U.S. FOOD & DRUG ADMINISTRATION

Cell and Gene Therapy Products: Inspectional Experience

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Learning Objectives

- ❑ Describe cell and gene therapies
- ❑ Discuss associated manufacturing challenges
- ❑ Name types of facility inspections
- ❑ Summarize FDA approach to inspections
- ❑ Correlate product-specific risks to frequent inspectional observations

Overview: Cell Therapy Products

- A spectrum of products
- Autologous or allogeneic
- Targeted to subpopulations of patients or designated for a single patient
- Unique regulatory concerns

Overview: Gene Therapy Products

- Modifies a person's genes to treat or cure disease
- Work by several mechanisms:
  - ✓ Replacing a disease-causing gene
  - ✓ Inactivating a disease-causing gene
  - ✓ Introducing a new or modified gene

Challenges: Cell Therapy Manufacture

- ***Stability*** of source material and final product
- ***Logistics*** of scheduling, manufacturing, shipping, and timely QC testing
- ***Aseptic*** manufacture from start to finish

Challenges: Cell Therapy Manufacture

- For patient-specific therapies - ***each lot is unique*** – segregation, changeover and line clearance are critical
- Ensuring adequate source material and product ***consistency*** and ***characterization***

Challenges: Gene Therapy Manufacture

- ***Containment,*** segregation, changeover and line clearance are critical
- Disinfectant effectiveness and ***cleaning***

Applicable Requirements

- *Compliance with **Section 501(a)(2)(b) of the FD&C Act** (statutory GMP)*

- ***Title 21 Code of Federal Regulations - 21 CFR:***
  - 210s & 211s – Current Good Manufacturing Practice Regulations (CGMP) regulations for Finished Pharmaceuticals
  - 600-680 – Additional biological products regulations
  - 1271 – Human Cells, Tissues, and Cellular and Tissue-Based Products

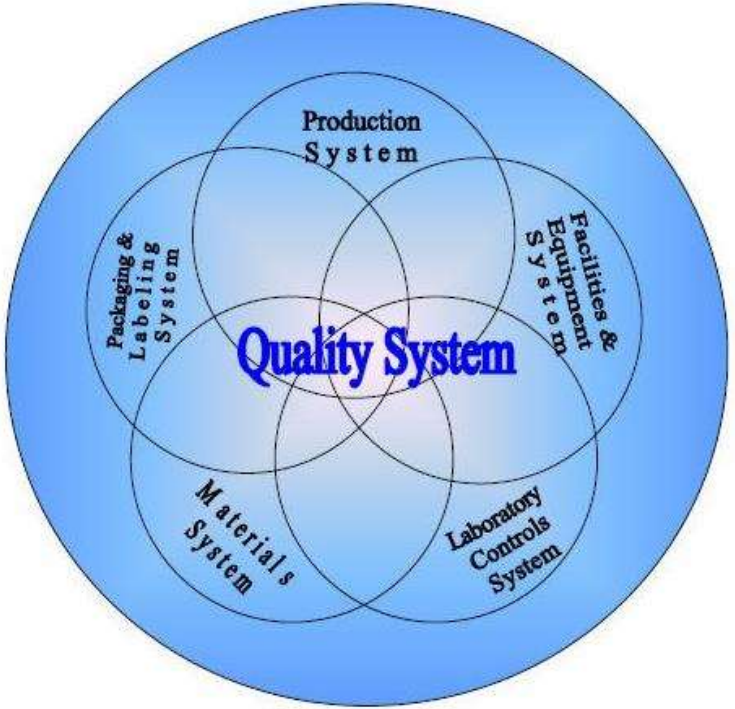
Types of Facility Inspections

- Pre-license inspections
- Pre-approval inspections
- Surveillance inspections
- For cause inspections

