Preparation for FDA Inspections

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We hope to provide answers to the following questions...

- When will the FDA come knocking?
  - Will focus primarily on FDA, but much applies to FACT and AABB preparation

- What do you need to do to prepare?
  - What SOPs and documents should be in place?
  - Roles and responsibilities of your staff?
  - How do you know you are adequately prepared?
And...

- What are the practical considerations for the day of the inspection?
- What is an inspector allowed to see?
- What information should not be disclosed at the time of the inspection?
- What are lessons learned?
  - Real-life experiences shared
Facility inspections can be stressful

Consequences of lack of preparation

- Key people 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
FDA’s Authority

“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 they 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,
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.

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 occurs through principal investigator
- FDA GTP inspections: typically unannounced, not routinely scheduled at this time

  W  Jan 2007: # of inspections 354 out of total of 2000 (mostly tissue recovery, 36 hematopoietic facilities)
  W  Latest FDA Human Tissue Task Force report recommends biennial for high risk facilities, and triennial for all others
First things 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
  - Identify Gaps
  - Good internal auditing helps
  - Periodic external audits useful
  - Fill gaps, improve systems
Organizational involvement

- Senior management
- Legal and Regulatory Affairs
- Quality Assurance
- Manufacturing and recovery operations
- All employees who may have interaction with inspectors require training
Identify inspection coordinator

- Represents the organization during inspection
- Answers Inspector’s questions in consistent manner, avoiding contradictions
- Possesses thorough knowledge of pertinent regulations
- Possesses good knowledge of facility procedures, quality systems, corporate policies/procedures
- Previous experience with regulatory inspections a plus
- Usually QA Manager, should have backup person(s)
- Stays with inspector at all times
- Interacts with key managers and other employees of various departments
- Responsible for documenting all aspects of inspection
Prepare documents

- List of key individuals to be notified
- Organizational overview and charts
- Facility description, including floor plans
- Summaries of recovery and manufacturing processes
- SOPs/policies guiding inspection preparation
Write SOP: “How to Prepare for an FDA Inspection”

- 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
- Tests staff
  - How are logistics of notification handled?
  - How are questions answered?
  - Are documents retrievable?
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
- 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 will the inspector want to see?

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

- 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
References

1) FDA, 21 CFR parts, 312.58, 312.68, 600.20, 600.21, 600.22, 1271.400


Thank you! Questions?

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Preparing Cell Therapy Production Facilities for Team Biologics Inspections

ISCT Regional Meeting
November 3, 2007

John Duguid
Preparing for an FDA inspection is like cramming for a final exam.

If you haven’t been doing the work all along, you’re probably not going to pass.
Team Biologics

Partnership between ORA and CBER to Address Inconsistency and Technical Depth

- Comprehensive regulatory posture
- Uniformity
- Highly trained, professional work force
- Inspections with clearly defined roles
- Rapid and effective process for resolving differences
- Approach that fits within FDA's existing systems
- Consistent quality
- Maximum efficiency
- New methods of implementing inspection and enforcement

ORA: Office of Regulatory Affairs
CBER: Center for Biologics Evaluation and Research
Current Agency Thinking

- Risk-based approach to Regulation
  - Target Inspections to High-Priority Sites
  - Reduce Inspections at Less Risky Facilities

- Reorganize ORA
  - Streamline Reporting Structure
  - Close 7 of 13 Field Labs

- Team Biologics Improvements
  - Implement Quality-Management Systems Approach
### US Regulations

<table>
<thead>
<tr>
<th>CFR Title 21</th>
<th>FOOD AND DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 11</td>
<td>Electronic records; electronic signatures</td>
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<tr>
<td>Part 210</td>
<td>Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general</td>
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<tr>
<td>Part 211</td>
<td>Current good manufacturing practice for finished pharmaceuticals</td>
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<tr>
<td>Part 610</td>
<td>General biological products standards</td>
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<tr>
<td>Part 820</td>
<td>Quality system regulation (medical devices)</td>
</tr>
<tr>
<td>Part 1270</td>
<td>Human tissue intended for transplantation</td>
</tr>
<tr>
<td>Part 1271</td>
<td>Human cells, tissues, and cellular and tissue-based products</td>
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CFR: Code of Federal Regulations
# GMP/GTP Background

