Compliance Overview and Compliance by Design [CbD] aka “Doing the Right Things at the Right Time”

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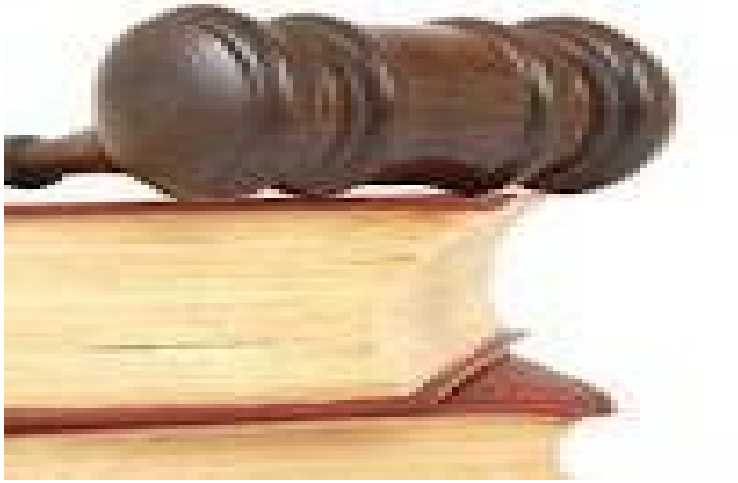
Dr. Raymond W. Brullo, DPM

