# Integration of Assessment and Inspection for Biological Products

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# Learning Objectives

- Learn the basis for assessment and inspection for biological products
- Learn the importance of both the assessment and inspection

# Presentation Outline

- Laws, regulations, and guidance
  - Provides the basis for application assessment and site inspection
- Overview of microbiology quality assessment of Biologic License Applications (BLAs)
- Case Study

# Laws, Regulations, and Guidance

- **Public Health Service Act** – Section 351 (a)(2)(C) – Licensure of biological establishments and products
  - The biological product must be safe, pure and potent
  - The facility in which the biological product is manufactured, processed, packed, or held must meet standards designed to assure that the biological product continues to be safe, pure and potent

# Laws, Regulations, and Guidance

- **Federal Food, Drug, and Cosmetic (FD&C) Act** (1938, 1962, 1997, 2007)
  - Biological products are also drugs
  - The FF&C Act applies to a biological product, except no application required under section 505
  - Inspection under both the provisions of both the PHS Act and the FD&C Act

# Laws, Regulations, and Guidance

Both PHS and FD&C Acts require biological products to be manufactured under cGMP as described in 21 CFR 210, 211, and 600-680

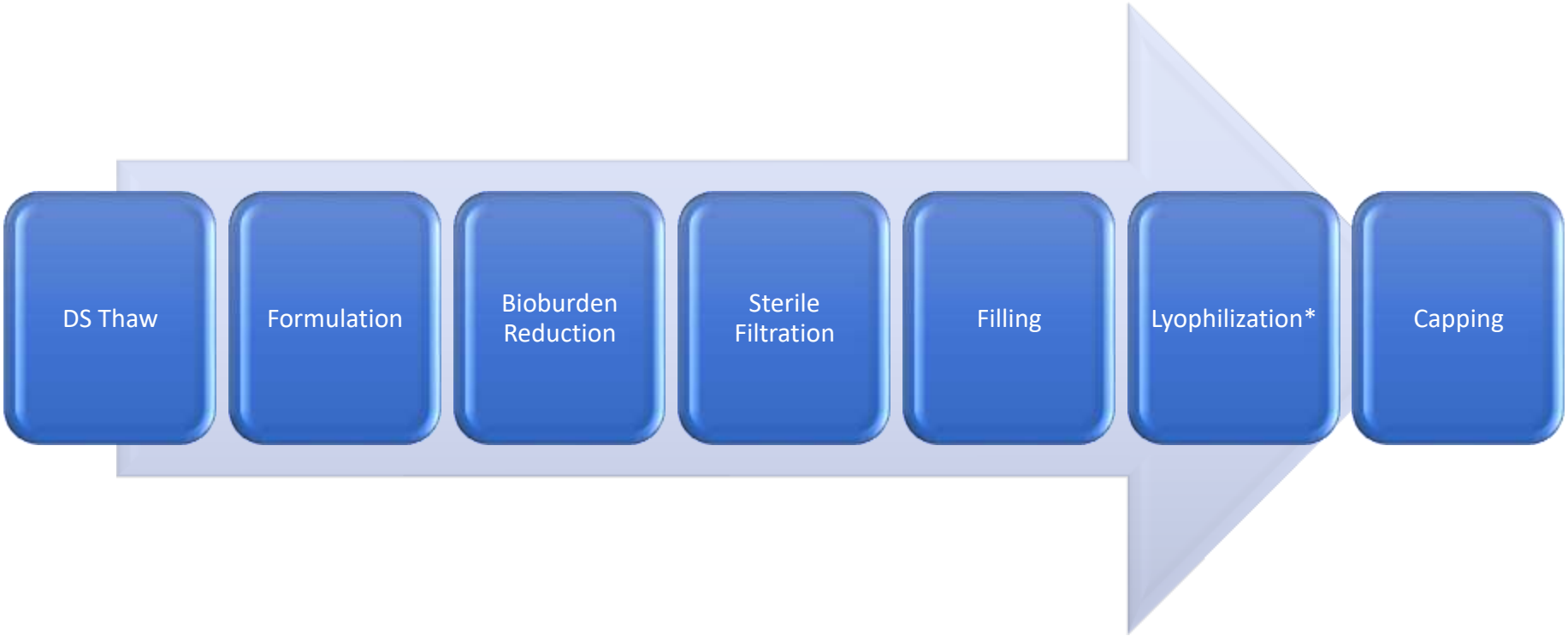
# Laws, Regulations, and Guidance

- Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (Nov. 1994)
  - Explains the type of information that should be submitted in applications in support of sterile drug applications manufactured using aseptic processing methods.
- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, 2004

