INDs, Warning Letters and Frestedt Incorporated Services

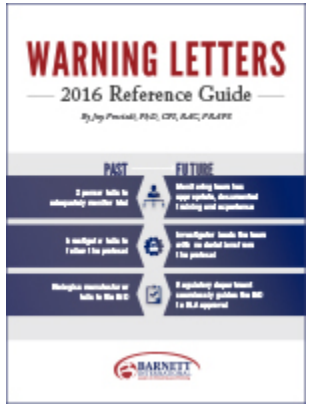
Dr. Joy Frestedt

11OCT2016

Gabe's by the Park, 991 Lexington Pkwy N, St Paul, MN 55108

5:30 Networking; 6:00 Dinner; 7:00 Presentation; 8:00 Finish

GRADUATE WOMEN IN SCIENCE



© 2016 Frestedt Incorporated.

Agenda

- Introduction
- INDs
- Warning Letters
- Role of Frestedt Inc.
- Two Warning Letter Books
- Conclusion

© 2016 Frestedt Incorporated.

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).

© 2016 Frestedt Incorporated.

Course Description

Today's talk will cover a high level discussion of Investigational New Drug Applications (INDs) and Warning Letters generally (e.g., what they are and who receives them), a little bit about the role of Frestedt Inc. (clinical, regulatory, quality and engineering affairs services), and a little bit about my two recent Warning Letters books.

Recently I've been speaking on CERs* in Minnesota (Oct 6) and San Francisco (Oct 7) and INDs in Philadelphia (Oct 13/14). In addition, I'll be attending Advamed (Oct 17/18) for a little networking. We can discuss those topics as part of this "smorgasbord" of topics if you like.

*CER=clinical evaluation report

© 2016 Frestedt Incorporated.

FDA History

1938 Federal Food, Drug, and Cosmetic Act

- Sulfanilamide (for strep throat) - diethylene glycol = 100+ deaths
- Requires NDA - new drugs shown "safe" (in animals) BEFORE mktg
- Form 356 – drug components, clinical trials, mfg. details, labeling
- FDA had 60 days to review; ok to proceed if no FDA response.

1952 NIH opens Clinical Center in Bethesda, MD

1962 Kefauver-Harris Amendments (removed 60 day approval "default")

- Thalidomide (sedative/hypnotic for morning sickness) causes birth defects
- Expands NDA – new drugs must be shown safe "and effective" before marketing .. Leads to need for IND…(1963)

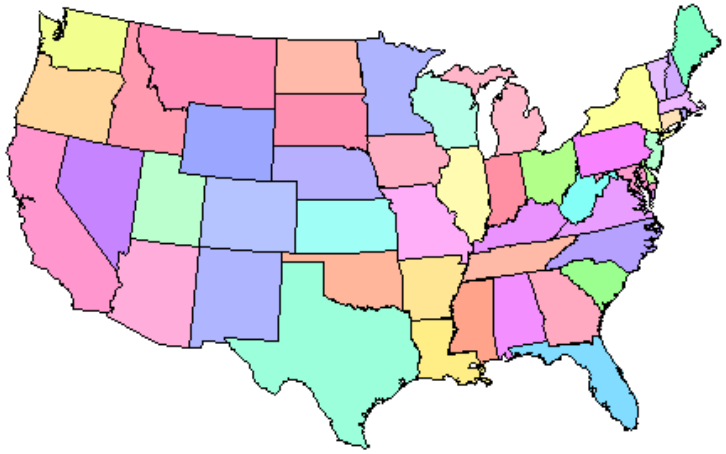
© 2016 Frestedt Incorporated.

FDA History continued…

- 1981 Revised regulations for Human Subject Protections
- 1987 IND revised to expand access for patients
- 1992 PDUFA requires fees for product applications
- 1998 Pediatric Rule –safety and efficacy in children (2003 PREA)
- 1999 Clinical trials.gov founded
- 2013 Drug Quality and Security Act
- 2015 Office of Pharmaceutical Quality (a super office)

© 2016 Frestedt Incorporated.

IND Submission



- IND is an "exemption" from normal NDA submission
  - Allows Sponsor to ship a non approved drug across state lines
- IND/s may be part of NDA, if IND/s successful
- IND/s required for previously approved drug, if:
  - Change to labeling/advertising
  - Change to dose/route of administration
  - Change to risk/benefit profile of original NDA approval
- IND process defines drug development phases I-IV

© 2016 Frestedt Incorporated.

Regulatory Responsibilities for INDs

Regulatory personnel are typically responsible to:

- Prepare and submit the IND (using appropriate IND strategies)
- Answer FDA questions about the IND
- Request and prepare FDA meetings (if needed)
- Write technical documents using outlines, style guides, templates
- Interpret FDA regulations and guidance
- Edit the work of others
- Publish information to meet FDA requirements
- Track key historical information sent to the FDA

IND submissions must meet regulatory requirements

© 2016 Frestedt Incorporated.

IND Purpose

Mechanism for FDA to control experimental therapy

Allows FDA 30 days from date of receipt to determine if:

- Nonclinical test data shows drug is reasonably safe to administer to humans and proposed protocol does NOT expose subjects to undue risk

Allows a Sponsor to ship a non approved drug across state lines "for investigational use only" after the 30-day wait.

© 2016 Frestedt Incorporated.

IND Functions

1. Alerts FDA (sponsor intends to begin clinical study/ies in the United States)
2. Provides preliminary animal toxicity data (reasonably safe to administer drug to humans)
3. Provides manufacturing process (and background chemistry)
4. Describes proposed clinical study (safety measures - qualifications of study staff, facilities; study population involved – healthy volunteers, sick patients, prisoners, women, men, children)
5. Provides IRB (Institutional Review Board) assurance (approval before study begins)
6. Provides signed **FDA Form 1572s** for every investigator participating in the study (maintained by the sponsor, indicating qualifications, location of research facility where study will be conducted, and name of IRB responsible for reviewing and approving the study protocol)

© 2016 Frestedt Incorporated.

IND Categories

Commercial IND

- Submitted by a Sponsor who intends to perform clinical trials to support a marketing application

Non-Commercial IND

- Also known as: “Investigator IND” or “Research IND”
- Submitted by a physician who both initiates (as the Sponsor) and conducts (as the Investigator) the study on a new drug or a drug already on the market for a new indication
  - Recently some academic institutions have been acting as the “Sponsor” for some Investigator Initiated INDs…
  - **CAUTION: Bigger sponsors are bigger targets for enforcement!**

© 2016 Frestedt Incorporated.

IND Submitters: Academic vs. Corporate

NOTE: Academic INDs are not the same as pharmaceutical company INDs

Why not? What are some similarities and differences?

Academic IND ≠ Company IND

© 2016 Frestedt Incorporated.

FDA IND Receipts

Historically, FDA gets far more Non-Commercial INDs than Commercial INDs

- FDA tracks numbers of INDs
- Shows roughly 2-3 times more Non-Commercial INDs are received than Commercial INDs (1986-2008)
- Databases changed in 2008
- Less clear for 2008-2016 as “expanded access” programs increase…

Calendar Year	Commercial	Non-Commercial	Total
1986	332	1286	1618
1987	311	994	1305
1988	371	929	1300
1989	310	1004	1314
1990	382	1123	1505
1991	369	1661	2030
1992	370	2111	2481
1993	384	1848	2232
1994	341	1660	2001
1995	340	1394	1734
1996	389	1194	1583
1997	396	1186	1582
1998	441	1626	2067
1999	425	983	1408
2000	410	974	1384
2001	409	995	1404
2002	417	1338	1755
2003	391	972	1363
2004*	621	1216	1837
2005*	637	1297	1934
2006*	713	1150	1863
2007*	779	1810	2589
2008*	883	1156	2039

© 2016 Frestedt Incorporated.

CDER Original INDs Received 1986-2013

Calendar Year	Commercial	Non-Commercial	Total
1986	332	1286	1618
1987	311	994	1305
1988	371	929	1300
1989	310	1004	1314
1990	382	1123	1505
1991	369	1661	2030
1992	370	2111	2481
1993	384	1848	2232
1994	341	1660	2001
1995	340	1394	1734
1996	389	1194	1583
1997	396	1186	1582
1998	441	1626	2067
1999	425	983	1408
2000	410	974	1384
2001	409	995	1404
2002	417	1338	1755
2003	391	972	1363
2004*	621	1216	1837
2005*	637	1297	1934
2006*	713	1150	1863
2007*	779	1810	2589
2008*	883	1156	2039

Calendar Year	Commercial	Research	Total
2013	10	0	10
2012	8	0	8
2011	7	1	8
2010	0	0	0
2009	0	1**	1

* Excludes Drug and Non-Biosimilar Biologic INDs, Expanded Access INDs, and Unknown INDs. Unknown refers to those INDs where the designation of Commercial or Research had not been made at the end of the calendar year.

**Following the passage of the Biologics Price Competition and Innovation Act of 2009, the sponsor of this IND decided to pursue development of their proposed product as a biosimilar.

