

# Microbial Contamination and Control Conference





## What will the focus be for this presentation

- Microbiological Contamination trends in warning letters and 483
- Case study
- Mitigation strategies



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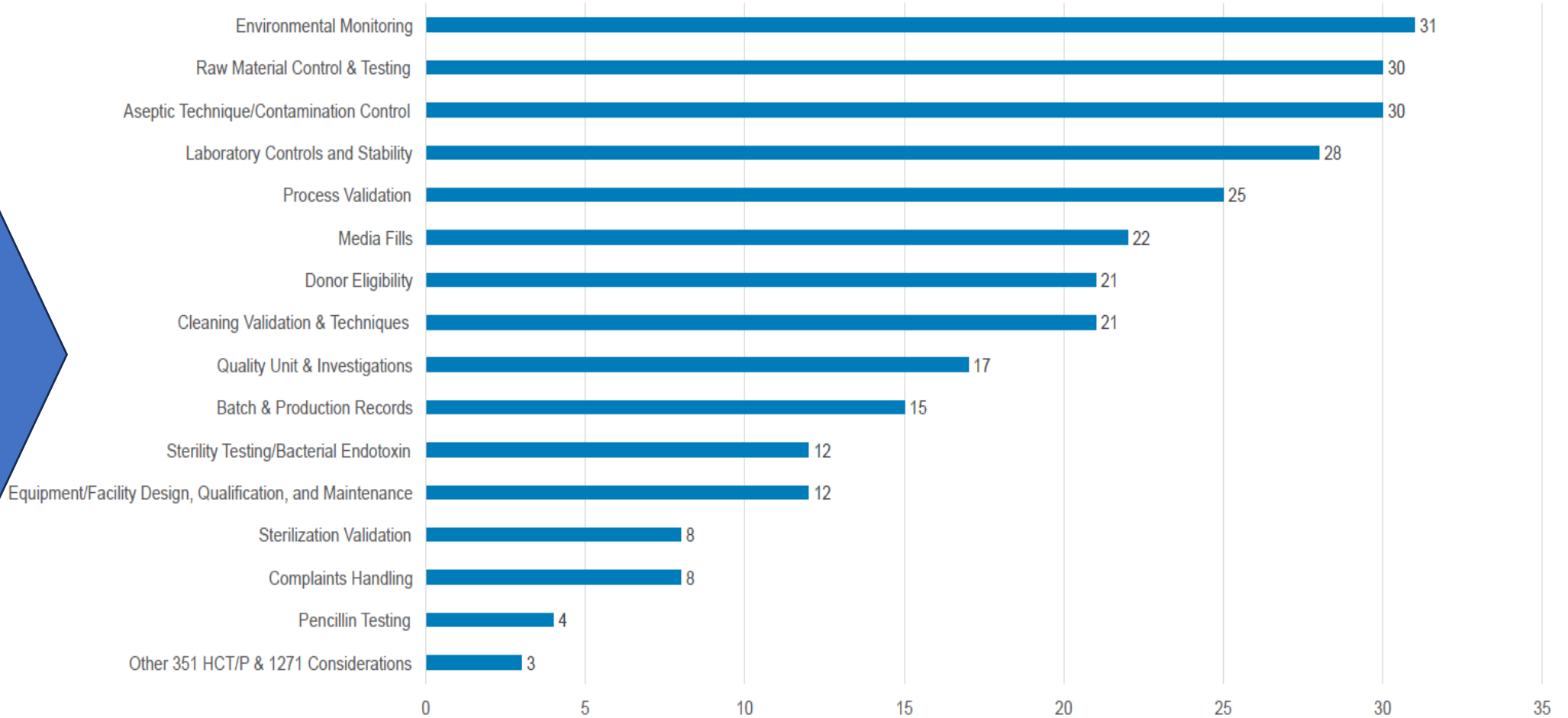
# Microbial Contamination and Control Conference

