



American Association  
of Bioanalysts

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## *What Type of Litigation Could I See for FDA Violations?*

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# Agenda

- Overview of FDA Enforcement Actions
- HCT/P Establishment Inspection and Enforcement Action Data
- FDA Guidelines and Enforcement (e.g. infectious disease tests)
- Errors and Risk Mitigation



# Overview of FDA Enforcement Actions



# Regulatory Authority

- FDA's authority to regulate HCT/Ps is under Section 361 of the Public Health Services Act (PHSA), not the Food, Drug and Cosmetic Act.
- The purpose of Section 361 is to prevent the introduction, transmission or spread of communicable disease.
- The FDA has the power to make and enforce regulations for this purpose.



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# COMPLIANCE ACTIONS



- FDA has a number of regulatory tools used to bring firms into compliance with the laws FDA administers.
- 3 types of actions:
  - *Advisory*
  - *Administrative*
  - *Judicial*

# ADVISORY ACTIONS



- Written communication to notify a firm that a product, practices or other activities are in violation of the law
  - *Untitled Letter*
  - *Warning Letter*

# ADVISORY ACTIONS

## Untitled Letters



- **Untitled Letter**: Violations that do not meet the threshold of regulatory significance for a Warning Letter; however, regulatory concerns exist.
- The letter does not include a statement that FDA will advise other federal agencies of the issuance of the letter.
- The letter does not include a warning statement that failure to take prompt correction may result in enforcement action.
- The letter does not evoke a mandated district follow-up.

# ADVISORY ACTIONS

## Warning Letters



- **Warning Letter**: Significant deviations in violation of the regulation, does not provide adequate protections against risks of communicable disease transmission; **or** the HCT/P is infected or contaminated, such that the conditions of manufacture do not provide adequate protections (i.e. risk of communicable disease transmission).
- Requires a written response to FDA within a given timeframe.
- Posted on the FDA website.
- Usually FDA's last attempt to get a company's attention before additional enforcement action.



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# ADMINISTRATIVE ACTIONS



Administrative actions are decided upon and taken by the agency, although they can be appealed to federal courts. These actions include:

- Product recalls.
- Debarment of individuals or companies who have been convicted of felonies.
- Withdrawals of product approvals.
- License revocations.
- Disqualification of clinical investigators.

# ADMINISTRATIVE ACTIONS

## Recalls



- Recalls are a method of removing or correcting products that are in violation of laws administered by FDA.
- Recall is a voluntary action that takes place because manufacturers and distributors carry out their responsibility to protect the public health.
- In rare instances, where the manufacturer or importer fails to voluntarily recall a product, FDA may issue a recall order.

# JUDICIAL ACTIONS



Judicial actions are decided upon and taken by federal courts, at the request of the Department of Justice and FDA.

- Seizure
- Injunction
- Prosecution

# JUDICIAL ACTIONS

## Seizure



- Attachment of goods through a court order by a U.S. Marshal pursuant to Section 304 of the FD&C Act.
- Action of choice when FDA wants to remove violative products (adulterated or misbranded products) from distribution channels.

# JUDICIAL ACTIONS

## Injunction



- A civil process initiated to stop or prevent a violation of the law and to correct the conditions that caused the violation to occur.
- When an injunction is granted, FDA has a continuing duty to monitor the injunction and to advise the court if the defendants fail to obey the terms of the decree.

# JUDICIAL ACTIONS

## Injunction



- To obtain an injunction, FDA must demonstrate:
  - Uncorrected deviations (prior warning).
  - Violative activities which present a health hazard.
  - A product or a component involved in its manufacture is shipped in interstate commerce.

# JUDICIAL ACTIONS

## Prosecution



- Institution of a criminal proceeding against an individual (U.S. Code 18, U.S. Code 21 [FD&C Act], U.S. Code 42 [PHS Act]).
- Prosecution recommendations should contain criminal charges that show:
  - Gross, flagrant or intentional violations, fraud or danger to health.
  - A continuous or repeated course of violative conduct.



