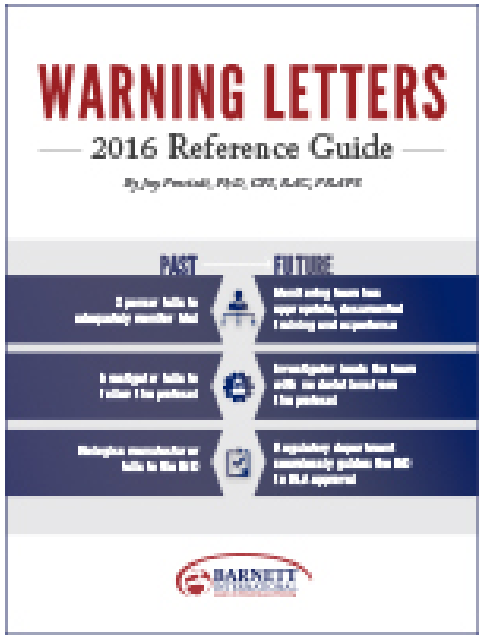
Warning Letters: 2016 Reference Guide



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Presented By:
Dr. Joy Frestedt
President and CEO
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About the Author

Frestedt Incorporated named ***Best for Biotechnology Clinical Research 2016 – Minnesota*** in the 2016 Healthcare & Pharmaceutical Awards by the GHP Magazine

Joy L. Frestedt, PhD, CPI, RAC, FRAPS is President and CEO of **Frestedt Incorporated** (www.frestedt.com) and **Alimentix, the Minnesota Diet Research Center** (www.alimentix.com).

Dr. Frestedt has managed clinical trials, negotiated regulatory submissions and updated quality systems for over 35 years in health care, pharmaceutical, medical device and food industries including the University of Minnesota Medical Center, Orphan Medical, Johnson and Johnson, Astra Zeneca, CNS Therapeutics, Mayo Clinical Trial Services, Medtronic, AMS, Cargill, Ecolab and others.

Dr. Frestedt holds a PhD in Pathobiology from the University of Minnesota Medical School and a BA In genetics from Knox College. She is a member of SOCRA, RAPS, ASCO, AAPS and other organizations. Dr. Frestedt is among the "**100 Most Inspiring People in the Life Sciences Industry**" (PharmaVOICE, 2011) and the **top 25 "Industry Leaders"** (Minneapolis/St. Paul Business Journal, 2011).

Course Description

- The author will discuss the "Warning Letters: 2016 Reference Guide" and will include discussion of the audience's interactions with the FDA (including FDA inspections, 483s, warning letters, consent decrees, etc.).

- The goal of the discussion is to understand the FDA inspection and Warning Letter processes and to learn from others experiences so we can develop better processes for our FDA-regulated products.

Learner Objectives

At the completion of this lecture, individuals should be able to:

- Describe the FDA inspection process
- Identify types of events leading up to a Warning Letter
- Use good processes to resolve (avoid) Warning Letters
- List a few Warning Letter statistics

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Audience/Acknowledgements

- Regulatory Affairs Directors/Managers
- Quality Assurance
- Research and Development
- Engineering
- Manufacturing
- Clinical Development
- Vigilance/Risk Management

Thank you to Dr. Lindsay Young, Kaitlin Cady, Megan Udermann and Matt Harris for assisting with the development of this presentation

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Agenda

- Introduction
- Warning Letter Procedures
- Recent Warning Letters
- How to Avoid and Recover from Warning Letters
- Summary/Review

Where ever possible exact words from the FDA Regulatory Procedures Manual (Chapter 4-1: Warning Letters) and other resources are included, please refer to the online documents for the entire texts.

http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM176965.pdf

http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm

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Introduction

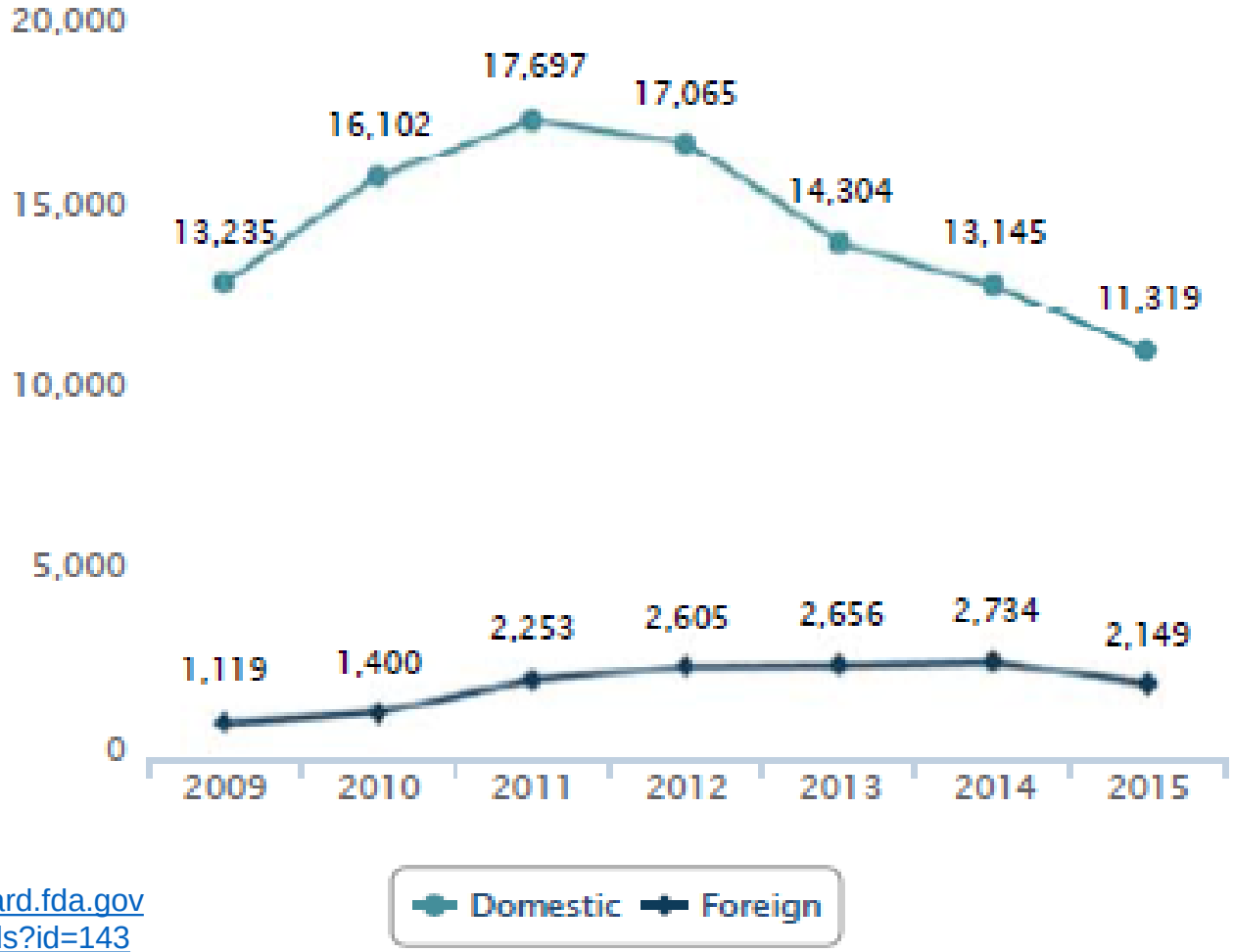
History and Purpose

Overview of FDA Inspections

The **Food, Drug and Cosmetic Act (the Act)** gives the FDA the authority to conduct inspections:

"...(A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein…" [21 U.S. Code § 374 – Inspection]

2009-2015 Inspections



http://govdashboard.fda.gov/public/dashboards?id=143

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FDA Inspection Forms

FDA Form 482 - Issued at the start of inspection

FDA Form 483 - Issued at end of inspection, should only be issued if violations to FDCA were observed

- If a company receives a FDA Form 483, the company should respond **within 15 days** and should describe (in detail) all actions taken to resolve issues and/or plans to address all unresolved issues. Timeline for hearing back from FDA varies according to criticality.

FDA form 484 - Issued to document samples taken during inspection

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Sidney H. Rogers	Sidney H. Rogers, Investigator	10/7/2008

FORM FDA 483 (9/08) PREVIOUS EDITION OBSOLETE **INSPECTIONAL OBSERVATIONS** PAGE 1 of 1 PAGES

Types of FDA Letters

Untitled Letter

- Cites violations not meeting regulatory significance

Warning Letter

- Cites violations meeting regulatory significance
- Indicates FDA is planning enforcement actions

Close Out letter

- Sufficient corrective action has been taken


Department of Health and Human Services

Public Health Service
Food and Drug Administration
San Juan District
Compliance Branch
466 Fernández Juncos
San Juan, Puerto Rico 00901-
3223

Telephone: (787) 729-8652
FAX: (787) 729-8826

June 30, 2016

WARNING LETTER
16-SJN-WL-07
CMS # 494483

SENT VIA – UNITED PARCEL SERVICE

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What is an Untitled Letter?

"An ***Untitled Letter*** is an **initial** correspondence with regulated industry that cites violations that do not meet the threshold of a Warning Letter. Untitled Letters are intended to cover those circumstances where the Agency has a need to communicate with regulated industry about violations that do not meet the threshold of regulatory significance as described above..."

http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM176965.pdf

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What is a Warning Letter?

"A Warning Letter is a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations."

http://www.fda.gov/downloads/ICECI/ComplicanceManuals/regulatoryproceduresmanual/UCM176965.pdf

Warning Letter Context?

"Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency's principal means of achieving prompt voluntary compliance with the Act."

http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM176965.pdf

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Who Oversees Warning Letters?

