were trained. The training program includes an introduction to Wyeth's organization and standard operating procedures and includes class room as well as on-the-job training. More senior experienced person is assigned to train a new employee and documentation of training is maintained. I also reviewed a job description for QC supervisor, and what education is needed to maintain this position. Part of the description for Quality Control Supervisor requires conducting assays, analyzing results, training and acting as a mentor, maintaining lab support records, developing and revising lab methods. No adverse findings were noted.

Physical Plant & Grounds

The maintenance of the warehouse and production areas were reviewed for building (b) (4) and complex (b) (4) (areas (b) (4)) and found sanitation requirements for the physical plant and grounds were established. Part of my review included a walk through of all areas where raw ingredients and finished products were stored, manufactured, and packaged to determine measures implemented to keep the grounds clean and free of pests, determine if appropriate lighting fixtures were installed, if appropriate temperature monitoring devices were installed, if food ingredients were stored away from chemicals, if Wyeth had adequate floor drainage systems, and water supply systems, and if adequate hand washing stations were present. My review revealed warehouse and manufacturing areas had adequate drainage systems, proper lighting, no signs of rodents and insects and appeared to be relatively clean.

I reviewed the firm's water treatment system. The water system converts portable water into purified water (contains an ozone generator) and all components belonging to water system are frequently inspected / maintained according to Preventative Maintenance schedules. The water is used to formulate film coat solution for all coated tablets. Both the portable water and purified water were analyzed and handled according to SOPs. No negative trends were found.

Also as part of my review of Physical Plant & Grounds, I reviewed areas for holding sanitizing agents/ chemicals and found all sanitizing agents were stored in a secured area. In general most areas where dietary ingredients are stored must be entered using an employee access card, and as such individuals from the outside would not have direct access into the production areas or warehouse.

As part of the overview of the physical plant and grounds, I reviewed pest control issues, (b) (4) alarm SOP, contractor cleaning of the warehouse and production areas, and temperature & humidity monitoring records for building (b) (4) Pest Control issues are handled by contractor: (b) (4) (b) (4) I reviewed pest control records and no adverse issued were noted.

The following records and SOPs were reviewed as part of the physical plant and grounds:

-Pest Control Management Procedure PPG 00020397

-Pest control logs

-Daily /Weekly/ Monthly schedules for cleaning building (b) (4)

-Temperature &Humidity Reports (July & Aug 2008) for Temp recorder for (b) (4) in Bldg (b) (4)

-Maintenance of Call Lists for (b) (4) system (SOP PPG 00001506) to include monitoring refrigerators, freezers, chillers, and remote alarm systems.

Hygiene Practices / Product Contamination

Written procedures were established for prevention of product and personnel contamination under SOP #20011(Exhibit 20) and this procedure appeared to be adequate. The SOP requires employees to wear lab coats and coverings over shoes, eyes, and hair when working in the production areas. In building there are different zones; each zone has restrictions. For example, in zone (b) (4) (manufacturing area) and zone (Packaging area) employees are can't bring food or beverages into these areas and must wash hands before entering the production area and report open lesions to the company's nurse.

Equipment & Utensils

Wyeth maintains a Preventative Maintenance program that includes requirements for monitoring, calibrating, and cleaning equipment. No adverse findings were noted. I reviewed calibration SOPs, PMO's, and cleaning logs. A supervisor in the maintenance area was designated as the QC personnel to ensure all equipment in the production area was adequately maintained, cleaned and calibrated. I reviewed cleaning logs for the following equipment: solution tank, (b) (4)

(b) (4) blenders, (b) (4) Pan Coaters, (b) (4) compressor and (b) (4) press machines. The PMOs I reviewed were for the (b) (4) Inverter, (b) (4) Sieve, and (b) (4) sealer. I also reviewed calibration records for digital thickness gauge, hardness tester, scales, and friability rollers. A review of the cleaning practices did not find any adverse issues. All instruments appeared to be clean, and cleaning agents were available, and had been stored away from dietary ingredients.

The preventative maintenance program for USP Purified Water System was reviewed. Wyeth maintains a program for maintaining air filters, mixed beds, (b) (4) units, and subparts to the UV sterilizer and ozone generator. These areas are maintained every (b) (4) months.

As an overview of the equipment cleaning I was provided with the following information:

- In the powder blending room, cleaning is performed after every product changeover, as well as every (b) (4) day. The blenders are cleaned if allowed to sit in a clean state for more than (b) (4) days

- The tablet compressors are cleaned after each product changeover, as well as every (b) (4) day when running the same product or cleaned after any repairs are performed in the room.

- The film coating machines (pan coaters and CTC) are cleaned every (b) (4) calendar days when running the same product, and cleaned when the equipment sits in a clean state for more than (b) (4) days.

In terms of automated, mechanical equipment the following validation reports were reviewed:

- Validation Report (b) (4) (manufacture of Centrum Silver tablets) using (b) (4) blender, (b) (4) tablet press, and Continuous Tablet Coater(CTC)

- Validation Report #s (b) (4) (Packaging Validation) Final Report for Centrum, Centrum Silver and Centrum Performance tablets using (b) (4) plastic bottles with a (b) (4) mm wave cap dated May 2005, December 2004 and October 2004

- Validation Report (b) (4) (manufacture of Centrum Performance tablets) under code (b) (4) using (b) (4) blender, (b) (4) tablet press, and (b) (4) pan coater dated March 2007

- Validation Report for Centrum Performance code [redacted] (b) (4) sing alternate suppliers of calcium carbonate, vitamin and mineral premixes, ascorbic acid, vitamin E, and a modification to lower vitamin D overage by [redacted]

- Validation Report [redacted] (b) (4) to remove ginkgo for Centrum Performance tablets under code [redacted]

- Computer Validation [redacted] (b) (4) software installed for the [redacted] (b) (4) Tablet Compressor) [redacted] (b) (4) dated 2/15/08

All automated, mechanical and electrical equipment used in manufacturing, packaging appeared to be capable of operating satisfactorily within the operating limits, and adequate controls were established.

