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FDA/ORA

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Help prepare you, an HCT/P establishment, for an FDA inspection by explaining the parameters, approaches and concerns of FDA investigators

Provide tips for resolving conflict during inspections
WHAT AM I NOT ATTEMPTING TO DO?

• Give you the entire history of FDA’s regulation of HCT/Ps
• 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
IS MY HCT/P “351” OR “361”? 

• HCT/Ps regulated solely under PHS 361 and regs in 1271 if all are met [21 CFR 1271.10(a)]: 
  • HCT/P is *minimally manipulated*, AND 
  • HCT/P intended for *homologous use* only, AND 
  • Manufacture of HCT/P doesn’t involve combination of cells/tissue with another article (except water, crystalloids or sterilizing/preserving/storage agent); AND 
  • Either: 
    - HCT/P doesn’t have systemic affect and not dependent on metabolic activity of living cells for its primary function, OR 
    - HCT/P has systemic affect or dependent on metabolic activity of living cells for primary function, AND 
      » Is for autologous use, 
      » Is for allogeneic use in a 1st or 2nd-degree blood relative, OR 
      » For reproductive use
If the HCT/P does not meet all of the 1271.10(a) criteria, then it is regulated:

- under FD&C Act and PHS Act 361 (21 CFR 820 and 1271 subparts A-D apply) as a medical device, or
- under FD&C Act and PHS Act 351, 361 (21 CFR 210, 211 and 1271 subparts A-D apply) as a biological drug product.
HCT/Ps regulated solely under PHS Act Section 361:

- 21 CFR 1271
- Must meet all of 21 CFR 1271.10(a)
- Premarket approval not required
- Reproductive, MS, ocular and heart tissue; hematopoietic stem cells (intended for autologous use or for allogeneic use in 1st or 2nd degree blood relative); skin; arteries and veins; dura mater
- CP 7341.002, Inspection of HCT/Ps

HCT/Ps regulated under the FD&C Act and PHS Act Sections 351 and/or 361:

- 21 CFR 1271, 210/211, 820
- Those HCT/Ps that don’t meet 1271.10(a)
- Premarket approval may be required
- Allogeneic pancreatic islets cells, cell-based cancer vaccines/immunotherapies (biological products)
- Demineralized bone combined with handling agent (medical device)
- CP 7345.848, Inspection of Biological Drug Products; CP 7382.845, Inspection of Medical Device Manufacturers
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.
INSPECTION FREQUENCY

• No statutory requirement for FDA to conduct routine biennial EIs of HCT/P manufacturers

• Each District chooses which firms to inspect based on resources and selection priorities:
  – Firms with history of compliance issues, especially those with non-compliant last EI
  – Firms which FDA has received info of potential 21 CFR 1271 violations
  – Newly registered firms with no inspectional history
FDA inspections are generally unannounced, with a few exceptions:

- Medical devices
- Inspections under the bioressearch monitoring (BIMO) program, unless they are for-cause/directed
- Pre-licensing biologics inspections
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 credentials displayed.
- FDA 482, Notice of Inspection, issued to MRI.
- Investigator(s) will explain the purpose of their “visit” and inform you of the records to review, personnel to interview and operations to observe.
“THIS IS NOT A DRILL”
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.
• 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 Compliance Programs (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/CompliancePrograms/ucm095207.htm) and Guidances for Industry (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/default.htm) apply to you.

• Stay current with the FDA (www.fda.gov/AboutFDA/CentersOffices/CBER/ucm125685.htm).
QUALITY PROGRAM

• Addressed in 21 CFR 1271.160
• Applies to all manufacturers (recovery, processing, storage, labeling, packaging, distribution of HCT/Ps; screening/testing donors) except for reproductive HCT/Ps
• Quality Program = comprehensive system for manufacturing/tracking HCT/Ps, designed to prevent, detect and correct deficiencies that may lead to circumstances that increase risk of intro, transmission or spread of communicable disease
QUALITY PROGRAM FUNCTIONS (1)

• Establish/maintain procedures relating to core CGTP requirements.
• Ensure procedures exist for receiving, investigating, evaluating and documenting info relating to core CGTPs, including complaints, and for sharing info relating to possible contamination/disease transmission.
Ensuring appropriate corrective action relating to core CGTPs are taken and documented.

Ensuring proper training/education of personnel involved in core CGTP activities.

Establishing/maintaining appropriate monitoring systems (e.g. environmental).

Investigating/documenting HCT/P deviations and trends relating to core CGTPs and reporting if required (per 1271.350).
QUALITY PROGRAM FUNCTIONS

• Quality audits of activities related to core CGTPs.
• Computer software validation, if its relied upon to comply with core CGTPs (if custom software or customized commercially available software.)
  – If not custom or customized commercially available software, and rely upon for core CGTPs, then its performance must be verified.
DURING THE INSPECTION – AVOIDING CONFLICT

- 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 – AVOIDING CONFLICT

• 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 DO YOU KEEP LOOKING AT?

- Investigations Operations Manual
- CP 7341.002, Inspection of HCT/Ps
- Guidances for Industry
- Previous Establishment Inspection Reports
- His/her assignment (FDA eyes only)
• 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 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.
A LITTLE MORE ON CONFLICT

• Conflict … where is it coming from?
  – MISCOMMUNICATION
  – Stress
  – Personality differences
  – Information interpretation differences
  – Defensiveness
WE ALL TRIED TO AVOID CONFLICT, BUT IT HAPPENED

• Take a minute to collect your thoughts … don’t let it escalate.
• Use paraphrasing.
• Don’t be sarcastic.
• If someone else at the firm can help with the issue at hand, consult with them.
• Remember … we all have the same bottom-line mission.
YOU’VE TRIED AND TRIED, BUT...

• If you feel that the investigator is conducting themselves in an unprofessional, unfair or irresponsible manner:
  – During the inspection, DO NOT contact CBER directly.
  – During and/or after the inspection, DO contact the District Office.
“STRAIGHT FROM THE HORSE’S MOUTH”

– “You just walk in the door and expect us to drop everything, yet still continue to operate per usual.”

– “The last investigator who was here didn’t request those documents so we didn’t think we had to keep them.”

– “You worded the FDA 483 items to make it sound like we are completely out of control.”

– “We have those documents, if you can just be patient.” (then the firm is observed “pre-reviewing” them)

– “Can you come back next week? Our regulatory affairs director is in Jamaica.”
“THERE’S TOO MUCH INCONSISTENCY AMONGST FDA INVESTIGATORS”

- All investigators receive initial FDA law training, including evidence development.
- For each program area, there are specialized classroom courses, as well as OJT and mentoring.
- While there might be differences in approach, each investigator is tasked with determining the firm’s compliance with applicable regulations.
CONTACTS

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