

FDA Updates and Recent Trends in the Inspection of Sterile Dosage Form

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One Agency. One Quality Voice.

- “
- *...ensure the Agency’s regulation of pharmaceutical products is a collaborative effort that best meets our public health mission.”*

Transmittal email for FDA's FY 2017 Strategic
Priorities for the Pharmaceutical Program

Four Major Types of Drug-Related Inspections

- **Pre-approval:**
 - supports the review of marketing applications for drug products to ensure high-quality manufacturing
- **Post-approval:**
 - is initiated after drug application approval to verify that the commercial-scale manufacturing produces the drug as it was designed and approved
- **Surveillance:**
 - monitors the state of pharmaceutical manufacturing quality to satisfy our legal obligation to inspect production operations
- **For-cause:**
 - is initiated in response to a specific event or observation that brings into question the quality of a manufacturing facility, process, or drug product;
 - is meant to determine whether recalls or enforcement actions are necessary, particularly as a result of the initial cause for concern

Concept of Operations Goals

Goals

Goals

- Create and implement a **formalized and streamlined facility evaluation and inspection program** that ensures:
 - Consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision-making for marketing applications across the FDA;
 - Strategic alignment across CDER and ORA functional units by clarifying roles and responsibilities;
 - Improved FDA’s operational capacity by enhancing collaboration between various CDER and ORA offices;
 - Enhanced quality and increased access to facility and regulatory decisional information across FDA;
 - Improved timelines for regulatory, advisory, and enforcement actions to protect public health and promote drug quality, safety, and effectiveness.

ConOps Highlights

What is new?

- Improved communication with stakeholders
decisional letters
- follow up engagements
- Defined timelines
- Parity between domestic and international inspections
- Improved collaboration, communication, and
information sharing between CDER and ORA
- Streamlined work flow
Consistent work processes
- Clear roles and responsibilities
- Better use of quality knowledge to support facility
evaluations (e.g., site dossiers)

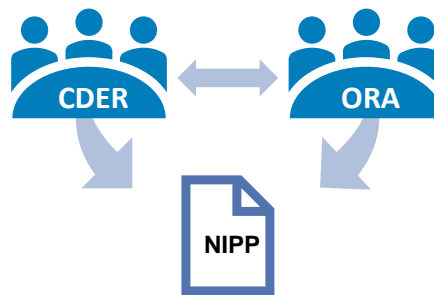


New Inspection Protocol Project (NIPP)

Overview

NIPP History and Background

- In February 2014, the Office of Regulatory Affairs (ORA) and the Center for Drug Evaluation and Research (CDER) began working together to support the advancement of pharmaceutical quality by developing a structured, consistent, efficient inspection and reporting paradigm.
- The sterile Pre-Approval and Surveillance Inspection protocols have each been piloted three times over the past four years.
 - Each new protocol version underwent extensive revision and refinement.
- The New Inspection Protocol Project (NIPP) inspections will not change the role of the investigator – which continues to be to collect and evaluate objective facts to assess the state of quality control and assurance practices of a site.





Why Are We Doing This?

The new inspection protocols aim to –

- Enhance consistent and comprehensive coverage of critical areas. The result of these inspections are structured data-rich reports that assess the state of quality of drug manufacturers.

The Goal of the program is to modernize inspections through collecting structured data that can be analyzed; this approach will enable FDA to efficiently analyze this data in order to –

- Better characterize and trend the state of pharmaceutical quality.
- Accelerate the pace of making informed/data-driven decisions.
- Lead to more targeted inspections in the future.

NIPP – Next Steps

Protocol development, IT implementation, piloting & refinement, training and operational implementation will continue and expand to include:

- Sterile dosage form
- Solid oral (non-sterile) dosage form
- Transdermal products
- Creams ointments & solutions
- Metered dose inhalers
- API's
- Terminally sterilized products

