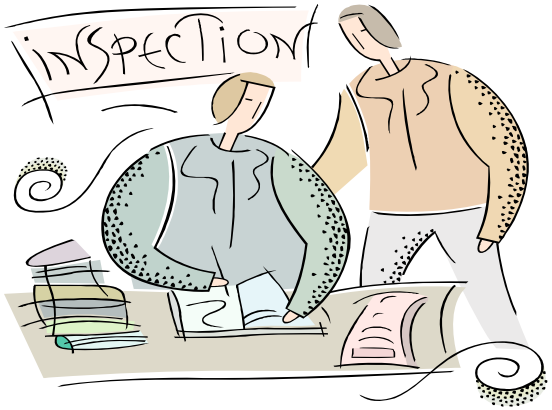
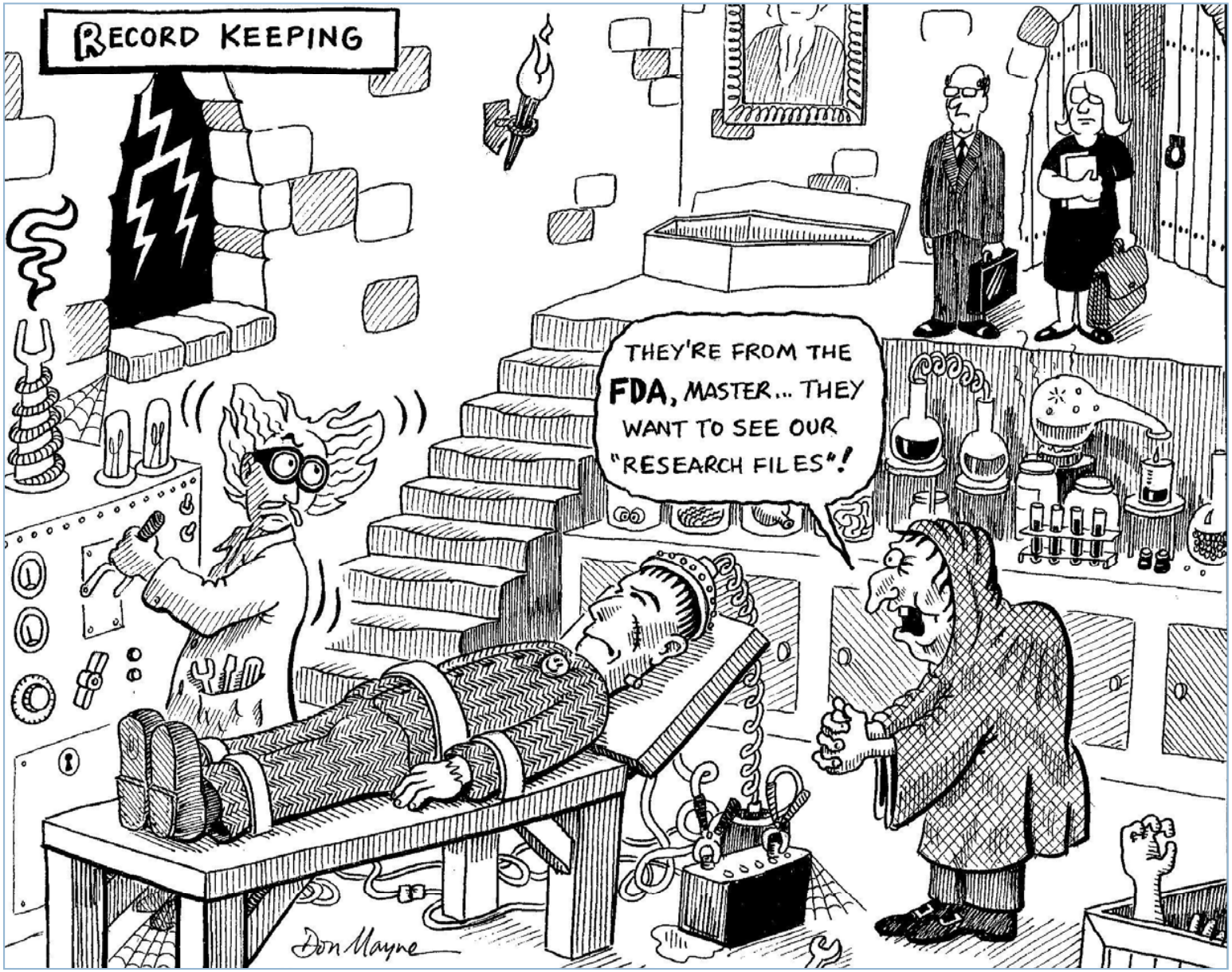
FDA Inspections: An Overview