<table>
<thead>
<tr>
<th>GMPs</th>
<th>GTPs</th>
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<tbody>
<tr>
<td>Well-established (decades)</td>
<td>Recently established (years)</td>
</tr>
<tr>
<td>Focused on product adulteration</td>
<td>Focused on transmission of communicable disease</td>
</tr>
<tr>
<td>Encompass all aspects of drug/biologics manufacture and require demonstration of potency, purity, identity</td>
<td>Encompass core GTPs as subset of broader regulation and tissue management practices</td>
</tr>
<tr>
<td>Include cell therapies meeting the definition of 351 products</td>
<td>Limited to HCT/Ps meeting the definition of 361 products</td>
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Autologous Products

- High volume - each patient constitutes a unique manufacturing lot
- 100% of lots tested
- Limited shelf life (48-72 hr) governing processing activities
- Variability in biopsy source material
- Patient-specific cell growth characteristics require control of in-process \textit{ex vivo} cell propagation
- Mechanism of action from biopsy through implantation should be characterized
- Inconsistency in critical raw materials (fetal bovine serum)
- QC assays need development and validation
- Potential variability in cellular product
- High degree of human involvement requiring aseptic processing techniques
- Emerging regulatory requirements
Essential Elements of Quality

- Standard Operating Procedures (SOPs)
- Personnel Training and Qualification
- Trend and Deviation Assessment
- Corrective and Preventative Actions (CAPA)
- Complaint Handling and Contamination Notification
- Management Review
- Facility Development
- Environmental Control
- Equipment Calibration/IQ, OQ, PQ
- Computer System Validation
- Raw Materials Inspection and Disposition
- Records and Documentation
- Process Validation
- Patient/Lot Segregation
- Test Methods – Safety, Potency, Identity
Assessment of Compliance

- Mock Audits
  - Assess current state of compliance
  - Useful before first regulatory audit

- Internal Audit Program
  - Assess ongoing state of compliance
  - Most useful when audited to standards

- Gap Analysis
  - Before first regulatory audit
  - After regulations change

- Remediation Plan
  - Specific: clear objectives
  - Measurable: defined deliverables
  - Accepted: organizational commitment
  - Realistic: available resources (staff, finances)
  - Timebound: concrete deadlines

- Risk Analysis
Compliance Development Program

**β Format**
- β Weekly Meeting
- β All Operations Departments

**β Agenda**
- β New Business/Emerging Issues
- β Business Updates
- β Customer Complaints
- β Deviations and CAPA
- β Material Review Board
- β Audits
- β Change Control
- β International Site Issues
- β Regulatory Activity
- β Safety
- β Training

![Graph showing the number of audits and average time to close over years 2002 to 2006](image)
Inspectional Guidance

- Display Credentials
- Provide Written Notice of Inspection (FDA Form 482)
- Review Recalls, Medical Device Reports (MDR), Biological Product Deviation Reports (BDR), Complaint Files
- Become Familiar with the Operation and Plan Inspection Strategy/Depth from Preliminary Tour
- Use a Systems-Based Approach
  - Quality
  - Facilities and Equipment
    - Environmental Controls
  - Materials
  - Production
  - Packaging and Labeling
  - Laboratory Controls
- Provide Written Inspectional Observations (FDA Form 483)
Preparations for Initial Meeting

- Inspection Readiness Kit
  - Floor Plan
  - Organizational Chart
  - Annual Report
- Tour
  - Prepared Script
  - Senior Management
- Technology Overview
  - Organized Presentation
  - Senior Scientist
FDA Inspection SOP

- Employee Interactions
- Practical Considerations
- Roles and Responsibilities
- Inspected Information Considerations
- Managing the Inspection
- Close out Meeting
- Dealing with Observations
Employee Interactions

Procedural Training
- Ensure all employees are trained in the FDA Inspection SOP

Attitude “DOs”
- DO Establish rapport based on mutual respect
- DO Remain positive and non-adversarial
- DO Be cooperative, but not unnecessarily revealing
- DO Tell the truth

Behavioral “DON’Ts”
- DON’T Take the opportunity to justify your existence (I told them…)
- DON’T Tell “war” stories (if you think that was bad…)
- DON’T Ask the inspector overly personal questions
- DON’T Complain about the government
- DON’T Guess
Practical Considerations

- Conference Room
- Restrooms
- Food
- Beverages
- Site Security (ID Badges)
- Safety (product and inspector)
  - PPE
  - Cleanroom garb
Roles and Responsibilities

★ Reception
  ★ Identifies and contacts escort
  ★ Notifies relevant departments

★ Main Point of Contact
★ Escort
  ★ QS, MFG OPS, RA
  ★ Facilitates inspection and interviews

