

Regulatory Observation Trends: Recurring Quality- System Learnings

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Theme: Raising the Standard: GMP Quality Systems for the Next Decade

DISCLAIMER: The views and opinions expressed in this presentation are those of the author and do not wholly represent the official position of the U.S Food and Drug Administration for all matters.

Agenda



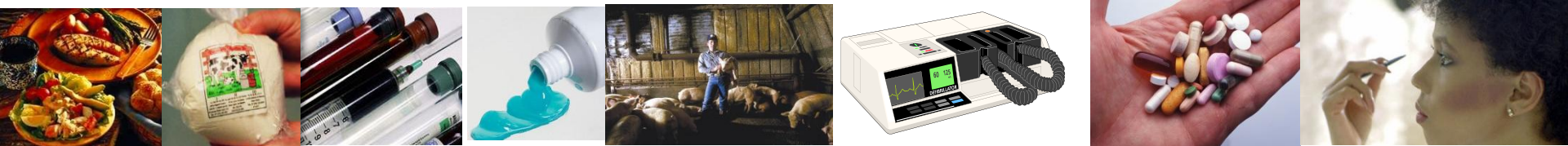
- **FDA Regulatory & Inspection Landscape**
CGMP foundation, inspection types and enforcement tools
- **Regulatory Observation Trends**
Warning Letter trends, foreign inspections and India-specific observations
- **Recent CGMP Inspectional Findings**
Sterile and non-sterile manufacturing trends
- **Recent Enforcement Examples**
Finished drugs, APIs, laboratories and OTC products
- **Recurring Quality-System Learnings**
Investigations • Data Integrity • Validation • Contamination Control • Quality Oversight

FDA's Mission:

Protecting the public health



- Assuring that the products the Agency regulates are safe and properly labeled
- Assuring that the products the Agency regulates are effective: human and veterinary drugs, vaccines and medical devices, food and cosmetics.
- Ensuring the safety of the nation's food supply and regulating tobacco products
- Advancing the public health by helping to speed product innovations



U.S. Federal Food, Drug, & Cosmetic Act

- 501(a)(1): Consists in part of filth
- 501(a)(2)(A): Insanitary conditions
- **501(a)(2)(B): Failure to conform with CGMP**
- 501(a)(3): Container composition renders a drug dangerous
- 501(a)(4): Contains an Unsafe Color
- 501(b): Strength, quality, or purity differing from official compendium
- 501(c): Misrepresentation of strength, etc., where drug is unrecognized in compendium
- 501(d): Mixture with or substitution of another substance
- 501(j): Deemed adulterated if owner/operator delays, denies, refuses, or limits inspection

Inspections - Types

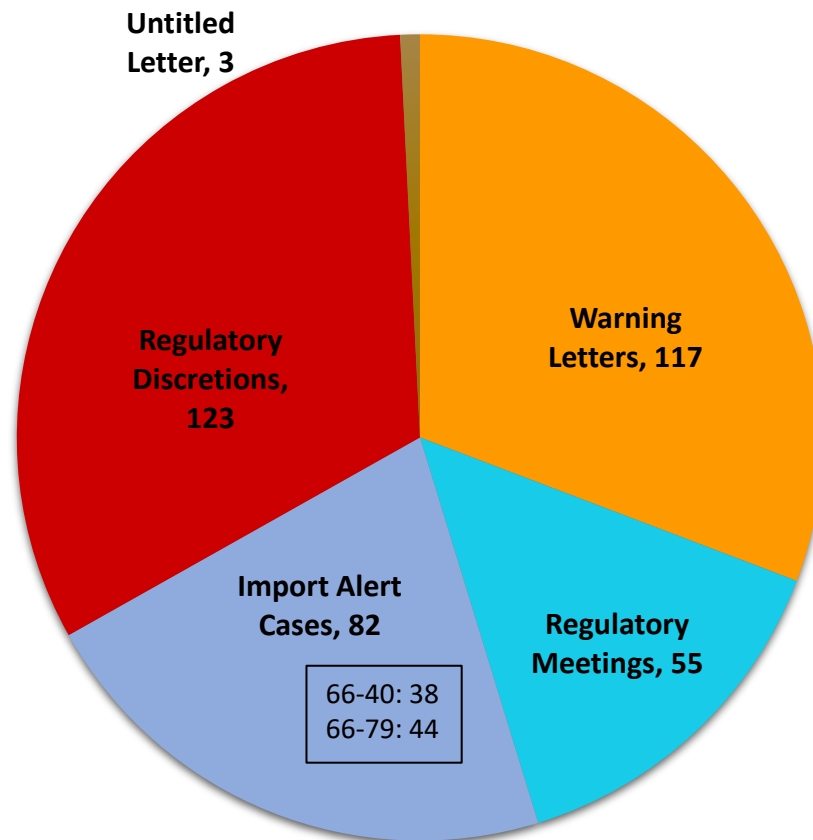
- **Surveillance (Routine) CGMP Inspections**
 - Comprehensive; risk-based frequency
 - To provide ongoing assurance that commercial products are of acceptable quality
- **CGMP inspections of newly-registered facilities**
- **Pre-Approval Inspections**
 - focused on the drug substance or drug product and manufacturing process in an application; may also conduct pre-approval inspections of analytical laboratories
- **Directed/For-Cause**
 - Compliance follow-up inspection
 - verify corrections following violative inspection
 - Specified coverage & purpose (e.g., f/u on complaint, evaluate a technology/technique)
- **Post-Approval**
 - Product-specific; soon after approval
 - Verify manufacturing processes and commitments in drug application