Mutual Recognition Agreement

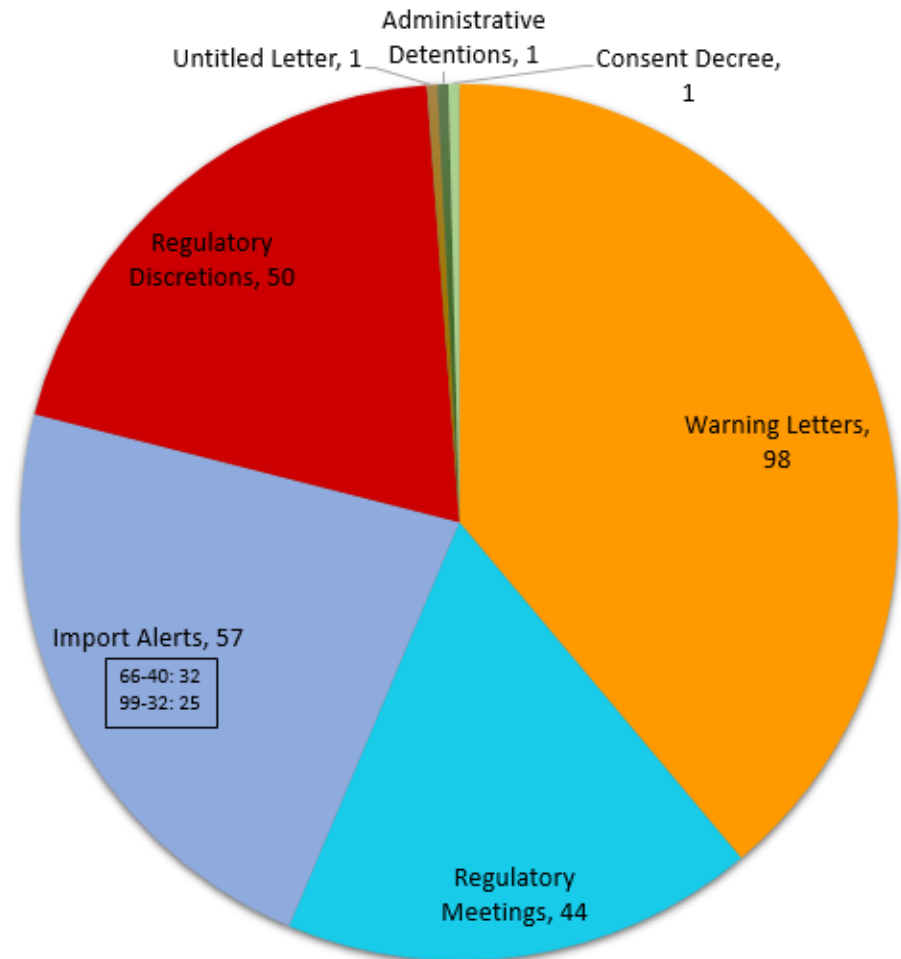
- MRA between FDA and the European Union allows drug inspectors to rely upon information from drug inspections conducted within each other's borders.
 - Evaluations and Negotiations started May 2014
 - Implemented November 1, 2017
 - July 2019 -28 EU countries capability
 - Ongoing evaluations to include Vet oversight
-
- <https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra>

Enforcement and Advisory Tools



FY2019 Regulatory Actions

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



Excludes compounding-related actions

Actions issued October 1, 2018 to September 30, 2019

Total CGMP Warning Letters by Country FY2015 to FY2019

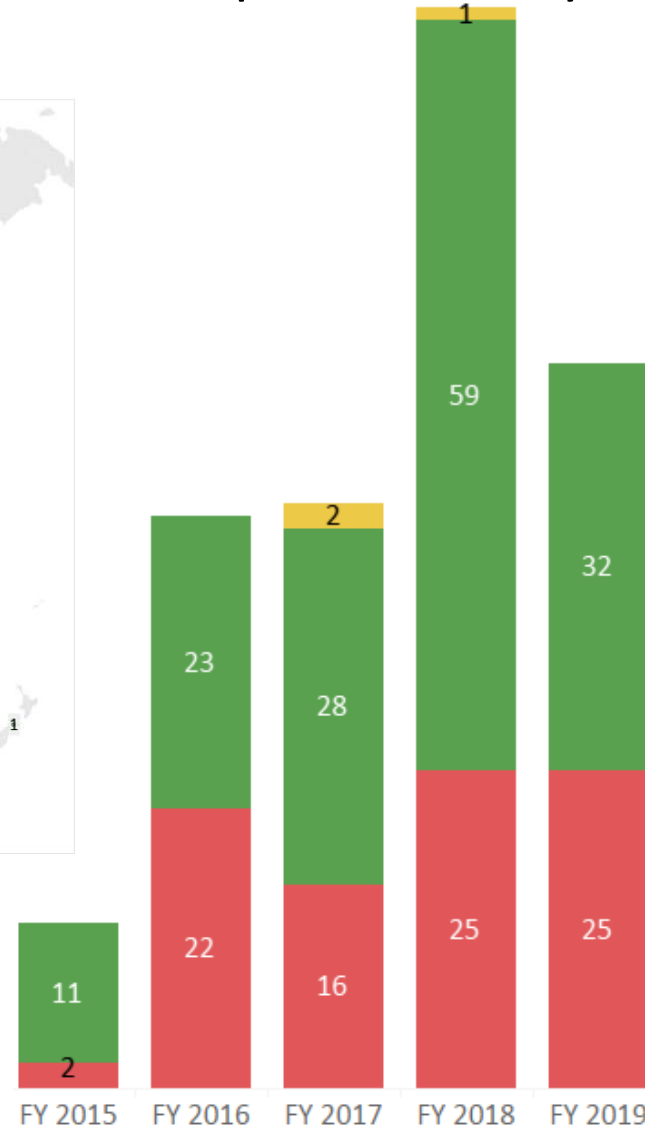
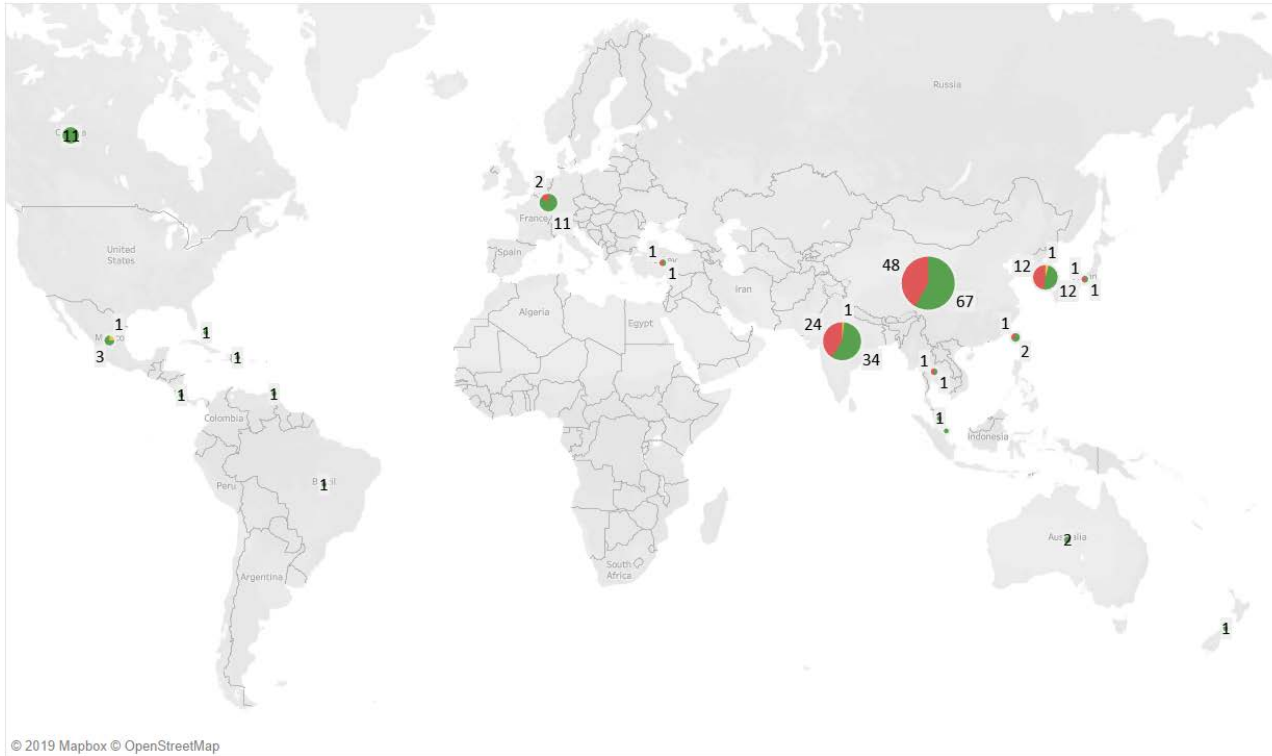


