PREPARING FOR AN FDA INSPECTION

August 11, 2011

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IS HE SPEAKING ENGLISH?

- **cGMP:** Current Good Manufacturing Practice
- **PHS Act:** Public Health Service Act
- **CFR:** Code of Federal Regulations
- **CP:** Compliance Program
- **BLA:** Biologics License Application
- **HCT/P:** Human Cells, Tissues and Cellular and Tissue-Based Products
- **BIMO:** Bloresearch MOnitoring
- **EI:** Establishment Inspection
- **EIR:** EI Report
- **IOM:** Investigations Operations Manual
- **FD&C Act:** Food, Drug & Cosmetic Act
- **IND:** Investigational New Drug
- **MS:** MusculoSkeletal
- **HPC:** Hematopoietic stem/Progenitor Cell

WHAT ARE WE ATTEMPTING TODAY?

- ME: Outline FDA's approach to inspecting cGMPs specifically for facilities processing cellular therapy products.
- YOU: Learn how to prepare for an FDA inspection and understand the parameters, approaches and concerns of FDA investigators.

WHAT AM I *NOT* ATTEMPTING TODAY?

- Give you the history of FDA's regulation of cellular therapy products.
- Make you an expert on all things FDA.
- Provide you with any secrets or shortcuts on how to not receive an FDA 483, Inspectional Observations.

DO I HAVE "361" OR "351" HCT/Ps?

- 361
  - PHS Act Section 361
  - 21 CFR 1271
  - Must meet all of criteria in 21 CFR 1271.10(a)
  - Premarket approval not required
  - Reproductive, MS, ocular and heart tissue; hematopoietic stem cells; skin; arteries and veins; dura mater
  - CP 7341.002, Inspection of HCT/Ps
- 351
  - PHS Act Section 351 & FD&C Act
  - 21 CFR 1271, 210/211, 600-680
  - Those HCT/Ps that don't meet 1271.10(a)
  - Premarket approval may be required
  - Vaccines; manipulated, cultured or expanded cell products
  - CP 7345.848, Inspection of Biological Drug Products

HPCs

- Regulatory framework for HPCs derived from peripheral or cord blood is dependent upon whether the product meets criteria in 21 CFR 1271.10(a) ***and*** the intended use:
  - If intended for unrelated allogeneic use, then they're regulated under PHS Act 351 as drugs, devices and/or biological products.
  - If intended for autologous use or allogeneic in 1st or 2nd degree blood relatives, and meet criteria in 1271.10(a), then they're regulated under PHS Act 361.

REMEMBER…

- Many HCT/P establishments that process HPCs derived from peripheral or cord blood manufacture the products for use in both (1) unrelated allogeneic and (2) autologous or 1st or 2nd-degree blood relative allogeneic use, i.e. it is common for manufacturers to produce both HPCs regulated solely under PHS Act 351 and HPCs regulated under PHS Act 361.

CORD BLOOD BANKS

- Ellen F. Lazarus, MD's presentation:
  - www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM200358.ppt

BIOLOGICAL DRUG PRODUCTS, WHO'S INSPECTING THEM?

- Team Biologics
  - Expert investigators in the areas of antitoxins, vaccines, plasma-derived products, in vivo diagnostics, allergenic products, hematopoietic cells and CELL/GENE THERAPIES.
  - Typically stationed in a field office.
  - Responsible for ensuring the quality/safety of biologic products and working with industry and Agency officials to quickly resolve inconsistencies and bring products into compliance.
  - Conducts inspections both domestically and internationally.

LET'S TALK NUMBERS

- Inventory of regulated firms:
  - Plasma derived products/recombinant analogues: 46
  - Vaccines/related products: 35
  - IVD: 25
  - Allergenic extracts: 11
  - CELL THERAPY: 2
  - Licensed cord blood banks: zilch, nada, none

ONLY 2 CELL THERAPY FIRMS?

- This means that most of you cell therapy folks are conducting studies under IND to prove that your product is safe and effective.

WHAT IS AN FDA INSPECTION?

- We call it an EI
  - An establishment inspection is a careful, critical, official examination of a facility to determine its compliance with the laws enforced by FDA.

WILL I KNOW YOU'RE COMING?