November 29, 2001 - Deputy Secretary of the Department of Health and Human Services directed the FDA "to submit all Warning Letters and Untitled Letters to FDA's Office of Chief Counsel (OCC) prior to their issuance so that they can be reviewed for legal sufficiency and consistency with Agency policy."

Procedures were established "to integrate OCC review into the agency's existing procedures for the review of enforcement correspondence... implemented in March 2002."

In 2009, the OCC review provisions of these procedures were modified "to apply only to the Warning and Untitled Letters" and finalized in December 2010.

http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM176965.pdf

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Why issue Warning Letters?

To correct violations of current statutes or regulations

To give individuals/firms an opportunity to take **voluntary** corrective action before an enforcement action will be taken

NOTE: Warning Letters are not final agency actions

- The FDA can also use **enforcement actions**
  - These include, but are not limited to: recall, seizure, injunction, administrative detention, civil money penalties, prosecution to achieve correction.. Consent decrees from a court of law...

When do Enforcement Actions Occur?

FDA can take enforcement action **without** issuing a Warning Letter

1. The individual/ firm has been notified and the violation reflects a history of repeated conduct of a similar or substantially similar nature

2. The violation is intentional or flagrant

3. The violation presents a reasonable possibility of injury or death

4. The violations are intentional and willful acts that once having occurred cannot be retracted

5. Adequate notice has been given by other means and the violations have not been corrected or are continuing

http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm

Who Receives Warning Letters?

Firms

- International companies
- Pharmaceutical companies
- Biologicals companies
- Combination products companies
- Medical device companies
- Sponsors
- Contract research organizations (CRO)
- Institutional review boards (IRB)
- Other companies: foods, dietary supplements, tobacco products, and animal and veterinary products companies

Individuals

- Monitors
- Investigators
- Study coordinators

How does a Warning Letter work?

FDA notifies manufacturer of findings showing the individual/firm has significantly violated FDA regulations

Warning Letter

- Identifies violations
  - poor manufacturing practices
  - problems with product claims
  - incorrect directions for use
- Makes apparent the problem(s) must be corrected
- Provides directions/timeframes to inform FDA of plans for correction

FDA checks to ensure company's corrections are sufficient

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What is included in a Warning Letter?

Title
- "WARNING LETTER"

Delivery
- Overnight, receipt of delivery

Addressee
- Highest official

Inspection Details
- Dates and description
- Note promised corrections

Response Request (15 days)

Warning Statement

- Impact
  - Government Contracts
  - Exports
  - FDA Approvals
- Response Instructions
  - Corrective/preventive action steps
  - Timeline for completion
  - Reason if not complete
  - Documentation
- Identify Response Recipient
- Issuer
- Standard Closing Text

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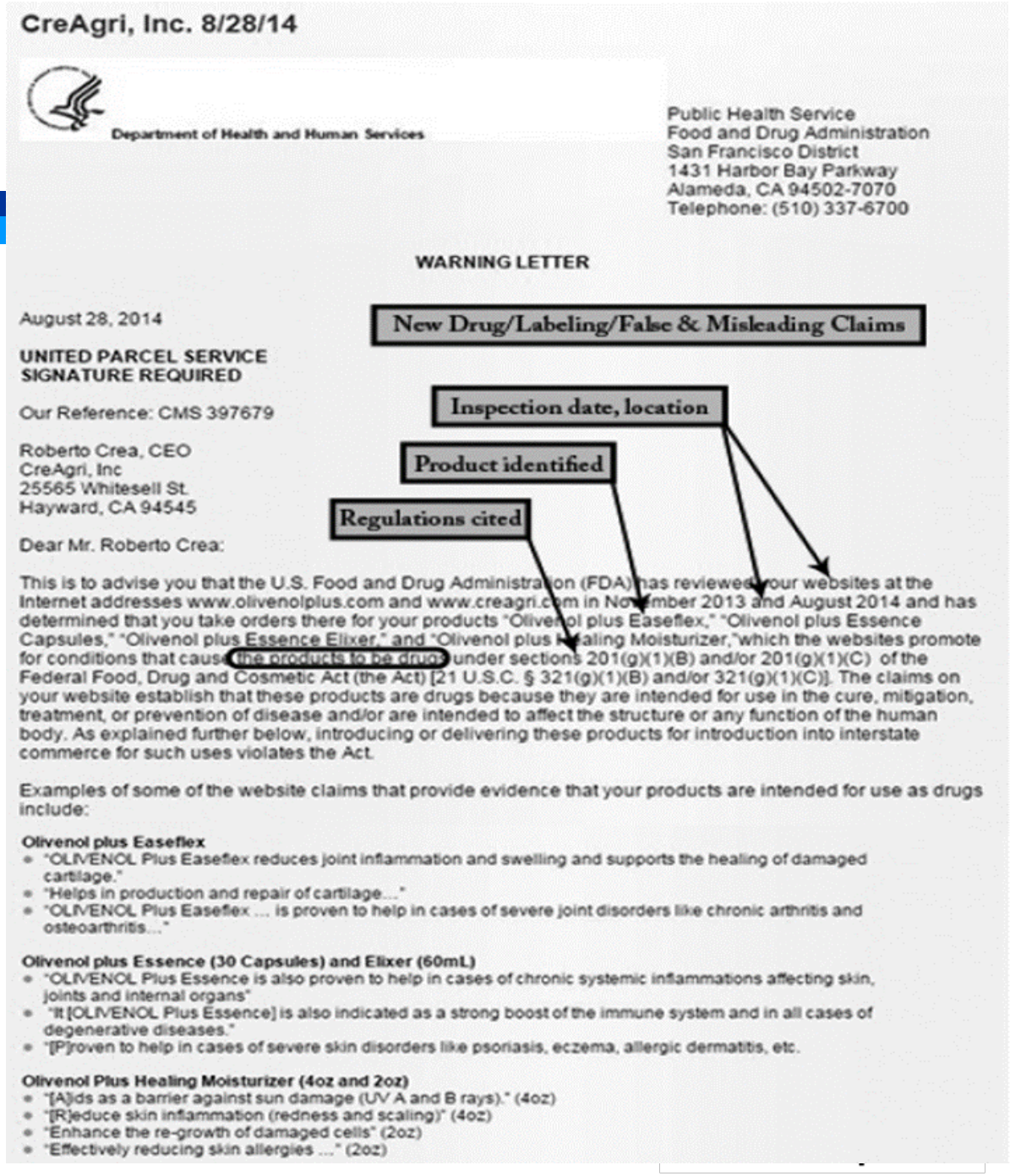
EXAMPLE

Title: WARNING LETTER

Delivery Type: overnight, receipt of delivery

Addressed to: highest official

Inspection Details: dates and description



CreAgri, Inc. 8/28/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94502-7070
Telephone: (510) 337-6700

WARNING LETTER

August 28, 2014

New Drug/Labeling/False & Misleading Claims

UNITED PARCEL SERVICE
SIGNATURE REQUIRED

Our Reference: CMS 397679

Inspection date, location

Product identified

Regulations cited

Roberto Crea, CEO
CreAgri, Inc
25565 Whitesell St.
Hayward, CA 94545

Dear Mr. Roberto Crea:

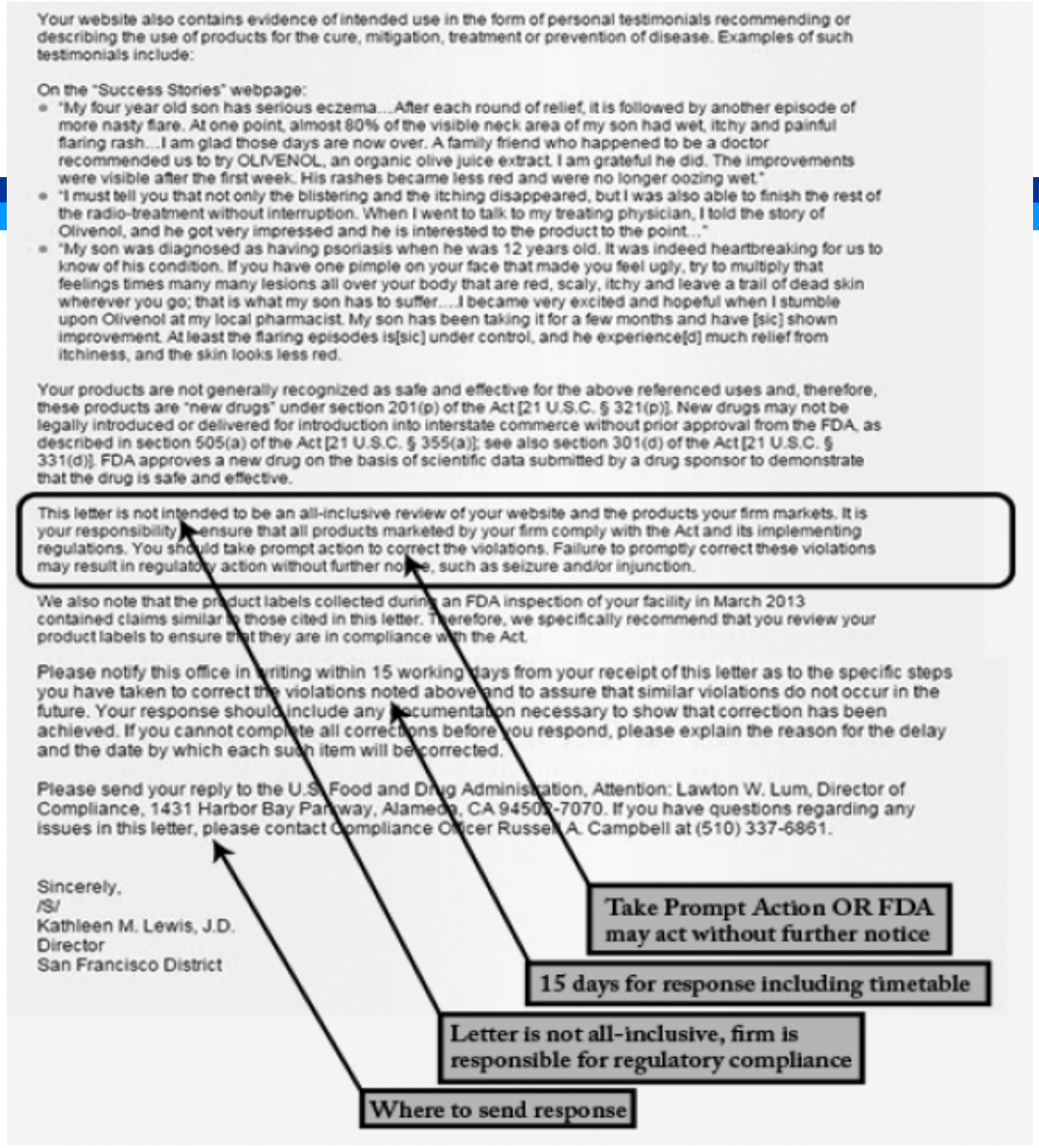
This is to advise you that the U.S. Food and Drug Administration (FDA) has reviewed your websites at the Internet addresses www.olivenolplus.com and www.creagri.com in November 2013 and August 2014 and has determined that you take orders there for your products "Olivenol plus Easeflex," "Olivenol plus Essence Capsules," "Olivenol plus Essence Elixer," and "Olivenol plus Healing Moisturizer,"which the websites promote for conditions that cause the products to be drugs under sections 201(g)(1)(B) and/or 201(g)(1)(C) of the Federal Food, Drug and Cosmetic Act (the Act) [21 U.S.C. § 321(g)(1)(B) and/or 321(g)(1)(C)]. The claims on your website establish that these products are drugs because they are intended for use in the cure, mitigation, treatment, or prevention of disease and/or are intended to affect the structure or any function of the human body. As explained further below, introducing or delivering these products for introduction into interstate commerce for such uses violates the Act.