Enforcement and Advisory Tools



Regulatory Meetings	Injunctions
Consent Decrees	Import Alerts
Seizures	Warning Letters
Untitled Letters	Administrative Detention

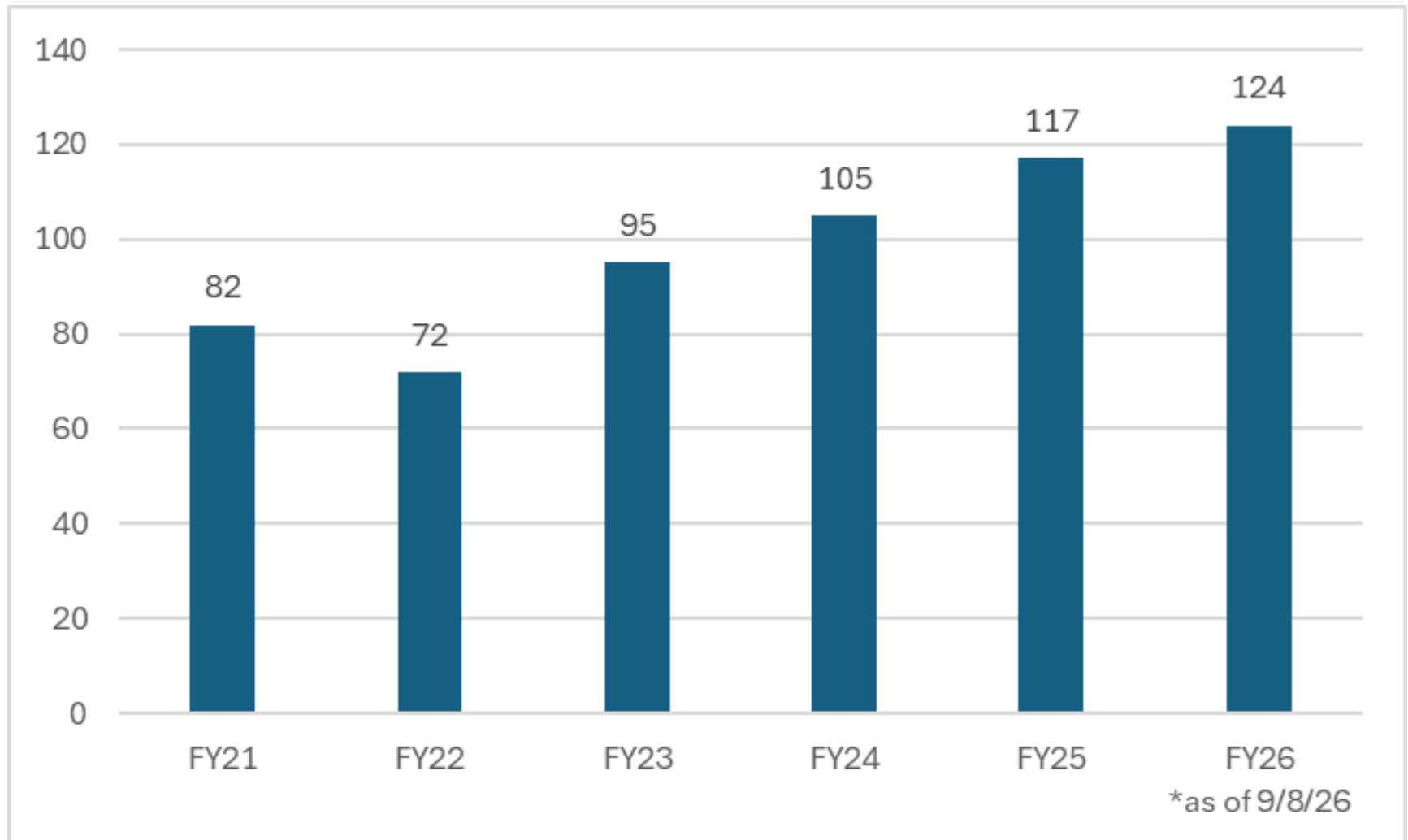
FY2025* Actions



Excludes compounding-related actions

