Industry Workshop for Reproductive HCT/P Establishments FDA Compliance

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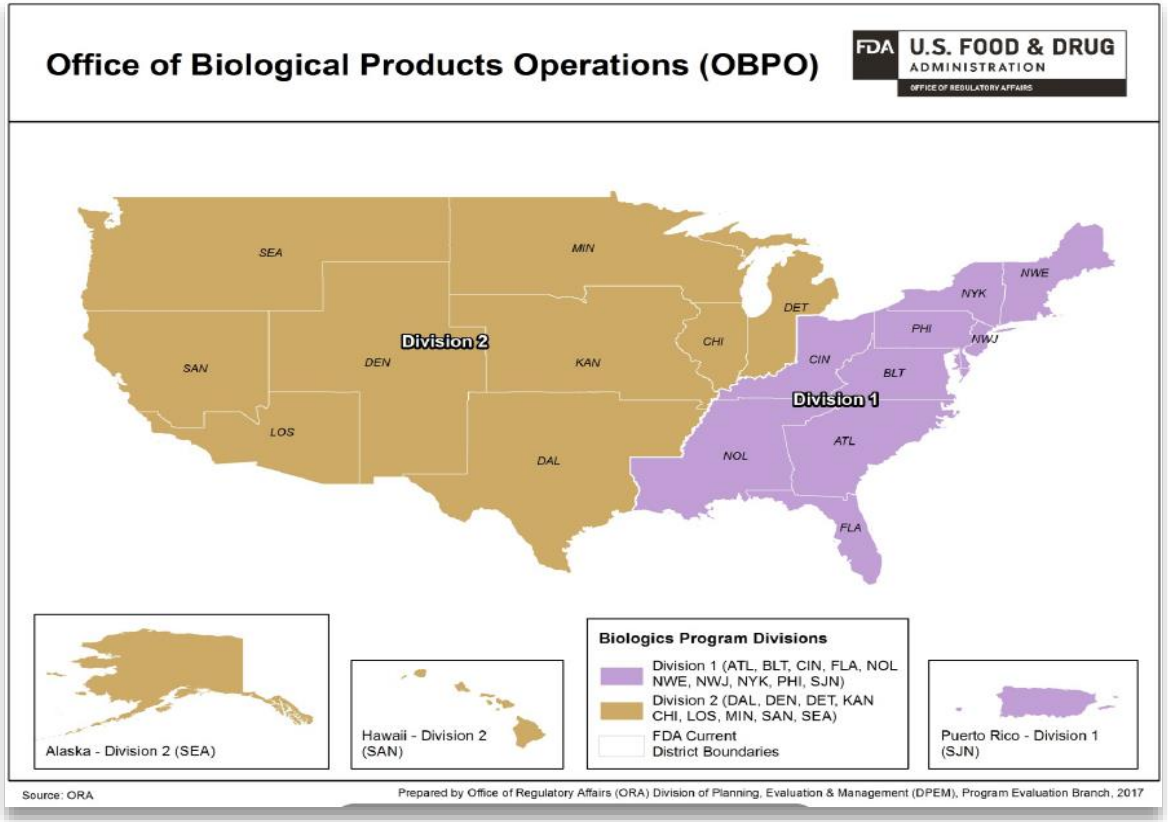
Topics to Cover

- Who Are We and What Compliance Does
- An Overview of the Review/Compliance Process After the Investigator's Establishment Inspection Report is Completed
- Common Issues/Top 10 Violations
- Compliance Actions/Statistics

Office of Biological Products Operations (OBPO) - Divisions



OBPO Compliance Branch Responsibilities

- Compliance activities that involve blood and tissue products as well as vaccines allergenics, and other biological products regulated by the Center for Biologics Evaluation and Research (CBER)

- Review and evaluate documented information gathered during inspections and investigations to ensure industry compliance with the Federal Food, Drug and Cosmetic Act, the Public Health Service Act and other related acts

- Recommend the most suitable course of action based on the seriousness of the documented deficiencies, and the most effective way to protect the public health. OBPO's recommendation is submitted to CBER's Office of Compliance