CDER Biosimilar Biologic INDs (above)
CDER Drug & Non-Biosimilar Biologic INDs (Below)

Calendar Year	Commercial	Research	Total
2013	732	697	1429
2012	636	648	1284
2011	644	760	1404
2010	601	729	1330
2009	730	824	1554

* Excludes Biosimilar Biologic INDs, Expanded Access INDs, and Unknown INDs. Unknown refers to those INDs where the designation of Commercial or Research had not been made at the end of the calendar year.

Roughly 50% non-commercial INDs are no longer tracked here…

* Includes INDs for Therapeutic Biologic Products transferred from CBER to CDER

IND receipt figures exclude INDs meeting the requirements for exemption in accordance with 21 CFR 312.2(b)(4

Frestedt incorporated

IND Types

Investigator-Initiated IND

- Physician initiates and conducts research (unapproved drug or old drug for a new indication)

Screening IND

- Allows exploratory studies to be conducted on a number of closely related molecules to choose the preferred compound or formulation

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm (last updated 6-2-16)

© 2016 Frestedt Incorporated.

Recently Defined/Re-Defined IND Types

Expanded Access IND (21CFR312.305)

- FDA determines serious or life-threatening disease with no alternative therapy; potential benefit justifies risk and potential use does not interfere with drug development
- New IND or IND protocol amendment marked "EXPANDED ACCESS SUBMISSION."

Emergency IND (EIND) (21CFR312.310)

- Request by phone, fax email (Compassionate Use or Single/Individual Patient IND).
- Desperate medical situation (i.e., an emergency) FDA authorizes drug shipment and use of experimental drug before an IND can be submitted for patients who do not meet the existing study protocol.

Intermediate-Size Patient Populations IND (21CFR312.315)

- Smaller than typical treatment IND or treatment protocol
- FDA may ask for “consolidated” expanded access in this category

Treatment IND (21CFR312.320)

- FDA allows experimental drug showing promise for serious or life-threatening conditions while final clinical work is conducted and FDA review is completed. Allows subjects access to promising drugs while clinical testing is wrapping up in preparation for a marketing application or during the marketing application review.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

© 2016 Frestedt Incorporated.

How to get started?

To begin writing the IND submission document:

- Print out applicable Regulations and Guidance documents
  - Read and understand the contents specific to the IND
- Create a Table of Contents for the IND Sections
  - Find available internal information
  - Document what is not yet available but is required for the IND
  - Create a spreadsheet to log where IND data are stored
- Create a Style Guide for IND writers to use
  - Formal document for a group or informal “rules” for single user
- Create a Content Template for each IND section
  - Outline input requirements for each section
  - Populate template with information from previous submissions
    - If no information available, leave blank for author to fill in with required content

© 2016 Frestedt Incorporated.

Resources Vary

- IND Submission Teams (commercial) vs. Individuals (academic)
- Quality Systems (SOPs, work instructions, templates…)
- Courses, Books, CD ROMs
- FDA Website Pages
- Regulations, Guidance, Slide shows, etc.

LOTS OF INFORMATION!

© 2016 Frestedt Incorporated.

Regulations

21CFR Part 312	Investigational New Drug Application
21CFR Part 314	INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
21CFR Part 316	Orphan Drugs
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies
21CFR Part 50	Protection of Human Subjects
21CFR Part 56	Institutional Review Boards
21CFR Part 201	Drug Labeling
21CFR Part 54	Financial Disclosure by Clinical Investigators
Final Rule (9/28/2010)	Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans
Final Rule (8/12/2009)	Final Rule: Final Rules for Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm (last updated 6-2-16)

© 2016 Frestedt Incorporated.

FDA Guidance Search

http://www.fda.gov/RegulatoryInformation/Guidances/default.htm

- Type in: “IND”
- Of 3391 total entries on 05JUN2016
  - 834 were about “IND”
  - 82 about “IND submission”
  - 10 about “IND CMC” alone

Finding lots of information at www.FDA.gov is “easy”

- *finding the right information is another matter entirely*

© 2016 Frestedt Incorporated.

Guidance Documents

Title	Issued Date
FDA IND, NDA, ANDA, or Drug Master File Binders	
Drug Master Files: Guidelines	09/01/89
Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (PDF - 42KB)	11/01/95
Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products. Questions and Answers (PDF - 14KB)	10/01/00
Immunotoxicology Evaluation of Investigational New Drugs (PDF - 100KB)	10/01/02
IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer (PDF - 172KB)	01/15/04
Exploratory IND Studies (PDF - 220KB)	01/12/06
Current Good Manufacturing Practice for Phase 1 Investigational Drugs (PDF - 92KB)	07/14/08
Safety Reporting Requirements for INDs (Investigational New Drug Applications) and BA/BE (Bioavailability/Bioequivalence) Studies (PDF - 227KB)	12/19/12
Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations (PDF - 805KB)	03/17/14
Safety Assessment for IND Safety Reporting Guidance for Industry (PDF - 411KB)	12/16/15

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm (last updated 6-2-16)

© 2016 Frestedt Incorporated.

Investigator-Initiated IND Applications

IND Applications for Clinical Investigations (*Product Development*)	IND Application Reporting	IND Application Procedures	IND Applications for Clinical Treatment (*Expanded Access*)
Overview	Overview	Overview	Overview
Contents and Format	Protocol Amendments	Exemptions from IND Requirements	Contents and Format
Regulatory and Administrative Components	Information Amendments	Interactions with FDA	Treatment of a Single Patient in Emergency Setting
Non-clinical Components	Safety Reports	Clinical Hold	Treatment of a Single Patient in Non-emergency Setting
Clinical Components	Annual Reports	Investigator's Responsibilities	Treatment of a Group of Patients

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm

© 2016 Frestedt Incorporated.

Understand FDA IND processes

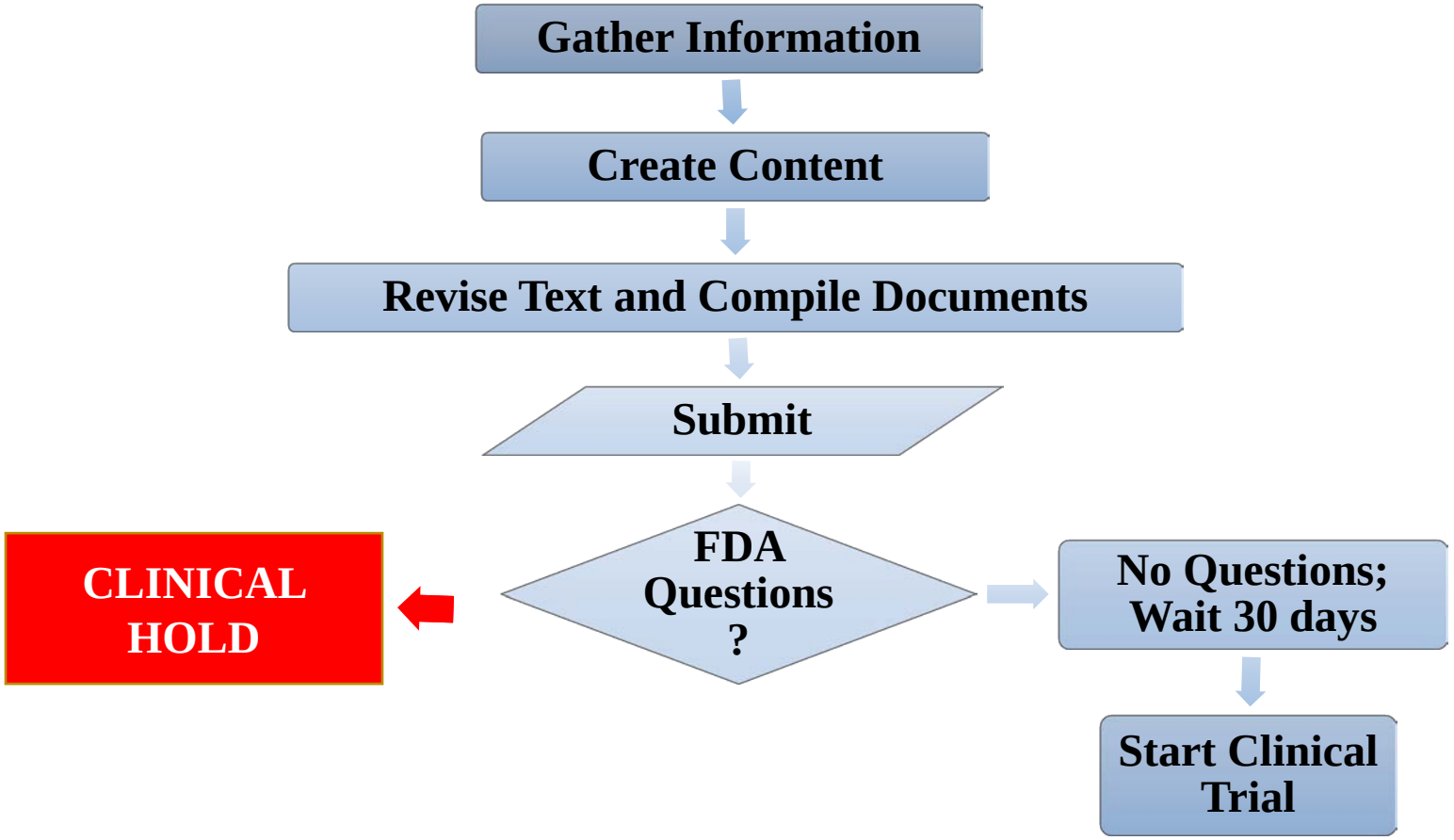
The FDA uses Manuals of Policies and Procedures (MAPPs) for consistent review/administrative oversight of INDs