Robert Lindblad, MD
The EMMES Corporation
August 11, 2011


RECORD KEEPING
THEY'RE FROM THE FDA, MASTER... THEY WANT TO SEE OUR "RESEARCH FILES"!
Don Mayne

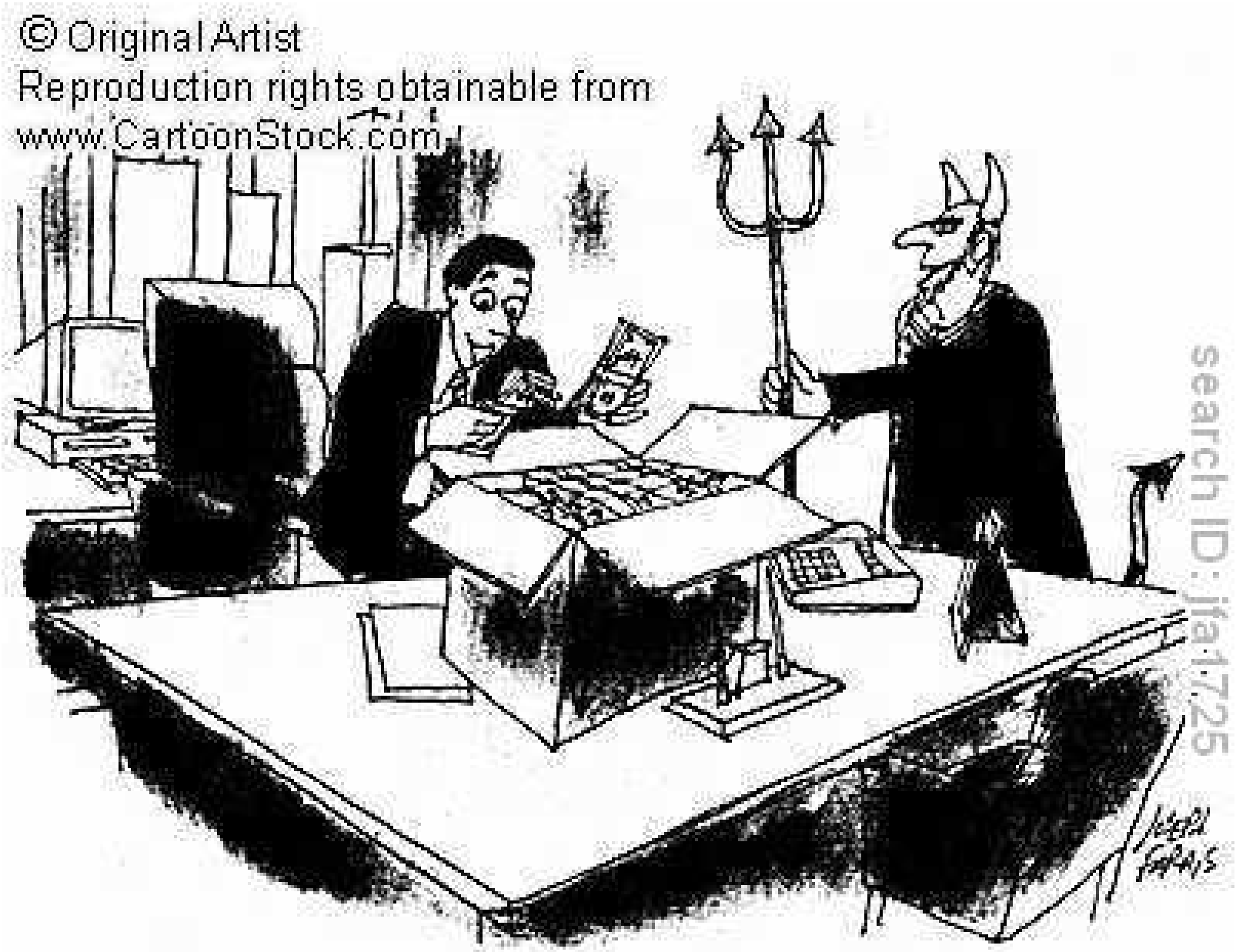
Why Inspections?