- FDA inspections are generally unannounced, with a few exceptions:
  - Medical devices
  - Inspections under the BIMO program, unless they are for-cause/directed
  - Pre-licensing biologics inspections

WE LOVE HAVING YOU HERE, BUT HOW LONG ARE YOU STAYING?

- Inspection length will depend on the complexity of operations, product(s) being manufactured, size of firm, number/type of problems found ***and the level of cooperation the firm provides.***

WHAT HAPPENS FIRST?

- Investigator(s) will identify themselves and ask to see the most responsible individual (MRI) available.
- FDA 482, Notice of Inspection, issued to MRI.
- FDA credentials displayed.
- Investigator(s) will explain the purpose of their "visit" and inform you of the records to review and personnel to interview.

WHAT CAN I DO IN ADVANCE (1)?

- Designate one or more persons to facilitate the inspection.
- Determine how you will handle requests for photocopies.
- Don't expect the facilitator(s) to have all of the answers to questions asked, designate in advance who is best suited to answer them.

IN ADVANCE (2)…

- Consider having an SOP on how to handle FDA inspections, e.g. think of logistics (space, etc.) ahead of time.
- SOPs: keep an updated hardcopy or at least a table of contents.

IN ADVANCE (3)…

- Know which CPs (www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/CompliancePrograms/UCM095419.pdf) and Guidances for Industry (www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm) apply to you.
- Stay current with the FDA (www.fda.gov/AboutFDA/CentersOffices/CBER/ucm125685.htm).

DURING THE INSPECTION (1)

- Don't be afraid to ask questions … avoid miscommunication.
- Okay fine, your policy is to never let the investigator roam around unescorted – but really … to the restroom?
- If you don't know the answer to a question … find someone who does.
- The investigator will take lots of notes … don't you hate it when someone attempts to read over your shoulder?

DURING THE INSPECTION (2)

- Don't be evasive.
- Investigators will need time alone to discuss amongst themselves.
- Provide requested records ASAP; explain why there might be any delay.
- You might use different terminology; ensure everyone is "on same page".
- At the end of each day, ask the investigator what he/she covered and if there are any deficiencies.

WHAT DOES THE FDA INVESTIGATOR KEEP LOOKING AT?

- IOM
- CP 7345.848, Inspections of Biological Drug Products (CBER)
- Guidances for Industry
- Previous EIRs
- His/her assignment (FDA eyes only)

CP 7345.848, INSPECTION OF BIOLOGICAL DRUG PRODUCTS (1)

- CPs are used by FDA investigators to, in conjunction with the CFR, help guide them through the inspectional process
- Current version: 10-1-10
- Addresses pre-approval, pre-licensing and post-market inspections

CP 7345.848 (2)

- EI is performed to ensure that manufacturers are making product that:
  - Meet provisions of regs: 21 CFR 200, 201, 210, 211, 600, 601, 610, 640, 660, 680, 1271
  - Meet BLA conditions (if licensed product)
- Systems-based, risk-management inspectional approach

SYSTEMS APPROACH

- SYSTEMS:
  - Quality
  - Facilities/equipment
  - Materials
  - Production
  - Packaging/labeling
  - Laboratory control
  - Donor eligibility
- CRITICAL ELEMENTS OF EACH SYSTEM:
  - SOPs
  - Training
  - Records

QUALITY SYSTEM, WHAT ARE WE LOOKING FOR?

- Has the QC unit fulfilled its responsibilities to review/approve SOPs related to production, QC and QA, and to ensure the SOPs are adequate/current for their intended use?
- We will review records related to release of components/in-process materials, product recall, product deviations, complaints, out of specification results, rejects and failure investigations.
- We will verify that the firm reviews its records pertinent to the manufacture of lots prior to their release or distribution.
- We will assess the data collected in order to identify quality problems that may be linked to other systems.

FACILITIES/EQUIPMENT SYSTEM

- We will verify the appropriateness of buildings/facilities, including maintenance; equipment qualifications (installation/operation); equipment calibration/preventative maintenance; validation of cleaning processes as appropriate; prevention of contamination/cross contamination; and utilities that are not intended to be incorporated into the product; such as HVAC, compressed gases, and steam and water systems.

MATERIALS SYSTEM

- This system includes the measures and activities to control finished products, such as components, source materials, water/gases that are incorporated into the product, and containers/closures.
- We will review the validation of computerized inventory control processes, product storage, distribution controls and records.
- We will evaluate routine monitoring of the utility systems.