Title	Issued Date
IND Process and Review Procedures (Including Clinical Holds) (PDF - 32KB)	05/01/98
Consulting the Controlled Substance Staff on INDs and Protocols That Use Schedule I Controlled Substances and Drugs (PDF - 89KB)	05/14/03
Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs (PDF - 125KB)	07/07/06
INDs: Processing Treatment INDs and Treatment Protocols (PDF - 164KB)	12/09/11
INDs: Review of Informed Consent Documents (PDF - 183KB)	05/02/14
INDs: Exception from Informed Consent Requirements for Emergency Research (PDF - 283KB)	11/17/14

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm (last updated 6-2-16)

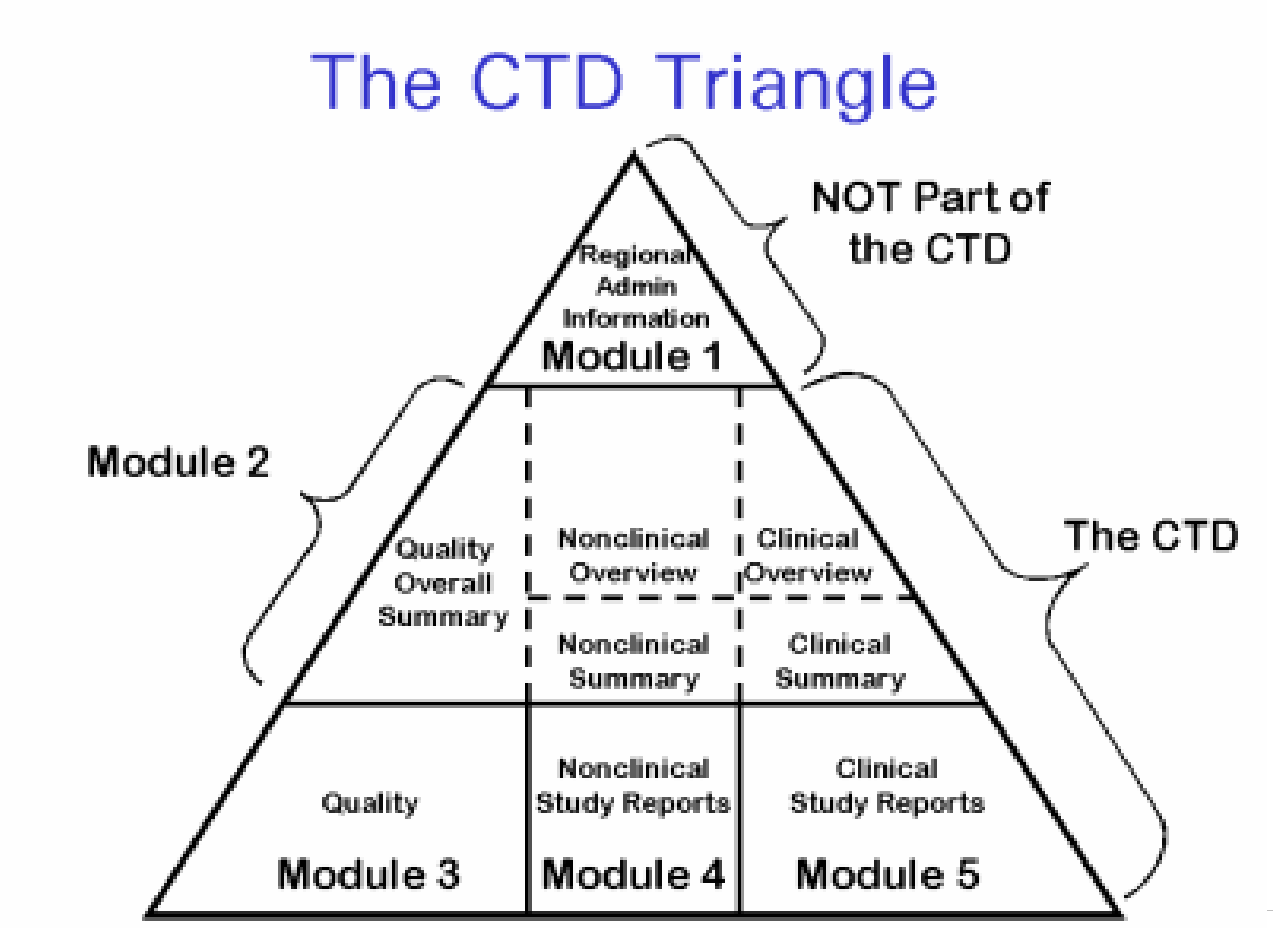
© 2016 Frestedt Incorporated.

IND Submission Flowchart



© 2016 Frestedt Incorporated.

CTD Format



Frestedt incorporated

IND Failures are Cited in Warning Letters

... to Principal Investigators

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)

© 2016 Frestedt Incorporated.

Warning Letters

History and Purpose

© 2016 Frestedt Incorporated.

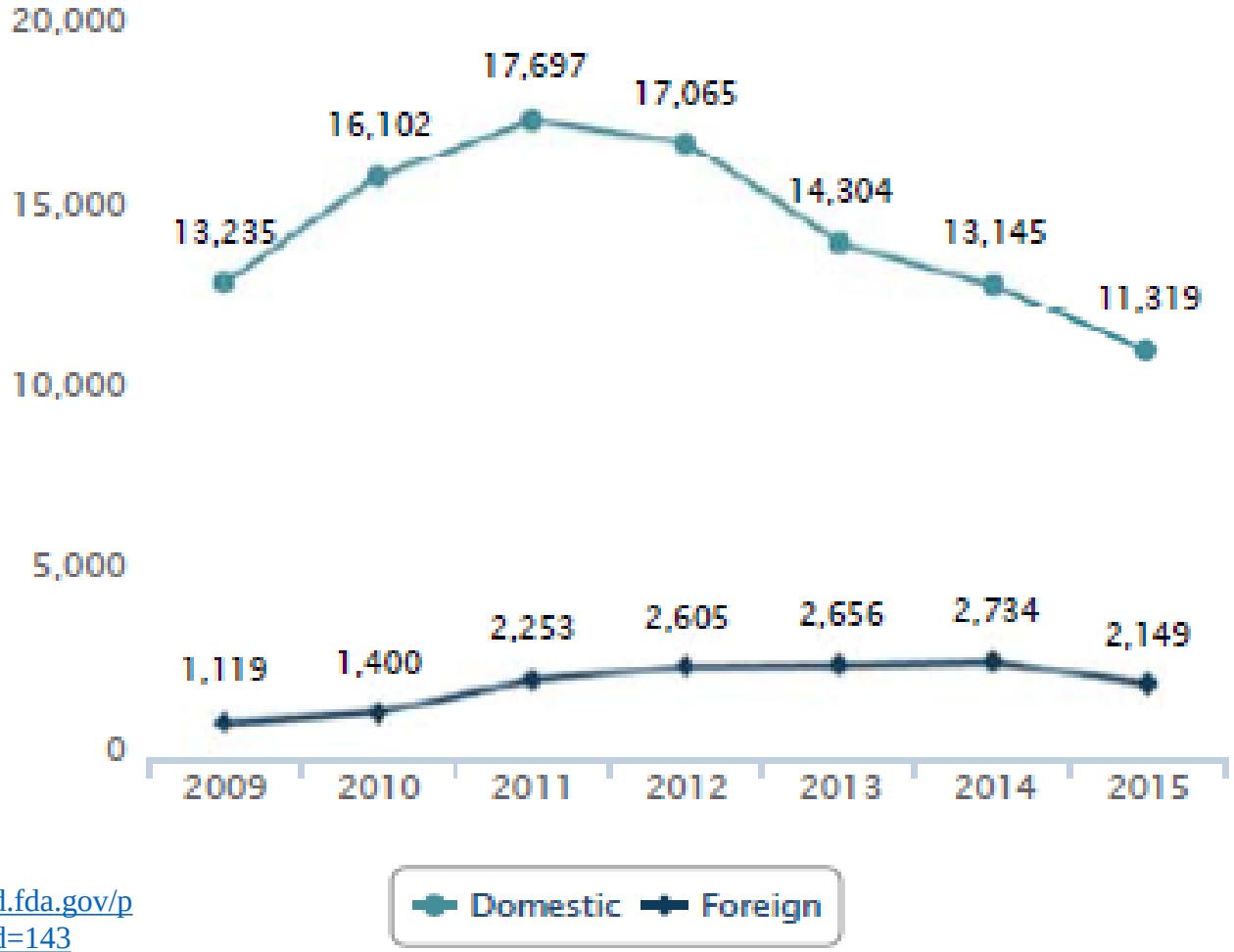
Overview of FDA Inspections

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]

© 2016 Frestedt Incorporated.