"Don't worry about doing the right thing. They'll be plenty of time for that when you're fired, retired, or reincarnated."

Why Inspections?

- To evaluate compliance with regulations
  - To establish that an entity exists
  - To establish there are written procedures
  - To establish the written procedures are followed

WHY NOT INSPECTIONS ?



"I don't want you to sell out because of the money.
I want you to sell out because it's the moral thing to do."

Categories of Inspections

- Routine = Surveillance
- For Cause = Directed

a) product complaint/problem reported by the PI or other entity
b) adverse events – too many or too few (as compared to other investigational sites)
c) patient complaint
d) sponsor reports concerns about investigator
e) too many research subjects enrolled (as compared to other investigational sites)
f) employee notification of "problems"

Types of FDA Inspections

- Compliance Audit – Unlicensed Product
  - 361 product
  - Manufacturer of devices (e.g. infectious disease test kits, Isolex)
  - Testing laboratory (e.g. donor screening, microbiological cultures)
  - licensed product
- Bioresearch Monitoring (BIMO)
  - Clinical trials – IND or IDE
- Biologics License Application (BLA) pre-licensure
  - review data used to support the application

7341.002 Compliance Program Objective

To assess whether all HCT/Ps intended for implantation, transplantation, infusion, or transfer are manufactured in accordance with the applicable provisions of 21 CFR Part 1271, to prevent the introduction, transmission, and spread of communicable disease

Compliance Program Manuals for Inspectors

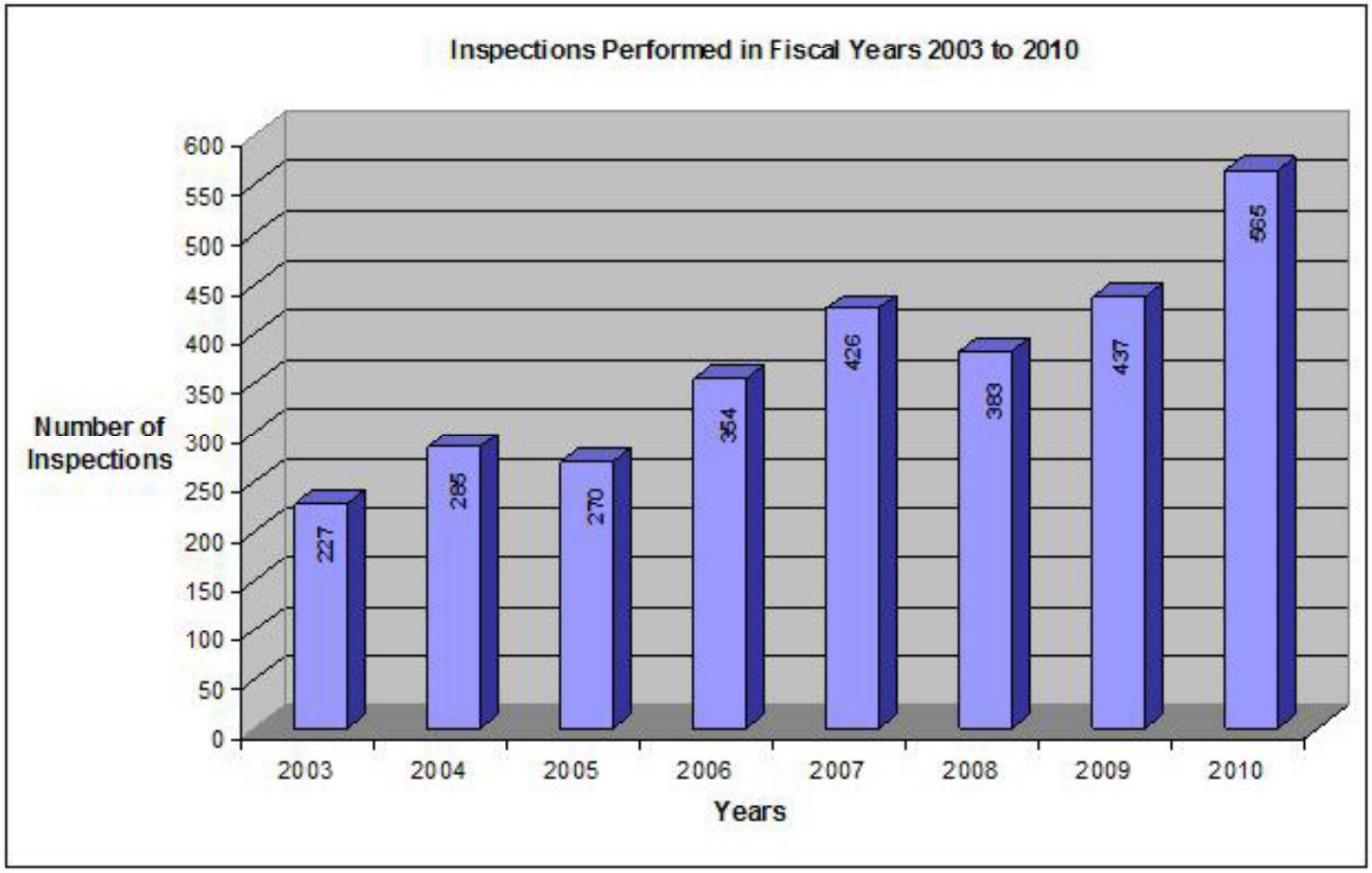
- 7341.002 – Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
(HCT/Ps recovered on or after to 5-25-05)