Examples of some of the website claims that provide evidence that your products are intended for use as drugs include:

Olivenol plus Easeflex
- "OLIVENOL Plus Easeflex reduces joint inflammation and swelling and supports the healing of damaged cartilage."
- "Helps in production and repair of cartilage...."
- "OLIVENOL Plus Easeflex ... is proven to help in cases of severe joint disorders like chronic arthritis and osteoarthritis...."

Olivenol plus Essence (30 Capsules) and Elixer (60mL)
- "OLIVENOL Plus Essence is also proven to help in cases of chronic systemic inflammations affecting skin, joints and internal organs"
- "It [OLIVENOL Plus Essence] is also indicated as a strong boost of the immune system and in all cases of degenerative diseases."
- "[P]roven to help in cases of severe skin disorders like psoriasis, eczema, allergic dermatitis, etc.

Olivenol Plus Healing Moisturizer (4oz and 2oz)
- "[A]ids as a barrier against sun damage (UV A and B rays)." (4oz)
- "[R]educe skin inflammation (redness and scaling)" (4oz)
- "Enhance the re-growth of damaged cells" (2oz)
- "Effectively reducing skin allergies ...." (2oz)



Response Request: 15 days

Impact: government contracts, exports, FDA approvals

Response Instructions: corrective/preventative action steps, timeline for completion and reason if not complete with full documentation and identifies response recipient/issuer

Standard Closing Text

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What Can Happen due to a Warning Letter?

- Investors, competitors, and customers hear and start asking questions
- Can result in problems with certain product submissions and prevent issuance of certificates to foreign governments for your international markets
- May be put on the import hold list for foreign establishment
- The cost of resolving can be expensive (millions)
- Increase inspection risk at subsidiaries in other districts

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Warning Letter Procedures

Process and Politics

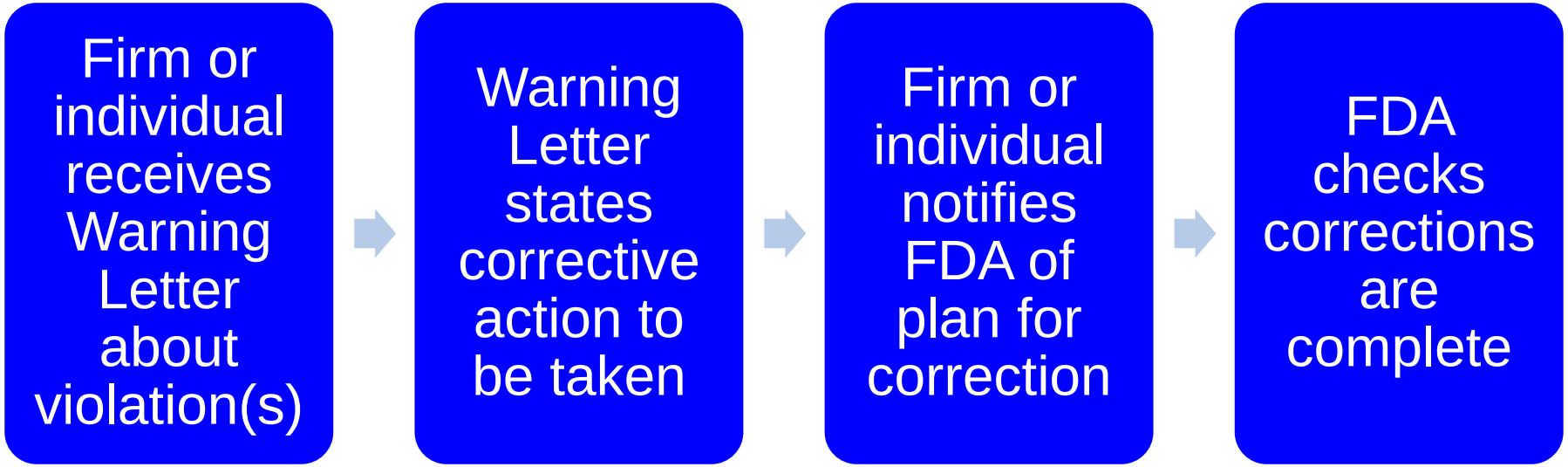
FDA Process Before Issuance

District should submit Warning Letter recommendation to the appropriate reviewing office (within 15 days after inspection)

The Center should review the Warning Letter and notify the District office of its decision (within 15 days after receiving the Warning Letter recommendation)

The District compliance officer assigned to the Warning Letter should monitor the progress of the case to its conclusion

Firm's Warning Letter Response Process



FDA Considers Several Factors

1. General Consideration
2. Ongoing or Promised Corrective Actions
3. Completed Corrective Actions
4. Response Letter
5. Verification or Corrective Actions

http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm

General Consideration

When issuing a Warning Letter, an official should consider whether:

- Evidence shows a firm, product, and/or individual is in violation and failure to achieve adequate/prompt correction may result in enforcement action
- Violation(s) of regulatory significance consistent with regulatory policy
- Reasonable expectation of quick corrective action

Ongoing/Promised Corrective Actions

With a written promise to take corrective action during/after inspection, an official should consider the following when determining whether to issue a Warning Letter:

- Firm's compliance history (serious, failed to prevent recurrence)
- Nature of the violation (prior awareness w/o correction)
- Risk associated with product and impact of violations on such risk
- Overall adequacy of firm's corrective action (addresses specific violations and contains provisions for monitoring and review to ensure effectiveness and prevent recurrence)
- Whether documentation of corrective action was provided for Agency to undertake an informed evaluation
- Whether corrective action ensures sustained compliance with the law or regulations

Completed Corrective Actions

In general, No Warning Letter should be issued if an individual/ firm's corrective actions are adequate and the violation(s) have been corrected

- Exceptions should recite history and consequences of recurrence

Response Letter

If no Warning Letter is issued because sufficient corrective action has been taken, is being taken, or has been promised then a “Response Letter” to the firms letter promising corrective action should be issued to document the violations and reflect the Agency's decision to rely on the firm's actions and/or promises.

A Response Letter describing firm’s promised corrective actions does not preclude future regulatory actions without further notice.

Verification of Corrective Actions

The next inspection should verify the corrective action/s are complete and effective

- Timing of the next inspection may be expedited or routine

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Center Concurrence

Required prior to issuance of Warning Letters for:

- **Labeling violations**
- **Computer application and software violations**
- **Bioresearch monitoring program violations**
- **Product advertising violations**

Warning Letter Response Evaluation

The issuing District or Center will evaluate the individual/ firms response to the Warning Letter

- If response is inadequate or absent, follow-up action will proceed as necessary to achieve correction
- If response is adequate, the District or Center will verify and notify that correction has been achieved (standard is to inspect again to verify corrections have been implemented)

Warning Letter Follow-Up

1. Acknowledgment of Response to a Warning Letter
   - Acknowledge receipt in writing
   - Evaluate firms response
2. Warning Letter Close-out Letter
   - Sufficient information demonstrates violations are corrected
   - Follow up inspection (as needed) shows adequate actions
   - No other significant violations exist
3. Follow-up Enforcement
   - Firm unable or unwilling to correct violations
   - Consider further regulatory action, evaluate prior/second notice/meeting with firm's management
4. Inspection Classification for Warning Letter
   - Official Action Indicated (OAI)

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Consequences of a Warning Letter

Once a Warning Letter has posted to the FDA website, others with interest in the company may take note including:

- Investors
- Competitors
- Customers

Warning Letters may take $Millions to resolve and result in the failed approval of FDA submissions, increased regulatory scrutiny of company subsidiaries, and refusal of product approval for international import and marketing.