Additional Compliance Responsibilities

- Review domestic FDA-483 responses and send acknowledgment letter
- Hold regulatory meetings with firms
- Assist investigators, if needed, in preparation for or during the inspection
- Review post action correspondence from the firm
- Assign follow-up inspections
- Collaborate with Office of Chief Counsel
- Monitor firm's compliance
- Issue FMD-145 to domestic firms
  - Release the EIR to the most responsible individual at the site
  - Inspection must be closed

CBER/BTCB Responsibilities

- Complete evidentiary review of all recommendations forwarded by either Compliance Branch in OBPO
- Drafting an Order for Retention, Recall, Destruction, and/or Cessation of Manufacturing (Order)
  - Preparation of Health Hazard Evaluation for review by medical staff
  - Coordination with FDA's Office of Chief Counsel for clearance of the Order
  - Documenting issuance of the Order
  - Review of correspondence from a firm that receives an Order

CBER/BTCB Responsibilities

- Review and classification of recall actions taken by all firms that manufacture products regulated by CBER
- Review and evaluation of complaints received by the agency related to blood and plasma establishments
- Attendance at Regulatory Meetings
- Coordination with OBPO, as needed, in regards to inspections conducted in follow up to an agency action
- Review and evaluation of all deviation reports submitted by HCT/P establishments
- As requested, review and comment on proposed Guidance documents relevant to the firms covered by BTCB

Compliance Actions

Advisory Actions issued by OBPO with CBER concurrence :

- Warning Letters
  - Significant violations related to communicable disease transmission
  - Reasonable expectation the firm will take prompt action to correct violations
- Untitled Letters

Compliance Actions (continued)

- Administrative Actions – Order for Retention, Recall, Destruction, and/or Cessation of Manufacturing (Order)
  - FDA may issue an Order upon an agency finding that there are reasonable grounds to believe:
    - An HCT/P is violative because it was manufactured in violation of the regulations at 21 CFR 1271 and the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission; or,
    - The HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or
    - An establishment is in violation of the regulations in 21 CFR 1271 and therefore, does not provide adequate protections against the risk of communicable disease transmission

Compliance Actions, Order (continued)

- CBER/BTCB drafts a Health Hazard Evaluation that is cleared through OCBQ management, FDA's Office of Chief Counsel and signed by a Medical expert
- CBER/BTCB drafts an Order for the action the agency expects the establishment to perform which is cleared by OCBQ and FDA's Office of Chief Counsel
- Final, cleared Order is signed by the Director of the Center for Biologics Evaluation and Research and issued by the Director of the Office of Compliance and Biologics Quality
- FDA will not issue an order for the destruction of reproductive tissue, nor will it carry out such destruction itself

Compliance Review Process

What criteria are used when assessing inspectional findings?

1. Inspectional findings
   - Significance
   - Frequency of occurrence
   - Evidence
2. Urgency for action
   - Public health concern
3. Firm's inspectional and compliance history
   - Repeat deficiencies
   - Failure to implement corrective actions

Compliance Review Process (Continued)

4. Level of firm's cooperation
5. Firm's commitment to correct
    - Statements made during inspection
    - Written correspondence i.e. response to the FDA-483 observations

After the Inspection

- The OBPO investigator prepares the Establishment Inspection Report (EIR) narrative with attachments and exhibits to support what is in the report

- The inspection receives an inspectional classification by the Investigations Branch.
  - NAI – No action indicated
  - **VAI – Voluntary action indicated**
  - **OAI – Official action indicated**

- OBPO Compliance Branch reviews the FDA-483s and EIRs for VAI and OAI classified inspections

After OBPO's Compliance Review

A decision is made whether to recommend an action.

- If no action is recommended, the Compliance Officer prepares a response to the firm's FDA-483 response (if available)

- If an action is recommended, the Compliance Officer prepares a recommendation and a proposed action for review and concurrence by CBER

Compliance Review by CBER

- For actions other than an Order, a recommendation together with a draft letter is received from either Compliance Branch in OBPO
  - In the case of an Order, OBPO submits a recommendation, CBER/BTCB drafts the Order
- CSOs perform an evidentiary review of all documents including the FDA-483 response submitted by the firm
- The decision to concur or not is reviewed by upper management in OCBQ
- CBER's decision to concur or not is communicated to OBPO

