Bioresearch Monitoring (BIMO)
Fiscal Year 2019
Metrics
Inspection Metrics Overview

• The following slides provide annual inspection metrics for the compliance programs within the Bioreserach Monitoring (BIMO) Program overseen by the Food and Drug Administration (FDA) six product centers:
  – Center for Biologics Evaluation and Research (CBER)
  – Center for Devices and Radiological Health (CDRH)
  – Center for Drug Evaluation and Research (CDER)
  – Center for Food Safety and Applied Nutrition (CFSAN)
  – Center for Tobacco Products (CTP)
  – Center for Veterinary Medicine (CVM)

• The inspections (domestic and foreign) were conducted by FDA’s Office of Regulatory Affairs (ORA). A portion of the CDER bioequivalence inspections were conducted independently by CDER subject matter experts.

• Metrics are based on the Center final classification determined in fiscal year (FY) 2019.
Metrics Terms

Organizations and Programs

• BE or BEQ: Bioequivalence - clinical and analytical
• BIMO: Bioresearch Monitoring
• CBER: Center for Biologics Evaluation and Research
• CDER: Center for Drug Evaluation and Research
• CDRH: Center for Devices and Radiological Health
• CFSAN: Center for Food Safety and Applied Nutrition
• CI or Clin: Clinical Investigator
• CRO: Contract Research Organization
• CTP: Center for Tobacco Products
• CVM – Center for Veterinary Medicine
• FDA: Food and Drug Administration
• GLP: Good Laboratory Practice
• IRB: Institutional Review Board
• M: Monitors
• PADE: Postmarketing Adverse Drug Experience
• PMR: Postmarketing Requirements
• RDRC: Radioactive Drug Research Committee
• REMS: Risk Evaluation and Mitigation Strategy
• Sponsor: Sponsor or Sponsor-Investigator

Classifications

• NAI: No Action Indicated
• OAI: Official Action Indicated
• VAI: Voluntary Action Indicated
# BIMO Inspection Classifications by Center – FY 2019*

<table>
<thead>
<tr>
<th>Center</th>
<th>CI</th>
<th>IRB</th>
<th>S/M/CRO</th>
<th>S/I</th>
<th>GLP</th>
<th>BEQ</th>
<th>PADE</th>
<th>REMS</th>
<th>Total</th>
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<tbody>
<tr>
<td>CBER</td>
<td>60</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>4</td>
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<td>CDER</td>
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<td>62</td>
<td>7</td>
<td>25</td>
<td>200</td>
<td>78</td>
<td>17</td>
<td>1053</td>
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<tr>
<td>CDRH</td>
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<td>3</td>
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<td>CFSAN</td>
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<td>0</td>
<td>4</td>
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<tr>
<td>CTP</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>CVM</td>
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<td>3</td>
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<td>19</td>
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<td>0</td>
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<tr>
<td>Totals</td>
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<td>140</td>
<td>113</td>
<td>13</td>
<td>62</td>
<td>200</td>
<td>78</td>
<td>17</td>
<td>1402</td>
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</tbody>
</table>

* Domestic and Foreign
Clinical Investigator Inspection Classifications
(FY 2019)

Domestic
n = 600

- NAI: 74% (n=445)
- VAI: 25% (n=152)
- OAI: 1% (n=3)

Foreign
n = 179

- NAI: 82% (n=147)
- VAI: 18% (n=32)

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Common Clinical Investigator
Inspectional Observations

• Failure to follow the investigational plan; protocol deviations
• Failure to comply with Form FDA 1572 requirements
• Inadequate and/or inaccurate case history records; inadequate study records
• Inadequate accountability for the investigational product
• Inadequate subject protection; informed consent issues
• Safety reporting; failure to report and/or record adverse events
• Failure to comply with 21 CFR part 56 (IRB) requirements.
Institutional Review Board Inspections Classifications (FY 2019)

Domestic
n = 140

Includes 2 RDRC (VAI)

- 20% (n=28)
- 79% (n=111)
- 1% (n=1)