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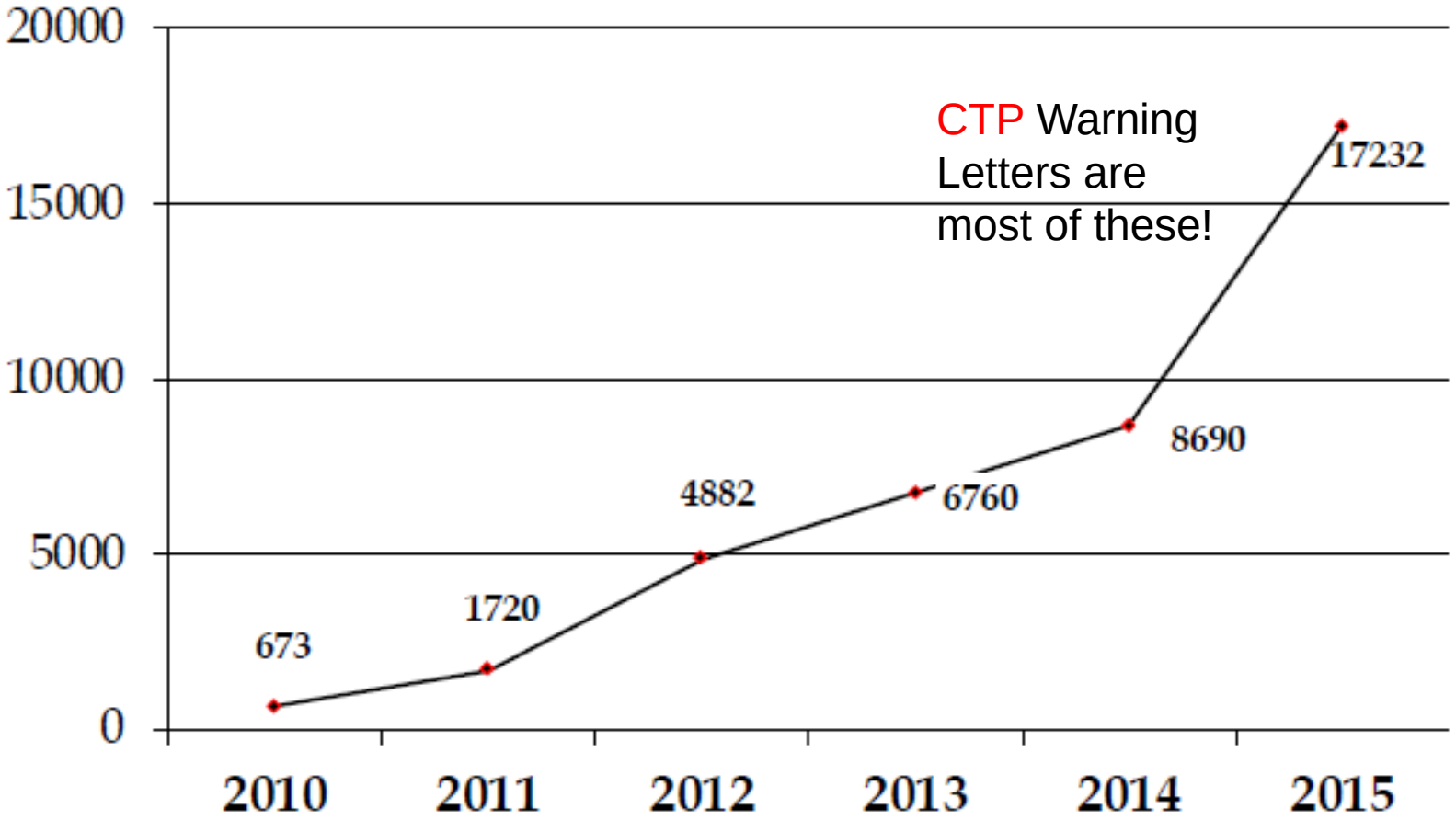
Recent Warning Letters

Current statistics and examples

2010-2015 FDA Warning Letters Increasing



http://www.fda.gov/downloads/ICECI/EnforcementActions/UCM484400.pdf

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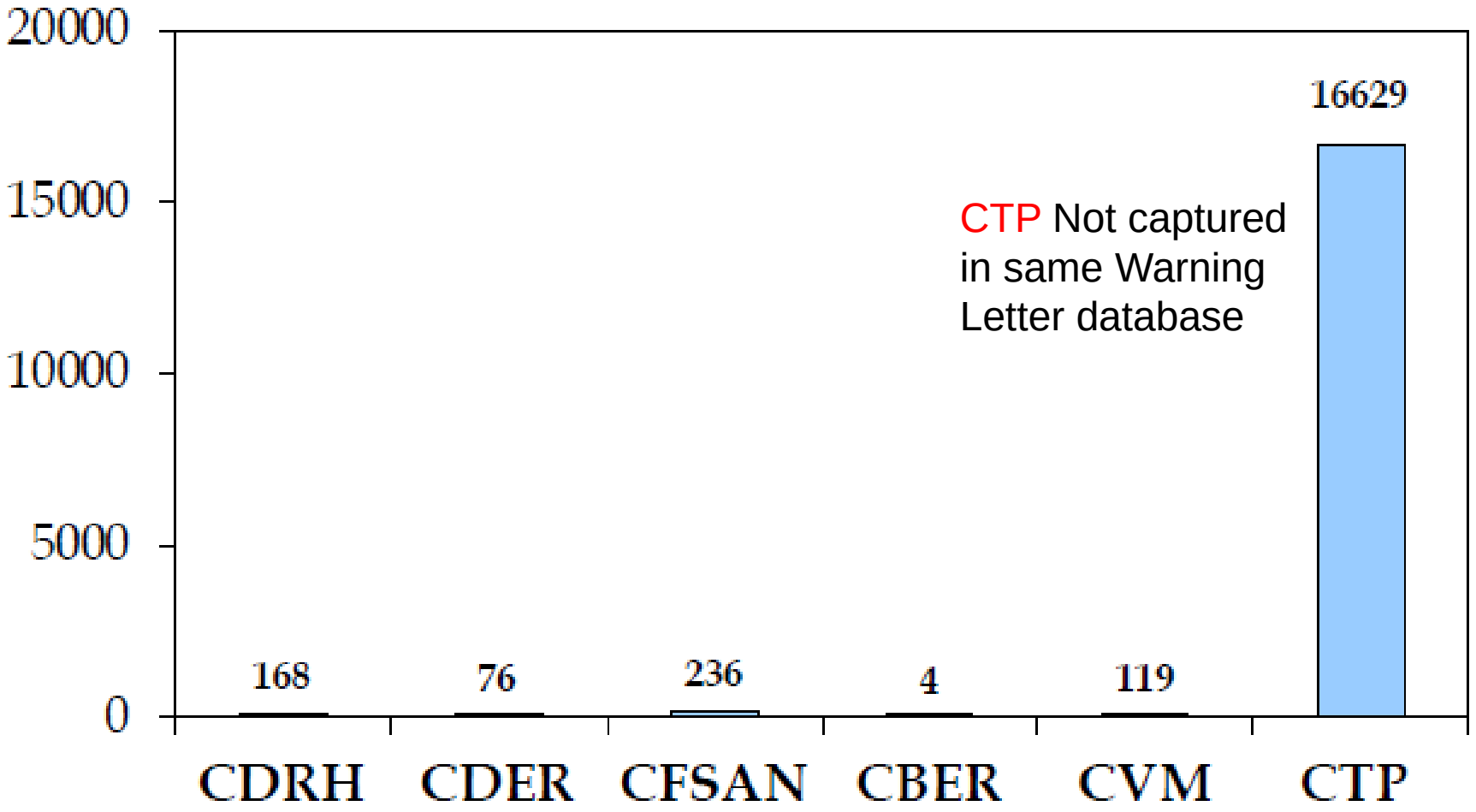
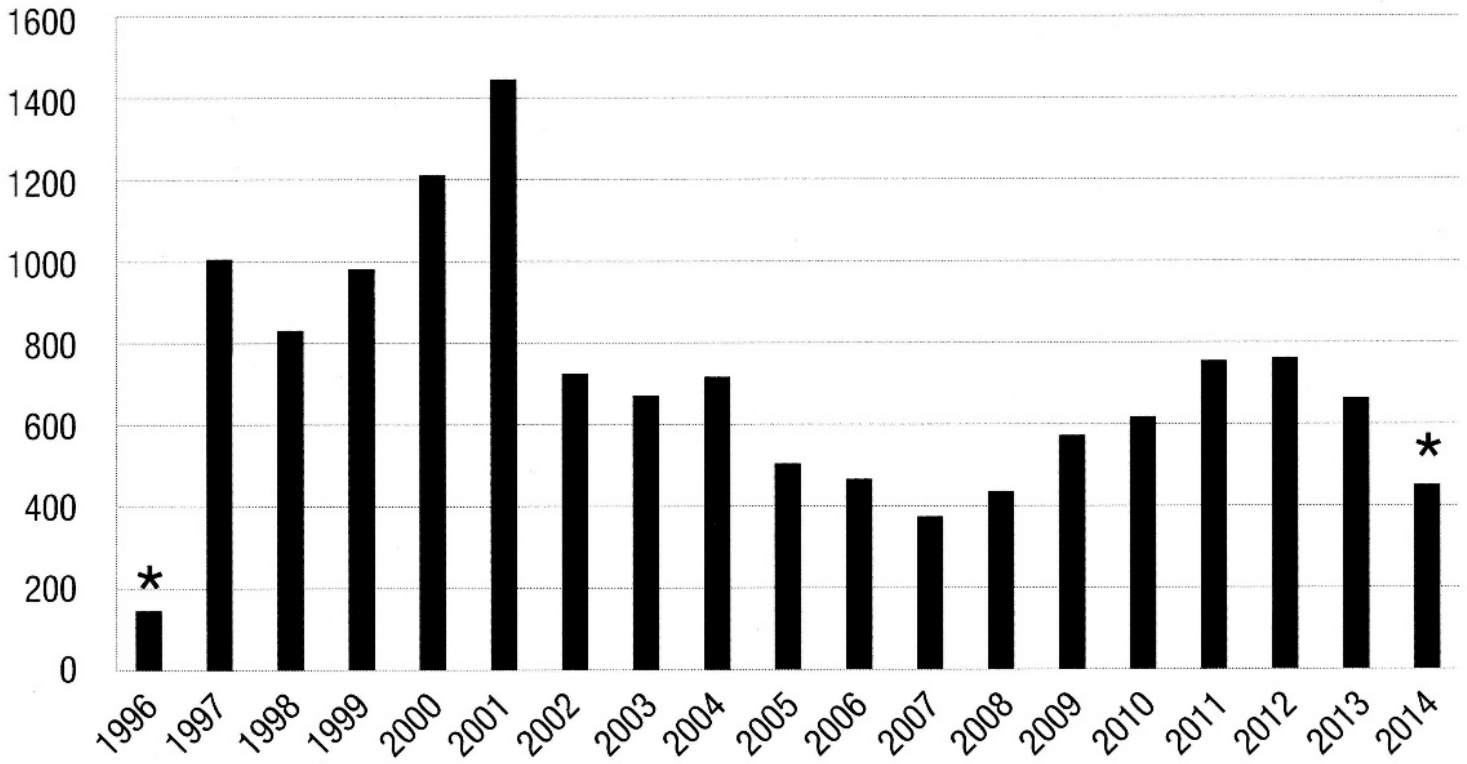
2015 Warning Letters by FDA Center