Production & Process Controls

A review of Production and Process Controls revealed all stages of manufacturing, packaging, labeling, and holding dietary supplements were defined, and both component and finished products are tested. Atleast one test or exam was conducted on each dietary ingredient to verify identity and all test reports (Lot Disposition Reports) are periodically reviewed by QA. At minimum all ingredients must pass ID test (verification of physical description and perform a HPLC or ICP assay). The finished product is tested for contaminants (lead and micro organisms) and all limits were defined. Specifically, on quarterly basis the lead and micro testing is conducted by external labs [redacted] (b) (4). Additional contaminants such as metal fragments are detected in the production area by installing metal detectors on tablet compressors and packaging line to ensure no metal parts (chips of metal from metal punches) are embedded inside the tablet). A MIR (Manufacturing Investigation Report) is completed for any deviations. **NOTE:** One verbal observation was discussed with the firm's management regarding storage of plastic ties in the blending room (over the entry door). Mr. Lucas explained the ties are needed as part of manufacturing process to secure plastic bags upon discharge of the powder from blenders. He believes plastic ties are part of utensils required for batch manufacturing process, and as such this observation was verbally discussed.

My review of process controls also verified process parameters were established inside the powder blending room. The blend speed is recorded as part of the machine's set-up. In the tablet press room every [redacted] (b) (4) samples are collected, and tested to verify correct weight, hardness and tablet thickness. All equipment shut downs are recorded as part of the Production Batch Record. I also reviewed pan coating process and all process target set points, ranges, and alarm limits were established.

Examples of process parameters are listed below:

[redacted] Tablet Press machine
Speed @[redacted]rpm, target [redacted] rpm;
tooling size: [redacted]"; avg target weight= [redacted]g
thickness: [redacted]"; hardness: [redacted]kp; disintegration of tablets: NMT [redacted]minutes w/discs, and Friability: Not More than [redacted]% loss.

Pan Coater[redacted]
Spray Gun Nozzle Size: Air Gap [redacted] Liquid Nozzle [redacted]
Atomizing Air and Pattern Air: [redacted] slpm and [redacted] slpm
Spray Rate: [redacted] ml/min(target [redacted] ml/min)

Pan Coaters [redacted]
Spray Gun Nozzle Size: [redacted]
Atomizing Air and Pattern Air: [redacted]psi (target [redacted]psi)
Spray Rate (using [redacted] ml/ min(the target= [redacted]ml/min)

As part of my review of requirements established for components and finished products, I reviewed monographs and incoming SOPs for testing dietary ingredients, packaging, and labels. Wyeth has a test schemes SOP PPG-000000890(Exhibit #64) and the following monographs are used to test dietary ingredients, the finished product, and inspect packaging.

- Ginseng Monograph [redacted] (Exhibit 65)
- Ginkgo Biloba Extract Monograph [redacted], Exhibit 66
- C. Silver Tablets Monograph [redacted] Exhibit 67
- C. Performance Tablets [redacted] Monograph [redacted] (Exhibit 68)
- Monograph [redacted] for C. Performance Tablets (code [redacted]) Exhibit 69
- Centrum Performance Mineral Premix, Monograph [redacted] Exhibit 70
- C. Performance Vitamin Premix Monograph [redacted] Exhibit 71
- C. Silver Vitamin Premix Monograph [redacted] (Exhibit 72)
- Centrum Silver Mineral Premix Monograph [redacted] Exhibit 73
- Monograph [redacted](caps) Exhibit 74

I verified an ID test is conducted for all raw materials. The ID test includes a visual verification of product's description ICP assay or HPLC assay or use of an in-house method.

Each supplier must provide a Certificate of Analysis (COA) to show ingredients were tested and on annual basis each supplier's COA is qualified. Copies of COAs for all dietary ingredients were provided, see Exhibit 75.

In terms of conducting a final test for dietary supplements, I was informed that the finished product is tested on a (b) (4) basis per Test Scheme SOP PPG-00000890(Exhibit 64). Every (b) (4) batch is tested. The test will include a test for the tracer ingredient and all other ingredients requested according to the monographs established for either Centrum performance or Centrum silver tablets. The test will include a water activity test. If the product is intended to be exported overseas, all batches are tested. The items for export are not place on the (b) (4) program only product intended for domestic sales.

NOTE: Each tablet will include a tracer test on detect if the lowest concentrated vitamin or mineral is correct. These items are usually contained in premixes purchased from suppliers. The lowest concentrated vitamin ingredient inside the premix for Centrum silver and Centrum performance tablets is (b) (4). The lowest concentrated mineral inside Centrum silver and Centrum performance tablets is (b) (4). If these two ingredients (b) (4) are tested using HPLC or ICP assays and meet all claims on the label, I was informed there is a higher probability that the other ingredients in premixes are OK. As such, other ingredients in the premix are not tested. The only other ingredients to test will be those ingredients specified per the monographs under Exhibit#s 67-69, as well as requirements ID per the SOP for the test scheme.

Wyeth approved the following vendors to supply vitamin and mineral premixes:

(b) (4)

The QA department is responsible for tracking all (b) (4) batches, and maintains a copy of all logs to show which batch was tested. Copies of logs for Centrum silver and Centrum performance tablets were provided see Exhibit 76. The Batch Production Record must be stamped (b) (4) to identify which batch received a final test. An example of one batch with all records showing it was stamped was provided for Centrum Silver Control No (b) (4) see Exhibit #77. If the batch does not include a stamp that shows a QA supervisor must go to the blend room and witness all ingredients added to the batch. This action is referred to a (b) (4)

If QA performs this task, the batch record must be stamped "(b) (4) (b) (4) One example of a batch record with this statement was provided, see Exhibit 78 (Centrum Performance tablets Control No. (b) (4)

NOTE: If the batch does not show a stamp with the following statement: "(b) (4) or (b) (4) (b) (4) a final test on the batch must be conducted using a Composite test. The composite test requires that (b) (4) batches of the same product be combined(either (b) (4) batches of Centrum silver or (b) (4) batches of Centrum performance) be combined and perform a tracer test and testing required by the monograph.

Lot Disposition Reports for Centrum Performance and Centrum Silver tablets were collected see Exhibits 79 & 80(shows summary of "pass" status and all test results).

All batch records must be stamped "(b) (4) to support QA reviewed documents.

