FDA Inspection/Facility Notification Case Studies

Fran Rabe, MS

Director of QA

University of Minnesota, MCT

Molecular&Cellular Therapeutics
University of Minnesota

I Thought We Met FDA Requirements, But …

Our Facility Received:

- A FDA Form 483
- A FDA Untitled Letter
- A FDA Warning Letter

All methods of notification are intended to notify facilities of practices that need to be amended.

FDA 483s and Other FDA Notifications Contain Valuable Information

- Use other organizations misfortunes to your advantage
- Review the finding to ensure the same problems don’t occur in your facility/operations

Handling 483

Response not “required”

- But, lack of response is viewed as a lack of concern

Immediately respond to report

- Response reviewed by FDA before determining if a Warning Letter will be issued.

FDA LETTERS – UNTITLED VERSUS WARNING

	Untitled	Warning
Expresses FDA's stance (based on statue or rules)	X	X
Intended to induce voluntary compliance	X	
Next step may be enforcement action if not promptly and adequately corrected		X
Includes statement about potential enforcement		X
Response required		X
Serious stuff (call your lawyer)		X

Warning Letters

- Letter states requirement time-line for response (usually 15 days)

- Letter of closure issued after corrective actions have been satisfactorily addressed

  - applicable to warning letters issued after 9/1/2009

[Example of Actual Untitled Letter]

CSL Biotherapies Untitled Letter
Brian McNamee
Chief Executive Officer (CEO)
CSL Biotherapies
45 Poplar Road
Parkville, Victoria 3052
Australia

Dear Mr. McNamee:

The Food and Drug Administration (FDA) conducted an inspection of CSL Biotherapies, located at 45 Poplar Road, Parkville, Victoria 3052, Australia, between April 19 and April 28, 2010. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP) requirements in the manufacture of licensed biological vaccine products and monovalent influenza bulks.

We would like to meet with you and other senior management at CSL Biotherapies to further discuss the issues cited in this letter and how you will address them going forward..

FDA Letters

FDA posts warning letters on their web site:

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

FOI

- The Freedom of Information Act (FOIA) and FDA's regulations governing disclosures require release of inspection information to the public

  - List of inspectional observations (FDA-483)

  - EIR (attachments and exhibits are excluded from requirement)

  - Warning letters communication with the regulated establishment must be disclosed upon request by any member of the public
- Mandate publicly accessible "electronic reading rooms" with electronic search and indexing features

FOI- Requests

Requests must be in writing (do not accept e-mail)

- **A**. Requestor's name, address, and telephone number.
- **B**. A description of the records being sought. The records should be identified as specifically as possible. A request for specific records that are releasable to the public can be processed much more quickly than a request for "all information" on a particular subject. Also fees for a more specific and limited request will generally be less.
- **C**. Separate requests should be submitted for each firm or product involved.
- **D**. A statement concerning willingness to pay fees, including any limitations.

FDA web:
http://www.fda.gov/RegulatoryInformation/FOI/HowtoMakeaFOIARequest/default.htm

Department of Health and Human Services

Food and Drug Administration

District Address and Phone Number

Dates of Inspection

FEI Number

NAME AND TITLE OF WHOM REPORT ISSUED TO

Jane Doe, Vice President and General Manager

FIRM NAME

Medical Device Unlimited

This document lists observations made by the FDA representative's) during the inspection ol your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance

OBSERVATION 1

Complaint handling procedures have not been implemented to ensure that all complaints are processed in a uniform and timely manner.

Specifically, during a review of xx complaint files were reviewed that did not have complete investigation documentation, and/or deviated from your investigation procedure.

The following are examples:

FORM FDA 483(04/03)

Note: This is not intended to be an exact indication of a Form 483

Respond and Correct

- When aware of FDA concerns via:
  - Issued FDA Form 483
  - Untitled letter
  - Warning letter

Establishment Inspection Report (EIR)

A detailed narrative of the inspection. Includes lists of all records reviewed, what aspect of the facility was audited. A detailed summary of the inspection. Includes identification of specific records reviewed, identification of participating staff, staff comments

- Available to inspected establishment after inspection process is *closed*
- Available to pubic through *Freedom of Information Act*

Example EIR

SUMMARY OF FINDINGS:

This inspection of a medical association Institutional Review Board (IRB) was conducted as follow-up to an inspection assignment dated 9/27/99 from Patricia A. Holobaugh, Center for Biologics Evaluation and Research, Bioresearch Monitoring, HFM-650. The assignment requests an unannounced, directed inspection of the referenced IRB and its operations. Additionally, the assignment requests specific information/documentation associated with the IRB's operations. Included in this request was the review of the files for at least six (6) studies that have been reviewed by the IRB. Three of the study files audited were specified in the inspection assignment while an additional three were selected from the IRB's list of studies approved since 1996 (*see Exhibit 1*). *The IRB files that were audited as part of this inspection were* associated with the following studies:

1. [redacted] (note the inspection assignment refers to this study and the Gene Activated Therapy or GAT study as two separate studies. However, this inspection revealed that the referenced studies were actually the same study);

2. [redacted]: Investigational Proposal for the Study of [redacted]

3. [redacted] (note-this study was never approved by the IRB as the Clinical Investigator (CI) never submitted all information needed to review the research proposal.);

Rengenerative Sciences, Inc
FDA Actions

July, 2008
Untitled Letter Recieved
Based on FDA's Review of Web Site

↓

February- March, 2009
FDA Inspection of Facility
483 Issued

↓

June, 2010
FDA Inspection of Facility
483 Issued
"Injunction Threatened"

↓

August, 2010
FDA Seeks Injunction

Regenerative Sciences, Inc
July 25, 2008

[Example of Actual Untitled Letter]

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Christopher J. Centeno, M.D.
Medical Director
Regenerative Sciences, Inc.
11080 Circle Point Road
Building 2, Suite 140
Westminster, Colorado 80020

Dear Dr. Centeno:

The Food and Drug Administration (FDA) has reviewed your website at Internet address: http://www.regenexx.com and has determined that you are promoting your use of mesenchymal stem cells under conditions that cause these cells to be drugs under section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(g)] and biological products, as defined in section 351(i) of the Public Health Service Act (PHS Act) [42 U.S.C. 262].

We request that you notify this office, in writing, of the steps you have taken or will take to address the violations noted above and to prevent their recurrence. Your response should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 N, Rockville Maryland 20852-1448.

FDA NEWS RELEASE
For Immediate Release: August 6, 2010
Media Inquiries: Shelly Burgess, 301-796-4651, shelly.burgess@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA
FDA Seeks Injunction Against Colorado Manufacturer of Cultured Cell Product

Example of Actual FDA News Release Regarding Action

The U.S. Food and Drug Administration is seeking an injunction in federal court against Regenerative Sciences LLC, of Broomfield, Colo., citing violations of current good manufacturing practice (cGMP) that cause its cultured cell product to be adulterated. The product is also misbranded due to the lack of adequate directions for use and the failure to bear the “Rx only” symbol.

uncements/ucm221656.htm

Enforcement

- Recalls
- Injunction

  - a civil action to prevent cease production and/or distribution
- Seizure of final product
- Fines
- Consent decree

  - an legal agreement to correct. Details exact requirements.
- Criminal investigations

  - allows FDA to hold employees legally liable for their actions

http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm

*FDA Issue of an Order to Cease Manufacturing
Vista Cord, LLC
September 24, 2009

- Ongoing investigation of the cord blood bank has identified deviations from requirements:
  - Donor eligibility screening and testing
  - Processing controls
  - Environmental control and monitoring
  - Equipment and facilities
  - Supplies and reagents
  - Process validation
  - Labeling controls
  - Receipt of products

*http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm183756.htm

Order to Cease Manufacturing of HCT/Ps - Vista Cord, LLC

- Facility

  Failure to provide plumbing, drainage, and access to sinks and toilets that are adequate to prevent the introduction, transmission or spread of communicable disease.

  – The restroom was not equipped with soap or paper towels.