http://www.fda.gov/downloads/ICECI/EnforcementActions/UCM484400.pdf

Database Warning Letters Issued per Year



Warning Letters Issued by Year as of 9-30-14 (* = incomplete years)

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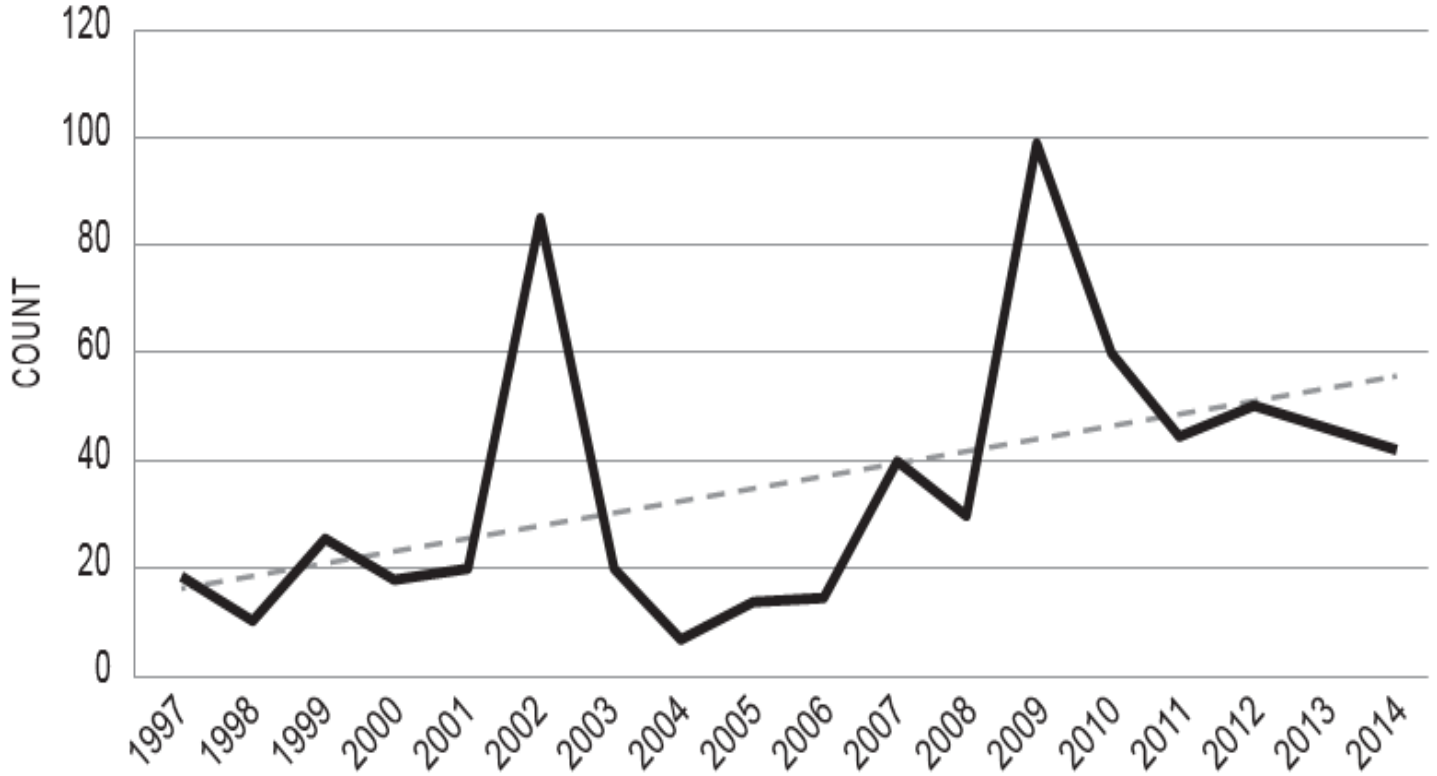
CDER Warning Letters Increasing



CDER Warning Letters Over Time (1997 – 2014)

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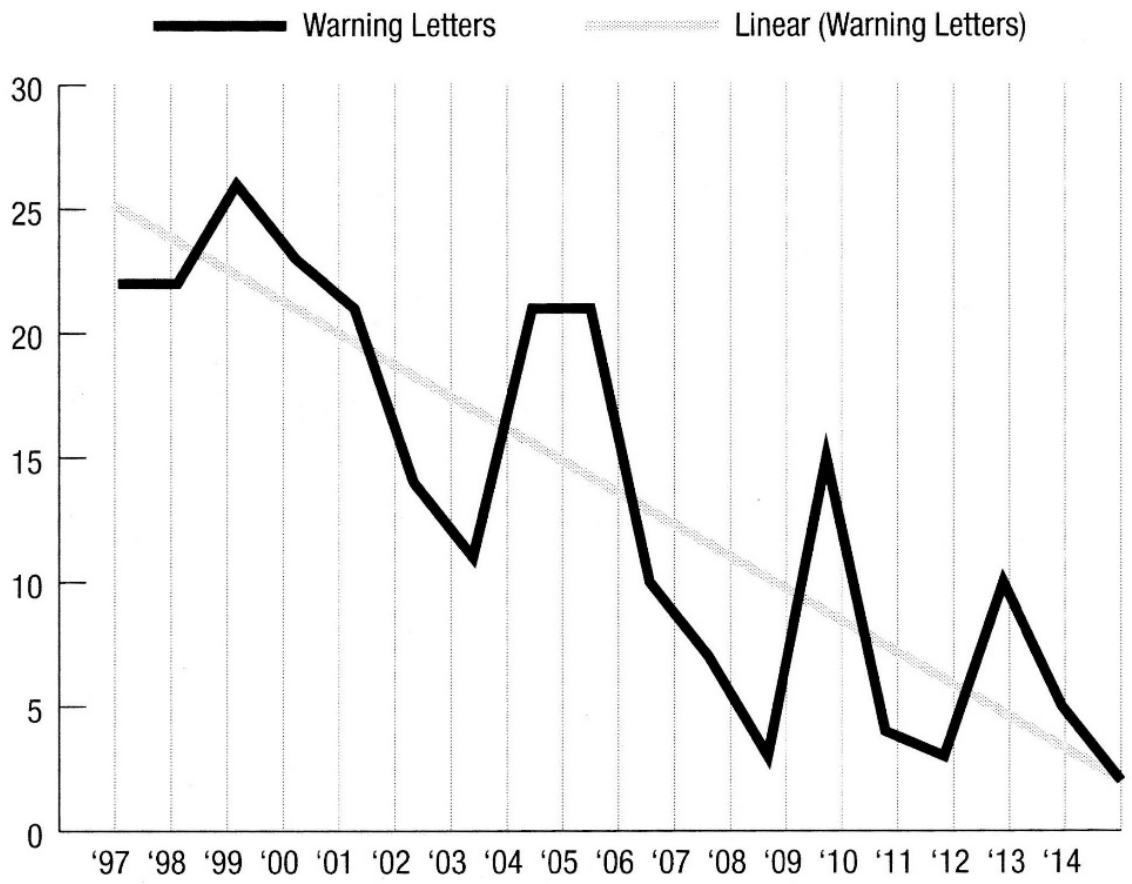
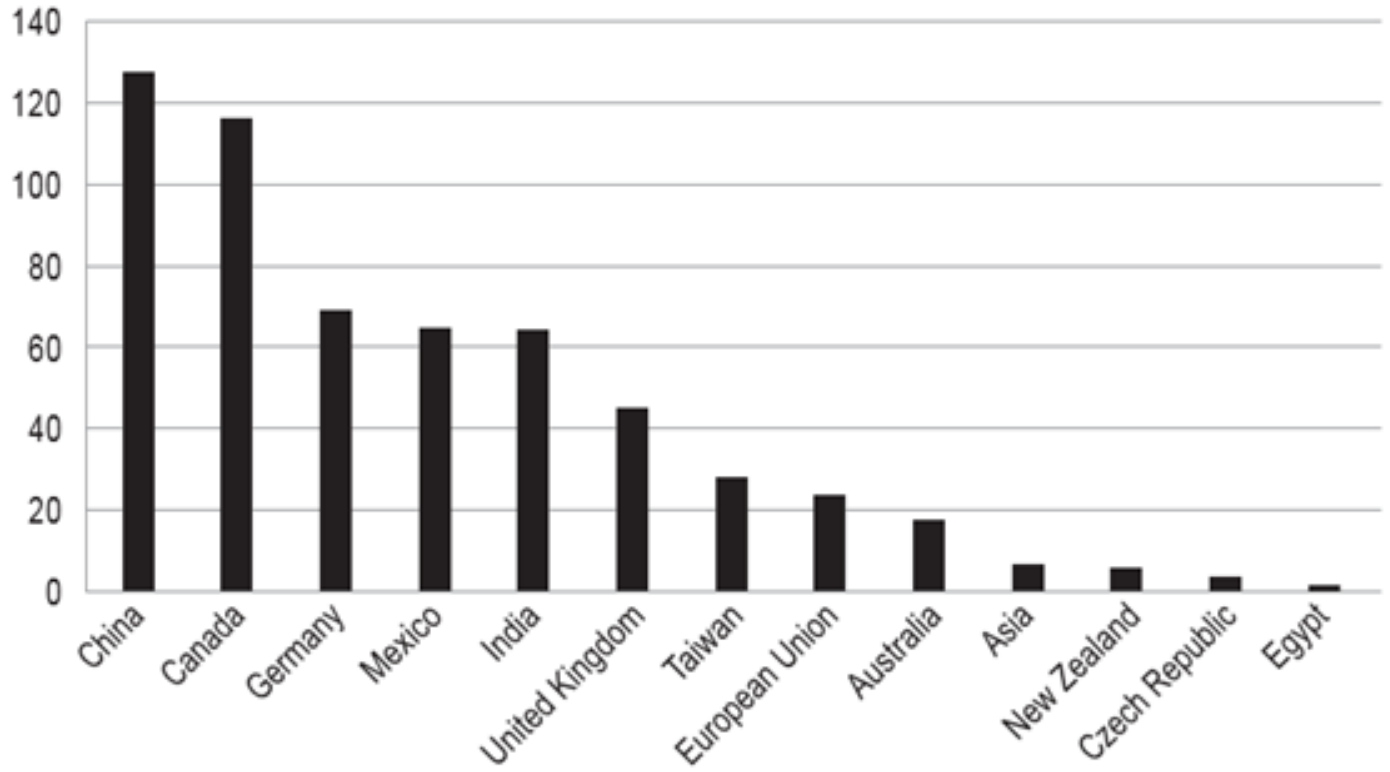
CBER Warning Letters Decreasing