On a quarterly basis dietary supplements are tested for Micro and Lead. The Micro test performed by (b) (4) (b) (4) The Lead test is performed by (b) (4)

The following records were also reviewed, as part of Production & Process Controls:

-Primary Document Job Aid for (b) (4) Tablet Press Set-up and Operation PPG00032101
-QA Shop Floor Verification(Exhibit #81) for Wyeth Consumer Healthcare PPG-0004009
-Testing Schemes for Wyeth Consumer Healthcare Materials PPG-0000089
-Maintenance and Destruction of Quality Assurance Reserve Samples PPG 000000974
- Processing Inventory Material for Receipt in Building (b) (4) and Complex (b) (4)
- Excipients, Critical Excipients, Dietary Ingredients, Critical Processing Aids, and Packaging Component Release PPG00001097
- Product Stability Program PPG 00030249
- MIR #(b) (4) (OOS lab test results for low Biotin due to wrong vitamin premix used)
-MIR #(b) (4) (OOS gain/ loss for Centrum silver batches for low magnesium) due to failure to follow charging /blending) process
- MIR #(b) (4) (high magnesium levels for Lot(b) (4))

- Quality Control Spec for Water, Purified Monograph (b) (4)
- Investigation of and handling of Discrepant Test Results PPG-0005695 (Exhibit 82)
- Portable water monograph (b) (4)
- Purified, de-ionized water for lab use Monograph (b) (4)
- Reduced Testing of Incoming Materials PPF000000979

Primary Doc Job Aid for Circular Inserts and Roll Label PPG 000005205

-Sampling Incoming Materials PPG 000009045

- Manufacturing Investigation Report(MIR) PPG-00000552 Exhibit 83

Quality Control Functions and requirements established for Supplier Qualifications, Lab Controls, Packaging & Labeling Material Reviews, Holding Distribution , Product Returns , Complaints , Master Batch Records, and Production Batch Records)

Based on a review of SOPs specific to QC's function to review and approve Master Batch records, supplier qualifications, laboratory operations, receipt of packaging and labeling issues , handling of Material Reviews& Disposition reports, product returns, I found that Wyeth's QC personnel was appointed to review and approve these functions and several requirements were established.

I reviewed Wyeth's supplier audit program and disclosed QC personnel reviews and approves suppliers. The supplier qualification process includes contractors and co-manufacturers. An Audit Checklist is completed and all suppliers of active dietary ingredients are audited every (b) (4) years. A contract agreement is created on a case by case basis, based on risk. Two copies of written contracts for (b) (4) (Exhibit 16) and (b) (4) (Exhibit 63) were provided.

The QC Personnel reviews the Master Batch Record. This document includes information, such as product name, strength, product code, expiration, dosage form, package configuration, manufacturing and packaging site, batch #, control numbers; dates, theoretical batch size/ yield, expiration date for packaging, a list of components (by assigned code), the calculated excess of components, theoretical weight of components, and the total weight of tablets, a list of packaging materials(to include all inspections on packaging/labeling), identification of equipment used, machine set-up, work instructions, # of samples tested, a cleaning checklist, verification of weights for components and tablets, operating parameters, in-process inspections, equipment downtimes, and equipment adjustments.

QC personal reviews and approves the material's final disposition. The following MIRs/ LIRs were reviewed to determine if QC personal reviews and approves process deviations, reworks, and all OOS issues: LIR (b) (4) (rejection of OOS for low copper), (b) (4) (a rework of (b) (4) batch with

Lightly coated tablets); (b) (4) rejection of eroded tablets; (b) (4) abnormal color of Centrum silver tablets/ code (b) (4) that resulted in re-validation of (b) (4) tablet press using reduced batch size for discharging (b) (4) of blended material to assure better product uniformity); (b) (4) OOS lab test result for low Biotin); (b) (4) OOS gain/ loss issue due to failure to follow charging process); (b) (4) to report high magnesium levels for Lot (b) (4) w/ approval to release; (b) (4) report that a foil bag was found in container of Vit E with a recommendation to improve instructions for how to open bags); and (b) (4) (plastic tie found in feeder)and (b) (4) copper OOS issue).

I also reviewed the Document Change Program to verify QC Personnel/ designated unit was identified to review and approve all process and product related changes. The following Change Control Records were reviewed: (b) (4) to transfer micro testing to a contract lab (b) (4) (b) (4) to remove ginkgo from Centrum Performance tablets); (b) (4) to revise monograph to add test for tricyclazole @ (b) (4) mg/kg and establish enterobacteria specification @ NMT (b) (4) cfu/ g); (b) (4) (b) (4) to change inspection interval from (b) (4) days based on stability data); (b) (4) updated monograph for ginseng extract due to typo error); (b) (4) add a new ginseng extract supplier: (b) (4)); (b) (4) to reduce testing for aflatoxin and Loss of Drying for (b) (4) ginseng); (b) (4) (to recommend reduce testing for ginseng for heavy metals); (b) (4) to revise Reduce Testing for Ginseng to include testing for Hist. Ginsenosides reflux, and Micro test); (b) (4) to reduce testing for gingko from (b) (4) for loss on drying and heavy metals) and (b) (4) to transfer testing for Gingko for microbial limits and have it displayed on supplier's COA).

All relevant SOPs were established for the following functions: packaging and labeling, qualifying suppliers, handling material reviews, holding & distribution, handling product returns , documenting complaints, and handling master batch and production records.

Some examples of SOPs, Policies, and Job Aids(Work Instructions) established at Wyeth are listed below:

- SOP that defines "Quality Unit Responsibilities" PPG 00001101.
- Investigation and handling Discrepant Test Results PPG-0005695
- QA Shop Floor Verification for Wyeth Consumer Healthcare PPG-00040093
- Testing Schemes for Wyeth Consumer Healthcare Materials PPG-00000890
- Production Reprocess, Rework, and Supplement Operating Instructions) PPG 00000678
- Qualification of GMP Suppliers SOP 00035766
- Auditing of Suppliers and Contractors
- Primary Doc Job Aid for Circular Inserts and Roll Label PPG 00000520
- Packaging Audit and Disposal PPG 00001044 V4.0
- Roll Label Inspection SOP PPG 000000425.