May 8<sup>th</sup> & 9<sup>th</sup>



Recent Data presented by FDA on Warning Letter Citations 2015-2023

2015-2023 Warning Letter Citations by Category



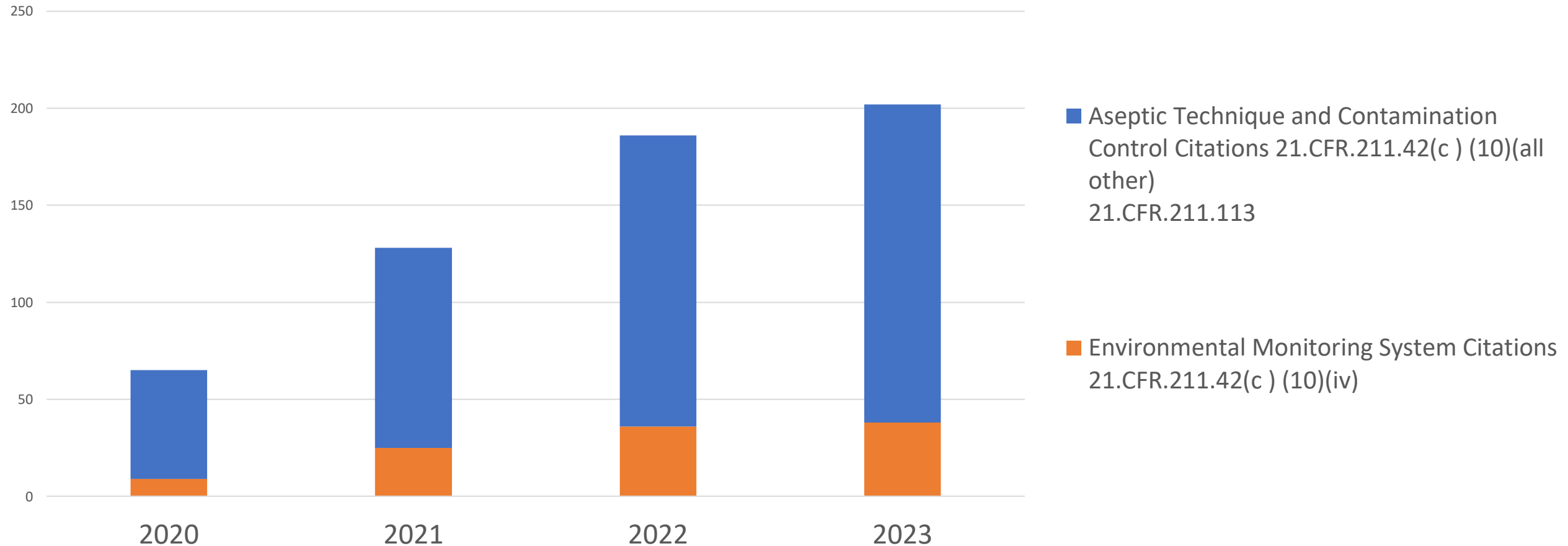


## Top GMP Violations Citations

- **Environmental Monitoring, Aseptic Technique and Contamination Control**
  - 211.113 Control of microbiological contamination
  - 211.42(c)(10) Design and construction features: aseptic processing
- **Raw Material Control and Testing**
  - 211.80 General Requirements
  - 211.84 Testing and Approval/Rejection of Components, Containers, and Closures
- **Laboratory Controls and Stability Testing**
  - 211.160 General Requirements
  - 211.166 Stability Testing
- **Process Validation**
  - 211.100 Written Procedures: Deviations



## Inspection citations EM, Aseptic Technique & Contamination control 2020-2023





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# Case Study



## Case Study



- European Biotech Company
- Pre- approval inspection in 2022
- Pre-announced
- 13 Observation 483 issued

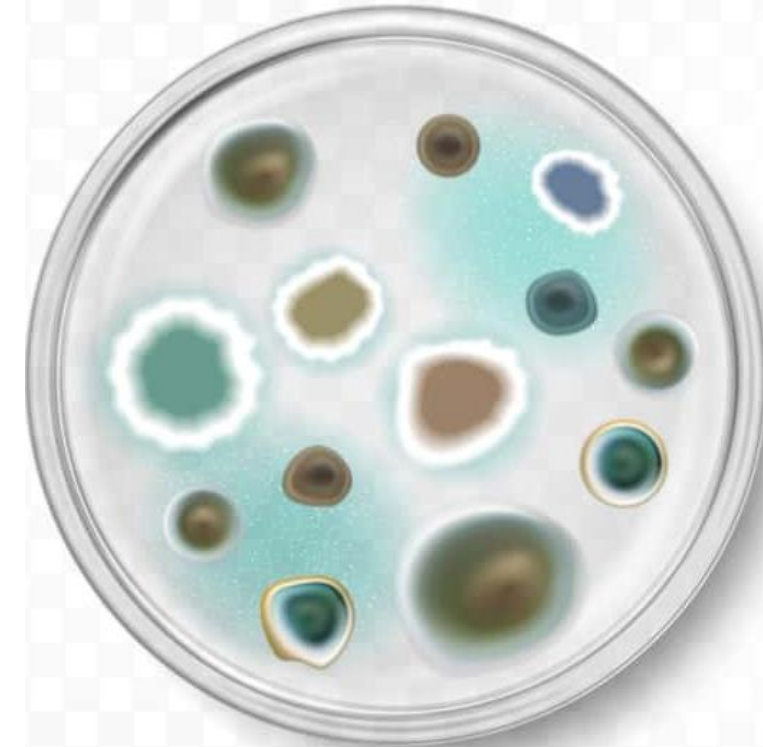


## Environmental Monitoring Deficiencies Cited

### 21.CFR.211.42(c ) (10)(iv) Environmental Monitoring

The manufacturing areas are not under control for bacteria and mold.

- There is an **unacceptably high number of mold recoveries in the classified rooms** used for (b) (4) manufacture of drug substance and drug product. Specifically, mold recoveries were 46(b) (4) and 176 in 2020 and 2021, respectively. The mold action limits (Grade C/D > CFU) are inadequate to initiate environmental monitoring investigation or deviation. In addition, the mold contaminants recovered via the EM Program have not been trended in a meaningful manner to identify trending patterns.
- There have been 91 and 89 **microbial excursions** in 2020 and 2021, respectively. The corrective and preventive actions (CAPA) implemented due to reoccurring microbial excursions were inadequate to avoid future occurrences of similar excursions.