*Europe WLS and China/Hong Kong WLS
Grouped into one dot respectively, but can be separated*

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Total Import Alerts by Country (FY15-FY19)

Total Import Alerts by FY



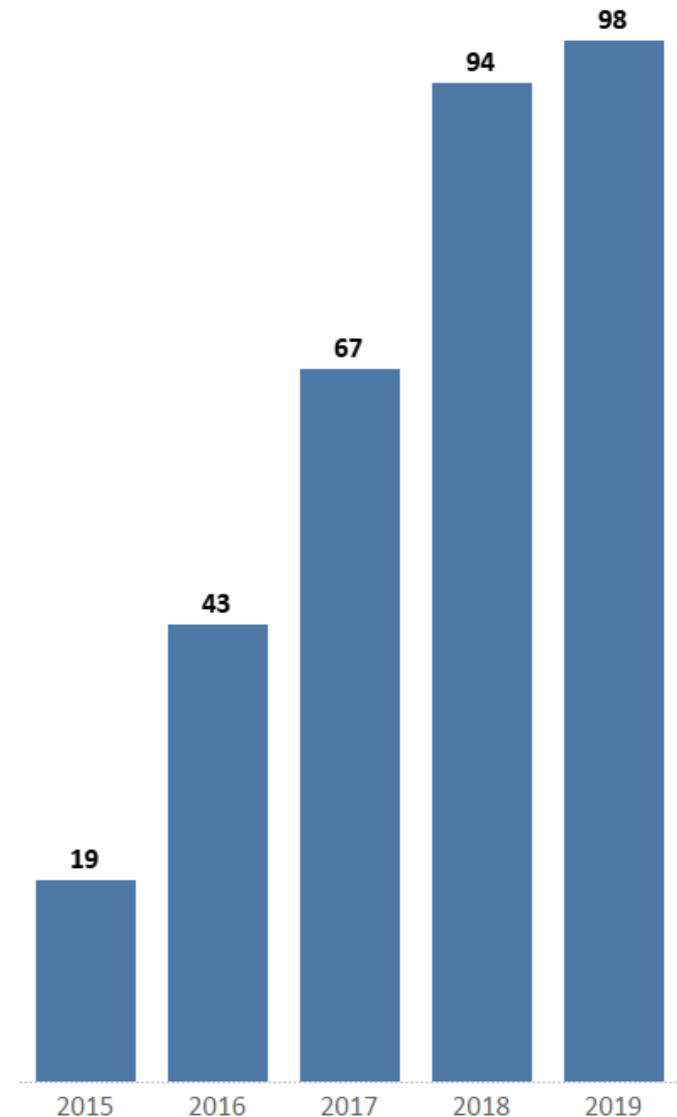
OMQ FY 2015-2019 Warning Letters



Warning Letters by Country

State	2015	2016	2017	2018	2019
United States	2	7	15	19	54
China	2	14	19	24	14
India	9	11	14	15	17
Europe	3	5	8	8	2
Korea			2	9	5
Canada	1		3	7	1
Japan		1	3	3	
Taiwan		3		2	1
Australia				3	
Brazil		2	1		
Mexico				3	
Singapore			1		1
Costa Rica					1
Dominican Republic				1	
Malaysia					1
New Zealand	1				
Philippines			1		
Thailand	1				
Turkey					1
Grand Total	19	43	67	94	98