- Master Batch Record SOP PPG 00021351
- Manufacturing Investigation Report (MIR) System
- Reduced Testing of Incoming Materials PPF000000979
- Sampling Incoming Materials PPG 000009045
- Maintenance and Destruction of Quality Assurance Reserve Samples PPG 000000974
- Processing Inventory Material for Receipt in Building (b) (4) and Complex (b) (4)

Returned Dietary Supplements

The location in NY does not receive returns from customers. Nevertheless, a general global policy was established on how to handle product returns, damaged materials, as well as how to salvage materials.

The following SOP's were reviewed:

- Receipt of Returned Goods SOP PPG 00008327
- Disposal and Documentation of Waste from Rejected Materials, Unsalvaged Returned Goods, and Clinical Supplies SOP PPG -00002045 , and
- Job Aid PPG -000042925 (Treatment of Potentially Damaged or Obviously Damaged Product).

Customer Complaints and Adverse Experience Reports (AERs)

Wyeth's location in Pearl River, NY does not evaluated and close out complaints; however all complaints are forwarded to Wyeth's Richmond, VA office and any adverse experience related to dietary supplements must be forwarded to Wyeth Consumer Healthcare(WCH) in Madison, NJ. The location in NY may handle investigations but all customer calls or emails are forwarded to Richmond, VA to be handled according to Customer Complaint Procedure (b) (4) (Exhibit 84). Product information is recorded into Wyeth's (b) (4) database. The Control # assigned on the bottle is researched to determine where the product was manufactured. Several dietary supplements are manufactured either in Canada, Puerto Rico or Pearl River, NY. A Consumer Contact Form is created and the complaint is assigned a priority status. A high priority status is a (b) (4) level and must be handled within (b) (4) hours whereas a low priority complaint is handled within (b) (4) days. All investigations are assigned to the production site to determine the root cause, as well as implement a corrective action if deemed necessary. Retained samples may be tested and the test results entered into the Wyeth's (b) (4) According to Farooq Moatter, Wyeth's location in the Richmond, VA is responsible for closing out complaints. On a monthly schedule Wyeth's Global Complaint Group is responsible for reviewing all complaints entered into the (b) (4) database and trends are reported to the location in Collegeville, PA. A

complaint that reports an adverse experience is handled at WCH in Madison, NJ according to Policy# (b) (4) A copy of this policy was collected, see Exhibit#85. Wyeth's global safety surveillance team (b) (4) will report all AER's to FDA according to SOPs PPG-00008135 and PPG-00000552.

The following AERs were reviewed from Dec' 07 to Aug 08:

- AER dated Feb 05 2008: gastrointestinal obstruction after using Centrum tablets Lot C23405
- AER dated 3/4/08: lip swelling issue for Centrum tablets Lot C33221;
- AER dated 3/18/08: allergic reaction to Centrum tablets Lot C51362;
- AER dated 7/23/08: skin hives after using Centrum tablets Lot C82000
- AER dated 3/20/08 : difficulty breathing associated with Centrum tablets;
- AER dated 6/18/08t: iron deficiency after using Centrum silver tablets dated;
- AER dated 3/20/08: increase in blood pressure after using Centrum cardio tablets Lot C48714
- AER dated 1-11-08 : suicide (Centrum tablets Lot C11328)
- AER dated 7/07/08: facial swelling, itching and hives (Centrum performance no Lot#)
- AER dated 7/09/08 : GI bleeding after using Centrum performance tablets(no Lot#)
- AER dated 3/20/08 :leukemia and skin rash after using Centrum silver Lot B43436
- AER dated 3/14/08 ;: medical important: hypercholesterolaemia, hypertension, glaucoma, and a blood sugar issue) for Centrum Lot #B67205
- AER dated 2/29/08; blood arsenic increased& energy increased after using Centrum silver Lot#C11339
- AER dated 4/16/08: a stroke after using Centrum silver Lot C11376
- AER dated 3/14/08: Coag. Time shortened after using c.silver Lot C54333
- an AER dated 8/07/08: irritable bowel syndrome after using Centrum silver Lot C82058
- an AER dated 3/20/08: stroke after using Centrum silver (no Lot# indicated)
- AER dated 5/27/08: thyroid cancer when used Centrum silver (no Lot# indicated)
- AER dated 6/17/08: low blood sugar, prostate cancer) for c. silver (no Lot#);
- an AER dated 6/24/08: diagnosed w/ low iron count for Centrum silver
- AER dated 6/26/08: severe anemia after using Centrum silver

A quick review of AER's also performed for Jan 04 to Aug '08.

A break down of the complaints received from 2004- 2008 was provided see Exhibit 86. The top reported issues associated with overall visual appearance of the product, the package seal quality, package fill, and alleged product mix-ups.

One product investigation was received during this inspection concerning an alleged product mix-up for Centrum Lot C61543 and a copy of the investigation was provided, see Exhibit #87 (Wyeth letter dated 8/4/08)

Holding and Distribution

Wyeth has written procedures to describe the receipt/ holding and distribution of goods. No major adverse findings were noted. All incoming goods(to include ingredients, packaging and labeling) are checked against Purchase Orders and employees must receive a copy of the Bill of lading or Manifest from the carrier to verify the correct item was received. The handling of incoming goods is conducted according to SOP 00001282(Processing Inventory Material for receipt inside Building (b) (4) and Complex (b) (4). An Inbound (b) (4) slip is generated and each shipment is issued a SAP#(Wyeth's control #). The employee in the warehouse will verify the vendor's name, PO# and quantity of containers and pallets received. A driver check-in is conducted to verify the truck's overall condition and temperature. All dietary ingredients must be delivered in sealed containers. In terms of distribution, all goods are further distributed to Wyeth's Distribution Centers (warehouses) for delivery to customers. There is a general procedure to describe how to handle distribution of dietary supplements to customers (Shipping of Finished Goods SOP PPG 0001391).

VOLUNTARY CORRECTIONS

Supplier Disqualifications

Although (b) (4) gingko was removed as an ingredient for Centrum Performance tablets, I found the material and supplier were not removed from the supplier's approved list (Exhibit 17) and continue to show "approved" although this material is no longer used in the product or any other FDA regulated products. As a corrective action, changes to the supplier's status and material status were implemented. The status "approved" was changed to "disqualified" for the supplier and "discontinued" for gingko.

