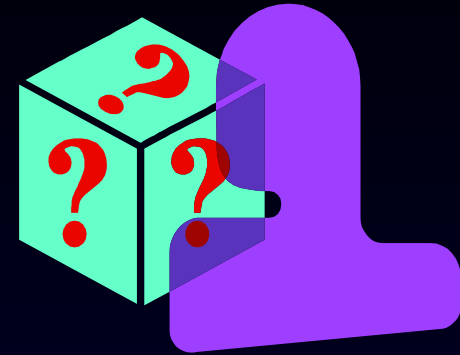


# Preparation for Facility Inspections and Audits

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# This session will provide answers to the following questions...



- Why are inspections/audits conducted?
  - Focus on TGA, FDA
- When will a regulator pay a visit?
- What are roles and responsibilities of the staff – senior management, QA, regulatory, manufacturing?
- What SOPs and other documents should be in place?
- How do I know I am prepared?

# And...

- What are the practical considerations for the day of the inspection?
- What is an inspector allowed to see?
- What information is not disclosed at the time of the inspection?
- What are lessons learned?



# Why are regulatory inspections conducted?



“The inspectional objective for biological products is to assure the products are safe, effective, and contain the quality and purity they purport to possess, and are properly labeled. The inspectional objective for HCT/Ps (human cells, tissues, and cellular and tissue-based products) is to assure that HCT/Ps are recovered, processed, stored, labeled, packaged and distributed, and the donors are screened and tested, in a way that prevents the introduction, transmission, or spread of communicable diseases. Facilities will be inspected for conformance with:

1. Provisions of the PHS Act and FD&C Act,
2. Applicable regulations in 21 CFR 210-211, 600-680, and 820.
3. HCT/P regulations in 21 CFR 1270 and 1271.
4. FDA Policies, which include guidance to the industry, and the Compliance Policy Guides Chapter 2.

# Facility Inspections can be stressful

## ■ What happens if you are not prepared?

- Key people are not available the day of inspection
- Practical aspects not in place: conference rooms, etc.
- Disruption of operations
- Employees not trained properly to respond to inspectors questions
- Can't find important documents
- Too much information revealed to the inspector putting organization at risk



# Facility Inspections can be stressful

## ■ Or worse.....

- Many observations (e.g. 483's)
- Warning letters
- Cease operations
- Loss of reputation



# When will they come?



- ✓ Licensed products : FDA Team Biologics schedules biennially
- ✓ Pre-approval (PAI) inspection: part of review of Biologics License Application (BLA) are scheduled
- ✓ Facility inspections for IND products: can happen, usually triggered through clinical protocol, notification through principal investigator
- ✓ FDA GTP inspections: typically unannounced, not routinely scheduled at this time
  - ◆ Jan 2007: # of inspections 354 out of total of 2000 (mostly tissue recovery, 36 hematopoietic)
  - ◆ Latest FDA Human Tissue Task Force report recommends biennial for high risk facilities, and triennial for all others

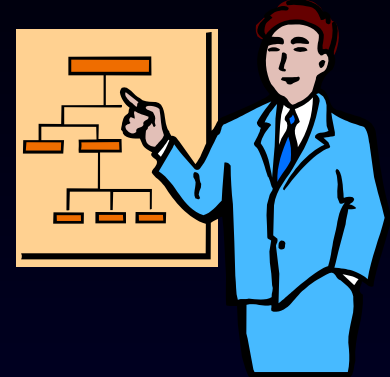
# First....make sure you are compliant with all pertinent regulations

- If accredited by AABB, FACT and other standard setting organizations, you should be reasonably prepared
- Assess quality systems periodically
  - ◆ Review current regulations/guidance docs
  - ◆ Good internal auditing helps
  - ◆ Periodic external audits useful
  - ◆ Fill gaps, improve systems



# Organizational involvement

- Senior Management
- Legal and Regulatory Affairs
- Quality Assurance
- Operations Management - “subject matter experts”
- All employees who may have interaction with inspectors require training