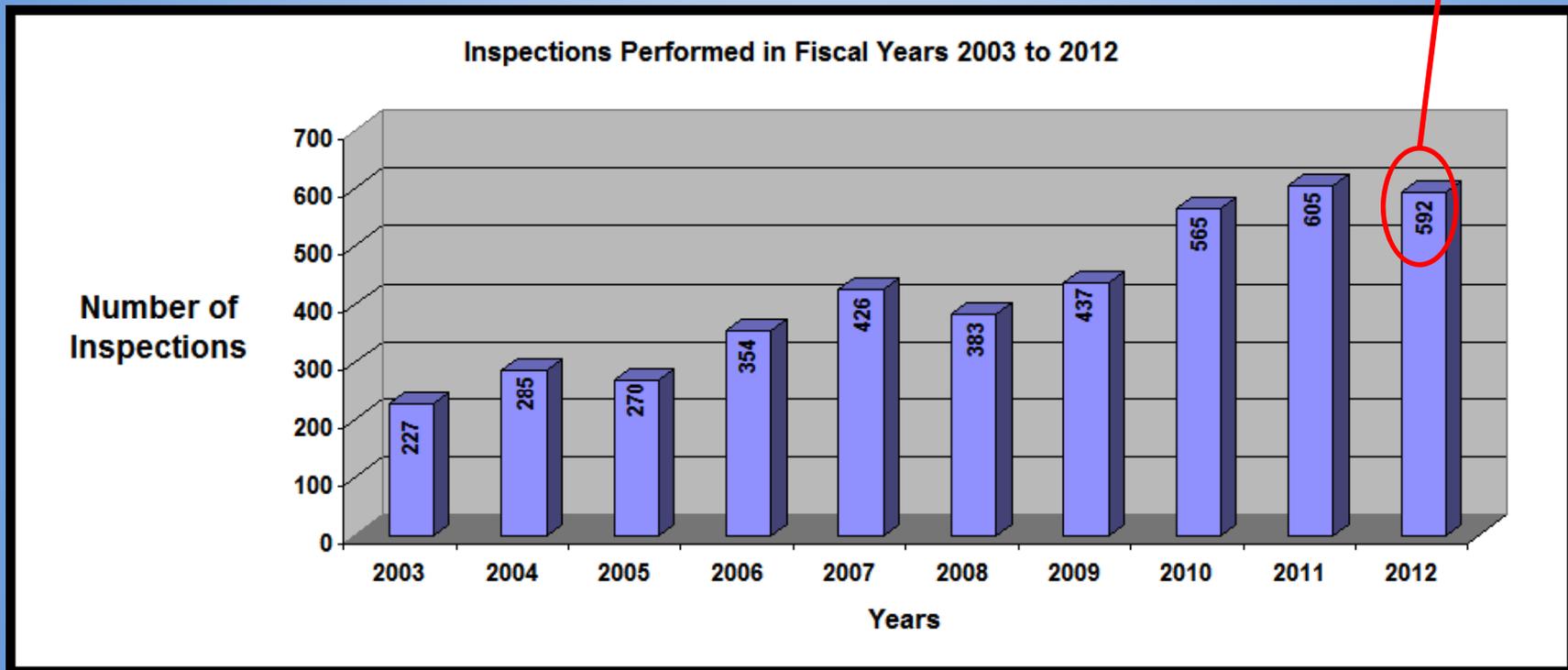
# HCT/P Establishment Inspection and Enforcement Action Data



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# HCT/P Inspections Performed



# FDA Form 483



- Lists observations made by the FDA representative(s) during the inspection of your facility.
- They are inspectional observations, and do not represent a final agency determination regarding compliance.
- Written response to FDA is not required – however it is recommended!!

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE

FORM FDA 483 (4/03) PREVIOUS EDITION OBSOLETE



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# Responding to an FDA 483

- **There is no regulatory requirement to respond to a 483.... So why respond?**
- Could possibly mitigate an FDA compliance decision for further action, e.g. untitled letter, Warning Letter.
- *“As a general rule, a Warning Letter should not be issued if the agency concludes that a firm’s corrective actions are adequate and that the violations that would have supported the letter have been corrected.”*



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# Inspection Classifications

- **NAI – No Action Indicated** – no objectionable conditions found (generally no FDA-483)
- **VAI – Voluntary Action Indicated** – Objectionable conditions found but do not meet the threshold for regulatory action
- **OAI – Official Action Indicated** – objectionable conditions found that warrant action

# FDA Enforcement Statistics

## HCT/P Inspection Conclusion

	2010	2011	2012
Inspections Classified NAI	414	494	432
Inspections Classified VAI	135	110	151
Inspections Classified OAI	12	13	15
Avg. hours per Inspection	41.7	39.9	39.4