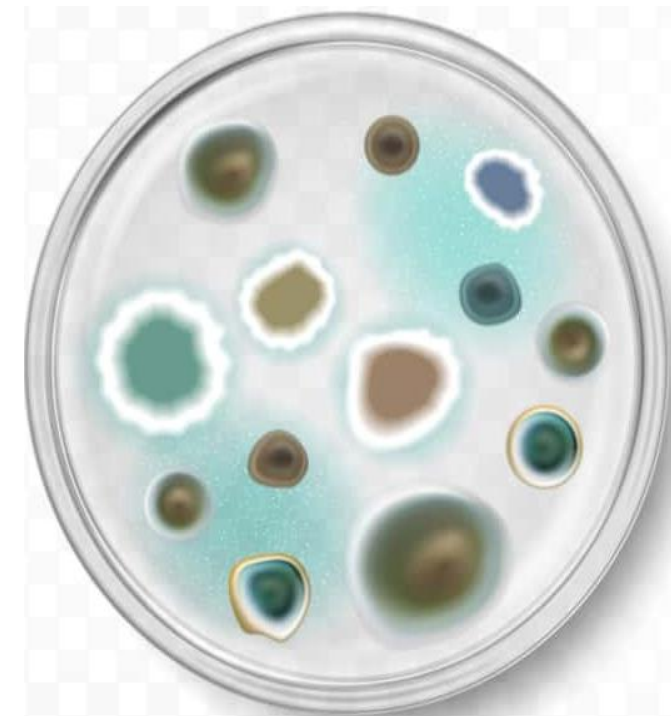
## Aseptic Technique & Contamination Control Deficiencies Cited

### 21.CFR.211.113 (b) Microbial Contamination Control

### 21.CFR.211.42 (c) 10 Design and construction features: aseptic processing

Procedures to control environmental conditions have not been adequately established. Specifically,

1. Materials to be used during filling operations are transferred into the Grade B filling suite through **the same path that personnel gown** into the Grade A filling suite. Examples Unwrapped items such as particle monitor; integrity tester and related parts; cleanroom tablets; cables; parts; maintenance tools, etc.
2. **RABS are inadequate** to meet acceptance criteria for Grade A (ISO 5). During the filling operation set up on March 16, 2022 the **operator did not wear sterile sleeve covers** and operator's lower forearm and the upper arms breached first air.





## Outcome

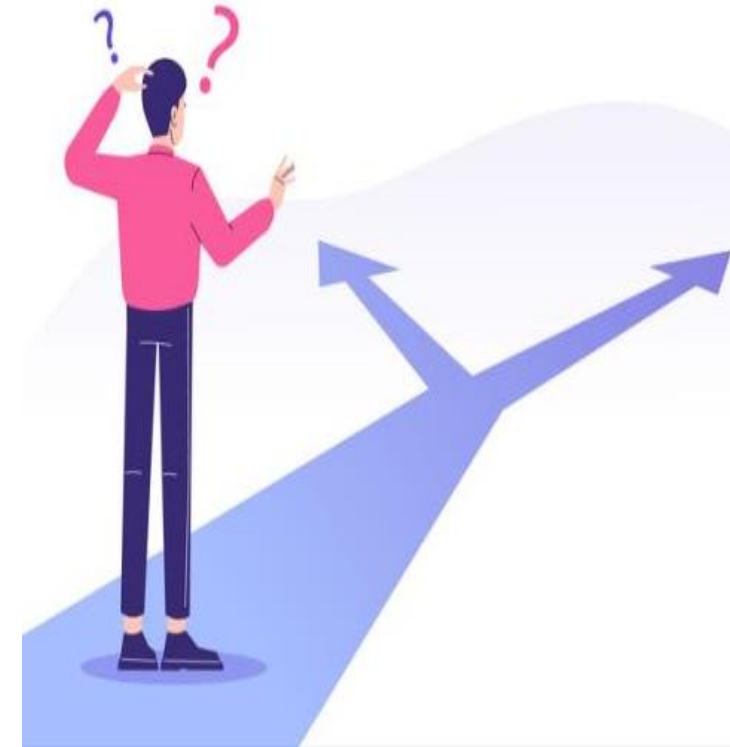
- Complete response letter citing facility deficiencies
- Warning letter issued
- Follow up inspections
- BLA Rejected





## How do firms get to this position

- Contamination Control Strategy deficient
- Inadequate Qualification and Training programs
- Not addressing Fit and Finish issues; Maintenance programs not in place
- Environmental Monitoring Signals not flagged
- Issues flagged by employees not corrected
- Management not in control
- Inspection readiness risks not properly assessed and mitigated





## Mitigation measures

- Develop a strong Contamination Control Strategy with risks identified and mitigated
- Don't focus on just the EM trends for excursions – look for emerging trends monthly from the recovery data.
- Gap assess against industry observations
- Invest in training
- Make maintenance, fit and finish a priority.
- Listen to the employee feedback