Most Common Deficiencies

- Failure to adequately screen and/or test for West Nile Virus
- Failure to adequately screen for ZIKA Virus
- Testing for Relevant Communicable Disease Agents and Diseases performed with diagnostic test kits
- Timing for collection of sample used for testing incorrect
- Inadequate SOPs for donor screening
- Donor Eligibility (DE) not performed or not documented
- DE not performed for directed donors

Top 10 HCT/P Violations (FY 2019 Data)

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations

1 – 21 CFR 1271.75(a)(1) – Risk factors, clinical evidence

2 – 21 CFR 1271.47(a) – Testing, screening, donor eligibility procedures

3 – 21 CFR 1271.47(a) – Procedures for all other requirements

> You did not establish and maintain procedures that address [the accompanying records after the donor eligibility determination is complete] [the retention of records related to testing, screening, and determining of donor eligibility] [storage of product from ineligible donors] [limited use of product from ineligible donors] [cases of use when the donor eligibility determination is not required or there is an exception for reproductive use] of HCT/Ps. Specifically, ***

4 – 21 CFR 1271.50(a) – Donor eligibility determination based on screening and testing

5 – 21 CFR 1271.85(a) – Testing for relevant communicable disease agents

Top 10 HCT/P Violations (Continued)

6 – 21 CFR 1271.90(c) – Required labeling

7 – 21 CFR 1271.50(a) – Responsible person to determine, document eligibility of an HCT/P donor

8 – 21 CFR 1271.80(b) – Timing of specimen collections

9 – 21 CFR 1271.50(b)(1) – Donor screening

Donor screening of HCT/P donors considered eligible indicated that the donor was not free of [risk factors for infection due to communicable disease agents] [clinical evidence of infection due to communicable disease agents] [risk factors associated with xenotransplantation]. Specifically, ***

10 – 21 CFR 1271.55(b)(2) – Listing and interpretation of communicable disease tests performed on Summary of Records

Warning Letters – 2018/2019
361 HCT/Ps

- Warning Letters - 2019
  - 5 Reproductive Establishments
  - 1 Musculoskeletal Establishment

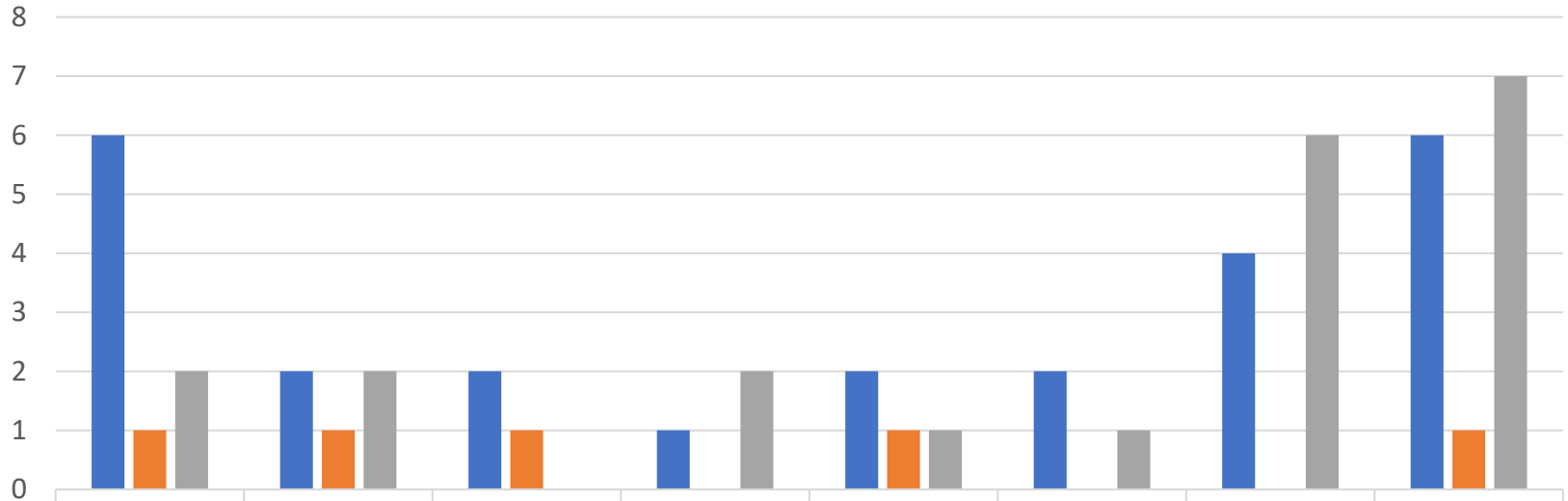
- Warning Letters - 2018
  - 3 Reproductive Establishments
  - 1 Musculoskeletal Establishment