Warning Letters by Fiscal Year



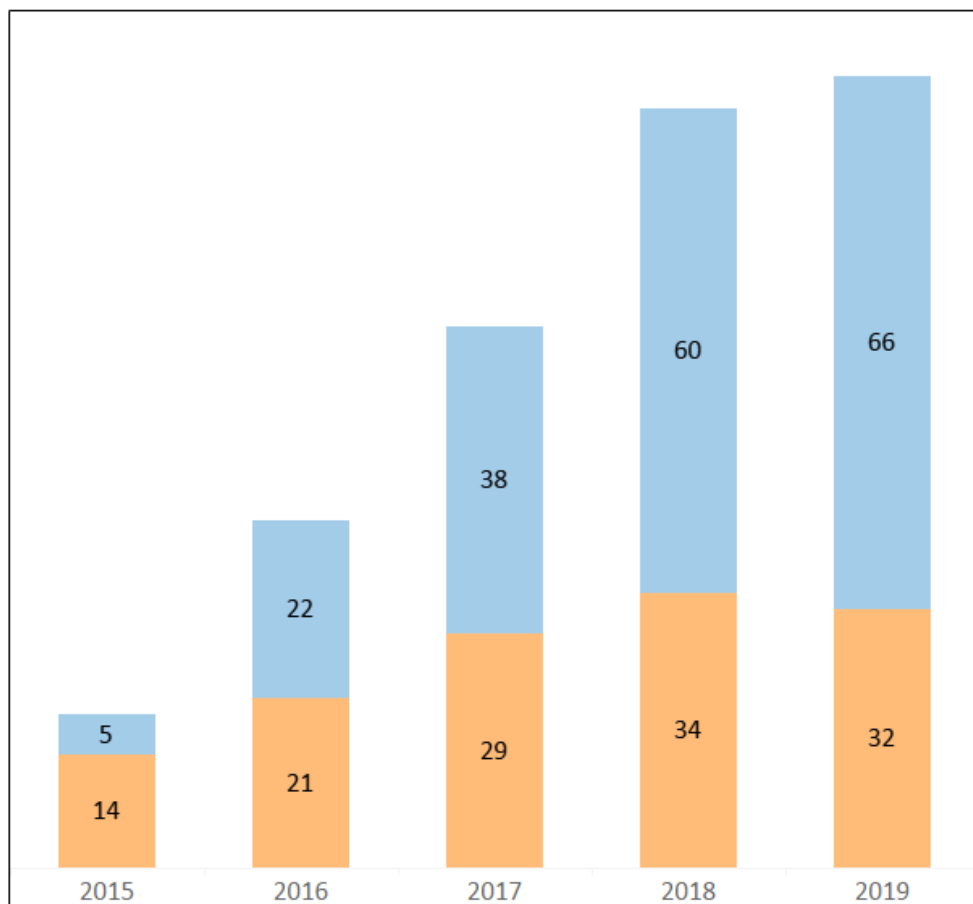
Compounding Warning Letters not included.

Europe and China/Hong Kong grouped for this slide

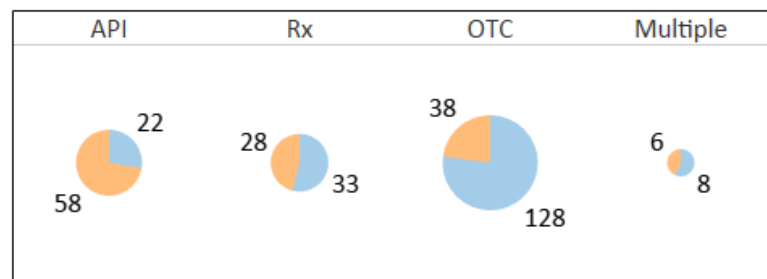
Data Integrity



Warning Letters Issued Containing Data Integrity Charges by Fiscal Year



Distribution of Data Integrity Charges by Drug Type





Sterile Dosage Forms

Sterile Dosage Forms

Parenteral: Preparation intended for injection through the skin (SQ, IM, IV, IP or IT) or other external boundary tissue so the active substances are administered directly into a blood vessel, organ, tissue or lesion.

- Large Volume Parenteral (LVP): Single-dose injection packaged in containers labeled as containing more than 100 mL



Sterile Dosage Forms

- Small Volume Parenteral (SVS, SVL, SVT): Injection packaged in containers labeled as containing 100 mL or less.
 - Single dose
 - Multiple dose usually includes substances to prevent microbial growth.



Vials made of glass or plastic and sealed with rubber stoppers



Ampoules are sealed glass containers with elongated necks that are broken off.