NAI  VAI  OAI
Common Institutional Review Board
Inspectional Observations

- Failure to have minutes of IRB meetings in sufficient detail to show attendance at the meeting; vote actions, quorum issues
- Failure to conform to membership criteria listed in 21 CFR 56.107; membership list
- Failure to conduct initial and/or continuing review of research
- Inadequate written procedures for prompt reporting of non-compliance, suspension or termination
- Failure to prepare and maintain documentation of IRB activities; inadequate copies of research proposals and related documents

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Sponsor/Monitor/CRO Inspections Classifications (FY 2019)

**Domestic**
- NAI: 73% (n=79)
- VAI: 23% (n=25)
- OAI: 4% (n=4)

**Foreign**
- NAI: 80% (n=4)
- VAI: 20% (n=1)
- OAI: 0% (n=0)

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Common Sponsor/Monitor/CRO Inspectional Observations

• Failure to select qualified investigators and/or monitors, ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan. (General responsibilities of sponsors)

• Failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; accountability for the investigational product.

• Failure to bring non-compliant investigators into compliance
Sponsor-Investigator Inspections Classifications (FY 2019)

Domestic
n = 13

46% (n=6)
54% (n=7)

NAI  VAI  OAI
Common Sponsor-Investigator Inspectional Observations

- Failure to submit an Investigational New Drug (IND) application
- Failure to ensure proper monitoring of the clinical investigation
- Failure to follow the investigational plan
- Failure to comply with Form FDA 1572 requirements
- Inadequate and/or inaccurate case history records; inadequate study records
- Inadequate accountability for the investigational product
- Inadequate subject protection; informed consent issues
- Failure to comply with 21 CFR part 56 (IRB) requirements.
Good Laboratory Practice Inspections Classifications (FY 2019)

Domestic
n = 54
- NAI: 46% (n=25)
- VAI: 33% (n=18)
- OAI: 21% (n=11)

Foreign
n = 8
- NAI: 50% (n=4)
- VAI: 50% (n=4)
Common Good Laboratory Practice
Inspectional Observations

• Inadequate labeling; test article, reagent
• Study Director requirements; failure to transfer data to archives, document unforeseen circumstances, assure data is accurately recorded and verified
• Missing standard operating procedures (SOPs)
• Conduct; not all studies were conducted in accordance with the protocol
• Final report; circumstances affecting data quality and integrity
Bioequivalence Inspections Classifications (FY 2019)

Domestic
n = 90

- NAI: 83% (n=75)
- VAI: 16% (n=14)
- OAI: 1% (n=1)

Foreign
n = 110

- NAI: 85% (n=94)
- VAI: 10% (n=11)
- OAI: 5% (n=5)
Common Bioequivalence Inspectional Observations

- **Analytical**
  - Validation
  - Reserve Samples

- **Clinical**
  - Blinding Codes
  - Recordkeeping
Postmarketing Adverse Drug Experience Inspections Classifications (FY 2019)

Domestic
n = 69

- NAI: 67% (n=46)
- VAI: 33% (n=23)

Foreign
n = 9

- NAI: 78% (n=7)
- VAI: 22% (n=2)
Common Postmarketing Adverse Drug Experience Inspectional Observations

- Failure to develop written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences
- Late submission of 15-day Alert reports
- Late submission of annual safety report
- Late submission of quarterly safety reports
- Failure to maintain records; compliant records for marketed drugs and/or PADE reports
Risk Evaluation Mitigation Strategies
Inspections Classifications
(FY 2019)

Domestic
n = 17

88%
(n=15)

12%
(n=2)

NAI

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Common Risk Evaluation Mitigation Strategies

Inspectional Observations

- Failure to comply with REMS elements to assure safe use (ETASU) B
- Failure to comply with REMS medication guide
- Late submission of 15-day report
- Failure to comply with REMS Implementation System
Reference

- FDA’s BIMO Compliance Programs:
  - Clinical Investigator (CP 7348.811)
  - Institutional Review Board (CP 7348.809)
  - Sponsors, Contract Research Organizations, Monitors (CP 7348.810)
  - Sponsor-Investigator (CP 7348.810, CP 7348.811)
  - Good Laboratory Practice (CP 7348.808)
  - Bioequivalence (CP 7348.003, CP 7348.004, CP 7348.007, CP 7348.808)
  - Postmarketing Adverse Drug Experience (CP 7353.001)
  - Risk Evaluation Mitigation Strategies (CP 7353.001c)