

Responding to 483s and Warning
Letters / Avoiding Consent Decrees
SoCalBio FDA Audit Workshop, LA
June 12, 2009

483 / EIR Enforcement Actions

- Application Action
 - Denial of Pending Application
 - Revocation of Approved Application
 - Ban
- Certification Withholding or Revocation
- Citation
- Civil Penalty
- Demand for Destruction
- Disqualification

483 / EIR Enforcement Actions

- Emergency Permit Disapproved
- Injunction
- License Action
 - Denial
 - Suspension
 - Revocation
- Prosecution
- Provisional Listing

483 / EIR Enforcement Actions

- Recall
- Remove from Shippers List
- Seizure / Detention
- Use Prohibited
- Warning Letter

FDA Form-483

- List of Inspectional Observations
- No Regulatory Requirement to Respond to a 483
- But Don't Miss the Opportunity To Do So



During the Inspection

- Set the Tone
- Discuss Observations in Real Time
 - Minimizes Surprises and Errors
 - Maximizes Dialog and Understanding
 - Creates Opportunity for Same Day Corrections
 - Often Lessens 483 Impact

Exit Interview

- 483 Observations
- Ask For:
 - Explanation and Details
 - Examples
- Write Down Exactly What Investigator Says –
 - some firms are videotaping (OK by FDA per IOM)

Exit Interview

- Make notes of your requested comments and include them in your 483 response
- Never “argue” with inspector
- Never make verbal promises, only written responses
- *Affidavits*
 - Never sign them and don’t even listen to a reading
 - If they push, ask them to send to your attorney for review
 - MAY BE USED AS EVIDENCE AGAINST YOU

Written Response to 483

- FDA Suggested Reasons to Submit
 - Could Mitigate Later FDA Compliance Action
 - From FDA Regulatory Procedures Manual
 - “As a general rule, a Warning Letter should not be issued if the agency concludes that a firm’s corrective actions are adequate and that the violations that would have supported the Letter have been corrected.”

Written Response to 483

- FDA Suggested Reasons to Submit
 - Demonstrates an understanding and acknowledgement of the observations
 - Demonstrates a commitment to voluntarily comply with regulations and correct deficiencies
 - Establishes credibility with the FDA
 - Source: Anita Richardson, Associate Director for Policy, Office of Compliance, *5th Annual FDA and the Changing Paradigm for HCT/P Regulation*, January 2009

Written Response to 483

- Address each observation separately
- Never agree that an observation is valid:
 - instead, state changes you intend to make
- Disagreements:
 - Present your argument – remember – Science wins!!
 - Be responsive, not argumentative
- Attach copies of changed documents
- Include a senior leadership commitment statement
- Don't forget time frames

Written Response to 483

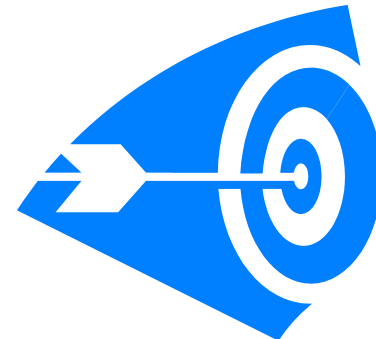
- Show the likelihood of recurrence of the problem/violation is low
- Show the company is doing all it can reasonably to remedy the situation: specific steps, timetable, monitoring
- Show problems attributable to a specific cause have/will be fixed with permanent remedies
- Show that senior management understands

Written Response to 483

- Observation Assessments
 - Do not limit to identified products
 - Consider root-cause analysis
 - Apply analysis globally
 - Specifically address cited regulations
- Think CAPA, even for non-device products
 - Correct easy issues
 - Plan and communicate larger issues
 - Develop prevention techniques / processes

Written Response to 483

- Critique from FDA Perspective
 - Does it specifically respond to the Observation?
 - Is it complete, thorough and technically robust?
 - Are you able to deliver what you promise and when?
 - IS IT TIMELY???