Prefilled syringes

Sterile Dosage Forms

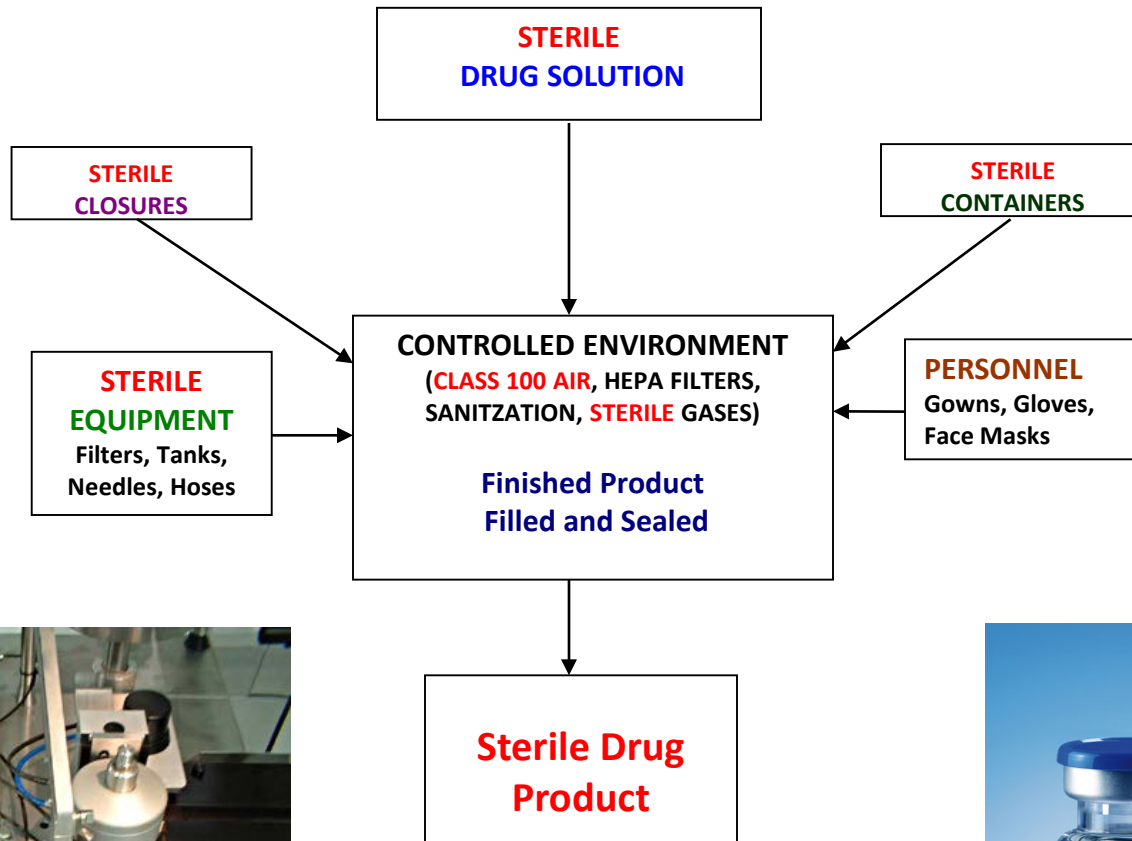
Sterile Non-Injectables

- Topical Ointments, Solutions, Lotions (SLQ)
 - Ophthalmic drugs (200.51)
- Implantable drugs (NEC)
- Aqueous based inhalers (200.50)



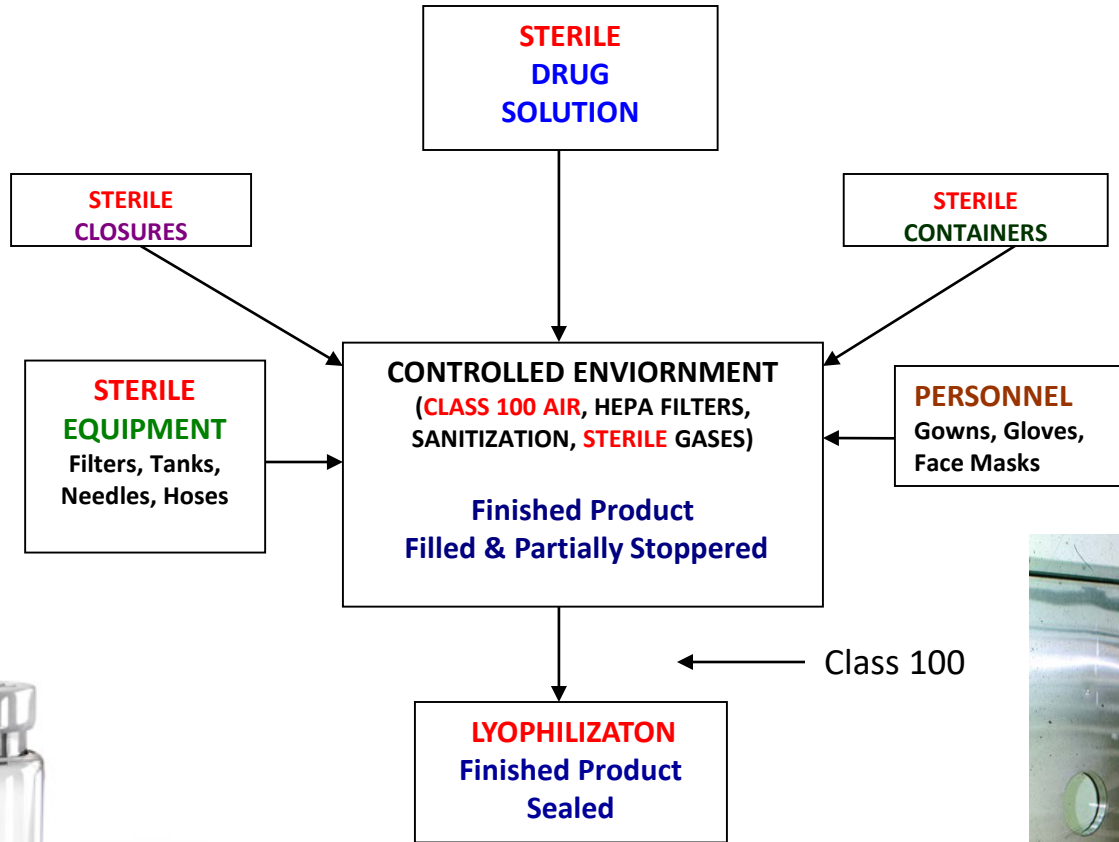
ASEPTIC PROCESSING

Drug containers and closures sterilized separately and assembled in an aseptic environment using sterile equipment