# Identify inspection coordinator



- Represents the company during inspection
- Understands government's inspection authority
- Answers questions in consistent manner, avoiding contradictions
- Possesses good knowledge of facility procedures, quality systems, corporate policies/procedures
- Possesses thorough knowledge of pertinent regulations
- Usually QA Manager, should have backup person(s)
- Previous experience with regulatory inspections a plus
- Stays with inspector at all times
- Interacts with key managers and other employees of various departments
- Documents all aspects of inspection or assigns scribe/runner

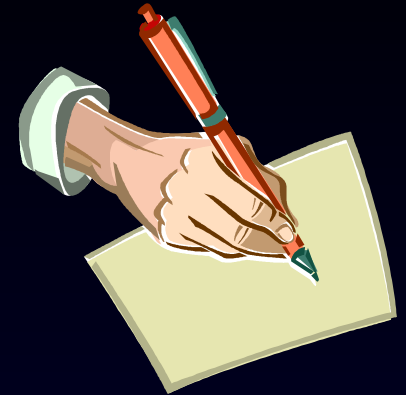
# Prepare documents



- ✓ List of key individuals to be notified
- ✓ Organizational overview and charts
- ✓ Facility description, including floor plans
- ✓ Summary of manufacturing process(es)
- ✓ SOPs/policies guiding inspection preparation

# Write SOP

- ✓ Notification
- ✓ Introductions, scheduling
- ✓ Organizational policies
- ✓ Employee behavior and responsibilities
- ✓ Inspection process
- ✓ Daily debriefings
- ✓ Exit interview
- ✓ Documentation and follow-up



# Practice

- A “Mock” inspection can help prepare and train the team for the real thing
  - Simulates the inspection process in your organization
  - Someone role plays as Inspector - either internal or external resource
  - If internal, should be someone with inspection experience
  - Important to have senior management support as preparation takes resources



# “Mock” inspections

- Use relevant regulatory guidelines as reference
  - e.g. FDA Compliance Program for Inspection of HCT/Ps
- Tests internal SOPs and documents
  - May need revising, updating
- Employee involvement important
  - How are logistics of notification handled?
  - How are questions answered?
  - Are documents retrievable?



# “Mock” inspections - lessons learned

- Summarize findings in a report
- Identify weaknesses, address shortcomings
- Develop and implement corrective plan
- Repeat periodically

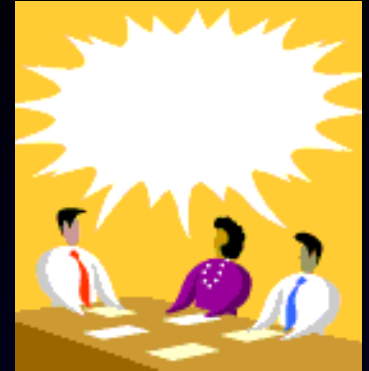


# Meet and greet



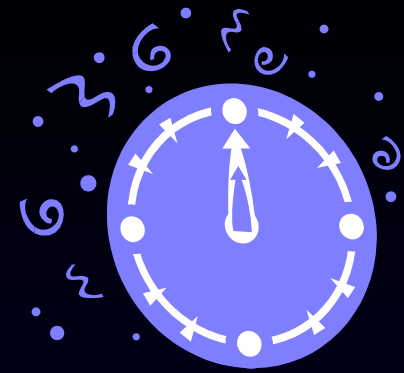
- ✓ Reception personnel need to be prepared in advance whom to contact (include backup personnel)
- ✓ Inspection coordinator greets and escorts inspector into appropriate conference room
- ✓ Request inspector credentials and record information
- ✓ Inspector should present document, e.g. FDA Form 482 “Notice of Inspection”

# Opening meeting



- Determine the purpose of the inspection
- Inform the inspector of organizational policies
  - Donor/recipient confidentiality
  - Company proprietary information
  - Operations - protocols in patient care areas, gowning and safety procedures
  - Taking of photographs - generally not allowed
  - Product samples - Many cell therapy products patient specific, contain protected health information (PHI)

# Schedule the day



- Immediately inform senior management and applicable staff that inspection is underway
- Inform the inspector of organizational policies
- Work out a schedule ensuring critical personnel are available
- Inspection coordinator should accompany the inspector at all times
- Assign additional staff to retrieve documents, scribe, etc.