*Actions Taken October 1, 2024 to August 31, 2025

CDER OMQ Warning Letters Per Year

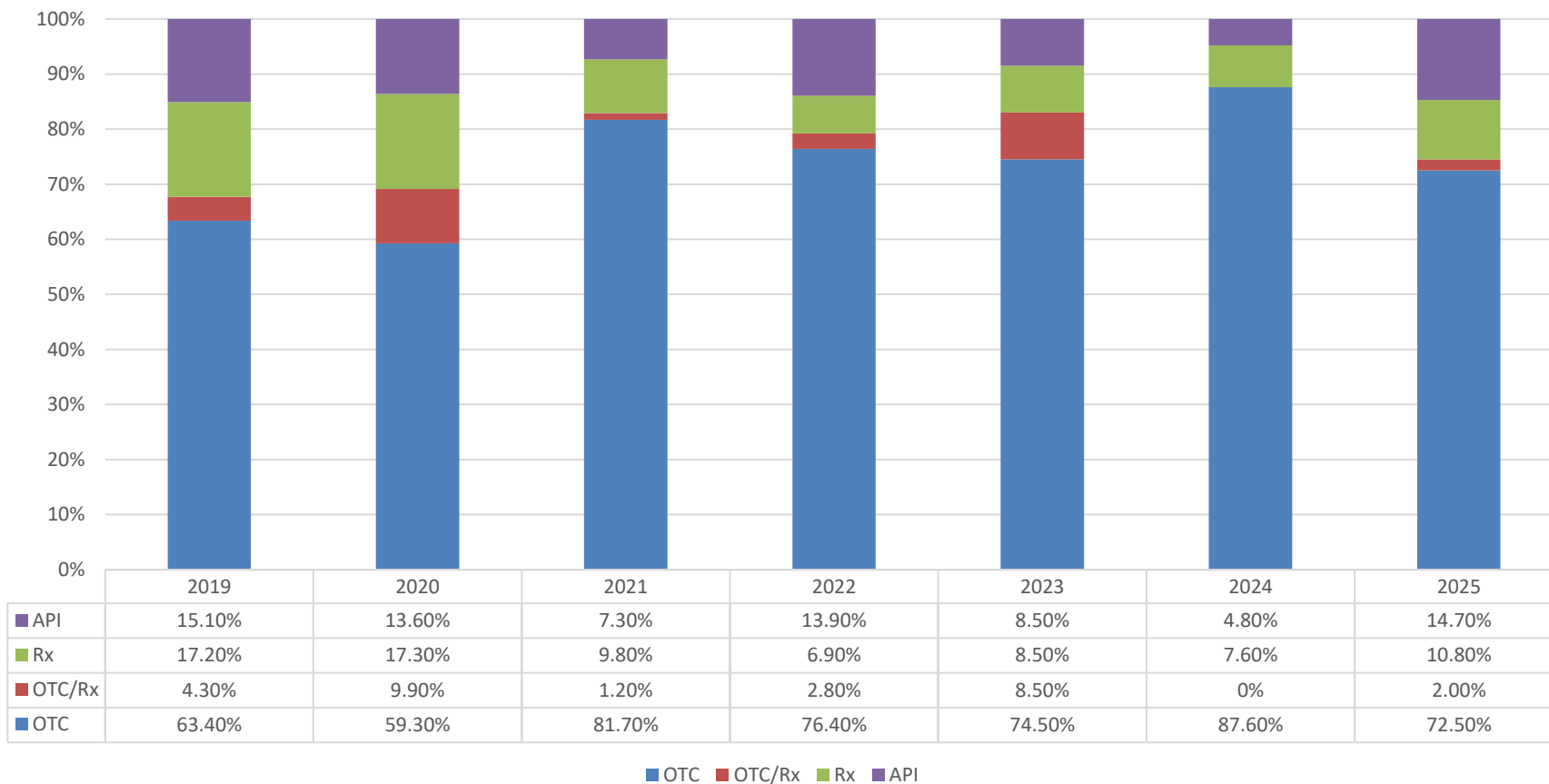


What's Driving the Record Number

- FDA's inspection of Ophthalmic facilities
- APIs for Pharmacy Compounding
- New OTC Entrants Lacking Fundamental CGMP
- Reduction of Inspection Backlog