Warning Letters from CBER are Declining

International Warning Letters Vary by Country



Number of Warning Letters sent to Various Countries as of June 21, 2015

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Search for FDA Warning Letters

Browse by year

View Recent letters

Search by term

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

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Search Example: “Medtronic”

FDA Warning Letters can be found on the “Inspections, Compliance, Enforcement, and Criminal Investigations” page of the FDA website:

http://www.fda.gov/iceci/enforcementactions/warningletters/default.htm

Search: “Medtronic” identified 14 Warning Letters

Warning Letters Search Results

Search all warning letters

Medtronic Search Advanced Search

Sort by: Go Reset

No. of Letters Found: 14

Company	Letter Issued	Issuing Office	Subject	Response Letter Posted	Closeout Date
Invatec S.p.A.[5]	05/06/2013	Center for Devices and Radiological Health	Quality System Regulation/Adulterated/Medical Device Reporting/Misbranded	No	02/02/2015
MedCentral Health System[6]	06/22/2010	Center for Devices and Radiological Health	Institutional Review Board (IRB)	No	
Medtronic Emergency Response System [7]	06/09/2005	Seattle District Office	CGMP Requirements for Medical Devices/Adulterated	No	
Medtronic Inc. Cardiac Rhythm Disease Managment	11/09/2009	Minneapolis District Office	CGMP/QSR/Medical Devices/Adulterated	No	

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CDRH Violation Examples

Danger to health violations (21 U.S.C. 352(j))

- Medical device reporting violations (failure to report malfunctions) (21 CFR 803.3(n))
- Restricted device violations
- Radiation Control for Health and Safety Act violations
- Violation of post market surveillance studies requirements
- Violation of device tracking regulations
- Violation of user reporting regulations
- Failure to submit a 510(k) (premarket notification) or PMA (Premarket Approval Application)
- All violations arising during pre-PMA inspections
- Mammography Quality Standards Act (MQSA) violations

Adulteration Charges

Class III device without approved PMA/IDE application

- Section 501(f)(1)(B), 21 U.S.C. 351(f)(1)(B), Section 513(f), 21 U.S.C. 360c(f), Section 515(a), 21 U.S.C. 360e(a), Section 520(g), 21 U.S.C. 360j(g)

Strength, purity, or quality falls below representations

- Section 501(c), 21 U.S.C. 351(c)

Methods, facilities or controls do not meet cGMP requirements for medical devices

- Section 501(h), 21 U.S.C. 351(h), Title 21, Code of Federal Regulations (CFR), Part 820

Misbranding Charges

Labeling for device represents or suggests device is adequate BUT these representations or suggestions are false or misleading

- Section 502(a), 21 U.S.C. 352(a)

Device is in package form and its label fails to contain the name and place of business of the manufacturer, packer, or distributor

- Section 502(b), 21 U.S.C. 352(b)

Labeling for the device fails to bear adequate directions for the purposes for which it is intended, because adequate directions cannot be written for (e.g., such purposes, etc.)

- Section 502(f)(1), 21 U.S.C. 352(f)(1)

More Misbranding Charges

Device was manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered and a notice or other information respecting the device was not provided to FDA

- Section 502(o), 21 U.S.C. 352(o), Section 510, 21 U.S.C. 360, Section 510(k), 21 U.S.C. 360(k)

Notice or other information was not provided to FDA when device was significantly changed or modified

- Section 502(o), 21 U.S.C. 352(o), 21 CFR 807.81(a)(3)(i)

EXAMPLE

Inspection date, location
Device identified
Regulation cited
MISBRANDED

- Failed to report correction /removal to reduce risk - balloon failing to deflate could result in airway obstruction; removed 18x40mm size (reported the Class I recall)
- Failed to report field correction - changes to IFU and MD training warning of airway obstruction

Department of Health and Human Services

Public Health Service
Food and Drug Administration
San Francisco District
1431 harbor Bay Parkway
Alameda, CA 94501-7070
Telephone: (510) 337-6700

WARNING LETTER

VIA UNITED PARCEL SERVICE

UIN # 394263

March 20, 2013

AIR Balloon Dilation System

Bridget A. Ross
President
Acclarent, Inc.
1525-B O'Brien Dr.
Menlo Park, CA 94025-1463

Dear Ms. Ross:

During an inspection of your firm located in Menlo Park, CA on January 29 through February 22, 2013, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures the Inspira AIR Balloon Dilation System, the Inspira AIR Balloon Catheter Inflation Device, and the Cyclops Multi-Angle Endoscope. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.

Our inspection also revealed that your firm's Inspira AIR Balloon Dilation System devices are misbranded under section 502(t)(2) of the Act, 21 U.S.C. § 352(t)(2), in that your firm failed or refused to furnish material or information respecting the device that is required by or under section 519 of the Act, 21 U.S.C. § 360i, and 21 CFR Part 806 – Medical Devices; Reports of Corrections and Removals. Significant violations include, but are not limited to, the following:

Failure to report to FDA in writing a correction or removal, conducted to reduce a risk to health posed by a device as required by 21 CFR 806.10(a).

For example: Due to the potential for the balloon of the Inspira AIR Balloon Dilation System (all sizes) to not deflate or to deflate slowly, which could potentially result in airway obstruction, you removed the 18 x 40 mm size Inspira AIR Balloon Dilation System. The removal was reported to FDA and classified as a class I recall.

You made additional changes to the Instructions-For-Use distributed with all sizes of the device, and you updated physician training materials to include a warning of the potential airway obstruction. However, you failed to report to FDA in writing the field correction affecting all device size.

Example p2

- Take Prompt Action OR FDA may act without further notice
- 15 days for response including timetable
- Where to send response
- Unique ID #
- Letter is not all-inclusive, firm is responsible for regulatory compliance

Your firm should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction, and civil money penalties. Also, federal agencies may be advised of the issuance of Warning Letters about devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing within fifteen business days from the date you receive this letter of the specific steps your firm has taken to correct the noted violations, as well as an explanation of how your firm plans to prevent these violations, or similar violations, from occurring again. Include documentation of the corrections and/or corrective actions (including any systemic corrective actions) that your firm has taken. If your firm's planned corrections and/or corrective actions will occur over time, please include a timetable for implementation of those activities. If corrections and/or corrective actions cannot be completed within fifteen business days, state the reason for the delay and the time within which these activities will be completed. Your firm's response should be comprehensive and address all violations included in this Warning Letter.

Your firm's response should be sent to: Lawton Lum, Director of Compliance, 1431 Harbor Bay Parkway, Alameda, CA 94502.

Refer to the Unique Identification Number 394263 when replying. If you have any questions about the contents of this letter, please contact: Sergio Chavez, Compliance Officer at (510) 337-6886 or (510)3376703 (fax).

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your firm's facility. It is your firm's responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, FDA 483, issued at the close of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality management systems. Your firm should investigate and determine the causes of the violations, and take prompt actions to correct the violations and bring the products into compliance.