ADDRESSES: 5 Wyeth Pharm Div of Wyeth Holding EI: 8/27/08-10/08/08 JW Pearl River, NY 10965	
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	
DISTRICT OFFICE ADDRESS AND PHONE NUMBER 158-15 Liberty Ave Jamaica, NY 11433 718-340-7000	DATE(S) OF INSPECTION 8/27/08-10/8/08* FEIN NUMBER 2410662
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Michael P. McDermott, Vice President Site Operations	

FIRM NAME Wyeth Pharmaceutical, Div Wyeth Holding Corp	STREET ADDRESS 401 N. Middletown Rd
CITY, STATE AND ZIP CODE Pearl River, NY 10965	TYPE OF ESTABLISHMENT INSPECTED Mfr of Dietary Supplements

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTORAL OBSERVATIONS AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION OR HAVE IMPLEMENTED OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

- DURING AN INSPECTION OF YOUR FIRM (S) ~~WERE~~ OBSERVED:
- Laboratory exam and test methodologies do not appear to be appropriate for their intended use. Specifically, the test method using ~~XXXX~~ instruments (~~XXXX~~) 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.
 - 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.
 - Specifications for dietary ingredient (ginseng) are listed under Monograph ~~XXXX~~ (code ~~XXXX~~) and this monograph requires verification on the supplier's COA that pesticide (tricyclazole) was tested, but COAs for code ~~XXXX~~ 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.
 - 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 your Master Corrective action plan established to test minerals under LIR commitment ~~XXXX~~ only 4 of 5 corrective actions were implemented.
 - 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 ~~XXXX~~ floor furnished only cold water.
- *DATES OF INSPECTION: 8/27-29/08, 9/3-5, 9-12, 15-18, 23-26, 29/08 #10/8/08

SEE REVERSE OF THIS PAGE 3RM FDA 483 (A03) PREVIOUS EDITION OBSOLETE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Jacqueline Warner, CSO	DATE ISSUED 10/8/08
INSPECTORAL OBSERVATIONS		PAGE 1 OF 1 PAGES	

Real Life Observations

- Observation A: The SOP for investigating out of specification test results (SOP 0006-QC) outlines principles of retest and re-sampling plans but fails to specify the predetermined re-testing/re-sampling procedures.
 - Response (1): SOP 0006-QC has been updated and is attached hereto.
 - Response (2): Attached is an updated version of SOP 0006-QC that incorporates the predetermined re-testing/re-sampling procedures. The re-testing procedure specifies a maximum number of tests (X) for the particular type of release assays and also provides retesting limits for the remaining assays used in the manufacture of Product (Y-Z). The methods used in these assays are [insert]. The updated SOP also outlines the criteria for reporting, evaluation of data, and closing the out-of-specification investigations.

Real Life Observations

- Observation B: Failure to adequately train employees engaged in the manufacture, processing or holding of a drug product in CGMP or in the particular operations performed by the employees [21 CFR § 211.25(a)].
 - Response (1): Company will train employees on existing policies on June 15, 2009, and will rotate employees through cGMP training in the future.
 - Response (2): Company will engage [insert consultant name] to train employees on the following policies: [insert policy numbers and names]. Such training will be completed by [date]. Ongoing training will be conducted on a yearly basis for warehouse employees and on a quarterly basis for manufacturing employees.

Then you wait...

- FDA
 - Prepares the Establishment Inspection Report
 - Recommends classification of the inspection
 - Supervisory review
 - Possible referral to your district's Compliance Branch for additional review and possible enforcement action

Establishment Inspection Report

Establishment Inspection Report

Wyeth Pharmaceutical, Division of
Wyeth Holding, Corp.
Pearl River, NY 10965-1215

FEI: 2410662
EI Start: 08/27/2008
EI End: 10/08/2008

TABLE OF CONTENTS

SUMMARY OF FINDINGS	1
ADMINISTRATIVE DATA	4
HISTORY OF BUSINESS	6
INTERSTATE COMMERCE	8
JURISDICTION	9
INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED	10
PRODUCTION OF CENRTUM SILVER & CENTRUM PERFORMANCE TABLETS	13
INVESTIGATION RE: GINSENG EXTRACT FROM SUPPLIER(INDENA)	18
INVESTIGATION OF GINKGO BILOBA FROM TSI(CHINA)	23
DIETARY SUPPLEMENTS CGMP's/ FACTS ASSIGNMENT #951846	28
VOLUNTARY CORRECTIONS	39
OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE.....	40
REFUSALS.....	46
SAMPLES COLLECTED	46
EXHIBITS COLLECTED	46
ATTACHMENTS.....	51

Classification of the Inspection

- NAI: No Action Indicated
- VAI: Voluntary Action Indicated
- OAI: Official Action Indicated



No Action Indicated (NAI)

- No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further action).