Systematic Approach to Inspections

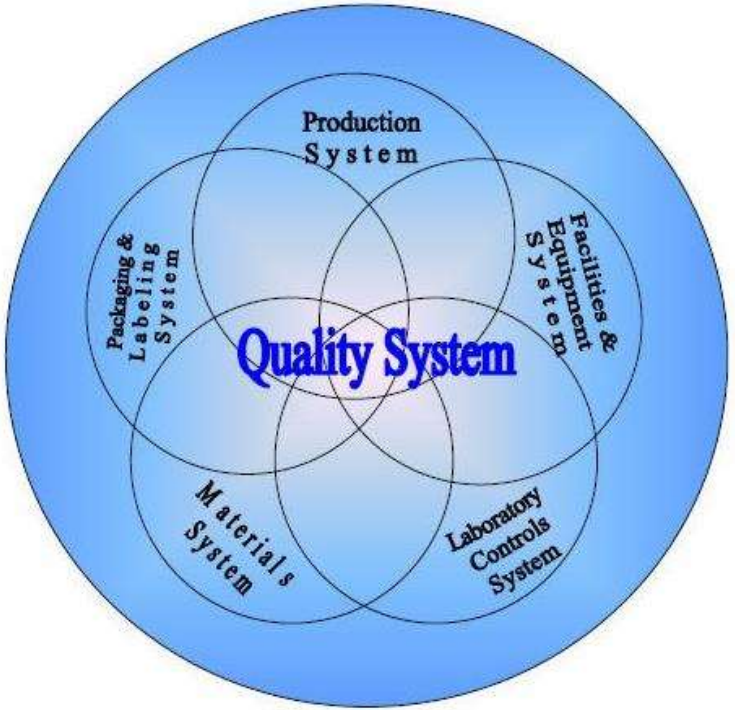
- ✓ Quality System
- ✓ Production System
- ✓ Facilities and Equipment System
- ✓ Materials System
- ✓ Laboratory Control System
- ✓ Packaging and Labeling System
- ✓ Donor Eligibility

Compliance Program Guidance Manual 7345.848



Systematic Approach to Inspections

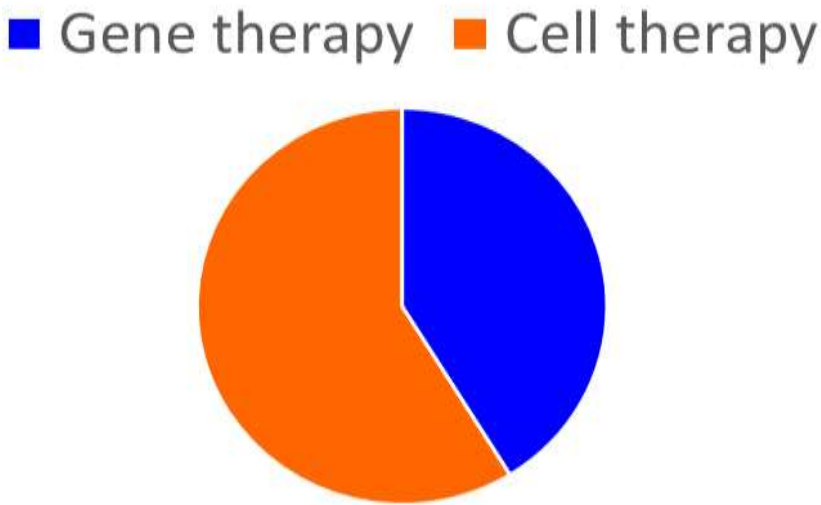
- ✓ Standard Operating Procedures
- ✓ Documentation
- ✓ Training



CGT Facility Inspectional Experience

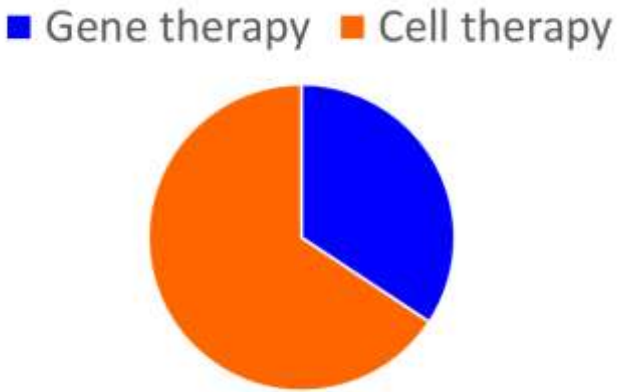
Facilities for CGT Inspected in 2007-2020

Facilities (*n=17)*



Inspections of CGT Facilities in 2007-2020

Inspections (*n*=35)



Systems Approach: Most Common FDA Form 483 Observations

Percent of inspections with observations, by system

	All (n=35)
Quality	89
Facilities/Equipment	66
Production	60
Materials	43
Laboratory Controls	34
Packaging/Labeling	20

Global Inspectional Issues

Standard Operating Procedures

- There are no written procedures for…
- Written procedures are incomplete/deficient.
- Written procedures for… are not followed.