2009-2015 Inspections



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

© 2016 Frestedt Incorporated.

Frestedt incorporated

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

© 2016 Frestedt Incorporated.

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

© 2016 Frestedt Incorporated.

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

© 2016 Frestedt Incorporated.

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...

© 2016 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

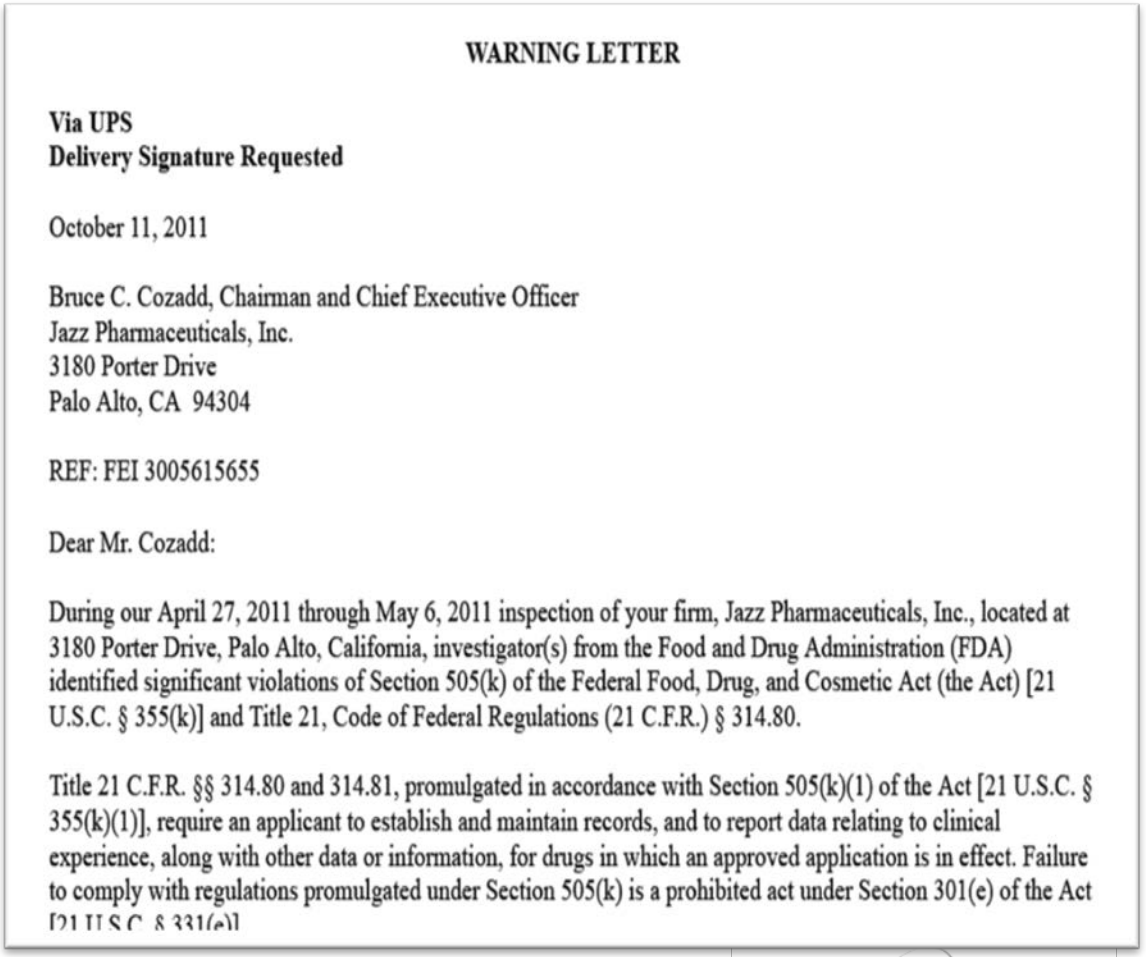
Clinical Trial Personnel

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

© 2016 Frestedt Incorporated.

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

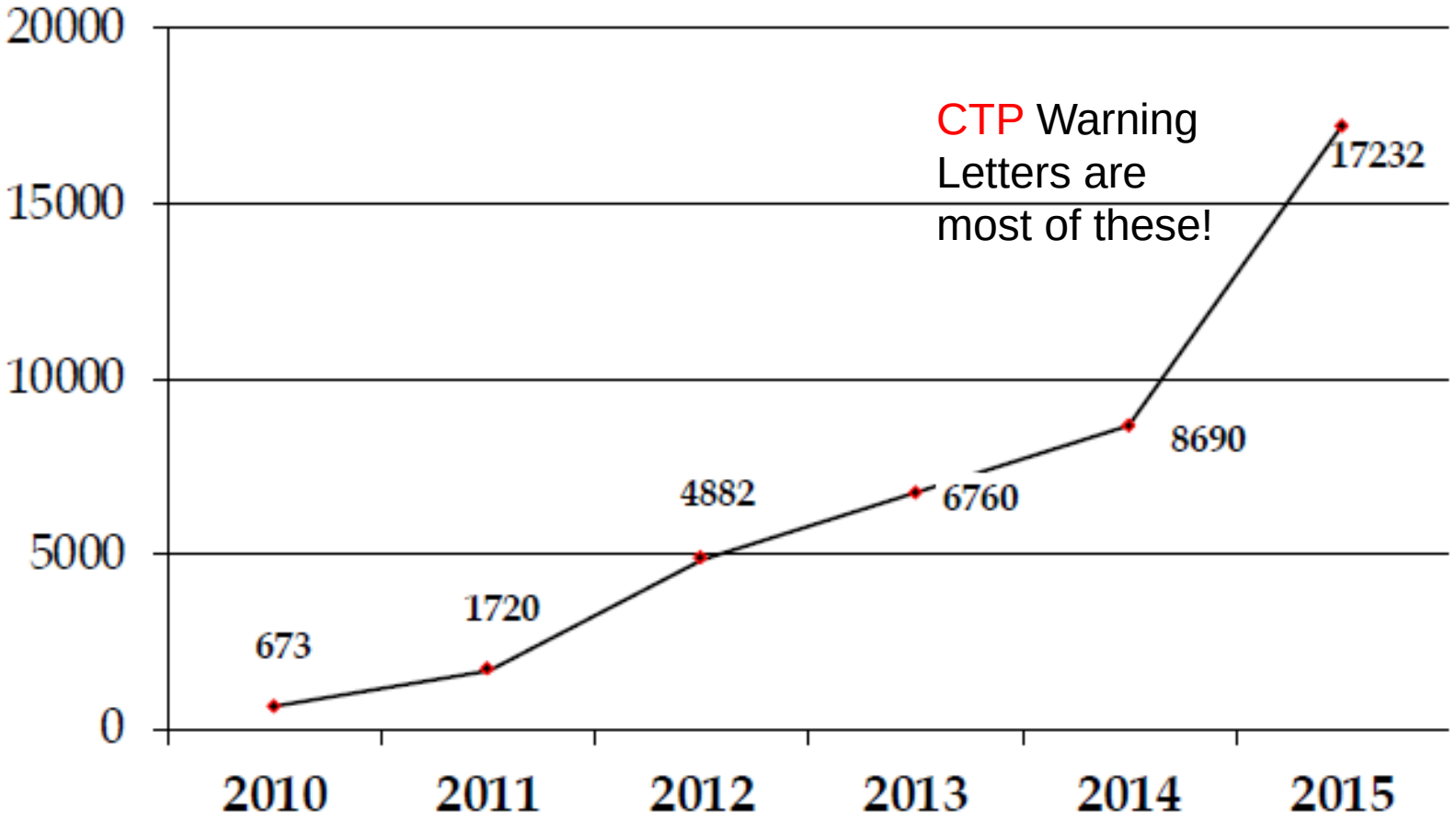
Dear Mr. Cozadd:

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)]

© 2016 Frestedt Incorporated.