# FDA Enforcement Statistics

## Fiscal Year 2012 (all of FDA)

Type of Action	Quantity
Seizures	8
Injunctions	17
Warning Letters	4,882
Recall Events	4,075
Recalled Products	9,469
Debarments	20

# Regulatory Actions HCT/Ps FY 2011

## – 3 Untitled Letters

- 1 Reproductive
- 2 Cell Therapy

## – 2 Warning Letters

- 2 Reproductive

## – 2 Order to Cease Manufacturing of HCT/Ps

- 1 Reproductive
- 1 Reproductive test laboratory



# Regulatory Actions HCT/Ps 2012/2013 (posted)

## – 5 Warning Letters

- 2 Reproductive
- 2 Cell Therapy
- 1 Tissue Bank

## – 3 Order to Cease Manufacturing of HCT/Ps

- 2 Reproductive
- 1 Tissue Bank



# JUDICIAL ACTIONS

## Injunction – Recent Examples



### **Order to Cease Manufacturing of HCT/Ps - New York Fertility Institute**

- March 1, 2013
- The agency has determined that because your Establishment is in violation of 21 CFR Part 1271, your Establishment does not provide adequate protections against the risks of communicable disease transmission through the use of these HCT/Ps. The agency has also determined that there are reasonable grounds to believe these violative HCT/Ps pose a danger to health, and, accordingly, this Order to Cease Manufacturing is effective immediately.

# JUDICIAL ACTIONS

## Injunction – Recent Examples



### **Order to Cease Manufacturing of HCT/Ps - Pacific Coast Tissue Bank**

- November 5, 2012
- Our review of the information and records examined and collected during the inspection revealed significant violations by Pacific Coast Tissue Bank. The agency has therefore determined that you do not provide adequate protections against the risks of communicable disease transmission, and accordingly, this Order to Cease Manufacturing is effective immediately. HCT/Ps subject to this Order will be recalled and destroyed within five (5) working days from the date of receipt of this Order.



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# JUDICIAL ACTIONS

## Injunction – Recent Examples



### Order to Cease Manufacturing of HCT/Ps - Center for Reproductive Medicine

- September 7, 2012
- Your firm performs donor screening, is responsible for donor testing and determines the eligibility of anonymous and directed donors of reproductive human cells, tissues and cellular and tissue-based products (HCT/Ps). The agency has issued an Order to Cease Manufacturing effective immediately. This Order to Cease Manufacturing relates to conduct occurring on or after May 25, 2005, the effective date of the applicable regulations and applies only to HCT/Ps from anonymous and directed donors.



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# FDA Guidelines and Enforcement

# Regulation vs. Guidance

- The Federal Food, Drug, and Cosmetic Act (FD&C Act) is a federal law enacted by Congress. It and other federal laws establish the legal framework within which FDA operates.
- FDA develops regulations based on the laws set forth in the FD&C Act or other laws under which FDA operates. This typically involves a process known as "notice and comment rulemaking" that allows for public input on a proposed regulation before FDA issues a final regulation.

# Regulation vs. Guidance

- Guidance represents the Food and Drug Administration's (FDA's) current thinking on a topic.
- FDA's guidance documents do not establish legally enforceable responsibilities. Guidance describes FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.
- **You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.**
- If you want to discuss an alternative approach, contact the appropriate FDA staff.

# Regulation vs. Guidance

**What are "relevant communicable disease agents or diseases (RCDADs)"?**

- There are two groups of relevant communicable disease agents and diseases. The first group consists of those communicable diseases and disease agents specifically listed in § 1271.3(r)(1). The second group consists of communicable diseases and disease agents described under § 1271.3(r)(2), that are not specifically listed in § 1271.3(r)(1).

# Regulation vs. Guidance

What are "relevant communicable disease agents or diseases (RCDADs)"?

- We intend to notify you through a guidance, if we determine that an infectious disease meets the definition of a relevant communicable disease under § 1271.3(r)(2). The guidance would include our comments or recommendations for donor screening and testing.
- Draft guidance documents for West Nile Virus and *Trypanosoma Cruzi* were never finalized. Although draft guidance reveals FDA's thinking, until it is approved they cannot be enforced.



# Errors and Risk Mitigation

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# Issue Awareness

- Once you become aware of an issue, it is important to document:
  - Identify the original source with which the issue became known.
  - Describe the issue as reported, and the root cause if known.
  - Describe the medical concern or problem that could result from the issue, based upon available information.

