

Navigating Challenges in Drug Manufacturing: Common Process Deficiencies and Pre-Approval Inspection Observations

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Learning Objectives

- Describe the common process deficiencies associated with major withhold recommendations for generic drug applications
- Describe the common pre-approval inspection deficiencies associated with major withhold recommendations for generic drug applications

USA Marketed Generic Drugs



- Generics and biosimilars: 90 percent of all U.S. prescriptions but less than 18 percent of spending (1)
- 2019 GAO-19-565 Report: 12% of generic applications approved in the first review cycle from FY15 to FY17
- FDA posted 88, 119, 91, product-specific guidance in years 2021, 2022, and 2023 respectively (2)
- 18% of generic applications approved in the first review cycle from FY22 to FY24 (3)

CRL Deficiencies

- Deficiencies Communicated in CRL
- Deficiencies Classified as Major or Minor
- Major Amendment: 6 or 8 or 10 months depending on various factors
- Minor Amendment: 3 months

(4)

Challenge Question #1



The review timeline for amendments in response to major deficiencies is:

- A. 180 days
- B. 9 months or 18 months
- C. 6 or 8 or 10 months
- D. 3 months

Major CRL Deficiencies



- Categories are listed in FDA, “ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA - Guidance for Industry.” September 2024.
- Process: Guidance lists 10 major deficiency categories
- Facilities:
 - “One or more facilities were found inadequate”
 - “The facility was not clearly identified in Form FDA 356h...”

(4)

Collection and Analysis of Data



- Limited to FY23 Generic Drug Applications
- First Review Cycle CRL, Major: 125 applications
- Major Process Deficiencies
- Major Facility Deficiencies
 - Categorized

Major CRL Manufacturing Process Deficiencies for FY23 by Dosage Form



| | | Liquid, parenteral | Liquid, otic, ophthalmic, nasal, inhalation | Semi-Solid, topical | Solid, tablet, capsule, film, oral powder, insert |
|--|---|-----------------------|--|------------------------|--|
| Manufacturing Process Deficiencies | New batches needed to support commercial scale-up | 3 | - | - | - |
| | PERLS | 2 | - | 1 | - |
| | New batches needed for formulation change | 1 | - | - | - |

- The results represent 7 applications (Total of 125 applications for CRL-Major)
- Process Equipment-Related Leachables (PERLS)

Challenge Question #2

For FY23, only 7 applications were associated with process deficiencies:

- A. True
- B. False

Major CRL Manufacturing Process Deficiencies for FY23 by Dosage Form



| | | Liquid, parenteral | Liquid, otic, ophthalmic, nasal, inhalation | Semi-Solid, topical | Solid, tablet, capsule, film, oral powder, insert |
|--|---|-----------------------|--|------------------------|--|
| Manufacturing Process Deficiencies | New batches needed to support commercial scale-up | 3 | - | - | - |
| | PERLS | 2 | - | 1 | - |
| | New batches needed for formulation change | 1 | - | - | - |

Dosage Forms: Only Liquid, parenteral and Semi-Solid, topical

Resources for Major Manufacturing Process Deficiencies for FY23



- New batches needed to support commercial scale up
 - Product Specific Guidance (PSG)
 - Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products Questions and Answers, May 2014
- Process Equipment-Related Leachables (PERLS)
 - Video: Generic Drugs Forum (GDF) 2024: Regulatory Considerations to Enhance Generic Drug Access-Day 2, Pt 3
 - Slides: Successful Practices for Pharmacology/Toxicology Justification in ANDAs SBIA 2024: Regulatory Considerations to Enhance Generic Drug Access

Facility Deficiencies

Major Facility Deficiencies by Dosage Form (FY23)



| | | Liquid, parenteral | Liquid, otic, ophthalmic, nasal, inhalation | Semi-Solid, topical | Solid, tablet, capsule, film, oral powder, insert |
|---|--|-----------------------|--|------------------------|--|
| Manufacturing Facility Deficiencies | GMP inspection observations | 41 | 13 | 4 | 38 |
| | Pre-approval inspection observations | 10 | - | - | 12 |
| | Facility not ready for inspection | 1 | - | - | 1 |
| | Lack of quality information for device component facility | - | 1 | - | - |