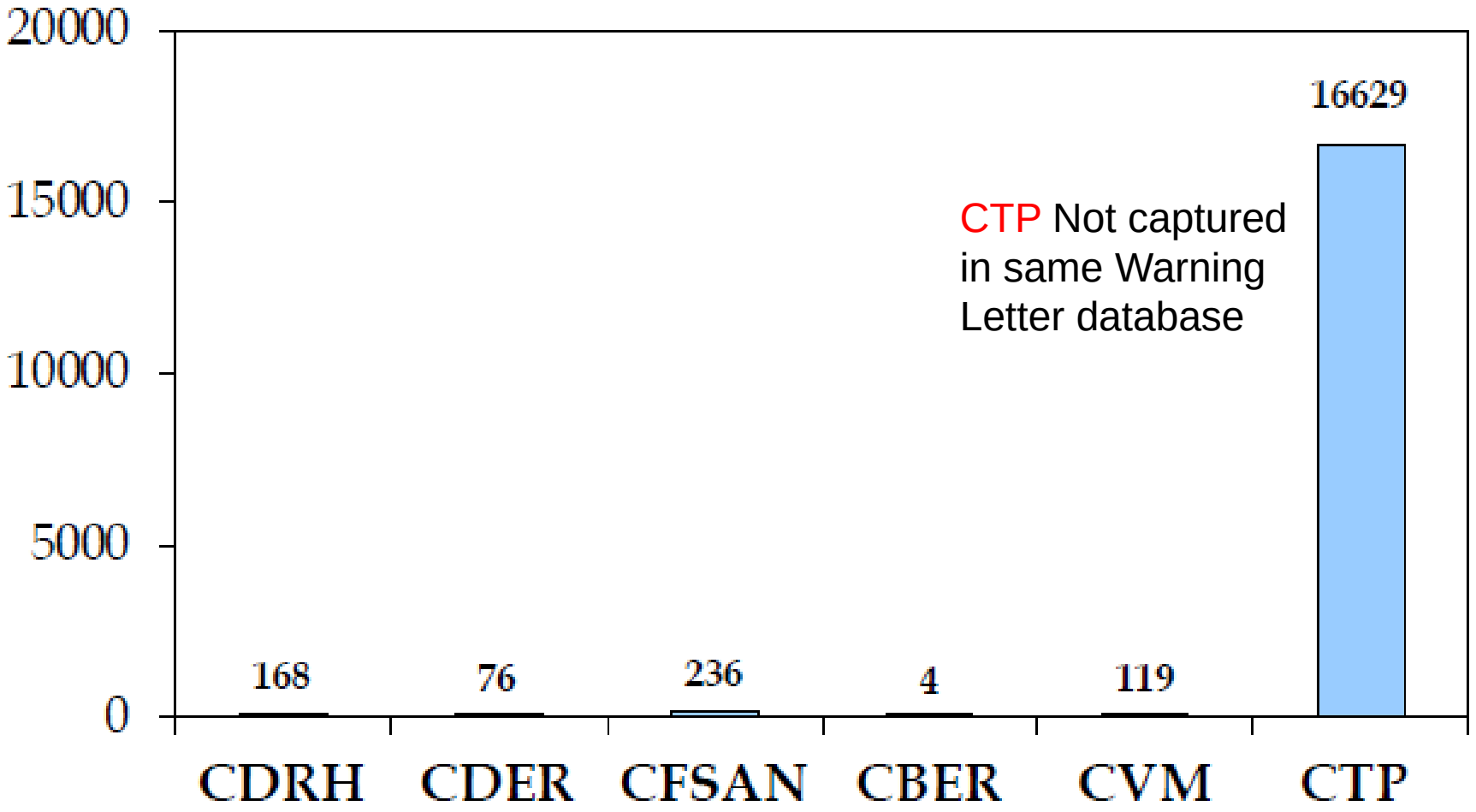
2010-2015 FDA Warning Letters Increasing



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

© 2016 Frestedt Incorporated.

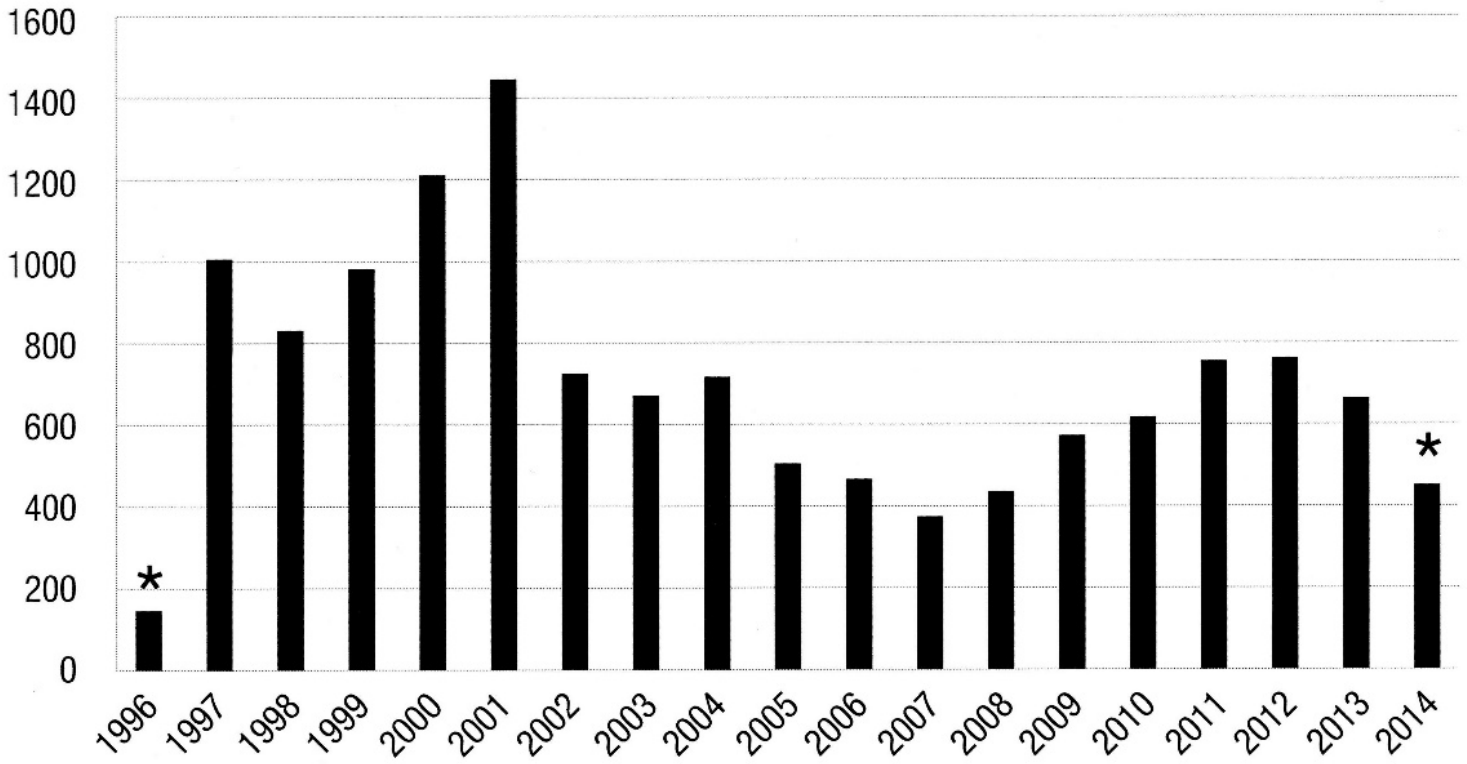
2015 Warning Letters by FDA Center



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

© 2016 Frestedt Incorporated.

Database Warning Letters Issued per Year

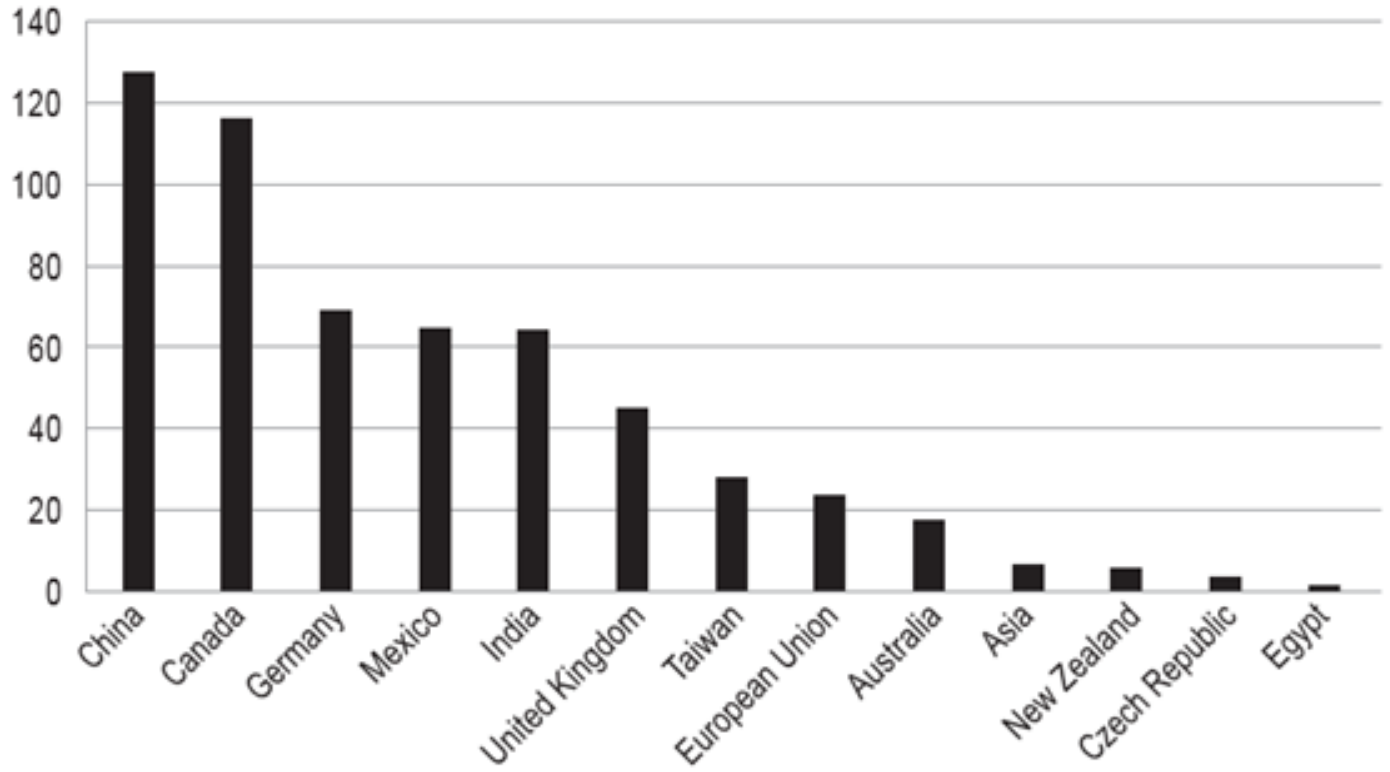


Warning Letters Issued by Year as of 9-30-14 (* = incomplete years)

© 2016 Frestedt Incorporated.