Sincerely yours,

/S/

Judy Strojny

Acting District Director

Clinical Investigator Charges

Failure to adhere to informed consent requirements

- 21CFR50.20, 50.25, 50.27, and 50.55(f)

Failure to conduct an investigation according to the signed agreement, investigational plan, and applicable FDA regulations

- 21CFR812.100 and 812.110(b)

Failure to maintain accurate, complete, and current records related to your participation in the investigation

- 21CFR812.140(a)

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Quality Services Reporting Charges

Failure to establish and maintain procedures for implementing corrective and preventive action

- 21 CFR 820.100(a)

Failure to document all activities and their results

- 21 CFR 820.10021, CFR 820.100(b)

Failure to establish and maintain procedures to control product that does not conform to specified requirements

- 21 CFR 820.90(a)

Frestedt incorporated

Medical Device Reporting Charges

Failure to develop, maintain, and implement adequate MDR procedures

- 21CFR803.17

For example

MDR Procedure failed to include address where Medical Device reports need to be sent

MDR procedure does not include a timeframe for submitting supplemental reports to FDA

- 21 CFR 803.56

MDR procedure combines language from requirements of other regulatory competent authorities

- 21 CFR 803

Frestedt incorporated

Common Warning Letter Topics

Firm

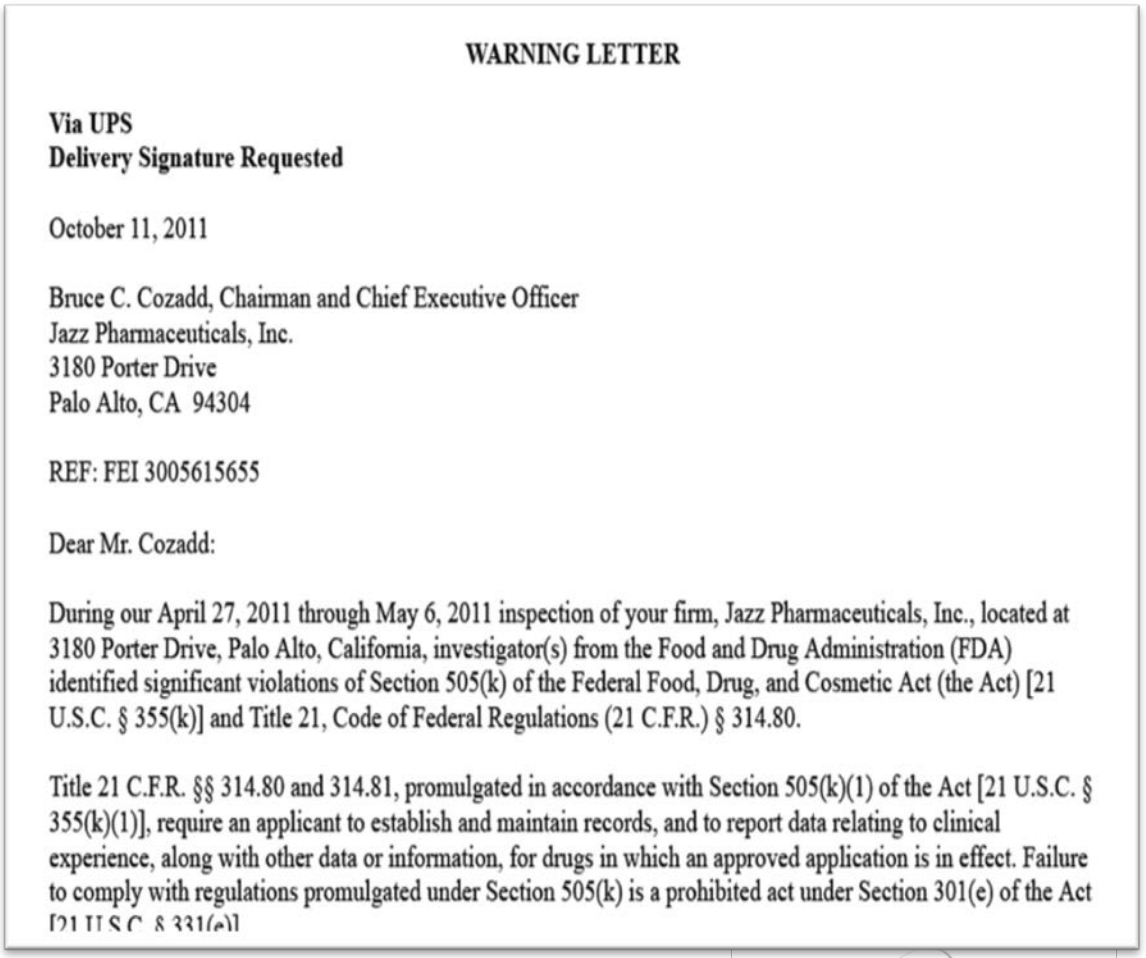
- Misleading or inaccurate labeling
- Failure to follow cGMPs
- Misbranding of products
- Failure to implement and Quality Management System
- Misleading promotional material
- Failure to manage complaints

Clinical Trial Personnel

- Protocol non-compliance
- Inadequate/inaccurate records
- Inadequate drug accountability
- Informed consent issues
- Inadequate adverse event reporting
- Failure to supervise study staff

Example – Jazz Pharmaceuticals, Inc.

- Failure to develop adequate written procedures for surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to the FDA [CFR314.80(b)].
- Failure to submit adverse drug experience (ADE) reports that are both serious and unexpected to FDA within 15 calendar days of initial receipt of the information by the applicant [21CFR314.80(c)(1)(i)].



WARNING LETTER

Via UPS
Delivery Signature Requested

October 11, 2011

Bruce C. Cozadd, Chairman and Chief Executive Officer
Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304

REF: FEI 3005615655

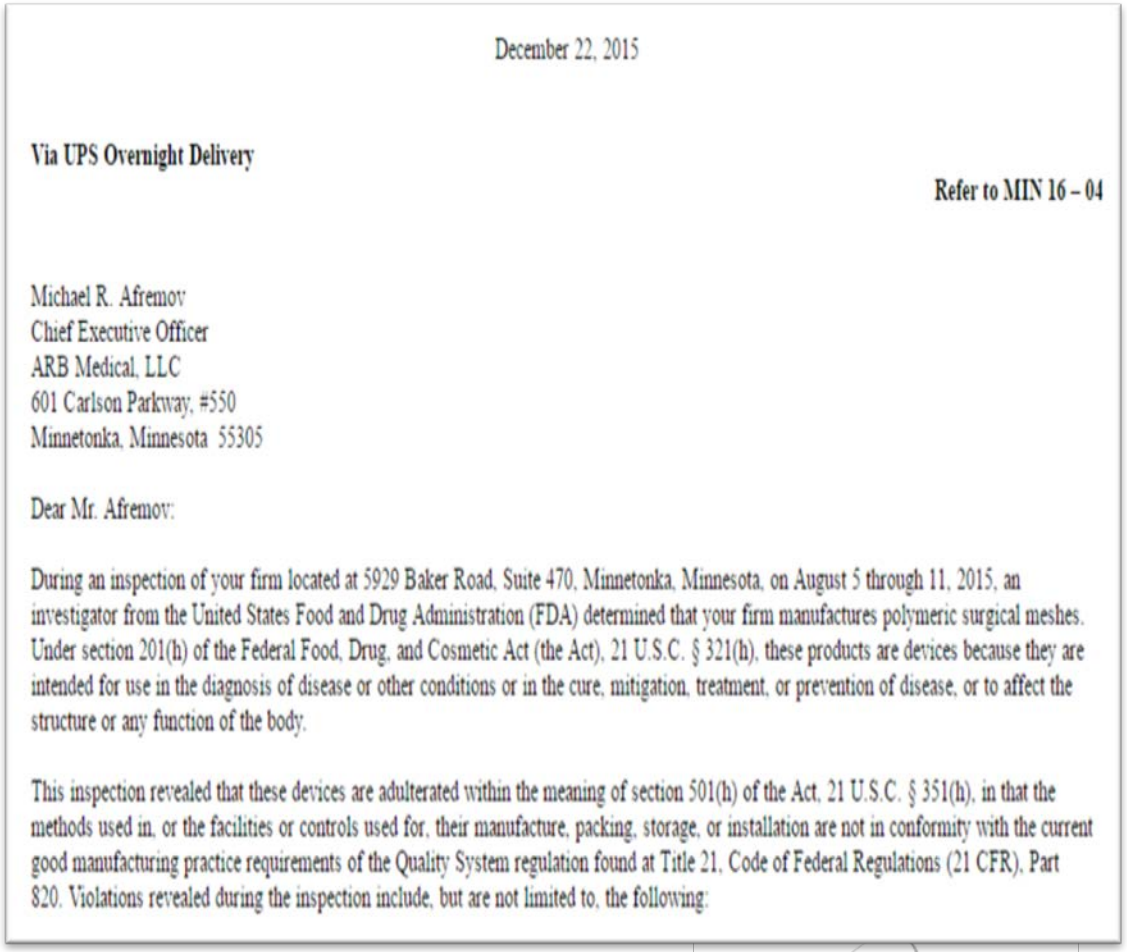
Dear Mr. Cozadd:

During our April 27, 2011 through May 6, 2011 inspection of your firm, Jazz Pharmaceuticals, Inc., located at 3180 Porter Drive, Palo Alto, California, investigator(s) from the Food and Drug Administration (FDA) identified significant violations of Section 505(k) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 355(k)] and Title 21, Code of Federal Regulations (21 C.F.R.) § 314.80.

Title 21 C.F.R. §§ 314.80 and 314.81, promulgated in accordance with Section 505(k)(1) of the Act [21 U.S.C. § 355(k)(1)], require an applicant to establish and maintain records, and to report data relating to clinical experience, along with other data or information, for drugs in which an approved application is in effect. Failure to comply with regulations promulgated under Section 505(k) is a prohibited act under Section 301(e) of the Act [21 U.S.C. § 331(e)]

Example – ARB Medical, LLC

- Failure to adequately validate... a process whose results cannot be fully verified by subsequent inspection and test, as required by 21CFR 820.75(a)
- Failure to review and approve design output before release, as required by 21CFR820.30(d)
- Design validation failed to ensure the device conforms to defined user needs and intended uses, as required by 21CFR820.30(g).