★ Regulatory Affairs
  ★ Maintains inspection records

★ Quality Systems
  ★ Provides documentation

★ Senior Management
  ★ Attends close out meeting
**Subject Matter Experts**

- Involve people in their area of expertise to give ownership
- Pride in organization comes through

**SME Matrix**

<table>
<thead>
<tr>
<th>FDA Team Biologics Inspection Coverage Matrix</th>
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<tbody>
<tr>
<td><strong>Major Area</strong></td>
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<tr>
<td>Quality</td>
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<tr>
<td>Production</td>
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<tr>
<td>Laboratory Controls</td>
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Information – What can they ask for

**FDA Authority**
- Broad, but not unlimited for inspection of equipment, materials, products, labeling, and certain records

**Records and Documentation**
- Readily available
- Data stored offsite retrievable within a day

**Photocopies**
- Provide if requested
- Make duplicates marked confidential, keep one
Information – Other Considerations

**Databases**
- Can be useful for rapid retrieval of requested information
- Exercise caution about how the data are presented
- Decision-making data systems must be validated – they’ll ask

**Photographs**
- Many firms declare by SOP that photography is forbidden to protect proprietary information
- US courts have rules that photographs may lawfully be taken as part of an inspection

**Affidavits**
- Legal document; formal sworn statement
- Employees do not have to sign them

**Contracts**
- Raw Material Vendors
- Contract Services
Information – What can’t they ask for

- Financial Data
  - e.g. audit records, financial statements
- Sales Data
  - unless related to shipments or volume
- Pricing Information
- Personnel Records
  - HR Files – No
  - Qualification Information – Yes
- Research
  - unless related to lifecycle of product inspected
- Internal Audit Reports
Managing the Inspection

- **Notes**
  - appoint a scribe for each inspector to record conversations and potential observations

- **Photocopies**
  - make duplicate photocopies of documents provided to inspectors

- **Document Log**
  - keep a log of all documents/records viewed, even if photocopies are not provided

- **Daily Debriefing**
  - meet after inspectors leave to discuss potential observations

- **Transcript**
  - combine notes/debriefing into a comprehensive transcript and distribute appropriately

- **Instant CAPA**
  - correct simple observations immediately and present to inspectors
    - shows that you take the process seriously
    - inspector may minimize or annotate 483 observations
Close out meeting

- Invite All Audit Participants
- Obtain Clarification of Ambiguous Observations
  - understand specific issues
  - determine what would be deemed acceptable
- No Point Arguing – Observations Already Written
- Ensure Senior Management Representation
  - important for future resource allocation
  - shows organizational commitment to compliance

Thank Inspector
Dealing with Observations

- Coordinate through Regulatory Affairs
- Respond in a timely manner
- Outline proposal to reestablish compliance with timelines
- Determine when and how to push back
  - Some issues to consider
    - Technical feasibility
    - Financial feasibility
    - Compromise product safety or effectiveness
- Sometimes it’s easier to comply with a simple request rather than argue the point, even if you’re right
What we’ve learned from FDA

FDA Inspectors – free consultants?
  No, but don’t be afraid to have discussions

Inspectors are well trained, have technical expertise, and have seen a lot of facilities

Just a few examples…
  Hand disinfectant not sterile
  Enzyme fermented from bacteria needs mycoplasma test because bacterial culture medium contains bovine components
  Optimal temperature for development of rapid sterility test
What FDA’s learned from us

- How to regulate cell therapy products
  - first US approved cell therapy product
  - first US approved xenotransplantation device
  - combination products (device/biologic)
- Revisions to biologics regulations
  - general safety test
- FDA has used our site for inspector training
- Improvements to compendial methodology
  - sterility test
Epicel™ Wins Marketing Approval for Severe Burn Victims

October 25, 2007!
Compendial Sterility Test

- Products with short shelf-lives need to have improved microbial detection times
  - Products have 2-3 day shelf life; sterility test takes 14 days
  - Significant sample handling
  - Costly in an environment where each patient constitutes a unique lot with multiple tests per lot
  - Cellular products may appear turbid due to cell suspension impacting microorganism detection
Improved Sterility Test for Cell Therapy

- BacT/Alert System will detect organisms faster than standard methods
  - Most organisms detected within 3 days
  - Minimal processing
  - Cost effective in an environment where each patient constitutes a unique lot with multiple tests per lot
- Turbidity of sample does not affect microorganism detection because detection is based on production of CO$_2$
Acknowledgements

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Thank you for your attention!

βQuestions?
References