Untitled Letters – 2018/2019
361 HCT/Ps

- Untitled Letters - 2019
  - 6 Reproductive Establishments
  - 1 Musculoskeletal Establishment

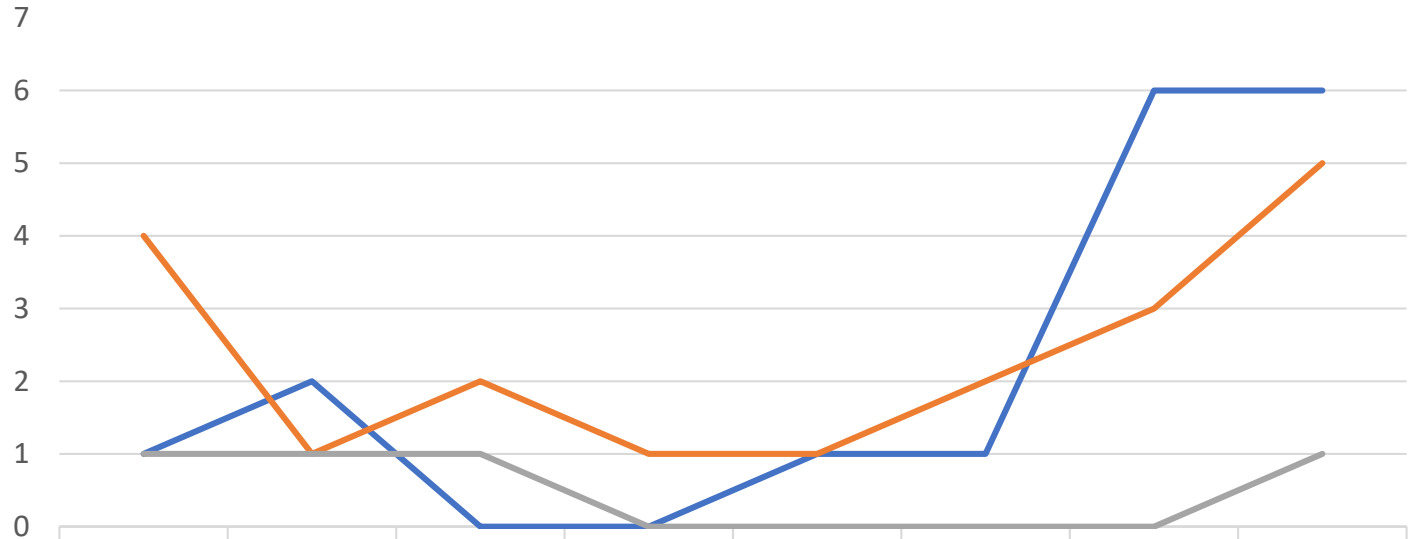
- Untitled Letters - 2018
  - 6 Reproductive Establishments

HCT/P Regulatory Actions
361 HCT/Ps



	2012	2013	2014	2015	2016	2017	2018	2019
WL's	6	2	2	1	2	2	4	6
Orders	1	1	1	0	1	0	0	1
UL's	2	2	0	2	1	1	6	7

Regulatory Actions: Reproductive Establishments



	2012	2013	2014	2015	2016	2017	2018	2019
Untitled Letters	1	2	0	0	1	1	6	6
Warning Letters	4	1	2	1	1	2	3	5
Orders	1	1	1	0	0	0	0	1

Resources

- Compliance Program Guidance Manuals (CPGMs)
  - CP 7341.002 – Inspection of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps) – Utilized for reproductive tissues
- Compliance Policy Guides
- Regulatory Procedures Manual (RPM)
- Investigations Operations Manual

Resources (continued)

- Guidance for Industry Documents
- 21 Code of Federal Regulations (CFR)
  - Part 1271 (utilized for reproductive tissues)
- Public Health Service Act (PHS Act)
- Warning Letters https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters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