# Rating Risk



- Do all issues present the same risk? NO
- Need a process to analyze and rate risk.
- Example:
  - Summary of Records does not indicate that the Lab is CLIA certified, but the Lab is.
  - Summary of Records does not indicate that the LAB is CLIA certified, because they are not.

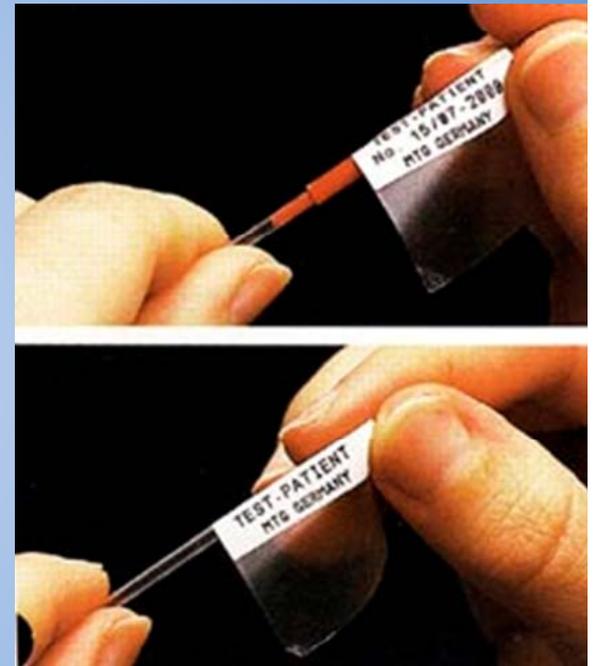
# Rating Risk



- Does the issue have a risk to health?
  - Missing an required infectious disease test
- Is the issue a violation of the laws administered by FDA:
  - Summary of records does not include a listing and interpretation of tests performed
- Is the issue in violation of client procedures and/or standard of care:
  - Inaccurate semen analysis – improper dilution

# Rating Risk

- The issue could effect more than one category:
  - Traceability – donor sample mislabeled with incorrect ID.
  - This is a violation of the regulation (1271.55) but is also a potential risk for disease transmission (positive directed donor improperly implanted due to mix-up)



# Rating Risk



- Mitigating factors or other conditions that are relevant to the issue.
  - Tissue not distributed (i.e. still within clinic control)
  - Donor ID mix-up, but both donors were determined eligible.
  - When did the event occur – e.g. use of a diagnostic test between May 25, 2005 and February 23, 2007 is addressed in an FDA guidance document.
  - Test was not performed on a particular cycle, but was performed and non-reactive on a subsequent cycle.

# Scoping the Problem

- Bounding is the process of determining when an issue started, when it stopped, and the identification of all tissue impacted.
- This often requires some investigation to determine the full extent of the problem.

For example, if an issue was caused by human error, it should not be assumed that the error only occurred once. If the error was a result of a procedure misinterpretation, it should not be assumed that the error is limited to one individual.



# Develop a Plan



- Need to develop a written plan to describe and document the activities associated with the issue.
- When developing a plan, there are three different aspects to consider:
  - How do I address the problem going forward?
  - How do I address the problem retrospectively?
  - How do I address affected HCT/P's still in storage?

# Developing a Plan



- HCT/Ps that are still in storage, should be quarantined (physical separation and/or quarantine labeling) and not implanted until risk mitigation is completed and a final disposition determined.
- Need to execute the plan promptly to minimize the magnitude of the issue. Once you become aware, it is your responsibility to act.

# Documentation

**All these activities need to be documented.**

The goal is to have a comprehensive story that explains:

- Explanation of the issue
- How the issue was identified
- The extent (bounding) of the issue
- Investigation and root cause
- Corrective action to prevent reoccurrence
- Disposition of HCT/Ps in storage
- Recipient notification



# Regulatory Reporting

## Do I need to notify the FDA?

- For **reproductive** HCT/Ps, **No.** For other tissue types, ***potentially if it meets certain criteria.***
- Because HCT/P deviation reporting requirements in 21 CFR 1271.350(b) do not apply to reproductive HCT/Ps, deviations of implanted/ distributed tissue identified through the risk mitigation plan do not have to be reported to FDA.
- If you determine there has been a case of disease transmission, ***Adverse Reaction Reports*** are not required for reproductive HCT/Ps either.

# Questions?



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