 - Further focusing inspections on higher risk sites
- Deficient Raw Material Testing
 - Talc and Asbestos
 - DEG/EG
 - Alcohol

New Record

CGMP Warning Letters by Drug Type



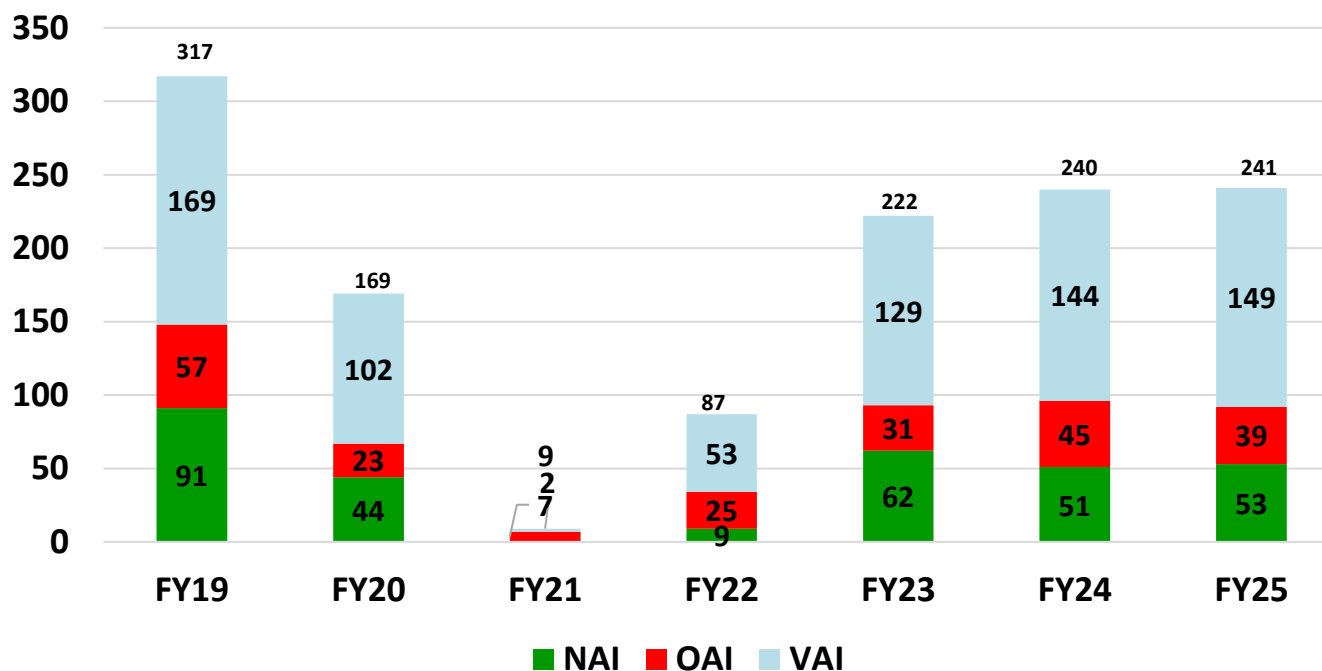
Warning Letters Issued 10/1/2018 to 8/31/2025