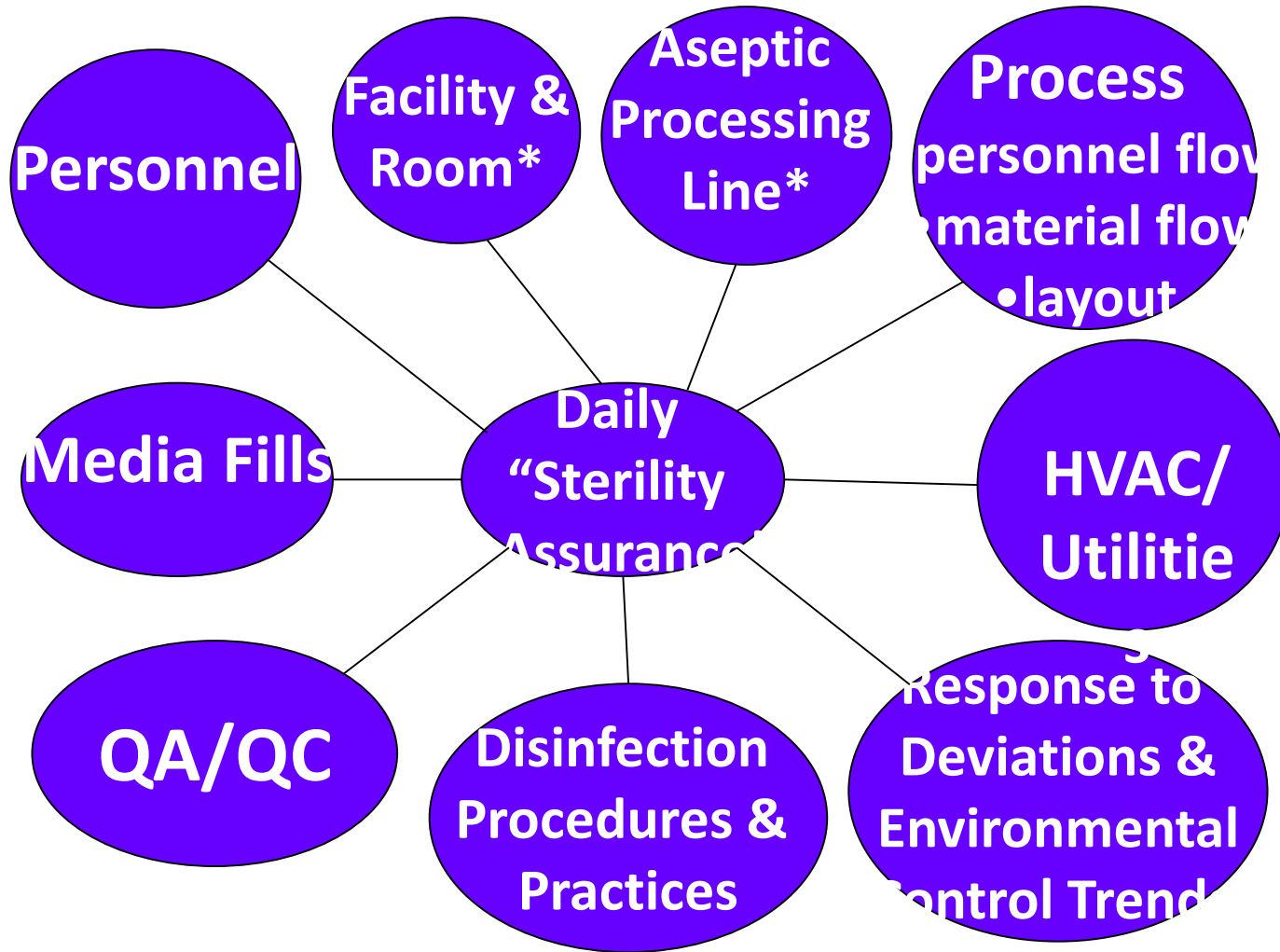
ASEPTIC PROCESSING & LYOPHILIZATION

Drug containers and closures sterilized separately and assembled in an aseptic environment using sterile equipment followed by lyophilization.



Aseptic Vs Terminally Sterilized

- There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization.
- Aseptic processing involves more variables than terminal sterilization.
- Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control.
- A terminally sterilized drug product, on the other hand, undergoes final sterilization in a sealed container, thus limiting the possibility of error.



**Includes both design and maintenance*

The Holistic Facility

Aseptic Processing requires “A strict design regime, not only on the process area, but on the **interactions with surrounding areas** and the **movement of people, materials and equipment** so as not to compromise the aseptic conditions.”