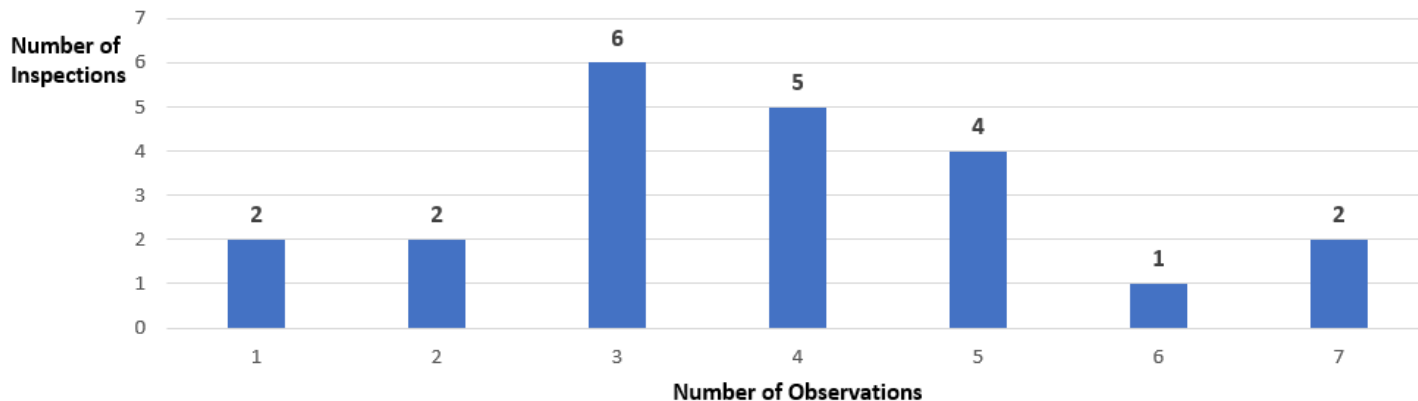
Total of 22 Applications for PAI Observations, 3 applications excluded due to API facilities

[fda.gov/cdersbia](https://www.fda.gov/cdersbia)

PAI Observations for Major Facility Deficiencies (FY23)



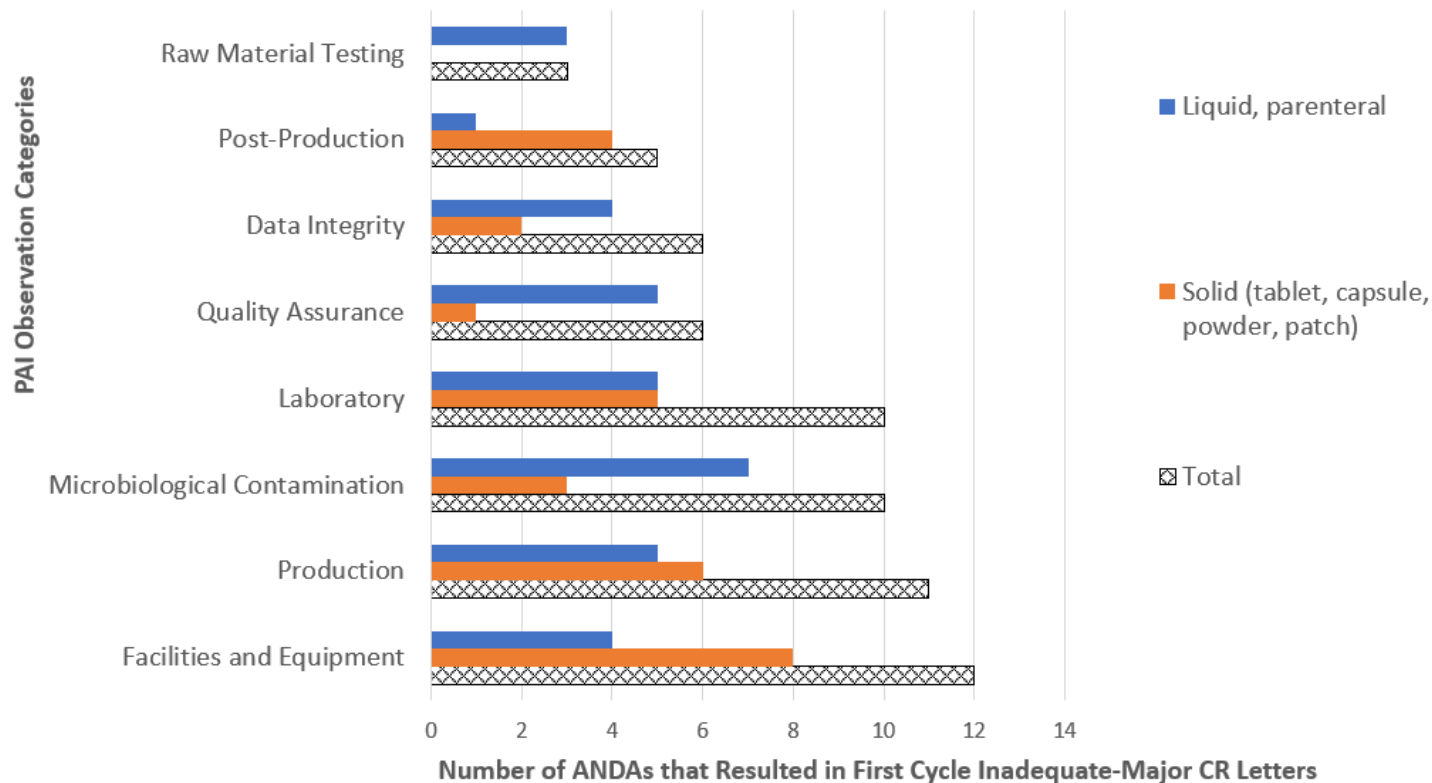
Number of Observations Cited for PAIs Associated with CRL-Major Facility Deficiencies (FY23)