PRODUCTION SYSTEM

- Are you following/documenting performance of approved manufacturing SOPs?
- We will review batch formulation, in-process testing, lot release, and process validation.
- Are records: complete and relate to the history/disposition of products produced/distributed; legible/indelible; identify the person performing the work, including dates of the various entries; show test results/interpretation; show expiration date assigned to specific products; and as detailed as necessary to provide a complete history of the work performed?

PACKAGING/LABELING SYSTEM

- We will review your SOPs regarding packaging/labeling controls.
- We will observe how you examine, store, issue and use labels.

LABORATORY CONTROL SYSTEM

- This system includes all the various measures and activities that are related to laboratory procedures; analytical methods development; validation or verification; and the stability program.
- We will review your SOPs for control of microbiological contamination and environmental monitoring; review of records for source materials, in-process and finished product testing;
- We will evaluate your methods for sampling and testing products for identity, potency, safety, sterility and conformance with final specifications.
- We will review a sampling of records for operations performed and verify that they are complete and maintained as required.

DONOR ELIGIBILITY SYSTEM

- This system includes the measures/controls that are related to determining the donor eligibility of allogeneic and family-related allogeneic HCT/P products, including donor screening and testing.
- We will review your SOPs for all steps performed in screening, testing and determining donor eligibility, including who made the determination, and the results and interpretation of all donor screening and testing for relevant communicable disease agents.
- We will assess your SOPs for quarantine of biological drug products pending completion of the donor eligibility determination, the identification and storage of products from donors determined to be ineligible, and the labeling and limited use of such products under the provisions of urgent medical need.

WITHIN EACH SYSTEM, WE COVER (1)…

- SOPs
  - For each system, you should have approved written procedures and associated records, e.g., testing, maintenance, cleaning, etc., that document adherence to the procedures.
  - We will verify through actual observation whether or not you adhere to the SOPs.
  - We will determine if the SOPs include all steps to be followed in the processing, testing, labeling, and distribution of biological drug products.
  - We will verify the most current version of approved SOPs is readily available for use by key personnel in the areas where the procedures are performed.

WITHIN EACH SYSTEM, WE COVER (2)…

- Training/personnel
  - Do you have an adequate number of trained personnel, including supervisors, for all assigned functions and operations, for each of the systems?
  - We will verify that all personnel responsible for supervising, processing, testing, packing, and distribution of biological drug products have the appropriate educational background, training and experience to perform their assigned functions. Training should also include CGMP regulations, as necessary; to ensure the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to posses.

WITHIN EACH SYSTEM, WE COVER (3)…

- Records
  - Are records maintained concurrently with the performance of each significant step in the processing, testing, and distribution of biological drug products so all steps can be clearly traced and documented?
  - If any records, which are required by regulation, are maintained in an electronic format in place of paper format, the record keeping system should comply with 21 CFR Part 11 (see Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application, August 2003).
  - Are records legible and indelible, and must identify the person performing the work, including dates of the various entries; show test results as well as the interpretation of results; show the expiration date assigned to specific products; and be as detailed as necessary to provide a complete history of the work performed?

THE INSPECTION IS OVER (☺), NOW WHAT?

- The investigator(s) will have a closing meeting with, at minimum, the MRI.
- If objectionable conditions/deviations/deficiencies were found, an FDA 483, Inspectional Observations, might be issued (☹).

FDA 483, INSPECTIONAL OBSERVATIONS

- Observations made by the FDA representative(s) during the EI.
- In the experience, judgment and knowledge of the FDA representative(s), the enumerated issues are potential violations of FDA laws and regulations.
- The citations do not represent the final Agency determination regarding compliance or whether/not the product or license is approved.

DISCUSSION ITEMS

- The FDA representative(s) may bring up issues of concern that are not placed on an FDA 483.
- These "discussion items" will be included on the narrative EIR and will be reviewed by Compliance Branch.

RESPONDING TO AN FDA 483

- It is encouraged, but not required, to respond to the discussion items or FDA 483.
- You can respond verbally during the final discussion and/or in writing to the District Office address as noted on the form.
- If you choose to respond in writing, do so within 15 business days.

GOOD LUCK!

I LOOK FORWARD TO MEETING YOU IN PERSON