Destruction of Gingko Biloba

A letter of Destruction was provided(Exhibit #45)

Master Packaging Record

The Master Packaging Record was updated to record all specifications on the Master Packaging Record for the (b) (4) Sealer's temperature output and for Cap Adjustments.

Disposing of labels (expired labels)

An audit of the Label Control area revealed expired labels were not destroyed as instructed. These labels were in the Label Control area but could not be used in the production area because there was a block placed on the labels. Nevertheless, as a corrective action, Wyeth's SOP was updated to require weekly reviews for the Label Control area to check all labels and remove labels for destruction.

C/A: SOP PPG-00002197 version 5 was revised and the new SOP (version 5.6) requires an inspection (b) (4) to review labels in stock to verify all expired labels using (b) (4) (b) (4).

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

On 10/8/08 a FDA-483(List of Inspectional Observations) was issued to Mr. Michael P. McDermott, Vice President Site Operation, in the presence of individuals: Joseph Vitanza, Managing Director of QCH Manufacturing, Farooq Moatter Director of QA; Mr. Paul Lucas, Sr. Director of Quality &Compliance; Josh Deutchman, Senior Auditor of Quality Assurance, and Kristin Fassett, Manager of Audit Compliance. (b) (5)

(b) (5)

After Mr. McDermott read all noted observations he mentioned Wyeth's overall commitment to complying with new GMP's and all corrective actions would be implemented and a written response sent to FDA's district office. However, I was advised that he would not commit to a date when the written response would be sent to the local FDA office, but would only mention that typically responses are sent within 30 days after receipt of a FDA-483. Mr. McDermott was informed that a Compliance Officer will review all documents and information contained in this report and if any significant GMP issues or violations were noted, regulatory actions could be recommended.

Prior to conducting this close out meeting, Mr. Paul Lucas asked that I have a pre-close out meeting with the staff to discuss all observations that could potentially be documented on the FDA- 483, and a telephone conference was set-up for 10/7/08 to discuss topics, such a(b) (4) instrument's invalid test results, seal integrity test, handling bulk tablets in metal detector bottles, handling plastic ties, product returns, and supplier COAs. Mr. Lucas was advised that the pre-close out teleconference was not intended to replace the actual close out meeting. On 10/8/08 at the close out meeting he provided me with document (Exhibit 88) to provide additional information related to ICP corrective actions.

The following observations cited on the FDA-483:

Observation 1

Laboratory exam and test methodologies do not appear to be appropriate for their intended use. Specifically, the test method using (b) (4) nstruments((b) (4) produced negative trends that report equipment drifts, OOS CV standards and/or invalid results that required a re-test on several mineral lots, but this test method continues to be used, and has not been replaced with a more reliable method.

Supporting documentation:

A copy of (b) (4) (Exhibit #89) was collected to document all invalid trends for ICP instrument and a copy of SOP titled Investigation and Handling of Discrepant Test Results PPG 00005695 also collected, see Exhibit 82.

Discussion:

During my review of batch records I reviewed batch records for Centrum performance and Centrum silver to include a review of test results for finished product, minerals, vitamins, and premixes that revealed some invalid test results. I asked to see what investigation was performed specific to minerals. Normally when there is a test repeated, a LIR(Laboratory Investigation Report) is completed and handled according to the procedure titled: Investigation and Handling of Discrepant Test Results. A Commitment report is created for a LIR in Wyeth's (b) (4) database to document all corrective actions. A trend report is also completed to determine if previous invalid test reports were found. For LIR(Laboratory Investigation Report) (b) (4) (Exhibit#89) this report showed an (b) (4) analysis for trace minerals disclosed final bracketing calibration verification (CV) standard for boron value exceeded the high limit. The document revealed the test method would need to be revalidated. Verbally I was advised that the revalidation would cover 2 parts (a test using multi-mineral premixes and a test for the finished product. Only one part of the validation was completed.

I was informed the test method was originally validated in 2006 but since that time the (b) (4) instrument had various issues with the injector tub clogging as well as invalid test results. No specific root cause was determined according to LIR (b) (4) I was advised that this instrument is sensitive and there are numerous factors that could contribute to the invalid test results. One temporary corrective action (not document on LI (b) (4)) was to reduce the amount of samples passed through the instrument to avoid equipment drifts. This was a band aid fix. It was not intended to be a permanent fix because all samples had to be completed within the allotted time. One major issue was the clogging of the injector tube due to calcium build-up from minerals. Some corrective actions were implemented to install a (b) (4) humidifier to reduce clogging, and modify the torch cleaning procedure. However invalid test results still continued and the injector was still clogged. I was informed the injector clogging issue can be decreased but will not be totally removed due to nature of the test (use of minerals) that cause the clogging. The target was to reduce the amount of clogs. A secon (b) (4) instrument was purchas (b) (4) and was installed in the lab

and the newer (b) (4) had similar issues see LIR (b) (4) Two individuals (Laura Ziegler, QC Mgr for AD (Analytical Development) and Mr. David Myhven, QC Scientist /Investigator) were interviewed and explained problem with this instrument. Mr. Myhven explained the injector clogging issue and Ms Ziegler explained that a new method was developed. A portion of the method was completed but the validation of the method for mineral premixes is still pending.

Observation 2

Failure to use an appropriate scientifically valid method to test the seal over plastic bottles to ensure uniformity of the sealing process across all plastic bottles. The current method requires testing the integrity of the seal by applying pressure (using finger pressure) over the middle of the seal and visually inspecting the rim over the mouth of the bottle. No specifications were established for the amount of pressure and dwell time to apply or use of measurable tool to evaluate the integrity of the seal.

Supporting documentation:

Copies of complaint breakdown list (Exhibit86) and SOP PPG-00002283"Container Monitoring)" see Exhibit #90 were collected. Under Exhibit 91 (section III In process Checks- Air Torque Inner seal) item #4 reads "(b) (4) (b) (4) ". A copy of document titled " Primary Document Job Aid for Heat Induction Cap Sealer Set-up & Operation" PPG-00010936 was also provided (Exhibit 91) that requires (see item 34) that each Packaging Operator remove (b) (4) containers at the start-up of the Process Order(PO) and verify seal is completely formed on each bottle, check foil seal for minimum wax reside, and verify pulp liner is not burnt inside the cap(all visual inspections).