FDA's Foreign Inspections



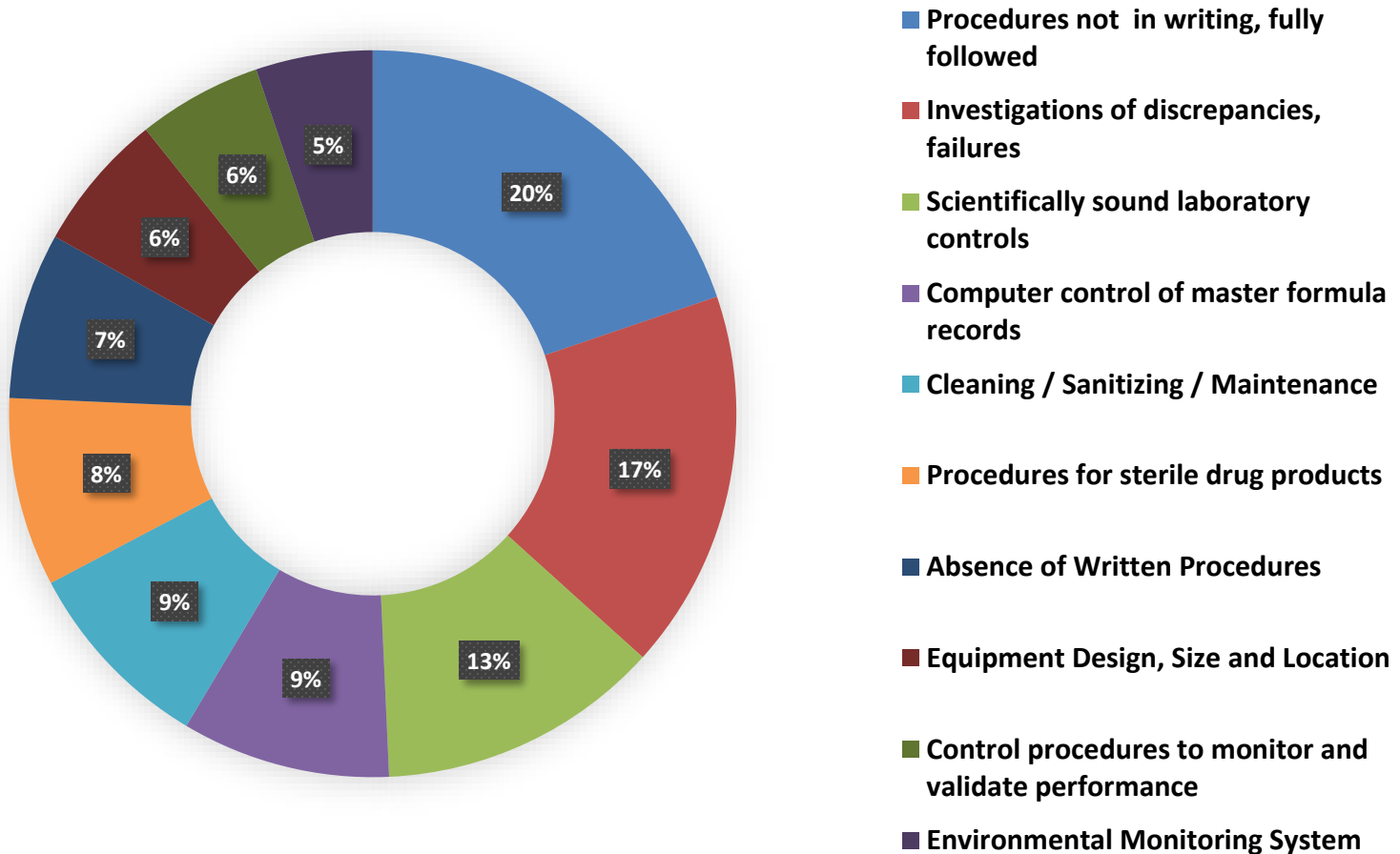
- FDA conducts approximately 12,000 domestic inspections each year.
- Across all FDA-regulated product programs, FDA conducts approximately 3,000 foreign inspections annually in more than 90 countries.
- Drug manufacturing represents a subset of this global inspection activity, with inspections prioritized using a risk-based approach.
- OHADI Foreign Inspections:
 - India
 - China
 - Canada
 - Latin America
 - Europe (*MRA)
 - ROW

Number & Classification of Pharmaceutical Inspections in India



Reference: Data from OQS

Top 10 citations issued in India for FY 2018-2025



Reference:

Recent CGMP Trends and Inspectional Findings

Sterile CGMP Trends



- Recently FDA has issued Warning Letters to multiple sterile drug facilities for:
 - Poor Aseptic Technique
 - Usually associated with poor training, or poor ergonomics/line design
 - Deficient Particulate Controls
 - Lack of visual inspection
 - Misclassification of particulates
 - Contamination with particulates such as Hair, Fiberglass, glass, fibers, etc.
 - Data Integrity of Microbiological Data
 - Disinfection directly prior to personnel monitoring sampling
 - Undercounting of colonies in the labs
 - Falsification of test results, even when no testing conducted

Sterile — Data Integrity / Destruction of Microbiological Evidence



Example from Recent FDA 483 Inspectional Observation:

- During the inspection, FDA investigators observed approximately 20 environmental and personnel monitoring plates with microbial growth discarded in red trash bags.
- Ten of these plates were associated with Grade A environmental or personnel monitoring locations; however, the corresponding laboratory records documented the results as 0 CFU or left them blank.
- Personnel finger-dab plates recorded as 0 CFU showed actual recoveries of 40, 11, 10, 9, and 7 CFU, while additional Grade A environmental plates exceeded established limits.
- FDA also found numerous EM/PM results left blank and monitoring plates that could not be located or accounted for, raising significant concerns regarding the completeness and reliability of microbiological data used to assess aseptic processing conditions.

Sterile — Smoke Studies / Loss of First-Air Protection



Example from Recent Warning Letter:

- “Smoke studies demonstrated a lack of unidirectional airflow in your ISO 5 aseptic processing operation.”
- FDA observed multiple instances of turbulent airflow in critical areas during interventions. During some interventions, an operator's head and upper body entered the Grade A area and blocked first air over critical operations. FDA also identified equipment operations that created unnecessary disturbances of airflow within the RABS.

Sterile — Smoke Studies / Loss of First-Air Protection



What was observed?
Curl or Eddy of
Smoke



What was observed?
Turbulence with smoke
contacting the covering on
the hopper and moving up
instead of down and away.

Sterile - poor ergonomics/line design



What was observed?
Vial loading- First air
breach



What was observed?
Volume check every 30
minutes – First air
breach

In addition, both these interventions were not simulated during media fill

Sterile — Inadequate Isolator Contamination Control and VHP Decontamination



Example from a Recent FDA Form 483: Grade A Isolator Contamination Control

- An aseptic process simulation showed microbial excursions at 13 locations. Microorganisms were detected at five locations after cleaning and VHP decontamination.
- The firm had not adequately assessed whether pre-decontamination cleaning introduced contamination or established the starting bioburden used to justify its VHP cycle.
- Key lesson: VHP is one control in a larger aseptic process. Its effectiveness depends on prior cleaning, controlled bioburden, exposure of all relevant surfaces, validated cycle conditions, intact gloves, and disciplined aseptic interventions. VHP cannot be assumed to reach shielded surfaces or correct contamination introduced after the cycle.

Sterile Finished Drugs — Recurring Contamination and Ineffective CAPA



Example from Recent Warning Letter:

- FDA found that the firm's **visual inspection program** was inadequate to ensure sterile injectable drug products were essentially free of visible particulates.
- FDA found that investigations of repeated contamination complaints for sterile drug products were not thorough, did not adequately expand in scope, and lacked scientifically supported root causes.
- Loose visible fibers were observed on aseptic-processing materials and tubing; unused protective material also contained loose fibers, identifying the material itself as a contamination source.

Non-Sterile GMP Trends

- Recently FDA has issued Warning Letters to multiple non-sterile drug facilities for:

Inadequate Investigations & CAPA

- Weak root-cause analysis
- Recurring OOS/deviations despite CAPA

Deficient Cleaning Controls

- Residues on equipment identified as “clean”
- Inadequate cleaning validation for shared equipment

Inadequate Material & Supplier Controls

- Over-reliance on supplier CoAs
- Inadequate DEG/EG testing of high-risk excipients

Laboratory & Data Integrity Deficiencies

- Incomplete/non-contemporaneous records
- Unjustified retesting or invalidation of results

Inadequate Process Control

- Weak process validation and in-process controls
- Insufficient monitoring of process performance

Non-Sterile Finished Drugs — Inadequate investigation



Example from Recent Warning Letter:

- FDA found that a finished drug product produced a failing TYMC result. After the contract laboratory was unable to identify the fungal species, the firm concluded **without supporting evidence** that contamination occurred during handling, transportation, or testing.
- The firm **invalidated the failure based on resampling results** and subsequently released the lot. FDA emphasized that microbial contamination may not be uniformly distributed within a batch.