  Failure to utilize a suitable facility maintained in a good state of repair

  – There was a hole in a section of the processing area ceiling, which opens to the exterior
  – Several water-stained ceiling tiles located directly above storage shelves containing processing supplies and in other parts of the facility.
  – Particles of dirt and dust were observed on …the top of an incubator
  – The lid was open on a large sharps receptacle containing used processing material. This was located adjacent to the laminar flow hood.
  – You failed to document, and maintain records of, all cleaning and sanitation

- Process validation
  – Failure to validate the two test methods for detection of bacterial/fungal contamination
  – Red blood depletion of cord blood using hydroxyethyl starch

483 Response Approach

- Root Cause Analysis ⇨Exact Cause

- Prevent reoccurrence through application of quality systems. E.G.:
  - design control
  - quality control
  - quality review (trending, etc.)
  - early detection of problems (through audit)

483 Response

- Factual
  - do not speculate
- Describe interim controls
- Demonstrate evaluation of root cause and systems that may have contributed to problem
- Provide comprehensive description of corrected system controls
- Address impact to past previously distribute product
- Address impact to quarantine product inventory
- Address prevention of future problems
- Provide dates for completion of all corrective action

483 Response

Ensure safety of this product/lot # identified. Determine disposition

Evaluate status of product collected and remaining in establishment quarantine/released inventory

Evaluate status of product (same type and/or lot #) that has been release and may be in (hospital) inventory

Ensure future products are problem free

Inaccurate Observation Findings

- Demonstrate where finding is incorrect
  - provide documents and/or references

Inspections, Compliance, Enforcement, and Criminal Investigations

Provident Pharmaceuticals LLC, 11/9/09

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Denver District Office
Building 20- Denver Federal Center
P.O. Box 25087
Denver, Colorado 80255-0087
Telephone: 303-236-3000

November 09, 2009

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Brian A. Crook, DVM, President
Provident Pharmaceuticals, LLC
4831 Centennial Blvd.
Colorado Springs, CO 80919-3308

Reference No.: DEN-10-03

Dear Dr. Crook:

Dr. Cook Warning Letter

- We acknowledge your July 2009 response and commitment to develop a **(b)(4)**. Please provide a copy of your **(b)(4)**.
  - **X** In addition, if not included in the **(b)(4)** provide corrective actions to prevent similar deviations from recurring.
  - **X** Note that failure to have an adequate number of qualified personnel is not justification to circumvent your adherence to CGMP requirements.

- We acknowledge your July 2009 response that indicates the **(b)(4)** in the completion of your APRs and your commitment to **(b)(4)** to complete APRs.
  - **X** Please provide timeframes for the completion of the **(b)(4)**. In addition,
  - **X** please provide corrective actions to prevent similar deviations regarding your failure to follow your procedure.

Dr. Cook Warning Letter

- We acknowledge your July 2009 response and commitment to complete stability testing, **(b)(4)** to ensure adherence to the stability procedure.

  X However, we believe your response does not provide adequate preventive actions because **(b)(4)** do not address the failure of the QCD to ensure your procedures are followed and training is effective. Please provide corrective action to prevent recurrence of similar deviations. For example, you may develop a contingency plan to send your stability samples for testing to a qualified contract laboratory, or you may reduce your product line to reduce the laboratory workload.

XXX Laboratories - Warning Letter Experts

- Your firm rejected 14 lots of product in 2008 due to contamination and the corrective action was to retrain employees on aseptic technique.

  X This corrective action was not effective. In 2009, your film received 23 complaints on contaminated product and rejected 13 lots of product due to contamination.

  X Additionally, your firm's failure investigations into nonconforming products do not include reviewing the results of environmental testing of the fill room for the days in which contaminated product has been produced.

  X You have failed to conduct a failure investigation that identifies the root cause of contamination

  X You have not taken a corrective action that reduces the trend of contaminated product.

XY, Inc. - Warning Letter Experts

- Broken glass was identified in filled 15 cc glass bottles of T-Gone Remedies on January 20, 2009, during product filling operations. This lot was rejected and destroyed on January 29, 2009. "Deviation Report," dated January 22, 2009, stated: "Broken glass was in the prepackaged and sealed bottles from the distributor. No risks were involved. Product was pulled and destroyed on January 29,2009. The broken glass inside the bottles accrued at the distributor's operation. The drug product with the broken glass was destroyed and all other products that were used with that component was rechecked and all were all were clear."

  X The investigation failed to identify other related products and lots manufactured with the implicated glass vials to assure no additional broken glass was present.

  X Finally, the specific lot number of the problematic glass bottles (components) used to fill T-Gone Remedies on January 20, 2009 was not documented in the investigation.

Note: Information not an exact replication of the information

In A Nut Shell

- Information on FDA website and information available by FOI can be used to your advantage to avoid the same pitfalls
- Respond to 483s thoroughly, accurately and using evidence
  - Consider impact of FDA finding across all systems and products
- Warning letters are a serious matter