Discussion:

During my review of packaging controls the integrity of the seal was evaluated and found pressure is exerted over the seal and to peel off the seal and check seal quality. The seal inspection is performed by the finger although not specifically stated. Mr. Moatter explained the finger is pressed over the seal and this technique has been used to test the seal during packaging validation. A copy of the validation report was collected and only mentions overall seal quality issues.

I discussed with the firm's management that the finger is not a calibrated tool and each person's finger force on the label can vary from employee to employee. Mr. Moatter mentioned he would found out what type of testing fixture could be used in the production area. I mentioned a peel test or air burst test for example, but Mr. Lucas mentioned the burst test was not suitable to use in the packaging area. In fact, it could introduce a contaminant in the packaging area. Wyeth created an

in-house tester and plans to validate this method. . A copy of the new Induction Seal Integrity tester was provided see Exhibit 92, along with a copy of Package Validation see Exhibit 93.

Observation 3

Specifications for dietary ingredient(ginseng) are listed under Monograph [redacted] code [redacted] and this monograph requires verification on the supplier's COA that pesticide(tricyclazole) was tested, but COAs for code [redacted] do not include test results for this pesticide, and was not revised to include the actual name and address of the lab currently responsible for furnishing this information.

Supporting documentation: Monograph [redacted] Exhibit 65) and Exhibit #94(COA issued by supplier [redacted] was collected along with lab reports issued by Lab Analysis(Exhibit 95).

Discussion:
One important point to clarify was that all testing for this ingredient for tricyclazole was performed by an external lab [redacted] although not specifically noted on the supplier's COA. At the close out meeting I was advised that this observation appeared to imply that no testing was conducted, and I should make it clear that testing was conducted by [redacted] (an external laboratory). This observation was documented because the monograph (Exhibit 65) mentions this information should be part of the supplier's COA and it was not. When I originally inquired about the test results on the supplier's COA I was advised the chemical name for this pesticide may have been written in [redacted], and they will determine if this was correct. At the time of my review of test reports QA personnel never mentioned precisely where the test results were documented, and did not attempt to interrupt and point out where to find the information. At the close of the day, I was advised that further information on this issue would be provided on my return to the facility. Upon my return I was shown test reports issued by [redacted] for all COAs issued by [redacted] and found information was acceptable. I explained that if the monograph pointed to the test reports issued by [redacted] as oppose to the supplier's COA there would have been no question where to find the test results.

Observation 4

In the packaging area, failure to demonstrate all requirements were met. Specifically as part of Master Packaging Record specifications for cap adjustments (distance from cap to bottom of sealing head) were established to show proper alignment to the sealer; however adjustments were not documented to support proper set-up. Also, when product changeovers occur bulk materials (to include tablets stored in metal detector challenge bottles) must be removed from the packaging line and destroyed; however there is no evidence that tablets inside metal detector bottles were emptied and removed from the packaging line.

Discussion with management

A typical packaging line will consists of a bottle unscrambler, a tablet filler, a capper, a metal detector, a cap detector, an induction sealer, a cap retorquer, and a printing station. Several adjustments are made to the packaging line before bottles are filled. There are two types of caps that can be used on bottles: a one-piece cap or a two piece cap. The packaging line's cap detectors must be adjusted to conform to specifications for each cap. Each cap has its own specifications. For example, monograph# (b) (4) Exhibit 74) was collected for a child resistant cap(wave caps) to show dimensions established for the cap to include the cap's inner lining (foil), height and outer diameter. The foil that is underneath the cap is sealed on the bottle's rim using a (b) (4) Sealer. The temperature output for the sealer will also be adjusted as needed. I was informed that minimum power setting should be at (b) (4) %. Several bottles are checked prior to start-up to confirm the seal on the bottle is adequate. A minimum specification at (b) (4) % is required but was not established on the Master Packaging Record. Also, the specification for the adjustment to make on the cap(to be measured in inches) was not recorded on the Master Batch Record although verbally I was informed the specifications were established. The Master Packaging Record (dated 8/11/08 Version 7) see Exhibit #96 was revised see Exhibit 97(Master Package Record Version 8 dated 9/11/08, bottom of pages 8 to show adjustment specifications (inches) for different types of caps and power output set at (b) (4) %.

The second issue with the Master Package Record concerned line clearance to check Metal Challenge bottles. The metal challenge bottles are used to challenge metal detectors installed on the line, to verify all metal detectors are working as intended. A few bottles marked as metal challenge bottles are set-up on the line and contain different types of metal fragments. Each bottle filled with the same product as filled on the packaging line. After the packaging process is completed I was informed these bottles (with tablets) are discarded and treated as bulk waste. For the next packaging process a different product is filled into new metal challenge bottle. However, upon interviewing an employee in the packaging area, I was informed the bottles are not discarded. The bottle remains on the packaging line and the tablets inside the bottles are removed. There is no record to verify all tablets were removed from bottles. I was informed that SOP titled WCH Packaging Process Order(PO) Completion PPG 00001622 (pg7 of 9) mentions Packaging Operator/ Packaging Line Mechanic must remove waste materials, and empty drums from the line(Exhibit 98). As a follow-up to complaints related to alleged product mix-ups, I reviewed all operations in the production area and requested that the Master Packaging Record also show all metal challenge bottles were emptied, as part of line clearance, to ensure no tablets from the previous batch were on the packaging line. As a corrective measure the Master Package Record (Exhibit 97) was revised (pg. 13 of 34) to include confirmation that all bottles were emptied.

At the close out meeting no objection to this observation was noted. The firm will send in a written response.

Observation 5

As part of your Master Corrective action plan established to test minerals under LIR commitment (b) (4) only 4 of 5 corrective actions were implemented.

Supporting evidence

A copy of LIR # (b) (4) was provided see Exhibit 99.