Frestedt incorporated

International Warning Letters Vary by Country

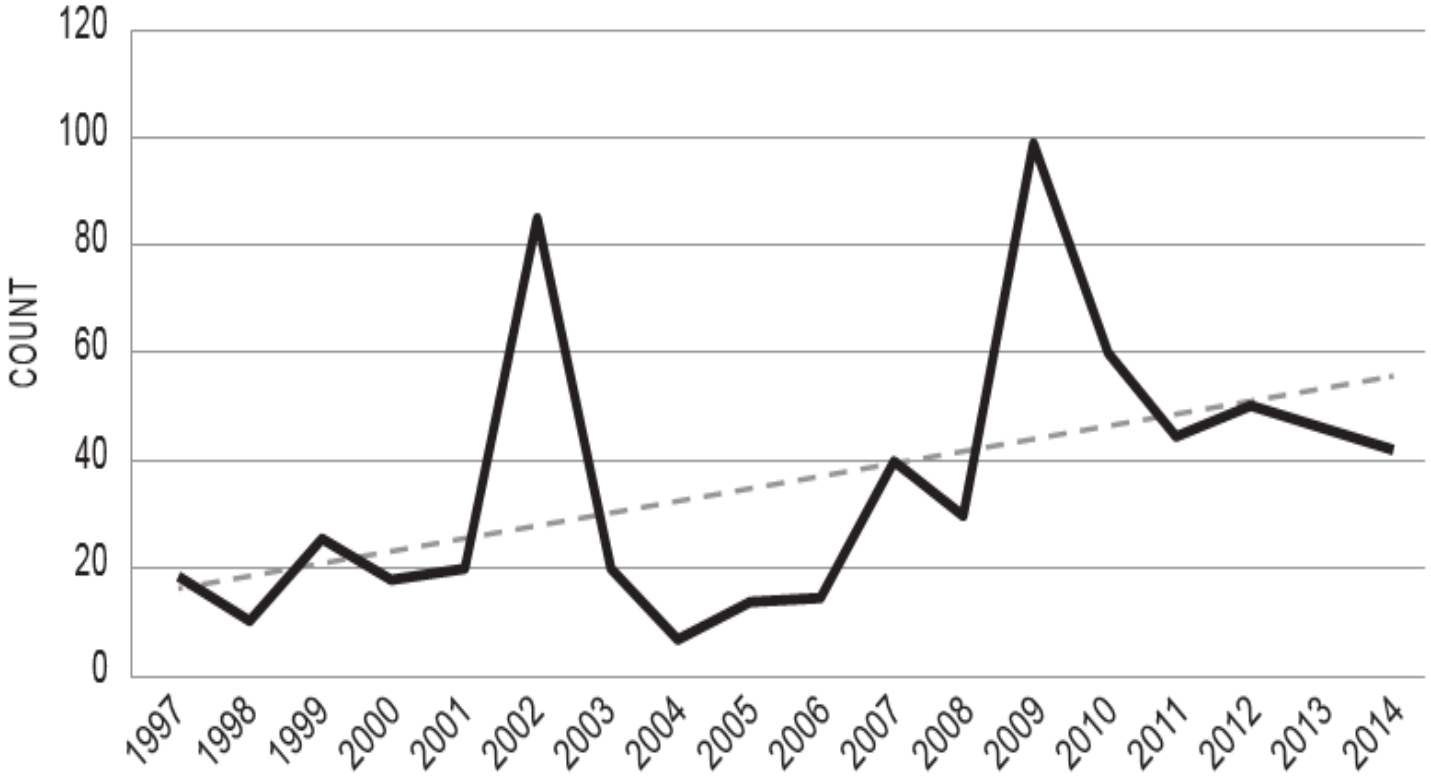


Number of Warning Letters sent to Various Countries as of June 21, 2015

© 2016 Frestedt Incorporated.

Frestedt incorporated

CDER Warning Letters Increasing

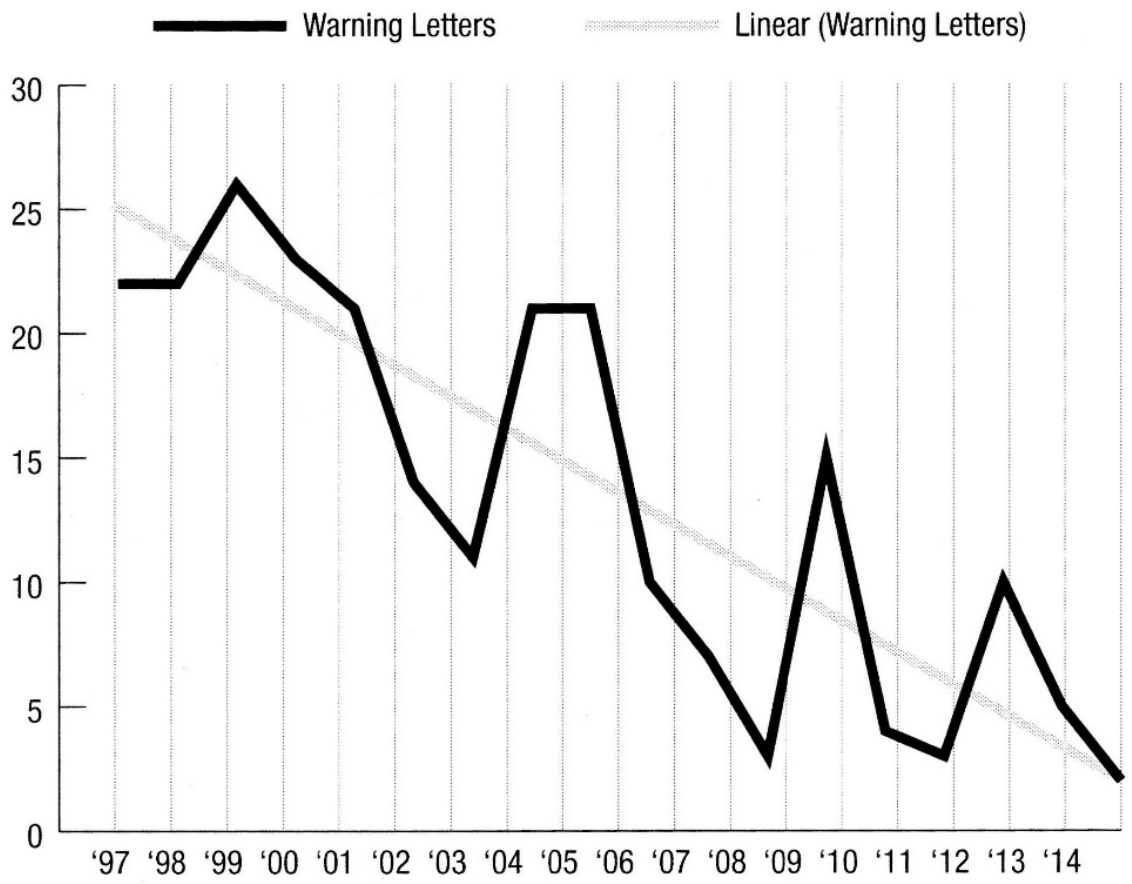


CDER Warning Letters Over Time (1997 – 2014)

© 2016 Frestedt Incorporated.

Frestedt incorporated

CBER Warning Letters Decreasing



Warning Letters from CBER are Declining

© 2016 Frestedt Incorporated.

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.

© 2016 Frestedt Incorporated.

Enforcement Actions

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

© 2016 Frestedt Incorporated.

Avoid the Warning Letter in the first place

Important things to do to avoid a Warning Letter:

- Use a robust quality management system (QMS)
- 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

© 2016 Frestedt Incorporated.

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

© 2016 Frestedt Incorporated.

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.

© 2016 Frestedt Incorporated.

Frestedt Inc.

What is our role?

© 2016 Frestedt Incorporated.