[ISPE Sterile Manufacturing Facilities Guide, Volume 3, January 1999]

Facility Equipment and Design

- It is essential for the equipment to be designed to prevent entrainment of lower quality [Surrounding] air into the critical area
 - *2004 Aseptic Guidance*

Human Factor

- Sciences of human factors engineering and human reliability analysis can provide valuable tools
- Human error may be more a symptom of an underlying problem rather than its cause.
- “...Errors can occur when a manufacturing process has not been sufficiently designed and validated... Also, problems may arise when work instructions, procedures, or policies are poorly written or designed,

- ... or when the operator-equipment or ***operator-process interface is poorly designed or difficult to use.***
- Therefore, it is useful to explore whether the existing manufacturing or other process may have contributed to the error or incident before assigning human error as the [primary] cause of the deviation or incident.”

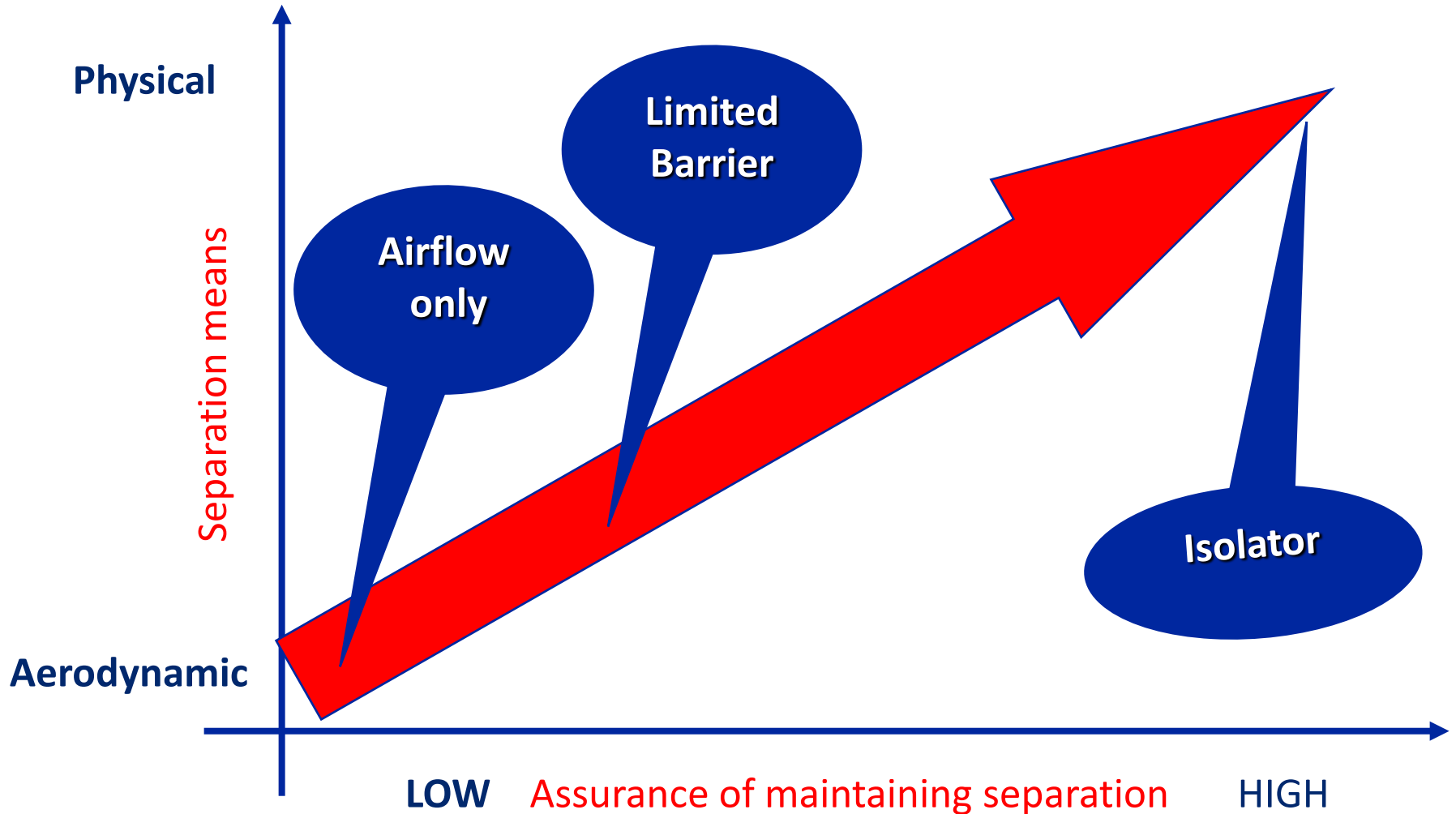
❖ [O'Donnell, K. “Human Error and Retraining,” *IVT Journal*, 2009]

Human Factor

Consider the variability in these critical Human-Machine interactions

- ✓ **Routine** Interventions
- ✓ **Non-Routine** Interventions: Fixing a Vial Jam or equipment malfunction
- ✓ **Setup** of equipment (Stopper Hopper, BFS Machinery, etc.)
- ✓ **Disinfection** of processing line and room
- ✓ **Charging containers or closures** onto a filling line
- ✓ **Aseptic connections**
- ✓ **Transfer of product** (transfer of half-stopped vials to the lyophilizer; loading the lyophilizer, etc.)
- ✓ **Aseptic addition** of a non-filterable ingredient
- ✓ **Wrapping parts and equipment** for porous autoclave load
- ✓ **Clearance of specified number (or all) units on the aseptic processing line** because of major/extended intervention

Open Vs Closed System



[Adapted from Farquharson, G. "ISO 14644...Part 7: Separative Devices," 8th Pharmaceutical Isolator Conference Warwick, U.K. December, 2004.]