Discussion with management

All corrective actions for LIR's/ MIR's are documented and transferred to a Commitment Report to be assigned to a specific person or team of people. There is a parent Commitment Report followed by a "child commitment" report. The child commitment report is assigned to each person for each task to complete. If there are 5 corrective actions reported on the LIR than five child commitments can be created or one child commitment with all five issues can be generated. The firm's (b) (4) database keeps track of all corrective actions and sets due dates for each task. This inspection revealed no "child commitments" had been generated in the electronic database to follow the progress of noted corrective actions as requested on LIR (b) (4) The 5 recommended corrective actions, as outlined under LIR (b) (4) were as follows: Install an (b) (4) humidifier, modify the torch cleaning process to include alkali(NH4OH) ammonium hydroxide wash, conduct more frequent injector tube changes, broaden the CV standard , and to increase the rinse time for the (b) (4) method. The first issue ((b) (4) humidifier) was verified when I visited the QC lab. This component was installed on the side of the instrument. The next three corrective actions were documented on work instructions (Job Aid for Operation of (b) (4) System) reviewed during the inspection and the actual documents provided on 10/8/08(Follow-up to pre close out meeting) see Exhibit 88 . The only issue that was not corrected was the rinse for the method for the instrument. I was informed this correction was only implemented for instrument (a second (b) (4) instrument installed in the QC lab). The firm will respond to this observation in writing. The firm's management was verbally advised to follow the SOP established for handling corrective actions, according SPPG0005695 (Exhibit #82: pgs 24-25) that requires QA maintain the database and performs trends and determined if corrective or preventative actions are necessary. QA must determine the responsible persons, due dates for completion, and evaluate the effectiveness of all implemented corrective actions for " child" commitments.

Observation 6

Your hand washing facility does not dispense water at a suitable temperature. Specifically, the automatic hand washing sinks for one side of men's restroom on the 4th floor furnished only cold water.

Supporting evidence

A copy of Product and Personnel Contamination Prevention SOP (PPG 00001964) was collected see Exhibit 100.

Discussion:

The firm's management was advised that cGMPs require that hand-washing facilities furnish running water at a suitable temperature and cold water was not considered suitable, as people would not want to place their hands in cold water. At the close out meeting I was advised there was one error. The restroom is actually located on the [redacted] floor, and not the [redacted] floor. I was also asked to include a statement that this observation does not reflect all restrooms in the building, as other hand washing facilities furnished running water at a suitable temperature. The hand temperature control device was repaired, as of 10/04/08.

A written response will be sent to the local office to respond to this observation.

REFUSALS

Wyeth officials refused to sign FDA484 (Receipt for Samples) and FDA-463a(Affidavit) otherwise no other refusals were encountered.

SAMPLES COLLECTED

On 9/26/08 samples of Centrum Performance tablets Control Nos: C02533, C02531, C02527, B51122, and C05315 were collected from Wyeth's reserve stock and prepared under Sample #s 491225, 491238, 491240 491241, and 491244. In addition a DOC sample # 496576 was collected to show I/s receipt of goods and distribution of finished product to one customer. A letter issued by Paul Lucas, Sr. Director of Quality was provided (Exhibit 101) to account for all bottles of Centrum Performance tablets collected on 9/26/08.

EXHIBITS COLLECTED

1. Site Operations
2. Wyeth's Quality Operations for Consumer HealthCare(CHC)
3. Organizational Charts
4. List of Site Addresses

5. Employee Headcount

6. Shipping (I/s) Records for Centrum Performance LOT [redacted]

[redacted] B/L Ref. [redacted]
[redacted] Packing [redacted],
Packing List issued by [redacted]
Wyeth Inbound Delivery [redacted], Wyeth
[redacted], B/L [redacted] stamped Jun 22, 06;
[redacted] Invoice# [redacted], Wyeth Inbound Delivery [redacted];
Wyeth's [redacted] slip #s [redacted]; Wyeth Canada B/L# [redacted];
[redacted] Lot [redacted] B/L [redacted]
Delivery Ticket 3/21/07 to [redacted] Shipping (I/s) Records

7. Shipping (I/s) Records for Centrum Performance LOT [redacted]

[redacted] Invoice [redacted]
In Bound Delivery [redacted], Wyeth [redacted],
[redacted] B/L [redacted], Packing list [redacted] B/L [redacted],
Wyeth [redacted] Delivery Ticket [redacted], [redacted] Lot [redacted]
B/L [redacted], and Wyeth Invoice [redacted]

8. Shipping (1/s) Records for Centrum Performance [redacted]

[redacted], Invoice [redacted]
In Bound Delivery [redacted] B/L [redacted]
[redacted] B/L stamped Jul 26,06; [redacted] Invoice [redacted] B/L [redacted]
[redacted] Packing Certificate [redacted], [redacted] B/L [redacted]
[redacted] Packing slip [redacted], Wyeth Inbound Delivery [redacted]
Wyeth's B/L [redacted], Delivery Packing List [redacted], Wyeth's Manifest Bill of Lading [redacted] and Invoice [redacted]

9. Product List(w/ product codes, description and material bulk codes)
10. Product labels
11. Product drawings (Centrum [redacted], Centrum Jr. with Extra Calcium, Caltrate 600, Centrum Silver, Centrum Performance [redacted]

12. FDA Inspection Sign-In Sheet
13. Wyeth Consumer Health Production Volumes (Pearl River Plant)
14. Lab Report (Ginseng Extract)
15. Product Recall, Market Withdrawal or Stock Recovery of Distributed Product 00000510
16. Quality Agreement between [redacted] and Wyeth (Ginseng Extract)
17. Approved Supplier List (Wyeth GMP Material List)
18. MIR Long Form# 270291
19. Incident Management PPG-00044410
20. Product Shipment Table (Original) Material [redacted] (Centrum Performance tablets)
21. Product Shipment Table: (Revised) Material [redacted] (Centrum Performance tablets)
22. Quantity of Finished Packaged Goods in Retention (Centrum Performance)
23. Material Rejection Report (Centrum Performance Tablets) dated 5/30/07
24. Material Rejection Report (Ginseng) dated 5/31/07