Compliance Officer, FDA Los Angeles District Office, Irvine, CA

Doctor of Podiatric Medicine and Surgery

FDA's Office of Regulatory Affairs Enforcement Philosophy

Effect and sustain compliance

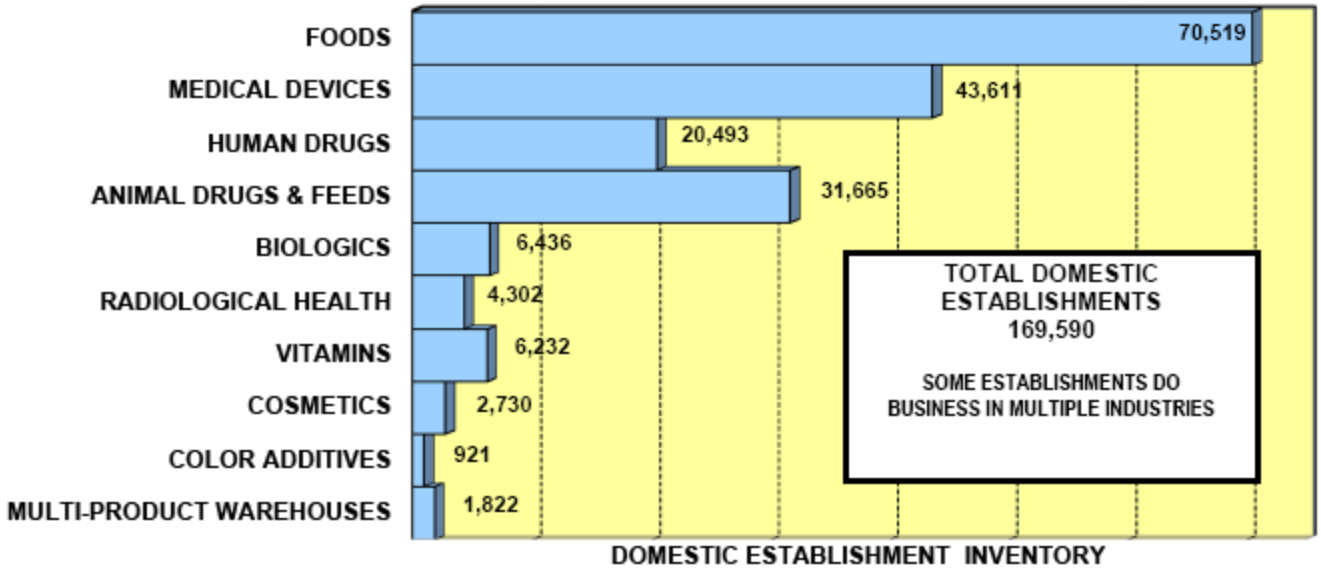


Today's Objectives

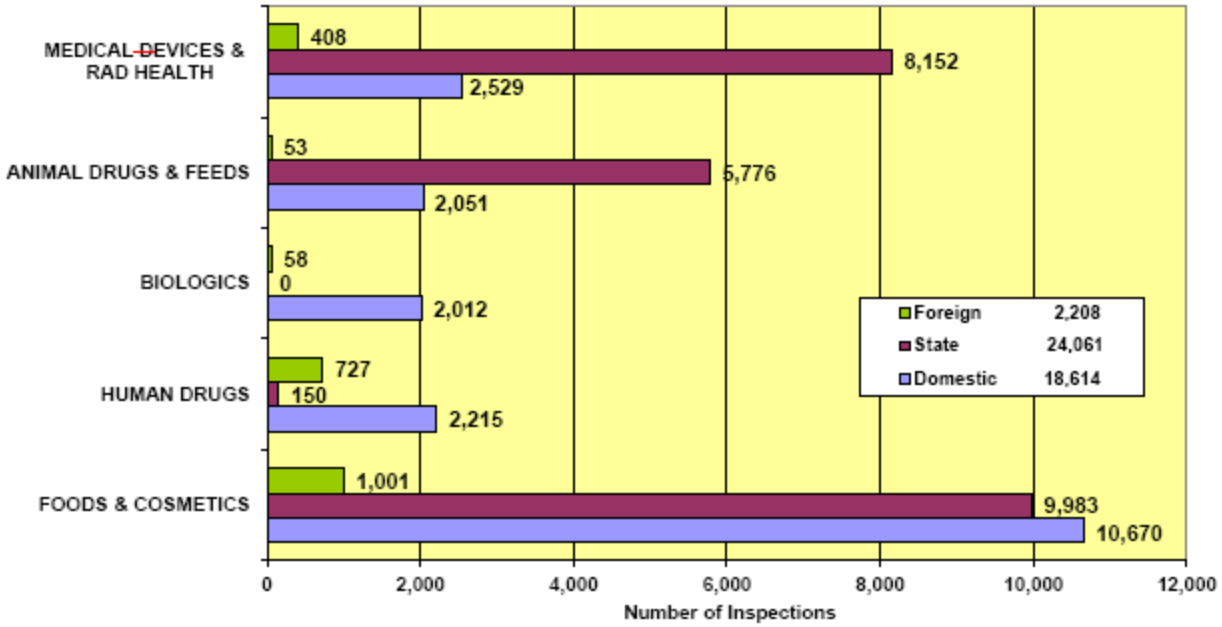
- Inform you of the **compliance and enforcement options available to FDA**
- Discuss **actual compliance and enforcement decisions** for a variety of regulatory actions
- Encourage and provide information for you to **effect and sustain compliance early** in the process [e.g. Compliance by Design]

DOMESTIC ESTABLISHMENT INVENTORY

(Establishments which are a recurring inspectional obligation)
By Product Category as of December 8, 2011