Contract Manufacturing

- “Not only are buyers unable to observe manufacturing quality, but firms that contract out manufacturing of their product ***often do not have the same level of insight into or oversight*** of the contract manufacturer’s quality systems as they would have into their own.
- ***Over-commitment on manufacturing capacity by a contract manufacturer can lead to*** an unsustainably high number of products on each line and ***substandard oversight of the process.***”

❖ [Woodcock, J and Wosinska M., Clinical Pharmacology & Therapeutics, “Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage,” Jan 2013]

Contract Manufacturing

- Senior Management Responsibility extends beyond local site or corporation. Includes management review and control of...
 - *Outsourced activities (CMOs)*
 - *Quality of incoming materials (ingredient manufacturers)*
 - **Prior to outsourcing operations or selecting material suppliers**, assess suitability and competence of the other party to -
 - *carry out the activity*
 - *provide the material using a defined supply chain*
 - Examples of program elements -
 - *audits, material evaluations, quality agreement, monitoring and **reviewing supplier performance**, etc.*
- ❖ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - *ICH Q10*

Managing Risk Everyday Throughout the Lifecycle

- A drug manufacturer is responsible for implementing dependable daily operations that assure consistent drug quality.
- Management's daily decisions on myriad issues involving
 - equipment, materials,
 - maintenance, staff qualifications,
 - supervision, process control, and investigations

will *ultimately determine the quality* of the drugs that are shipped from a given facility.

❖ [Woodcock, J and Wosinska M., Clinical Pharmacology & Therapeutics, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage," Jan 2013]



Warning Letter Examples



“Your firm **failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination** of drug products purporting to be sterile, and that include **validation of all aseptic and sterilization processes** (21 CFR 211.113(b)).”

January 26, 2018 Warning Letter cited poor aseptic behavior, such as reaching over open vials and disrupting unidirectional airflow, without removing affected units; failure to include set-up and routine aseptic manipulations and interventions in smoke studies; rejection of integral vials during a media fill that would not have otherwise been removed during production; not all personnel authorized to enter aseptic processing were required to participate in a media fill at least once a year; no procedures for training and qualification of personnel performing examination of media fill units; and lack of active air monitoring in ISO 5 areas.

Also described failure to thoroughly investigate 140 complaints of a particular defect.

<https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm594395.htm>

Various GMP Deficiencies

April 24, 2018 Warning Letter cited failure to test incoming components; the release of batches without reviewing all production and control records (microbiological testing); equipment design deficiencies (dead legs); lack of air handling systems and control/monitoring of temperature and humidity in production and warehouse.

“Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).”

May 31, 2018 Warning Letter cited several environmental monitoring plates from ISO 5 and ISO 8 areas which exceeded action limits, and for which no investigations were initiated (and “your firm had reported no results outside limits for over a year prior to the inspection date”); inadequate collection of surface samples, which “had been occurring for approximately 1–2 years”; late and missed stability pulls, for which no investigation was raised; failure to include 15 investigations of product yield failure in annual product reviews.

“Visible particles in some of the drug vials for injection”

April 13, 2018, FDA alerted health care professionals of a voluntary recall of all non-expired products marketed as sterile made by a particular firm, after a recent inspection found visible particulates in vials and poor sterile production practices.

The **483 issued April 6, 2018** describes inadequate environmental and personnel monitoring samples, pressure differential data not reviewed, inadequate gowning, inadequate conditions for visual inspection of finished vials, incomplete media fill records missing the number of vials filled, and rust observed on HEPA return grates in ISO 7.

“Lack of sterility assurance”

July 10, 2018, FDA alerted health care professionals, patients, veterinarians, and animal owners of a voluntary recall following our observation of insanitary conditions and poor sterile production practices at a particular firm.

Our **follow-up inspection** to a **March, 2017 Warning Letter** found personnel touching non-sterile surfaces without sanitizing their hands or changing gloves prior to returning to the ISO 5 hood; handling components with bare hands while disinfecting those items, prior to placement in the pass through; failure to use a sporicidal disinfectant at the appropriate concentration and contact time; use of non-sterile cleaning wipes in ISO 5; and white residue on the face panel of the HEPA filter supplying air to the ISO 5 area, as well as dirt and residue on the floor of the ISO 7 area. On **June 7, 2018, the firm informed FDA it was ceasing sterile operations.**

“Continued to produce and distribute...even after identifying instances of microbial contamination in your ISO-5 and ISO-7 areas”

April 4, 2018 Warning Letter also describes use of non-sterile wipes to clean the ISO 5 work surface, failing to disinfect gloves frequently between operations, failing to adequately clean after handling hazardous drugs, and the presence of cardboard boxes and a paper note pad in the ISO 7 room.

“Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written and followed.”

This **483** issued **September 26, 2017** describes repeated media fill failures, after which product continued to be distributed. Discrepancies were observed in the media fill records, and the failures were inadequately investigated.



Thank You