Non-Sterile Manufacturing — Electronic Data & Audit Trails Not Reviewed



Example from FDA 483 Inspectional Observation:

- FDA investigators found that electronic data generated by manufacturing equipment were **not adequately reviewed, documented, or investigated as part of batch-record review**. Electronic records included process alarms, operator login/logout activity, recipe step changes, and operator privileges. FDA also found that the firm's procedure requiring **audit-trail and event-log review for production equipment had not been followed since its implementation**, raising concerns regarding the completeness and reliability of electronic manufacturing records.

Non-Sterile Finished Drugs — Manufacturing Without Completed Process Validation



Example from Recent Warning Letter:

- FDA found that the firm had **not performed process validation for a substantial portion of its drug products** manufactured on multiple production lines.
- Although the firm committed to developing and executing validation protocols, its response did not provide adequate schedules or timelines for completing process validation for each affected product.
- FDA also found that the firm had not adequately assessed the potential impact on **drug products already manufactured and distributed without a validated manufacturing process.**

API — Dirty Equipment Released as “Cleaned and Ready for Use”



Example from Recent Warning Letter:

- FDA investigators observed unidentified residues, apparent rust, and unidentified liquids on or inside product-contact surfaces of **non-dedicated API manufacturing equipment that had been identified as cleaned and ready for use**. Investigators also observed discolored and scratched manufacturing containers. FDA concluded that the firm's cleaning and equipment-maintenance controls were inadequate to prevent contamination or carryover.

API — Dirty Equipment Released as “Cleaned and Ready for Use”



API / Laboratory — Destruction of Original GMP Records



Example from Recent Warning Letter:

- FDA investigators found **original laboratory records in shred bins**, including an original pH-meter printout, an analytical-balance printout, and reviewer-signed analytical-data checklists. The firm could not associate some discarded records with specific batches or explain why they had been discarded.
- FDA also found that laboratory personnel reviewed photocopies rather than original records, while shred bins had historically been removed for off-site destruction without Quality Unit review.

API / Laboratory — Destruction of Original GMP Records



Bags of Documents to
be Shredded

Data Integrity Violations



Hidden GMP Documents

- Whole blue binder
- Tucked inside the drum between used clothing and used fluid-bed filter socks.
- Dated 1-2 weeks prior to Inspection.
- Management first response is that it was procedurally allowed. “First time”, “oversight”, then “insignificant or non-critical GMP documents”.. Then came the apology.

API — Inadequate Stability Program and Retest/Expiry Support



Example from Recent Warning Letter:

- FDA found that the API manufacturer lacked a documented ongoing stability program to demonstrate that API quality attributes remained acceptable throughout the labeled expiry period.
- The firm did not provide requested stability data for certain APIs.
- FDA concluded that, without an appropriate stability program, the firm lacked adequate scientific evidence to support storage conditions and retest or expiry periods.

OTC — DEG/EG and Methanol

Testing of High-Risk Components



Example from Recent Warning Letter:

- FDA found that an OTC manufacturer failed to adequately identity-test incoming glycerin, propylene glycol, and ethanol before use. The firm also used **nonpharmaceutical-grade propylene glycol**.
- Glycerin and other high-risk components were not adequately tested for DEG/EG, and incoming ethanol was not adequately tested for methanol or demonstrated to meet applicable impurity specifications.

In Summary — Recurring Quality-System Learnings



- Fundamental CGMP controls remain critical — procedures, investigations, laboratory controls, cleaning, validation, and material controls continue to drive significant findings.
- Adverse signals require scientifically sound investigation — OOS results, microbial excursions, contamination events, and adverse trends should be investigated to determine root cause and product impact.
- Data must be complete, accurate, and reliable — whether microbiological, analytical, paper, or electronic.
- Quality oversight extends across the product lifecycle — from suppliers and incoming materials through manufacturing, laboratories, contractors, and distribution.
- A mature quality system should detect and correct problems before they become regulatory findings.

The goal is not simply inspection readiness — it is maintaining a state of control.

Questions?