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

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Generic Drugs Forum (GDF) 2025 – April 10, 2025

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

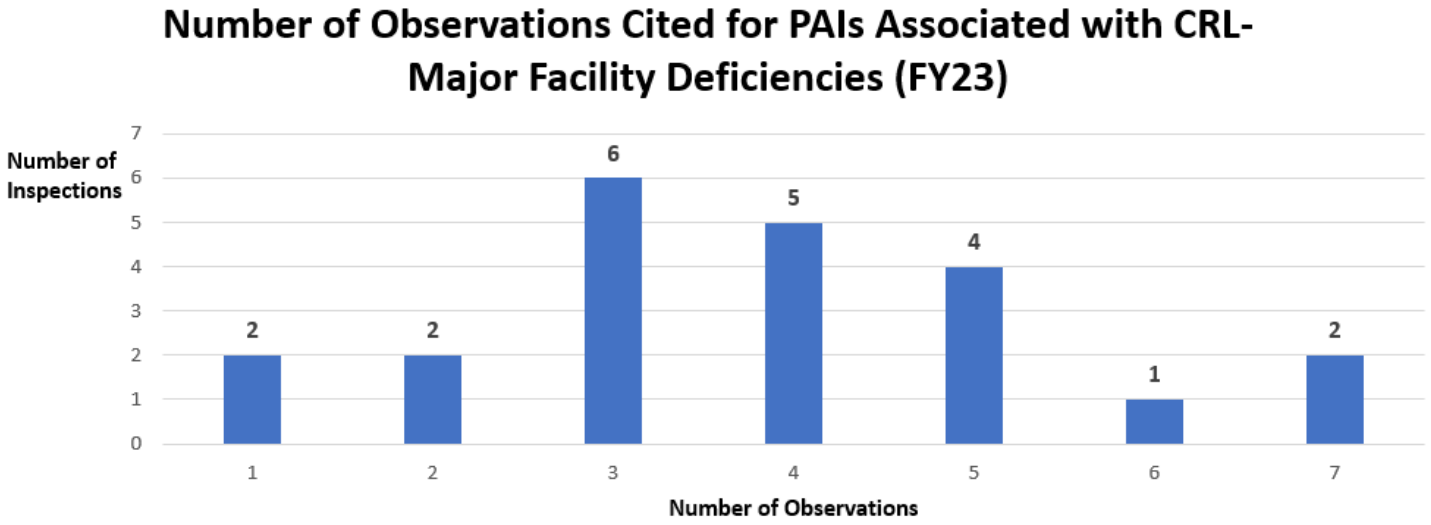
Facility Deficiencies

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	-	-

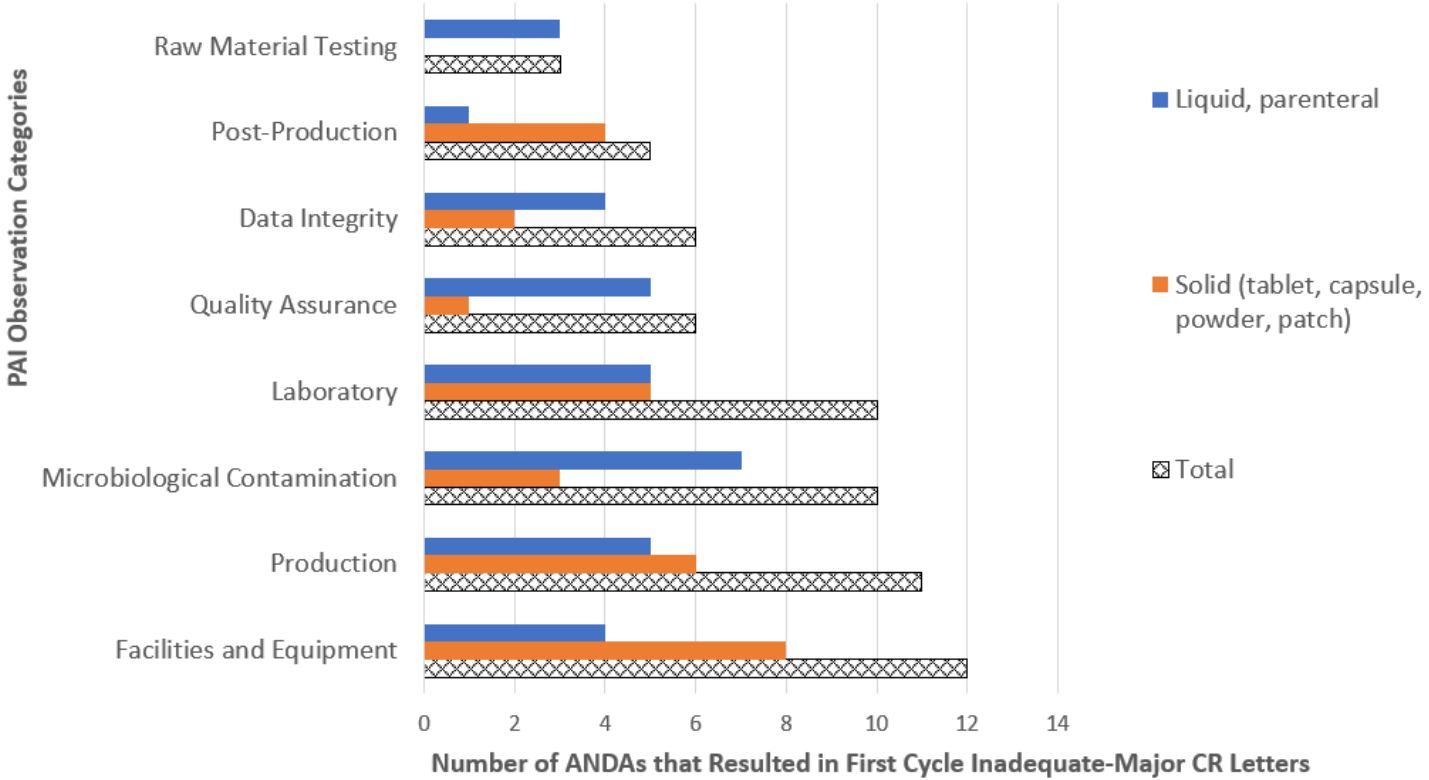
Total of 22 Applications for PAI Observations, 3 applications excluded due to API facilities

PAI Observations for Major Facility Deficiencies (FY23)



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

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

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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.


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