Clinical Research

Prepare

- Assess feasibility, review literature, and create budgets, protocols and essential documents

Initiate

- Train personnel, submit FDA & IRB documents, register trials and adhere to timelines

Conduct

- Monitor trials, manage site staff, collect data, analyze and report relevant information

Close Out

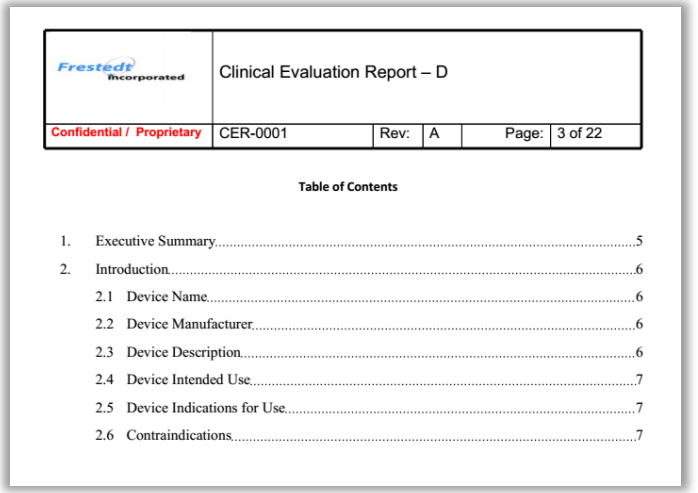
- Close site, compile documents and create comprehensive reports

© 2016 Frestedt Incorporated.

Case Study 1: Clinical Evaluation Report (CER)

Situation

Mid-sized medical device company required CER to remediate Notified Body findings



Frestedt incorporated | Clinical Evaluation Report – D

Confidential / Proprietary | CER-0001 | Rev: A | Page: 3 of 22

Table of Contents

Frestedt Approach

- Reviewed documentation and conducted systematic literature searches
- Integrated findings and trained in-house staff to create suitable reports and templates
- Managed client costs by allocating appropriate expert's resources for at each level of the CER development process

Results

CER completed and staff members trained. Notified Body cleared CER without further remediation. Working relationship established with Frestedt to conduct several other projects in client's clinical, quality and regulatory departments.

© 2016 Frestedt Incorporated.

Frestedt incorporated

Case Study 2: Risk Based Monitoring

Situation

The IRB determined a small company's clinical trial did not meet regulatory requirements

Frestedt Approach

- provided an appropriate risk-based monitoring plan
- Received IRB approval
- trained the study staff accordingly
- completed the risk-based monitoring and advised changes to the company's Quality Management System (plan, work instructions, forms)

Results

The clinical trial issues were resolved in a timely manner with good clinical practices (GCP) in place for future clinical endeavors.

© 2016 Frestedt Incorporated.

Case Study 3: Clinical Trial Management

Situation

A leading smoothie type beverage supplier wanted to make a claim about weight loss regarding their beverage. In order to make product claims, they required scientific substantiation.

Frestedt Approach

- Selected and trained company on appropriate claims
- Defined the trial design and developed the protocol
- Created informed consent, CRF, source documents
- Created database and statistical analysis plan
- Selected IRB, and submitted and tracked all documentation through IRB approval
- Generated a recruitment campaign and enrolled all study subjects
- Conducted the trial within Alimentix: The Minnesota Diet Research Center
- Wrote final study report and authored several abstracts and a manuscript for publication
- Won several awards for this work

Results

Frestedt Inc. designed the clinical trial with an intended goal for subjects to safely lose approximately 1 pound of excess weight per week. During the 12 week trial, study subjects (on average) lost the expected weight, stated they were not hungry and they felt satiated (which were measured attributes followed during the trial). At the request of the sponsor, an abstract for a poster presentation and manuscript were submitted. The poster was presented at a national clinical research conference, and was a finalist in the poster competition.

© 2016 Frestedt Incorporated.

Regulatory Affairs

Strategies

- Create comprehensive strategies to approach any regulatory body

Submissions

- Create documents, secure approvals and prepare reports

Negotiations

- Correspond with stakeholders using clear, transparent communication to ensure timely submissions to facilitate approvals and clearances

© 2016 Frestedt Incorporated.

Case Study 1: Regulatory Submissions

Situation

Start-up pharmaceutical company needed regulatory to bring a drug to market.

Frestedt Approach

- Formulated and negotiated generic drug regulatory strategy for 505(b)(2) submission
- Devised novel combination regulatory product plan to limit testing for kitted products
- Obtained data from competing companies manufacturing the same drug/device combination product
- Updated and trained in-house staff on quality system improvements, including new device testing requirements
- Marketed a new convenience kit

Results

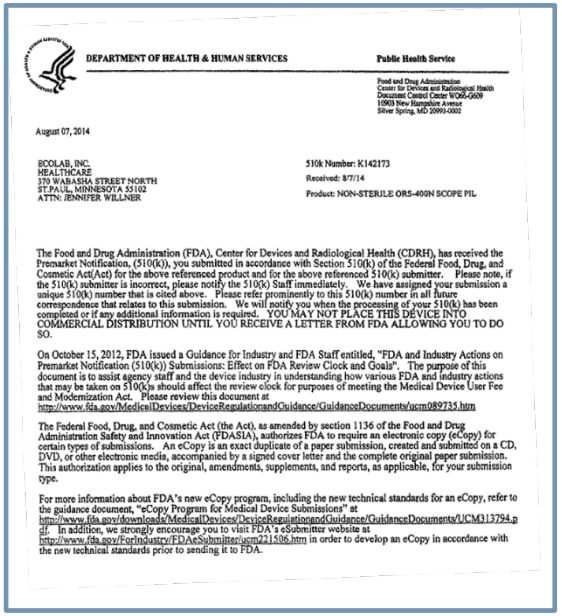
Frestedt provided both in-house and virtual regulatory support/strategy to successfully bring generic drug and convenience kits to market — one of the first product approvals for a combination drug/device manufactured by competing companies.

© 2016 Frestedt Incorporated.

Case Study 2: Two Special 510(k)s

Situation

Hospital supply company needed a non-sterile version of approved sterile devices, but lacked medical device experience.



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

August 07, 2014

ECOLAB, INC.
HEALTHCARE
370 WABASHA STREET NORTH
ST.PAUL, MINNESOTA 55102
ATTN: JENNIFER WILLNER

510k Number: K142173
Received: 8/7/14
Product: NON-STERILE ORS-400N SCOPE PIL

The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), has received the Premarket Notification, (510(k)), you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act(Act) for the above referenced product and for the above referenced 510(k) submitter. Please note, if the 510(k) submitter is incorrect, please notify the 510(k) Staff immediately. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in all future correspondence that relates to this submission. We will notify you when the processing of your 510(k) has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

On October 15, 2012, FDA issued a Guidance for Industry and FDA Staff entitled, "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals". The purpose of this document is to assist agency staff and the device industry in understanding how various FDA and industry actions that may be taken on 510(k)s should affect the review clock for purposes of meeting the Medical Device User Fee and Modernization Act. Please review this document at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089735.htm

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA), authorizes FDA to require an electronic copy (eCopy) for certain types of submissions. An eCopy is an exact duplicate of a paper submission, created and submitted on a CD, DVD, or other electronic media, accompanied by a signed cover letter and the complete original paper submission. This authorization applies to the original, amendments, supplements, and reports, as applicable, for your submission type.

For more information about FDA's new eCopy program, including the new technical standards for an eCopy, refer to the guidance document, "eCopy Program for Medical Device Submissions" at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf. In addition, we strongly encourage you to visit FDA's eSubmitter website at http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm221506.htm in order to develop an eCopy in accordance with the new technical standards prior to sending it to FDA.

Frestedt Approach

- Set regulatory strategy
- Worked with the company to update design records
- Created essential labeling
- Assisted with packaging changes and testing
- Avoided costly technical changes to device
- Performed risk analyses on changes made
- Recommended strategies to complete development and launch ahead of schedule

Results

Frestedt submitted special 510(k) to FDA ahead of deadline, and secured clearance (without questions) for highest priority products. Also, trained company's newly hired regulatory staff and device design teams to meet regulatory requirements.

© 2016 Frestedt Incorporated.

Case Study 3: International oversight

Situation

Large medical device firm needed assistance with world wide governmental approvals to introduce a new device to the market, support development of clinical evidence and risk documentation and to create world wide regulatory submission strategies and documents.

Frestedt Approach

- Integrate with team to execute regulatory strategy
- Worked with internal writing, engineering and international regulatory groups to train and develop CERs, risk management reports, manuals/IFUs, and regulatory submissions, etc.
- Training provided for required regulatory submission components to meet international standard and regulatory requirements (e.g., council directive 90/385/EEC and ISO 14971, MEDDEV 2.7.1, Rev 4 and others)

Results

Project is ongoing after over one year with multiple regulatory interactions. Training and development is impacting all departments associated with the project.

© 2016 Frestedt Incorporated.