- 7341.002A – Inspection of Tissue Establishments
(HCT/Ps recovered prior to 5-25-05)

- 7345.848* – Inspection of biological drug products

**HCT/Ps that don't meet all the criteria will more than likely be inspected as biological drug products*

HCT/P Inspections Performed



FDA website 5/21/2011

Top 3 citations issued on 483s for HCT/Ps

(2 refer to donor eligibility)

- ✓ Procedures for all steps performed in the testing, screening and/or determining of donor eligibility of HCT/Ps were not established, maintained, defined, documented, implemented, followed, reviewed and/or revised. [21 CFR 1271.47(a)]

- ✓ Procedures appropriate to meet core CGTP requirements for all steps that you perform in the manufacture of HCT/Ps were not established, maintained, defined, documented, implemented, followed, reviewed and/or revised. [21 CFR 1271.180(a)]

- ✓ Donors were not screened by a review of relevant medical records for risk factors and/or clinical evidence of communicable disease agents and diseases. [21 CFR 1271.75(a)(1)]

Top 3 citations issued on 483s for drugs

(including biological drugs)

- ✓ The responsibilities and procedures applicable to the quality control unit are not in writing and/or fully followed. [21 CFR 211.22(d)]
- ✓ Written production and process control procedures are not followed in the execution of production and process control functions and/or documented at the time of performance. [21 CFR 211.100(b)]
- ✓ Control procedures are not established which monitor the output and/or validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. [21 CFR 211.110(a)]

What is BIMO?

Background

- Investigational New Drug (IND) Regulations went into effect in 1963

- FDA has exercised oversight of the conduct of clinical studies involving FDA regulated products

- The Bioresearch Monitoring (BIMO) Program was established in 1977 by a task force that included representatives from the drug, biologic, device, animal drug, and food areas

- Compliance programs (CP) were developed to provide uniform guidance and specific instructions for inspections of Clinical Investigators , Sponsors , Institutional Review Boards , and Non-Clinical Laboratories

Top 3 BIMO citations issued on 483s

(i.e. while product is still being investigated under protocol)

- ✓ An investigation was not conducted in accordance with the signed statement of investigator and/or investigational plan. [21 CFR 312.60]
- ✓ Failure to prepare or maintain adequate and/or accurate case histories with respect to observations and data pertinent to the investigation and/or informed consent. [21 CFR 312.62(b)]
- ✓ Investigational drug disposition records are not adequate with respect to dates, quantity and/or use by subjects. [21 CFR 312.62(a)]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