Surveillance Inspections and Recent Trends

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Agenda

- Office of Global Policy and Strategy
- Human Drug Inventory
- Site Selection Model (SSM)
- Concept of Operations (ConOps)
- Inspection Trends
OGPS MISSION STATEMENT: OGPS works to protect and enhance the public health of Americans by ensuring that global considerations are fully integrated into the Agency's policies and operational activities.

STRATEGIC PRIORITY 1: POLICY COHERENCE
Promote mutually reinforcing policy actions to advance FDA's public health and regulatory interests globally.

STRATEGIC PRIORITY 2: GLOBAL PARTNERSHIPS
Build and leverage global partnerships to protect and promote public health.

STRATEGIC PRIORITY 3: HIGH QUALITY INFORMATION
Collect, analyze, and share high-quality information, including inspections data, to advance FDA's public health mission.
CDER’s Tools for Regulating Quality

- Inspection
- Assessment
- Engagement
- Surveillance
- Enforcement
- Outreach
- Policy
- Testing
- Research

Improving Patient Access Without Sacrificing Quality
Human Drug Inventory - Approximate Numbers

- **Facilities:**
  - ~6,000 human drug manufacturing sites
  - ~2,000 Medical Gas (MG) manufacturers (nearly all in U.S.)
  - ~4,000 Non-Medical Gas manufacturers
    - 44% domestic
    - 56% foreign

- **Products:**
  - 120,000 unique finished dose
  - 35,000 unique Active Pharmaceutical Ingredients

- **Foreign:** ~2200 Sites
  - India: 476 sites
  - China: 347 sites
  - Rest of the World: 1455 sites

- The hierarchy for this analysis tags a site that makes both FDF and API as FDF facilities and a facility that makes both application and non-application products as an application site.

- **Note:** Based on July 2019 Surveillance Catalogs and current eDRLS listings.
Human Drug Inventory - Approximate Numbers

Percentage of Active Pharmaceutical Ingredient Manufacturing Facilities for All Drugs by Country or Region, August 2019

- China: 13%
- USA: 28%
- India: 18%
- EU: 26%
- Canada: 2%
- Rest of World: 13%

Percentage of Finished Dosage Form Manufacturing Facilities for All Drugs by Country or Region, August 2019

- USA: 47%
- EU: 18%
- India: 11%
- Rest of World: 13%
- Canada: 4%
- China: 7%
Facilities* are also categorized through a hierarchy of industry sectors:

- 20% of all facilities are listed in new and biotech drug applications only
- 14% of all facilities are listed in generic drug applications only
- 26% of all facilities are listed in both generic and new drug applications
- The remaining 60% of facilities are not listed in any applications (non-application sites including some over-the-counter and homeopathic products)

- 60% of all facilities are listed in application products
- 40% of all facilities manufacture non-application products

* Medical Gas not included
FDA’s Domestic and Foreign Drug Inspections (FY2000 – FY2019)

Implemented a risk-based approach

FDASIA & GDUFA I

GDUFA II
CDER-ORA Site Selection Model (SSM)
Sources of Information for Quality Surveillance

- Inherent Product Risk
- Facility Type
- Patient Exposure
- Inspection History
- Time Since Last Inspection
- Hazard Signals

Fairly Static
Dynamic

www.fda.gov
Median Years Between Drug Inspections By Risk Level (December 2011 – June 2019)

- China: High Risk 1.9, Medium Risk 3.2, Low Risk 2.6
- India: High Risk 2.1, Medium Risk 2.7, Low Risk 3.0
- European Union: High Risk 2.1, Medium Risk 2.7, Low Risk 3.2
- Rest of World: High Risk 2.1, Medium Risk 2.6, Low Risk 3.0
- USA: High Risk 2.1, Medium Risk 2.7, Low Risk 3.4
Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations

On June 6, 2017, the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) have entered into an unprecedented concept of operations (ConOps) agreement to integrate facility evaluations and inspections for human drugs. The agreement, Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations, outlines the responsibilities and the workflow for Pre-Approval, Post-Approval, Surveillance, and For-Cause Inspections at domestic and international facilities.

ConOps will enable CDER and ORA to more effectively manage the growing complexity of the pharmaceutical landscape and to meet new challenges by:

- Ensuring consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision-making for marketing applications across FDA;
- Advancing strategic alignment across ORA and CDER functional units by creating clear roles and responsibilities;
- Improving FDA’s operational capacity by enhancing collaboration between various CDER and ORA offices;
- Enhancing the quality of and increasing access to facility and regulatory decisional information across FDA; and
- Meeting user fee commitments and improving the timelines for regulatory, advisory, and enforcement actions to protect public health and promote drug quality, safety, and effectiveness.

Related Resources:
- Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations
- Questions and Answers on the Concept of Operations
- FDA Voices Blog: New Steps to Strengthen FDA’s Inspection and Oversight of Drug Manufacturing
ConOps – Surveillance Facility Inspections

1. Manufacturing facility catalogue

2. OS develops and uses SSM to select sites for Surveillance Inspection

3. ORA schedules Surveillance Inspection

4. ORA prepares site dossier to provide information on site and suggested areas of product(s) of inspection focus

5. ORA investigators develop on-site inspection strategy

6. ORA completes report and initial classification in 45 days post-inspection (VAI/NAI/OAI)

7. ORA issues FDA 483 as necessary

8. ORA performs the on-site inspection

9. Are major/critical conditions identified and observed?
   - Yes
     - ORA and CDER discuss inspection findings, as appropriate
     - OC issues OAI decisional letter in 5 days
     - OC/ORA implements appropriate action for OAI within 3 months of decisional letter
     - OS conducts trend analysis
   - No
     - OS updates site dossier

10. No
    - ORA completes final classification in 40 days
    - ORA issues VAI and NAI decisional letter in 5 days post final classification
    - OC issues downgraded VAI and NAI decisional letter in 5 days post final classification

11. During inspection
    - Is evidence sufficient to make a final decision?
      - Yes
        - OC/ORA implements appropriate action for OAI within 3 months of decisional letter
      - No
        - OS updates site dossier
% of Manufacturing Facilities with Acceptable Final Outcome (as of August 2019)

- European Union: 98%
- Rest of World: 94%
- United States: 93%
- China: 90%
- India: 83%
Quality Management Maturity

• **Basic Quality Management Systems**
  – *Reactive*: focused on Current Good Manufacturing Practice (CGMP) compliance

• **Strong, mature Quality Management Systems**
  – *Proactive*: focus on performance, especially outcomes that affect the patient
Resources

• Inspections Classification Database
  https://www.accessdata.fda.gov/scripts/inspsearch/

• Drug Shortages
  https://www.accessdata.fda.gov/scripts/drugshortages/Drugshortages.cfm

• Drug Recalls

• Drug Quality Sampling and Testing Programs
  https://www.fda.gov/drugs/science-and-research-drugs/drug-quality-sampling-and-testing-programs

• FDA Social Media
Acknowledgements

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• Office of Regulatory Affairs