FY 2011 ESTABLISHMENT INSPECTIONS
(Foreign, State and Domestic) by Program Area

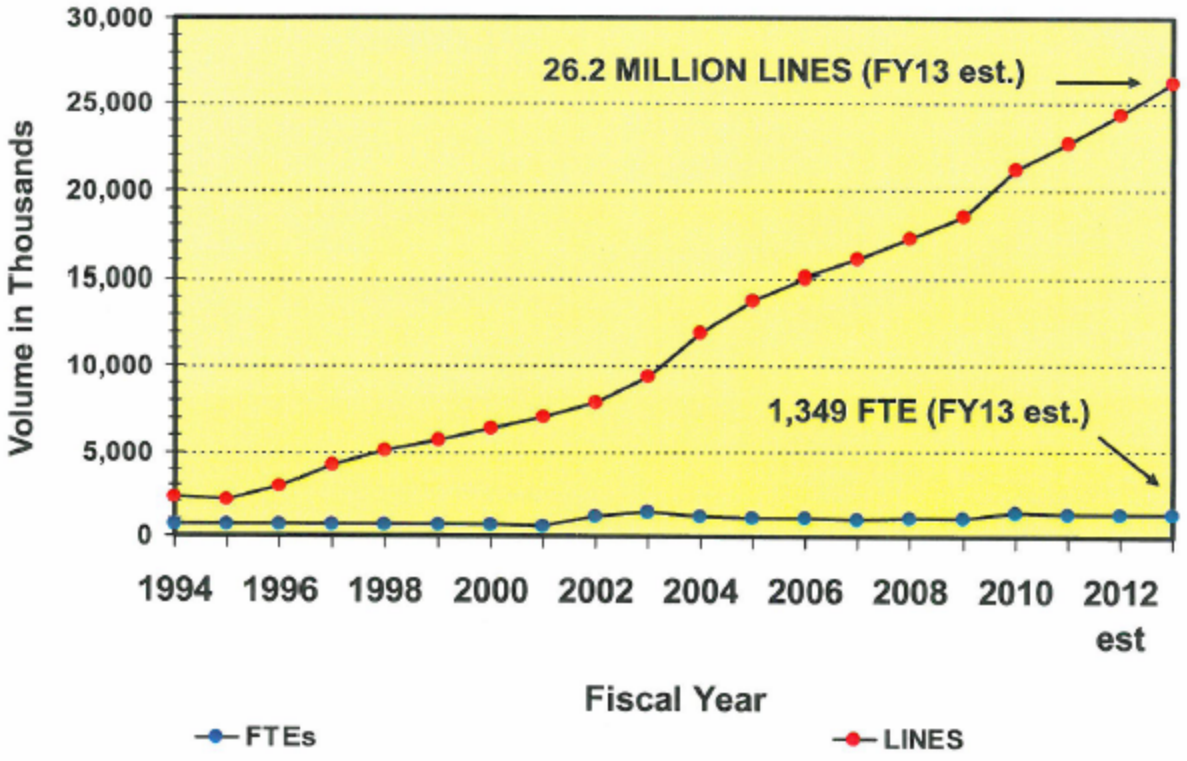


44,883 Foreign, State & Domestic Establishment Inspections*

*An establishment inspection may include one or more program inspection.
Inspections reported in FACTS as of 12/8/2011.

Import Volume History vs. Import FTE History

(FTE include staff conducting foreign inspections, import exams and related support)



Inspections - Resulting Work Products

- The **FDA-483…**
  - notifies top management in writing of significant objectionable conditions observed by our investigator.
  - is not intended to be an all-inclusive list of objectionable conditions
- The **EIR**
  - Accurate description of investigator's findings
  - Endorsed by supervisor with recommended action

Compliance Information – Recalls

- Definition: 21 Code of Federal Regulations, Section 7.3(g)
- **A firm's removal or correction** of a marketed product that the **Food and Drug Administration considers to be in violation of the laws** it administers and against which the agency would initiate legal action

Compliance Information – Recalls

- Classifications:
  - A **Class I** recall is a situation in which there is a **reasonable probability** that the use of or exposure to a violative product will cause **serious adverse health consequences or death**
  - A **Class II** recall is a situation in which use of or exposure to a violative product **may cause temporary or medically reversible adverse health consequences** or where the probability of serious adverse health consequences is remote.
  - A Class III recall is a situation in which use of or exposure to a violative product is **not likely to cause adverse health consequences.**

Compliance Information – Recalls

- Reasons for Recalls
  - Labeling
  - Stability
  - Sterility
  - Product Approval
  - Counterfeit
- Correlation to GMP compliance

Compliance Information – Other Sources

- Adverse Events
- Complaints
- Reports from other agencies (federal, state, foreign)
- Other Surveillance

Compliance & Enforcement Options

- No action
- Reliance on voluntary action
  - **Ability and willingness to: fully correct observations**, evaluate all systems and correct as appropriate, and prevent recurrence
  - **Significance of observations** listed on Form FDA-483 and public health impact
  - **Compliance history**

Compliance & Enforcement Options (cont.)

- When FDA Action is Indicated, What Actions Could FDA Pursue?
  - **Advisory**: Warning Letter, “Untitled” Letter, Meeting
  - **Administrative**: license suspension/revocation, detention, debarment/disqualification, civil money penalties
  - **Judicial**: seizure, injunction, prosecution

Compliance & Enforcement Decision Making (cont.)

How Are Compliance Decisions Made?

- **Assess the Violations**
- **Analyze** the Violations
- Consider the **Desired Outcome**
- **Optimize** the Compliance or Enforcement Decision
- Pursue the Decision with **Vigor**

Warning Letters

- A Warning Letter...
  - is the Agency's **principal means of achieving prompt, voluntary compliance**.
  - affords individuals and firms an **opportunity to take corrective action**
  - is issued only for violations of **regulatory significance**
  - is **not appropriate for** certain situations (e.g. intentional or flagrant violations, **immediate health hazard**, failure to heed previous warnings)

Warning Letter to Albert Browne Ltd., Leicester, UK [29-May-12]

- During an inspection of your firm ..., an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures chemical indicators for sterilization processes.
- These violations include, but are not limited to, the following:1. **Failure to establish and maintain adequate procedures for validating the device design**, as required by 21 CFR 820.30(g). For example, acceptance criteria were not established prior to the performance of validation activities.