Documentation

- Good documentation practices are not followed.
- GMP data are not adequately secured, maintained, and managed.

Reminder Regarding Form 483 Observations

"This document 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 your compliance.** If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above…."

Quality System Observations

Type of Observation	Frequency (n=35)
Deviations Management	51%
CAPA	40%
Training	31%
Document Control	29%
Oversight of Operations	26%
Change Control	23%
Product Adverse Events and Complaints Procedures	20%

- Deviations were not initiated.
- Investigations did not include a complete root cause analysis.
- Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product.

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Training	31%
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Change Control	23%
Product Adverse Events and Complaints Procedures	20%

Follow-up to investigation was:

- not implemented and/or
- documented or
- was inadequate to prevent recurring deviations.

Quality System Observations: CGT-Specific

Type of Observation	Frequency (n=35)
Deviations Management	51%
CAPA	40%
Training	31%
Document Control	29%
Oversight of Operations	26%
Change Control	23%
Product Adverse Events and Complaints Procedures	20%

- Timeline for closures of manufacturing non-conformances is not justified (e.g. procedures allow up to 45 days after the product is used to close sterility failure investigations).
- Aseptic technique training is inadequate.

Facilities and Equipment System Observations

Type of Observation	Frequency (n=35)
Environmental Monitoring	37%
Equipment Cleaning	31%
Equipment Qualification	23%
Facility Cleaning	14%
Calibration/Maintenance	14%
Disinfectant Effectiveness	11%
Alarms/Redundancy	11%
EMPQ	9%

- No dynamic active air monitoring (viable and non-viable) of ISO5 BSC or ISO7 areas.
- No surface viable sampling of ISO7 pass-throughs or ISO5 BSC post-operations.
- Sampling sites did not represent the sites where most critical operation took place.

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- Cleaning procedures were not specific enough to allow for consistent execution.
- Cleaning of product contact material transfer ports is not validated for removal of detergent.
- Disinfectant effectiveness study has not been performed or is deficient.

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Calibration/Maintenance	14%
Disinfectant Effectiveness	11%
Alarms/Redundancy	11%
EMPQ	9%

- Qualification of ISO5 BSC has not been performed or is deficient.

Production System Observations

Type of Observation	Frequency (n=35)
Batch Record	23%
Aseptic Process Validation	17%
Process Validation	17%
Retain Program	9%
Microbial Controls	6%
Stability Program	6%
Changeover/Line Clearance	3%
Reprocessing/Rework	3%

- The BR does not document the completion of each significant step.
- The BR does not document that all critical in-process parameters were met.

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- APV does not simulate all critical aseptic processes executed during the production.
- Growth promotion testing was not performed.

Production System Observations

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Process Validation	17%
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- The process performance qualification (PPQ) study was based on clinical batches made before the commercial process was defined in the commercial master batch record.
- Adequately validated in-process time limits for various steps are not established.

Materials System Observations

Type of Observation	Frequency (n=35)
Incoming Specification and Sampling	34%
Inventory Control and Storage	17%
Extractables/Leachables	9%

- Failure to reject any lot of components that did not meet the appropriate written specifications for identity, strength, quality, and purity.
- Suppliers' CoA for components used during production are not periodically verified through testing of incoming lots.

Materials System Observations

Type of Observation	Frequency (n=35)
Incoming Specification and Sampling	34%
Inventory Control and Storage	17%
Extractables/Leachables	9%

- Materials are not properly segregated.
- Receiving/incoming materials area is overflowing with received materials. Storage areas are not adequately labeled.

QC Laboratory System Observations

Type of Observation	Frequency (n=35)
Testing Methods	29%
Sample Storage and Tracking	9%
In-process and Release Specification/OOS Investigation	6%

- The suitability of all testing methods is not verified under actual conditions of use.
- No documented system is in place to track and manage the flow of the samples.

Packaging and Labeling System Observations

Type of Observation	Frequency (n=35)
Final Package Inspection	9%
Shipping	9%
Labeling and Tracking	6%

- Visual inspection parameters have not been fully defined.
- Visual inspection reject rate is not based on suitable statistical procedures.

Packaging and Labeling System Observations: CGT-Specific

Type of Observation	Frequency (n=35)
Final Package Inspection	9%
Shipping	9%
Labeling and Tracking	6%

- Reinspection of a batch that failed visual inspection could not be performed due to the temperature-sensitive nature of the product. No alternative strategy or remediation plan was developed.