December 22, 2015

Via UPS Overnight Delivery

Refer to MIN 16 – 04

Michael R. Afremov
Chief Executive Officer
ARB Medical, LLC
601 Carlson Parkway, #550
Minnetonka, Minnesota 55305

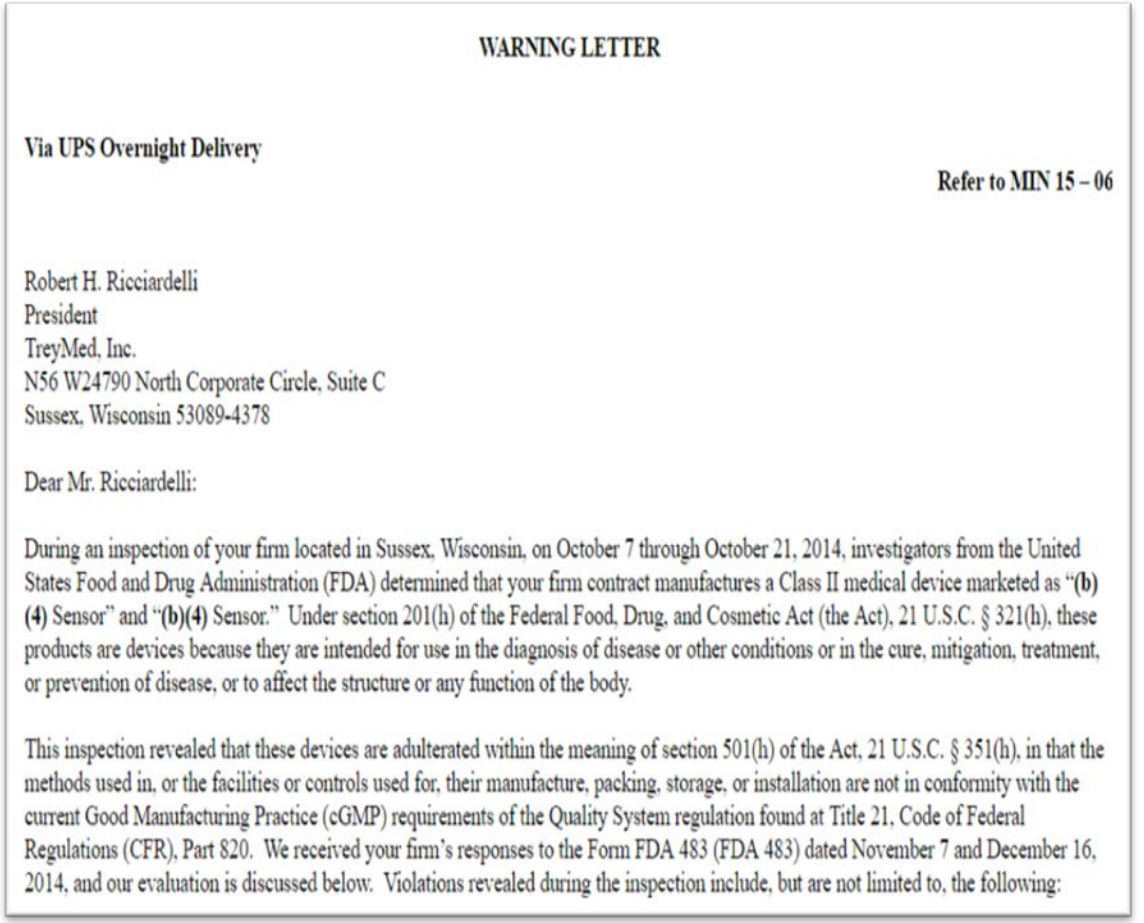
Dear Mr. Afremov:

During an inspection of your firm located at 5929 Baker Road, Suite 470, Minnetonka, Minnesota, on August 5 through 11, 2015, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures polymeric surgical meshes. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (21 CFR), Part 820. Violations revealed during the inspection include, but are not limited to, the following:

Example – TreyMed, Inc.

- Failed to adequately establish procedures to control product that does not conform to specified requirements, as required by 21 CFR 820.90(a)
- Device history record does not demonstrate that the device was manufactured in accordance with the device master record, as required by 21 CFR 820.184
- Device master record not adequately maintained, as required by 21CFR820.80(b)



WARNING LETTER

Via UPS Overnight Delivery

Refer to MIN 15 – 06

Robert H. Ricciardelli
President
TreyMed, Inc.
N56 W24790 North Corporate Circle, Suite C
Sussex, Wisconsin 53089-4378

Dear Mr. Ricciardelli:

During an inspection of your firm located in Sussex, Wisconsin, on October 7 through October 21, 2014, investigators from the United States Food and Drug Administration (FDA) determined that your firm contract manufactures a Class II medical device marketed as "**(b)(4)** Sensor" and "**(b)(4)** Sensor." Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current Good Manufacturing Practice (cGMP) requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820. We received your firm's responses to the Form FDA 483 (FDA 483) dated November 7 and December 16, 2014, and our evaluation is discussed below. Violations revealed during the inspection include, but are not limited to, the following:

Consent Decree Example - Medtronic

The US District Court issued a Consent Decree to Medtronic in 2015 to halt direct or indirect designing, manufacturing, processing, packing, labeling, holding, storing, distributing, importing or exporting SynchroMed devices until the firm's facilities corrected their manufacturing and quality systems processes.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MINNESOTA

UNITED STATES OF AMERICA,

Plaintiff.

v.

MEDTRONIC, INC., a corporation, and S. OMAR ISHRAK and THOMAS M. TEFFT, individuals,

Defendants.

Case No. _____

CONSENT DECREE OF PERMANENT INJUNCTION

Plaintiff, the United States of America, by its undersigned attorneys, having filed a complaint for permanent injunction against Medtronic, Inc. ("Medtronic"), a corporation, and S. Omar Ishrak and Thomas M. Tefft, individuals (collectively, "Defendants"), and Defendants, having appeared and having consented to entry of this Decree without contest, without admitting or denying the allegations in the Complaint, and disclaiming any liability in connection therewith and before any testimony has been taken, and the United States having consented to this Decree,

Frestedt incorporated

How to Avoid and Recover from a Warning Letter

Be Knowledgeable

- Be compliant and familiar with laws and regulations
- Implement and follow a 21CFR820 compliant Quality Management System (get your SOPs in order!)
- Implement and follow Good Manufacturing Practices (GMPs) and Good Clinical Practices (GCP)
- Do not anticipate FDA Regulators will develop special rules for you
- Avoid approaches to bypass rules or personnel; better to examine all options and find what works best

Furr, D; Dealing with fda 483's, warning letters, and other enforcement actions. FDA Medical Device Industry Coalition. Accessed on 21Mar2013 at: http://fmdic.org/wp-content/uploads/2012/05/Furr-Recovery.pdf

Frestedt incorporated

Follow Key Elements of a Quality System

Documented procedures developed, implemented, and up-to-date	**Training of sponsor personnel**	**Validation of computerized systems**
Monitoring of trial sites and technical facilities on-site	**Data management and quality control**	**Internal and external audits performed by independent personnel**

Use Standard Operating Procedures!

Frestedt incorporated

Use Current Good Manufacturing Practices

- Supports early adoption of new technological advances/promotes using risk-based approaches
- Facilitates modern quality systems approaches to all aspects of production and quality assurance
- Increases consistency/coordination with FDA by incorporating improved quality systems approaches aligned with the FDA's business processes, regulatory policies, review and inspection activities
- Ensures review, compliance, and inspection policies are based on the most advanced level of development

U.S. Food and Drug Administration. Pharmaceutical cGCMPs for the 21st Century- A Risk-Based Approach. FDA.gov, Fall 2004; Accessed on 12-18-12 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm

Frestedt incorporated

List Action Items, Set Timelines

- Respond to Warning Letter appropriately and promptly (within 15 days of receipt)
- Assemble a team to address issues and create Quality Improvement Plan
- Consult with expert external consultants if you do not have the in-house knowledge
- Assign each issue to an individual/committee/group to review findings for accuracy
- Draft and review written response before submission (describe cause of failure, corrective action and timeline for implementation)

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Plan for Close out Meeting

- Written response should list each violation (as written by FDA), followed by your reply
- Once FDA agrees your action plan is complete, you will be informed of a follow-up inspection and close out date
- Conduct a thorough and rigorous mock follow-up audit for security, completeness, competence of implementation of corrective and preventive actions
  - Be prepared to answer questions
  - Be prepared to justify timelines

Avoid the Warning Letter in the first place

Three important things to do to avoid a Warning Letter:

- Follow cGMPs during all manufacturing steps (from starting materials to finished product on the shelf)
- Require all marketing materials/labeling to be truthful and not misleading
- Design appropriate tests to certify products are pure and not contaminated

Recover from Warning Letters: it happens!

Be prepared and follow good practices:

- Be familiar and compliant with applicable laws and regulations
- Implement and follow a well designed Quality Management System (SOPs designed to fully comply with regulations)
- Follow cGMP, cGCP, cGLP
- Stay informed about product risks and benefits
- Implement product-related special controls
- Use guidance documents
- Review past Warning Letters and consider implications
- Identify appropriate standards and follow them during product development and marketing

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Summary / Review

In Summary...

- The warning letter is a tool used by the FDA to gain voluntary compliance with federal regulations

- Published warning letters can be used as a tool to learn from other's mistakes and how to prevent regulatory violations that surface during FDA inspections.

One Minute Review

FDA can take enforcement action without a Warning Letter

The Warning Letter identifies violations such as:

- poor manufacturing practices
- problems with product claims
- incorrect directions for use

FDA checks to ensure the company's corrections are sufficient and issues a Close out Letter when completed

“Sing in the Choir”

Stay Informed and Up-to-Date

Be familiar and follow changes in current laws and regulations

Develop and follow a compliant Quality Management System (21CFR820)

Implement and follow current Good Manufacturing and Good Clinical Practices and Good Laboratory Practices

Frestedt incorporated

Learner Objectives

At the completion of this lecture, individuals should be able to:

- Describe the FDA inspection process
- Identify types of events leading up to a Warning Letter
- Use good processes to resolve (avoid) Warning Letters
- List a few Warning Letter statistics

Questions?

Any suggestions about Warning Letters: 2016 Reference Guide content for next edition?