# Inspection “Dos...”



- Communicate clearly and effectively
- Project a positive, courteous and professional attitude
- Focus on the positive
- Direct questions to “subject matter experts”
- Answer the question directly and honestly

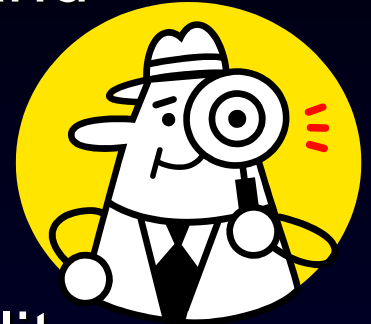
# Inspection “Don’ts...”



- Guess, lie, or make misleading statements
- Get too uptight, overly anxious, or defensive
- Volunteer more information than necessary to answer the question
- Engage in unconstructive argument
- Offer to buy lunch!

# What can the inspector view and review?

- ◆ Tour facilities as long as appropriately attired and adhering to safety SOPs
- ◆ Observe actual manufacturing processes
- ◆ Review SOPs, policies and plans describing manufacturing processes, QA testing, and quality systems
- ◆ Review completed MBRs, forms, worksheets, reports, training records, audit reports, and other data (e.g. validation and stability data, data to support IND)
- ◆ Request copies of documents
  - Documents containing Protected Health Information (PHI) should be redacted such that patient identifiers are not readable



# What information is not disclosed at the time of the inspection?

- Financial Data
- Personnel data, except qualifications, competency and training records
- Research data, except to support safety or efficacy claims
- Donor or recipient PHI



# Daily Debriefings



- Good idea if the inspection lasts more than one day
- Include appropriate management personnel specific to each area under inspection
- Discuss any issues that require clarification
- Discuss any corrections made
- Ask the inspector if there are any problems, concerns
- Document the debriefing
- Establish an agenda for the next day

# Exit Interview



- Include key operational and management staff (including senior management, legal and regulatory affairs)
- If the inspector issues observations (e.g. FDA form 483, List of Observations) review each one for accuracy and interpretation
- If it is the opinion that the observation is erroneous, request the inspector change the observation or note the disagreement in their report
- Inform the inspector of any corrections or confirmed plans for correction
- Indicate the intent to respond to all observations and determine a timeframe

# Inspection Documentation

- Inspector's credentials
- Facilities and other area inspected
- Names of all key personnel involved in the inspection
- Records, data, procedures inspected
- All key questions asked during the inspection and responses
- Minutes for all meetings
- Corrective actions and response



# FDA References

- 1) FDA, 21 CFR parts, 312.58, 312.68, 600.20, 600.21, 600.22, 1271.400
- 2) FDA, Investigations Operation Manual:  
[http://www.fda.gov/ora/inspect\\_ref/iom/iomtc.html](http://www.fda.gov/ora/inspect_ref/iom/iomtc.html)
- 3) Biotechnology Inspection Guide:  
[http://www.fda.gov/ora/inspect\\_ref/igs/biotech.html](http://www.fda.gov/ora/inspect_ref/igs/biotech.html)
- 4) Inspection of Biologic and Tissue Establishments:  
<http://www.fda.gov/cber/cpg/7341002tis.htm>  
<http://www.fda.gov/cber/cpg/7345848.pdf>
- 5) FDA/CBER Human Tissue Task Force Report  
<http://www.fda.gov/cber/tissue/httfo7report.htm>

*Thank you! Questions?*

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