Quality Systems

Develop and Provide Training

- Create/update quality manuals, SOPs, work instructions and forms
- Stay current with new/upcoming regulations and guidances and standards

Conduct Audits and Audit Support

- Identify, establish and schedule visit
- Complete audits and assess straining effectiveness
- Follow up until findings are resolved

Risk Management

- Assess plan and risk remediation efforts, identify gaps and recommend improvements

© 2016 Frestedt Incorporated.

Case Study 1: Quality Management System (QMS)

Situation

Client needed QMS oversight to support overall improvements and upcoming audits

Frestedt Approach

- Used combination on-site and virtual support methods
- On-site for all audits, team meetings and training sessions
- Completed pre-audit paperwork, preparations and identified potential audit findings
- Created an action plan
- Developed an improved QMS (document revisions compliant with regulations)
- Updated the approval process and conducted interactive trainings

Results

Frestedt Inc. developed the QMS to reflect current working practices to meet the regulatory requirements and customer needs. Frestedt team developed 2 quality manuals, 20 SOPs, 5 detailed work instructions and more than 30 templates, forms and checklists and conducted an internal audit as well as an external vendor audit for the client and facilitated more than 8 external client assessments / audits in a 6 month period.

© 2016 Frestedt Incorporated.

Case Study 2: Clinical Trial QMS

Situation

Start up active implantable medical device (AIMD) manufacturer needed development of a QMS to control conduct of an international clinical trial, managed through a CRO.

Frestedt Approach

- Created quality documents for CRO/vender management
- Created a quality system to support clinical manager role and responsibilities
- Trained clinical manager and senior management on QMS

Results

Client successfully launched clinical trial and re-hired Frestedt Inc. to modify QMS as they brought CRO functions in house.

© 2016 Frestedt Incorporated.

Case Study 3: Recall Quality System

Situation

Midsize class II device manufacturer needed risk management quality support and recall advise.

Frestedt Approach

- Updated SOP,WI and template for ISO 14971 compliant system
- Met with team and trained on implementation
- Continuing service as quality and regulatory service provider for issues like a class III recall for a device dysfunction

Results

Frestedt continues as the quality and regulatory support for this company. Company is fully operational with an active and successful updated RM program in place.

© 2016 Frestedt Incorporated.

Engineering Affairs

Develop and Provide Training

- Create Technical and Design History Files

Verify and Validate

- Test Method verifications and validations
- Process validations

Unique Device Identification

- Product marking
- Labeling requirements
- Assess plan and risk remediation efforts, identify gaps and recommend improvements

Project Management

- Organize planning activities
- Gantt chart development
- Team leadership and accountability

© 2016 Frestedt Incorporated.

Case Study 1: Unique Device Identification (UDI)

Situation

Medical device class II low risk manufacturer was updated labeling per UDI regulation and called on Frestedt Inc. to train and project manage the implementation.

Frestedt Approach

- Provided training in partnership with subject matter experts
- Created project plan and tracking efforts for cross function teams to meet the required deadline
- Engaged venders and supported vender management activities
- Selected needed equipment (e.g., bar code verification systems) to meet regulations set by accredited FDA issuing agencies

Results

Frestedt Inc. provided all necessary equipment, documentation and training to allow the client meet UDI regulations.

© 2016 Frestedt Incorporated.

Case Study 2: Test Method Validation

Situation

Client was a midst transferring manufacture sites from an out of state facility to Minnesota. During the transition period the clients customers asked for verification and validation activities to ensure the transfer resulted in quality products

Frestedt Approach

- Reviewed and updated manufacturing procedures during manufacturing transitions
- Reviewed the clients internal validation procedures to develop validation test methods which would assess the performance of the final product
- Reviewed associated production test methods
- Completed requested procedures and delivered documents ahead of schedule

Results

Frestedt Inc. delivered several test method validation protocols to the client using their development process to ensure continuation of their practices within their QMS. All documentation review and provided to the client was created in compliance with all parts of the clients internal QMS.

© 2016 Frestedt Incorporated.

Case Study 3: Labeling Support

Situation

One of the largest medical device companies in the world hired Frestedt Inc. to provide support for the development of documentation necessary for FDA submission. Engineering support provided to ensure technical aspects of IFU and labeling is ensured.

Frestedt Approach

- Reviewed 25+ documents (not including review cycles, i.e., revisions)
- Reviewed governing standards in conjunction with client provided specification documents
- Provided comments to ensure accuracy in regards to technical specifications

Results

Engineering support continues to ensure technical aspects are not overlooked as regulations are changing

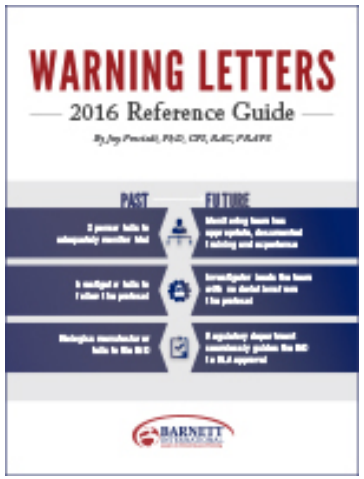
© 2016 Frestedt Incorporated.

How Does Frestedt Meet Client's Needs?

- Thousands of new products are brought to the marketplace every year
- Regulations, clinical requirements and quality solutions change frequently
- Corporate teams sometimes need a little help

Frestedt's experienced people negotiate this complex network to hasten the progress of your product towards its full potential

© 2016 Frestedt Incorporated.



Recent Books

Warning Letters: 2016 Reference Guide

FDA Warning Letters About Food Products:
How To Avoid Or Respond To Citations (pending)

© 2016 Frestedt Incorporated.

Warning Letters: 2016 Reference Guide

This unique guide begins with the framework of Warning Letters, laying out a course to learn from others' mistakes. Readers can expect guidance on understanding current trends in Warning Letters, avoiding Warning Letters, and responding to a Warning Letter if necessary.

This reference guide provides examples of key Warning Letters of pharmaceutical, drug, biologic, and device products.

"This book will be helpful to "managers, directors, younger CRC's, (and) other people for training operations." The book answers questions like "Who's getting WL and why – software, electronic capabilities, electronic systems validations (future trends)" and gives answers to "questions you can't answer." **- Director Clinical Affairs**

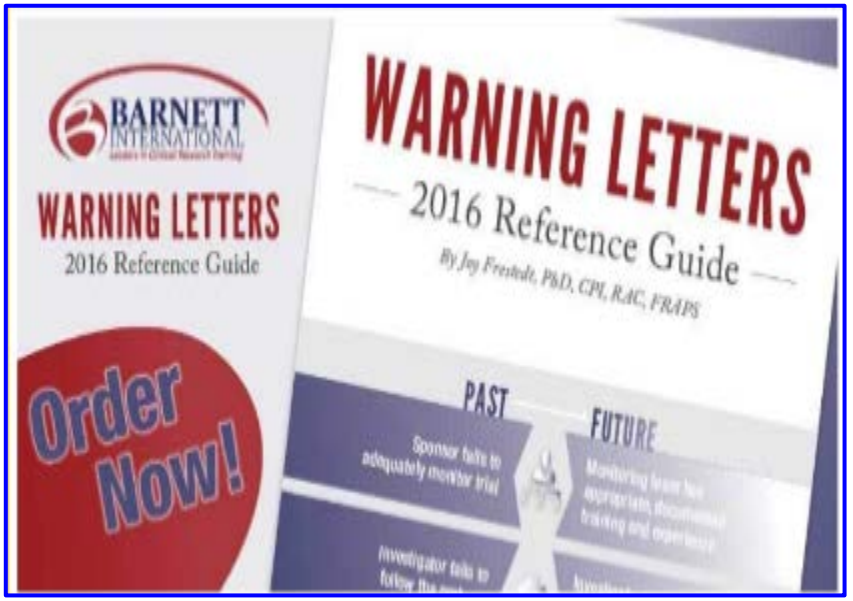
© 2016 Frestedt Incorporated.

Warning Letter: 2016 Table of Contents

1) History of Warning Letters

Warning Letters To ...

2) International Companies
3) Pharmaceutical Companies
4) Biologicals Companies
5) Combination Products Companies
6) Other Companies
7) Sponsors
8) Contract Research Organizations
9) Monitors
10) Investigators
11) Institutional Review Boards
12) Study Coordinators and Others



http://www.barnettinternational.com/Publications/Warning-Letters-Reference-Guide--2016-Edition/

13) Warning Letter Trends and Future Directions

© 2016 Frestedt Incorporated.

Food Warning Letters: Table of Contents

FDA Warning Letters About Food Products: How To Avoid Or Respond To Citations

1. History of FDA, Food Regulations and Warning Letters to Food Companies
2. Introduction to Quality Systems
3. HACCP
4. Imports/Exports
5. Food Contract Products
6. Clinical Trials for Foods and Dietary Supplements
7. Food Safety Modernization Act (FSMA) in 2016
8. Future Trends and Directions

© 2016 Frestedt Incorporated.

Thank You for attending!

Questions?

Dr. Joy Frestedt
Frestedt Incorporated
President and CEO
612-219-9982
jf@frestedt.com

952-426-1747
info@frestedt.com
www.frestedt.com

© 2016 Frestedt Incorporated.