What should you do if you get a WL?

- **Top Management** Must Engage
- **Act promptly**
- Recognize **this could be the start**, not the end, **of an enforcement action**.

Complete Response - D.R.U.M.

- Direct – face the problem head on
- Related – collect all associated information and review applicable systems
- Universal – look a the big picture of complete compliance with the CFR/Act
- Monitoring – follow up responses and on going assessments

Seizure

- Pursued to **remove violative products from the market.**
- “Prior notice” considered.
- Violations aren’t easily corrected
- **Other means of control aren’t viable**
- **Voluntary action not forthcoming** or reliable

Seizure of ultrasound gel at Pharmaceutical Innovations Inc., Newark, NJ [18-April-12]

- U.S. Marshals, acting at the request of the Food and Drug Administration, have seized Other-Sonic Generic Ultrasound Transmission Gel located at Pharmaceutical Innovations Inc. in Newark, N.J., after an FDA analysis found that **product samples contained dangerous bacteria.**
- The FDA received a report involving 16 surgical patients infected with ***Pseudomonas aeruginosa***. The patients had transesophageal ultrasound procedures, while undergoing heart valve replacement, using Other-Sonic Generic Ultrasound Transmission Gel.

Injunctions

- Pursued to **stop or prevent violation of the law, particularly when a health hazard** is present.
- “Prior notice” considered.
- **Significant out-of-compliance** situation, often involving chronic violative practices.
- **Other means aren’t viable**.
- In exigent circumstances, could pursue TRO

Michigan heart-lung bypass machine manufacturer enters into consent decree [22-Mar-11]

- The U.S. Food and Drug Administration today announced that Terumo Cardiovascular Systems Corporation (TCVS) of Ann Arbor, Mich., **and two of its officers**, Mark A. Sutter, president and chief executive officer, and Mark Lincoln, vice president of Quality Assurance and Operations, have **signed a consent decree of permanent injunction.**
- TCVS **also agreed to pay the federal government $35 million** in disgorgement of profits derived from past sales and additional disgorgement amounts should it fail to comply with the provisions of the consent decree in an effective and timely manner.

Other Regulatory Actions – Import Alert

- **Alert 89-08: Devices listed in the attachment for this alert have not been determined substantially equivalent or lack either a 510(k) or a Pre-Market Approval (PMA) for commercial distribution or, alternately, lack an Investigational Device Exemption (IDE).**

  Savec Health Systems
  Date Published : 09/16/2009

  120 Deramore Avenue , Northern Ireland , Belfast, UNITED KINGDOM

  Notes:Omnivir Device Possibly listed as oxygen generator 12/17/2008

Other Regulatory Actions – Order to Cease Manufacturing

- Sunrise Medical Laboratories, Inc.
- The agency has determined that because your Establishment is in violation of 21 CFR Part 1271, **you do not provide adequate protections against the risks of communicable disease transmission through the use of the HCT/Ps for which you perform testing for relevant communicable diseases.**
- 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.

Other Regulatory Actions - Prosecution

- U.S. **Department of Justice** Press Release
- ...a multi-count **indictment charging eight men** with participation in the unlawful distribution of the **controlled substance referred to in drug parlance as "bath salts**," as well as synthetic marijuana.
- ...the indictment was returned by the grand jury on April 4, 2012 but was **kept under seal to allow law enforcement agencies to arrest those indicted**, to execute eight search warrants simultaneously in multiple locations and to coordinate the **seizure of over $6 million dollars** of suspected drug-related funds in banks in Maryland and Texas.

Other Regulatory Actions – Civil Money Penalties

- FDA reaches $1 million settlement with **Pennsylvania medical device firm**
- This action is in response to FDA learning that the company had **marketed** its NuBone Osteoinductive Bone Graft product **without proper premarket approval or clearance**, as required by law.
- The settlement requires **Globus Medical to pay a $550,000 penalty and David C. Paul, the firm's CEO, to pay a $450,000 penalty**, for a total of $1 million.