Total of 22 Applications for PAI Observations, 3 applications excluded due to API facilities

[fda.gov/cdersbia](https://www.fda.gov/cdersbia)

PAI Observations from FY23 First Cycle ANDA Inadequate-Major CR Letters by Dosage Form



| | Sub-Category | Liquid, parenteral |
|---|--|---|
| Quality Assurance | Training are Inadequate or Not Followed | 1 |
| | Inadequate Investigations, Corrective and Preventative Actions (Excluding OOS Investigations) | 5  |
| Laboratory | Microbiological Testing Procedures are Inadequate or Not Followed | 1 |
| | Microbiological Contamination, Test Result Failures, OOS Investigation | 1 |
| | Chemical and Physical Testing Procedures are Inadequate or Not Followed | 1 |
| | Chemical and Physical Results, Test Result Failures, OOS Investigation | 3 |
| | Laboratory Equipment Cleaning and Maintenance Procedures are Inadequate or Not Followed | 0 |
| Causes of Microbiological Contamination | Microbiological Controls, Procedures, Environmental Monitoring are Inadequate or Not Followed | 5  |
| | Facility Design Does Not Support Aseptic Conditions | 2 |
| | Lack of Microbiological Data to Support Manufacturing Steps | 5  |
| | Cleaning and Maintenance of Facilities and Equipment Does Not Adequately Prevent Microbiological Contamination | 2 |
| Production Procedures and Development | Lack of Data to Support Manufacturing Steps | 3 |
| | Deficient In-Process Controls for Manufacturing Steps | 2 |
| | Visual Inspection Program | 0 |

| | Sub-Category | Solid (tablet, capsule, powder, patch) | |
|---------------------------------------|--|--|---|
| Laboratory | Microbiological Testing Procedures are Inadequate or Not Followed | 2 | |
| | Microbiological Contamination, Test Result Failures, OOS Investigation | 0 | |
| | Chemical and Physical Testing Procedures are Inadequate or Not Followed | 2 | |
| | Chemical and Physical Results, Test Result Failures, OOS Investigation | 3 | |
| | Laboratory Equipment Cleaning and Maintenance Procedures are Inadequate or Not Followed | 1 | |
| Facilities and Equipment | Equipment is Not Qualified or Not Available | 6 | ← |
| | Cleaning and Maintenance Procedures are Inadequate or Not Followed | 4 | ← |
| | Water System Deficiencies (may be both an equipment problem and a contamination problem) | 1 | |
| Production Procedures and Development | Lack of Data to Support Manufacturing Steps | 4 | ← |
| | Deficient In-Process Controls for Manufacturing Steps | 5 | ← |
| | Visual Inspection Program | 3 | |

Top 3 Categories / Sub-Categories for PAI- Major Facility Deficiencies (FY23)



- Liquid, Parenteral Drug Products:
 - Inadequate Investigations, Corrective and Preventative Actions (Excluding OOS Investigations)
 - Microbiological Controls, Procedures, Environmental Monitoring are Inadequate or Not Followed
 - Lack of Microbiological Data to Support Manufacturing Steps
- Solid, (tablet, capsule, film, powder) Drug Products:
 - Equipment is Not Qualified or Not Available
 - Cleaning and Maintenance Procedures are Inadequate or Not Followed
 - Deficient In-Process Controls for Manufacturing Steps
 - Lack of Data to Support Manufacturing Steps

Challenge Question #3

For FY23, what was the most frequent PAI observation sub-category associated with a CRL due to major process deficiencies for Solid dosage forms:

- A. Equipment not qualified or not available
- B. Facility Design Does Not Support Aseptic Conditions
- C. Lack of Data to Support Manufacturing Steps
- D. Facility Design Does Not Support Aseptic Conditions

Summary



- Process Deficiencies: Liquid, parenteral and Semi-Solid
 - New batches needed to support commercial scale up
 - Process Equipment-Related Leachables (PERLS)
- PAI Facility Observations: Liquid, parenteral and Solid
 - Investigation, Microbiological Controls, Microbiological Data
 - Equipment is Not Qualified or Not Available
- Limited to FY23 First Cycle Major CRL actions for Generic Drug Products

Questions?

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References



- 1- Association for Accessible Medicines, The U.S. Generic & Biosimilar Medicines Savings Report September 2023
- 2- Food and Drug Administration, Office of Generic Drugs 2023 Annual Report. 2024.
- 3- Food and Drug Administration, Generic Drugs Program Monthly and Quarterly Activities Reports (FY2022-FY2024)
- 4- Food and Drug Administration, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA - Guidance for Industry. September 2024.