Packaging and Labeling System Observations

Type of Observation	Frequency (n=35)
Final Package Inspection	9%
Shipping	9%
Labeling and Tracking	6%

- Shipping validation is inadequate in that no testing was performed to confirm the robustness of the shipping container, such as a drop test. The temperature during the shipment does not represent a worst-case temperature challenge.
- Shipper temperature and integrity are not verified upon receipt.

Packaging and Labeling System Observations

Type of Observation	Frequency (n=35)
Final Package Inspection	9%
Shipping	9%
Labeling and Tracking	6%

- The firm does not require secure access to label templates or excess printed labels that are dispositioned for destruction. Labels returned from production are stored in a fire rated cabinet that is unlocked.

Summary

- More observations noted for: Quality System, Facilities & Equipment, and Production System.
- Some differences might exist for PLI vs Surveillance and Gene vs Cell Therapy establishment inspections.
- Quality system inspectional observations are the most common, but generally not unique to CGT products.
- Special sterility considerations for CGT products reflect other frequent observations:

  APV, EM, BSC cleaning and qualification, aseptic technique, method validation (often sterility and endotoxin).

Challenge Question 1

Risks specific to cell therapy product manufacture ***exclude***:

A. Lack of lot-to-lot consistency

B. Introduction of adventitious agents

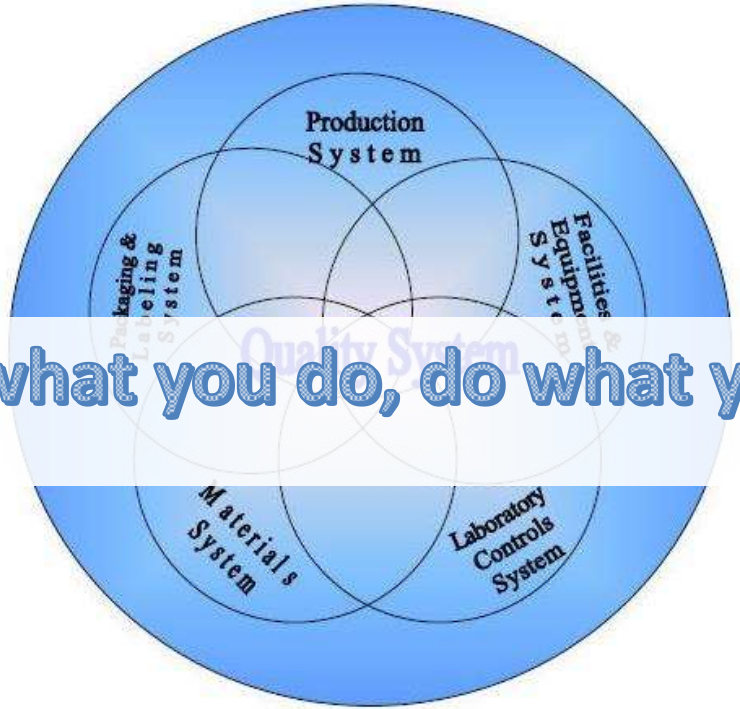
C. Drug product sterile filtration failure

D. Failure to maintain chain of custody and identity

Challenge Question 2

Key system that is evaluated on all facility inspections:

A. Donor Eligibility
B. Facilities and Equipment System
C. Laboratory Control System
D. Materials System
E. Packaging and Labeling System
F. Production System
G. Quality System



Document what you do, do what you document

Special Thanks

- Lily Koo – Reviewer, OCBQ/DMPQ/MRB2
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- Jay Eltermann – Director, OCBQ/DMPQ
- Mary Malarkey – Director, OCBQ

Resources

- Compliance Program Guidance Manual Chapter 45 Biological Drug Products, Inspection of Biological Drug Products (CBER) 7345.848
- FDA Guidance for Industry “Sterile Drug Products Produces by Aseptic Processing – Current Good Manufacturing Practice”, 2004

List of Abbreviations

- APV – aseptic process validation
- BR – batch record
- BSC – biosafety cabinet
- CAPA – corrective action and preventive action
- CGT – cell and gene therapy
- CoA – certificate of analysis
- GMP – good manufacturing practices
- ISO - International Organization for Standardization
- OOS - out of specification

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Questions?

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