Voluntary Action Indicated (VAI)

- Objectionable conditions were found and documented but the District and/or Center is not prepared to take or recommend any of the regulatory (advisory, administrative, or judicial) actions
- The district may use an Untitled Letter, Regulatory Meeting or other communication with responsible individuals to inform the establishment of findings that should be corrected
- A written response by the establishment may be an option, but is not necessary
- Any corrective action is left to the establishment to take voluntarily

Official Action Indicated (OAI)

- Objectionable conditions were found and one of the regulatory actions listed below should be recommended
- Includes voluntary recalls where the district has decided conditions warrant regulatory (advisory, administrative, or judicial) action
- Typically, an OAI classification should be made only if a FDA-483 has been issued and the documented evidence supports the action recommended

OAI Enforcement

- **NOV's**
 - **Call attention to a Minor Violation**
 - Routine
 - Does not Jeopardize Public Health
 - Can be Easily Remedied
 - Typically Requests Cessation of Certain Behavior, i.e. Dissemination of Certain Materials
 - Rarely Requests Correction or Alteration of Behavior / Materials

OAI Enforcement

- **Warning Letters**

- Most Common Enforcement Tool
- Posted on FDA website
 - Easy to locate
- Requires a Reply to FDA, Usually Within 15 Days of Receipt
- Details Company's Response to FDA's Allegation and Actions, as appropriate
- Right To Appeal Exists

OAI Enforcement

- **Warning Letters**
 - Violations are Alleged with more Specificity
 - Remedies are Required
 - Cessation of Behavior / Materials
 - Correction of Behavior / Materials
 - Corrective Action Plan
 - Requires Aggressive Action by Company
 - Never Forget to Respond
 - Failure Leads to Heightened Enforcement



February 5, 2009

WARNING LETTER

VIA Federal Express

WL No. 320-08-04

Barrie Levitt, M. D.
Chairman and CEO
Taro Pharmaceuticals U.S.A., Inc.
3 Skyline Drive
Hawthorne, NY 10532

Dear Dr. Levitt:

This letter is regarding an inspection of your pharmaceutical manufacturing facility in Brampton, Ontario, Canada, by FDA Investigator Daryl A. DeWoskin and Chemist Marianela Aponte Cruz during the period of July 28-31, 2008. The inspection revealed significant deviations from Current Good Manufacturing Practices (CGMP) Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211) in the manufacture of non-sterile cream and ointment finished drug products.

These CGMP deviations were listed on an Inspectional Observations (FDA-483) form issued to Mr. (b) (6), General Manager, at the close of inspection. These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351(a)(2)(B)] in that they were not manufactured, processed, packed, and held in compliance with current good manufacturing practice.

We have reviewed the Establishment Inspection Report (EIR) and your September 26, 2008 response to the FDA-483 observations. We acknowledge that some corrections appear to have been completed, or will soon be completed. However, your response fails to adequately address multiple serious deficiencies. Specific areas of concern include but are not limited to the following aspects of your firm's quality system:

1. The written stability testing program is inadequate to assess the stability characteristics of drug products and for determining appropriate storage conditions and expiration dates [21 CFR 211.166(a)]. In addition, expiration dates on drug product labeling have not been determined by appropriate stability testing [21 CFR 211.137(a)]. For example:
 - A. Three out of twenty four lots of Fluocinonide cream USP, 0.05% (36-month shelf-life), failed the ANDA limit of 6.0% for the relative standard deviation (RSD) of

Warning Letter Format

- Allegation: Failure to ensure proper monitoring of a clinical investigation. Examples of your failures include, but are not limited to, the following: You did not assure that the Data Coordinating Center monitored each of the investigative sites as stated per protocol. You did not assure, according to the protocol and the Monitoring Plan that data collection was overseen by an independent study monitor.
- Acknowledgment of 483 Response: You submitted the monitoring plan and included a copy of a participating site monitoring schedule.
- Face Slap: Your response is inadequate in that your plan does not provide for on-going oversight of the study.

Warning Letter Format

- Allegation: These devices are adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for their manufacture.... Are not in conformity with cGMP requirements of the QS regulation.
- Acknowledgment of 483 Response: Your response indicates that Company now has procedures for the violations noted in this letter.
- Face Slap: Your response is inadequate as it is unclear whether any of the procedures have actually been implemented.

Warning Letter Response

- Get Serious
- Shower Deference to the Agency
- Have a Solid Plan to Address and Correct the Deficiency
- Have Reasonable Expectations
- Do What You Say You Will, When You Say You'll Do It
- Respond No Later Than 15 Days from the Date of the WL

Failure to Respond to WL?