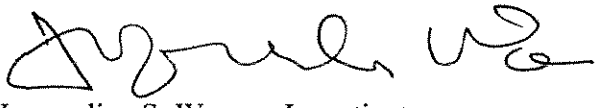
25(A) Table display [redacted] lots of Centrum Performance tablets (120's, 150's, 75's and 45's)
25(B) Destruction List [redacted] re: Centrum Performance Tablets
26 Domestic Centrum Performance (involved in Tricyclazole issue within expiration (Retains)
27. Centrum Performance [redacted] Query dated Sept 25, 2008
28. Ginseng Pesticides Issue (P. Lucas w/ stamped date 9/ 18/08)
29. Ginseng Pesticides Issue (P. Lucas w/ stamped date 8/29/08)
30. Lab Analysis Test Report attached to [redacted] product requirements for ginseng extract
31. [redacted] COA for [redacted] Ginseng Dry Extract Batch [redacted]
32. Supplier Audit (Visit to [redacted] Plant dated 4/27/07)
33. Change Control Request [redacted]
34. Internal Correspondence (M. Willoughby to P. Lucas) re: June 2007 audit at [redacted]
35. Letter issued by P. Lucas re: Response to Request by FDA Investigator Ms. Jacqueline Warner
36. Letter re: The value of destroyed goods: Centrum Performance tablets w/ tricyclazole issue
37. Rejected lots of Ginseng from 2006- 2008
38. Customer Distribution List (Centrum Performance tablets)
39. [redacted] Analytical Report #s [redacted]
40. Material Document List (original) 3 Lots of Ginkgo at Wyeth [redacted] kgs)
41. Material Document List (revised) 3 Lots of Ginkgo [redacted] kgs)
42. Disposal Request for Hazardous / Problem Waste [redacted]
43. [redacted] Shipping Document [redacted]
44. Labels affixed to 3 lots of Ginkgo (headed for destruction) on 9/26/08
45. [redacted] Certificate of Destruction (Disposal by Incineration)

46. [redacted] B/L [redacted] dated Oct 17, 2007
47. Packing List [redacted] dated Oct 17, 2007
48. [redacted] Straight B/L (Shipper's No. [redacted]
49. [redacted] Memorandum Shipper's No. [redacted]
50. Bill of lading issued by [redacted], dated 12/10/07
    Ginkgo Biloba 2 Lot No.s: [redacted] drums or [redacted] kgs)and [redacted] drums or [redacted] kgs)
51. Wyeth's Inbound Delivery Ticket [redacted]
52. Wyeth Canada's Purchase Order [redacted]
53. Packaging Order [redacted] issued by Wyeth Canada
54. Bill of Lading issued by [redacted] (Shipper's No. [redacted]
55. Final Report Process Validation [redacted]
56. Final Report Protocol [redacted]
57. Wyeth GMP Material List (Approval status for [redacted]
58. Wyeth GMP Suppliers List Disqualification of supplier
    [redacted] and Wyeth's Material List (discontinue gingko# [redacted]
59. Ginkgo labels (3 lots w/ pesticides [redacted])
60. Cost of Ginkgo lots sent for destruction on 9/26/08
61. [redacted] Certificate of Analysis(Ginkgo) Lot [redacted]
62 [redacted] Certificate of Analysis(Ginkgo) Lot [redacted]
63 Quality Agreement between [redacted] and Wyeth
64. Testing Schemes for Wyeth Consumer Health care Materials PPG 00000890
65. Monograph [redacted] Ginseng
66. Monograph [redacted] Ginkgo Biloba Dry Extract
67. Monograph [redacted] Centrum Silver Tablets
68. Monograph [redacted] Centrum Performance w/ ginseng & gingko
69. Monograph [redacted] Centrum Performance Tablets w/ ginseng & gingko biloba
70. Monograph [redacted] Centrum Performance Mineral Premix
71. Monograph [redacted] Centrum Performance Vitamin Premix
72. Monograph [redacted] Centrum Silver Vitamin Premix
73. Monograph [redacted] Centrum Silver Mineral Premix
74. Monograph [redacted] (caps, child resistant)
75. Copies of all COA's for Dietary Ingredients used in Multivitamin/ Multimineral supplements
76. [redacted] Batch Logs (Centrum Performance/ Centrum Silver)
77. Centrum Performance Batch Record [redacted]
78. Centrum Silver Batch Record [redacted]
79. Lot Disposition Reports Centrum Performance

80. Lot Disposition Reports Centrum Silver
81. QA Shop Floor Verification for Wyeth Consumer Healthcare 00040093
82. Investigation and Handling of Discrepant Test Results PPG 00005695
83. Manufacturing Investigation Report(MIR) System
84. Wyeth Consumer healthcare Complaint Investigations
85. Policy (b) (4) Worldwide Adverse Event Data
86. Customer Complaints 2004-2008
87. Follow-up Investigation re: Consumer Complaint Centrum Lot C61543 dated 8/4/08
88. Follow-up to Oct 7 Pre-closeout teleconference
89. Lab Investigation Report Form(LIR (b) (4)
90. Container Monitoring PPG-0002283
91. Primary Document Job Aid for Heat Induction Cap Sealer Set-up & Operation PPG00010936
92. Induction Heat Seal Integrity Tester
93. Prospective Packaging Validation Final Report (b) (4)
94. (b) (4) Certificate of Analysis(COA) for Ginseng Root Extract
95. Copies of Lab Analysis Reports (Ginseng) pesticide test for tricyclazole
96. Consumer Health Products (Master Packaging Record v7)
97 Consumer Health Products (Master Packaging Record v8)
98 WCH Packaging Order(PO) Completion SOP PPG00001622
99 Wyeth Internal Correspondence dated 6/29/07 (Commitment (b) (4))
100. Product and Personal Contamination Prevention Procedure PPG00001964
101. Wyeth's Note to File dated 9/26/08 issued by Mr. Paul Lucas, Sr Director o& Compliance

ATTACHMENTS

1. FDA-482 (Notice of Inspection) dated 8/27/08, Joseph T. Vitanza, Managing Director
2. FDA-484 (Receipt for Samples), Mr. F. Moatter, Director of QA Compliance & Product Release
3. FDA-463a(Affidavit) dated 10/08/08, issued to Mr. Farooq Moatter
4. HFS-615 CFSAN/OC/ Div of Field Program Assignment #951846
5. FDA-483(Inspectional Observations) dated 10/8/08, Michael McDermott, V.P of Site Operations



Jacqueline S. Warner, Investigator