# Microbiology Quality Oversight

- Microbial control during drug substance manufacturing
- Sterility assurance for drug product manufacturing
- Microbial product quality attributes at release
  - Sterility
  - Endotoxin
  - Preservative effectiveness (if applicable)
- Maintenance of sterility through expiry
  - Container closure integrity

# Drug Product Manufacturing Process Unit Operations (Vial Presentation)




* If applicable

# Aseptic Processing: Contributing Factors

# Microbiology Drug Product Quality assessment

- Process description (facility design, equipment, filling environment)
- Microbial attributes
- Conditions for DS thawing, formulation, and hold conditions
- Sterile filtration
- Sterilization of product contact equipment and container closure components

# Drug Product Process Validation

- Process Validation including sterilization of product contact equipment and container closure components
- Media fill program
- Environmental monitoring

Case Study

# New Fill Line for An Approved Product

# Prior Approval Supplement

- Second fill line for an approved product
- No changes to unit operations
- Increase in batch size
- Minor differences in equipment

# Prior Approval Supplement

- In-process controls were unchanged
- Specifications were unchanged
- No changes to analytical methods
  - Endotoxin
  - Sterility

# Validation Studies

- 3 PPQ lots
  - acceptance criteria met
- Sterilization Validation Studies
  - Dry heat tunnel
  - Autoclave
- Three successful media fills
- Successful Method Verification

# Recommendation

- The submitted application was considered satisfactory based on the data submitted
- The supplement was recommended for approval from a microbiology product quality perspective
- However……

# Inspection

- Required for new filling line
- Objectionable conditions observed at the facility
- Form FDA 483 issued
- Recommended withhold

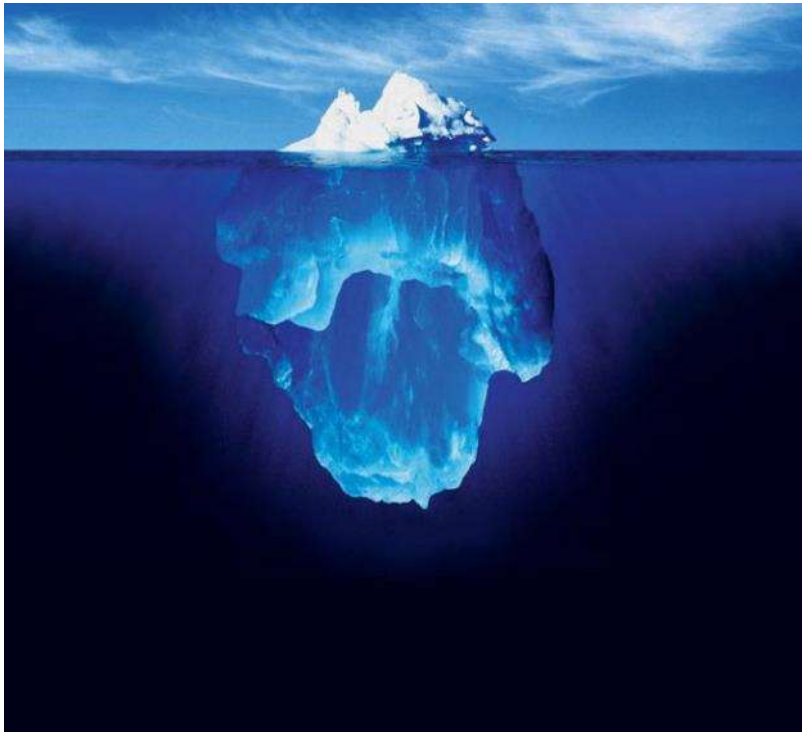
# 483 Items

- Procedures designed to prevent microbiological contamination of the drug product are not established, written, adequately validated, and/or followed
- Written records of investigations into discrepancies do no consistently include adequate conclusions or follow-up

# Inspection Findings

- Media fill failures
  - Only successful media fills were submitted in the application
- Microbial recovery from filling needles
- Corrective actions not implemented in timely fashion
- **Application was not approved based on these findings**

# It’s All About Perspective



- Submissions give a limited perspective
- Inspection provides a full view of what is happening in a facility
- Both are necessary to make adequate regulatory decisions

# Conclusions

- Adequate validation studies are necessary to demonstrate consistent aseptic processing for sterile drug products
- assessment and inspection are equally important in assessing applications

# Challenge Questions

- What gives the FDA the authority to inspect a facility?
  - The law (PHS Act, FD&C Act)
- True or false: The demonstration of sterility assurance is not critical.
  - FALSE
- Which is more important, assessment or inspection?
  - Neither, they are equal in importance

# Thank You

- Peter Qiu, Ph.D.
- Diane Raccasi
- Scott Nichols, Ph.D.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