Proposed Concept: Compliance by Design [CbD]

- **Disclaimer:**
- Compliance by Design used here is a concept only, loosely comparable to the concept of Quality by Design [QbD]. This proposed concept used here by Raymond Brullo does not imply any connection to products or services of any company or entity of similar or same name.
- Compliance by Design is terminology used by Raymond Brullo and of his opinion only and not of the Food and Drug Administration.

Quality

- Quality is often broadly defined as **suitability for the intended use**. For pharmaceuticals, quality is usually **related to the attributes** that allow a product to achieve its desired safety and efficacy, such as identity, strength, purity, and bioavailability.
- **Historically**, pharmaceutical manufacturers have used an **empirical approach** toward ensuring product quality that has sometimes been characterized as "**quality by testing**."

Summary of Quality by Design

- Quality by Design (QbD) calls for the use of modern **science- and risk-based approaches** to pharmaceutical development and manufacturing. Emphasis is placed on **understanding the factors that influence pharmaceutical quality** and how these may be monitored or controlled during the manufacturing process.
- The anticipated benefits of following a QbD approach include a **clear understanding of the potential causes of manufacturing variability and poor quality**, as well as the corresponding **controls to mitigate or eliminate threats to quality before they have an effect.**

What could happen if we viewed Compliance in a similar context?

- Compliance by Design (CbD) calls for the use of modern **regulatory science and risk-based approaches to compliance** with the Code of Federal Regulations [CFR] and the Food Drug and Cosmetic Act [the Act]. Emphasis is placed on **understanding the factors that influence compliance and how these may be monitored or controlled** during the pre/post inspectional and regulatory action process.

Benefit?

This approach allows compliance and regulatory affairs personnel to achieve a higher level of assurance of compliance with the regulations. With problems caught early, and completely, fewer FD483s are issued as well as fewer, and possibly, less significant regulatory actions such as enforcement.

Basic Principles

- Proactive not reactive [identify risks early];
  preventive not remedial
- Integrate compliance considerations into business models
- Compliance is the default, the starting point
- Visibility and transparency both internal and external
- Conduct internal assessments of compliance status
- Use consultants and attorneys but be aware that YOU/YOUR COMPANY is ultimately responsible

Scenario 1: Pre-Inspectional

- If never inspected, review marketed products for potential for FDA audit
- Be aware of the regulations for your product area [e.g. 21 Part 800 for devices]
- If inspected before, review prior EIR reports and FD483s for potential weaknesses/issues
- Device inspections are generally preannounced which should help in prep
- Understand your company's SOPs and policies

Scenario 2: Intra-inspectional

- Be available for consultation to other personnel at your firm
- Assist with providing information and documents to the investigator as needed
- Work with personnel to correct deficiencies as found during the inspection
- Be present at least at the close out and possibly the end-of-day summaries

Scenario 3: Post-Inspectional

- Assist in securing information and working on the FD483 response due within 15 working days
- Assist with follow up on items not fully completed in the initial response
- Assess inspectional history and possibility of regulatory action to be taken by the Agency
- Consider reaching out to Compliance Branch of the District Office [e.g. “pick up the phone”]
- Possible need for consultants and/or attorneys

Scenario 4: Advisory Action

- Collect information and assist in replying to the regulatory letter as warranted [e.g. within 15 or 30 working days]
- Maintain open, transparent line of communication with the District's Compliance Officer/Branch
- Focus on timely implementation of corrective actions and preparation for verification inspection
- Be aware of charges within the Food, Drug and Cosmetic Act [the Act]
- Consider requesting and attending any Regulatory Meeting at the District Office

Scenario 5: Enforcement Actions

- Understand the violations of the Act that can lead to enforcement [e.g. seizure, injunction, etc]
- Review prior Warning Letters, history of compliance to assess if seizure or injunction is a real possibility
- Under the Agency's policies [e.g. unapproved new drugs] to assess whether an enforcement action is a real possibility
- Be prompt and complete in working with the Compliance Officer/Branch to minimize the time and stress of a seizure or injunction
- Work closely and promptly with your consultants/attorneys

Summary

- Compliance with laws and regulations, the purpose of which is protection of public health, is a mutual objective and the end game.
- Invest in compliance.
- Communicate well, often, and early, with your local Compliance Officer/Branch as well as FDA's Centers' Offices of Compliance.

Quality and the Compliance Officer

- Dr. Raymond W. Brullo
  FDA – Los Angeles District Office
  19701 Fairchild
  Irvine, CA 92612

  949.608.2918
  raymond.brullo@fda.hhs.gov