- Other
- Enforcement
- Tools



Heightened FDA Enforcement

- **Seizures**

- Brought in Federal District Court by US Attorney
- Seizure: Product may not be Distributed Pending the Outcome of the Case
- Injunction: Enjoined from taking some Specific Action
- Time Intensive, Drain on Resources, Adverse Publicity
- Both are Rare and Come About Because the Relationship between FDA and Company Has Soured

Heightened FDA Enforcement

- **Criminal Prosecution**
 - Brought Against Company and Individual(s)
 - Typically Only Use in Cases where Fraud is Suspected or Against Recidivists
 - May be Misdemeanor or Felony (intentional act)

Other Civil Enforcement

- **Competitors**
 - File a Complaint with the PhRMA, AdvaMed
 - Complain to the FDA or FTC
 - General Letter, May be anonymous
 - File a Civil Complaint
 - Federal
 - Lanham Act
 - State
 - Unfair Competition Statutes
 - Deceptive Trade Practice Statutes

Civil Actions

- False Claims and Deceptive Behavior
 - Mannatech, Texas
 - False Product Claims
 - Required to pay \$850,000.00 in opposing counsel fees
- Recidivist Action
 - SeaSilver
 - \$3,000,00000 grew to \$120,000,000.00 for failure to comply with an earlier order

State Civil Actions

- cGMP Violations, Texas
 - Licensing
 - Product Labels
- Sale of Expired OTC Drugs, NY
 - Large Chain Pharmacies

Criminal Enforcement

- DOJ represents FDA and the FTC in Federal actions
- Medical Device
 - At least 150 companies are being investigated
 - Marketing practices
 - March 18, 2009 Fed Grand Jury Investigation of device company based on off-label promotional activities

Criminal Penalties

- False Claims and Deceptive Behavior
 - Enzyte, Southern District of Ohio
 - Conspiracy, Fraud, Money Laundering
 - 11 employees
 - 1 – 25 year prison terms
 - \$500,000,000.00 penalty

Consent Decree

- After 483
- After Warning LetterS
- Perhaps After Detention
- Perhaps After Seizure
- Complaint is Filed
- Settle via Consent Decree

Consent Decree

- Most Devastating Consequences:
 - Against Individuals as well as the Company
 - Provisions Limit and Haunt People for 20 Years or More
 - Triggers Cascade of Other Horribles

Consent Decrees

- In the Pharma and Device Context
 - Consent Decrees Drive Permanent Injunctions
 - Change Behavior Until Facility or Methods are in Compliance
 - Require a Third-Party Expert, which the Company Pays for and which is \$\$\$\$\$\$\$\$\$\$\$\$ because the Expert must inspect and Certify to the FDA that Co. is in Compliance

Consent Decrees

- Contain Overarching Provisions
 - Permanently restrained from
 - Introducing any product until NDA / ANDA / PMA is approved, IND / IDE is in effect, etc.
 - Introducing any Misbranded product
 - Introducing any Adulterated product
 - Must Notify FDA in Writing
 - Of its intention to submit any NDA / PMA
 - Of its intention to distribute any otc drug, and provide additional data as requested by the Agency

Consent Decrees

- More Invasive Provisions
 - Auditor must draft an Audit Report
 - Any observations must be corrected in 30 days
 - FDA has authority to pop in for an inspection at any time
 - Inspection is compliance with the CD
 - Company must pay for these FDA Inspections
 - Must Post a Copy of the CD in Common Areas

Consent Decrees

- Personal Invasions of Life, Liberty, Property
 - Advise FDA within 15 Days BEFORE any Change in Ownership or Change of Personal Address
 - Agree to Allow FDA to Institute Recalls, Shut-Downs, Discontinue Clinical Trials
 - Avalanche Clause
 - Failure to Comply with CD → liquidated damages

Consent Decree Triggers

- Distribution of Adulterated Goods
- Failure to Take Corrective Measures as stated in Warning Letter Responses
- Gross Manufacturing Defects
- Recidivist Activity
- Failure to Comply with cGMP's

Consent Decree Avoidance

- Maintain a Good Relationship with District Inspectors
- Hire a Good QC / RA Team
- Good Faith Regulatory Compliance
- Respond to all FDA Correspondence with Good Intentions

- Be Good.

Not Done

- Other Horribles....



Thank You

- Questions ??
- Contact:
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