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Risk-based approaches for a sterility assurance application review: a microbiologist's perspective

Dr. Yeissa Chabrier-Roselló
Product Quality Microbiologist
Division of Microbiology Assessment
Office of Process & Facilities
Office of Pharmaceutical Quality
Center for Drug Evaluation & Research

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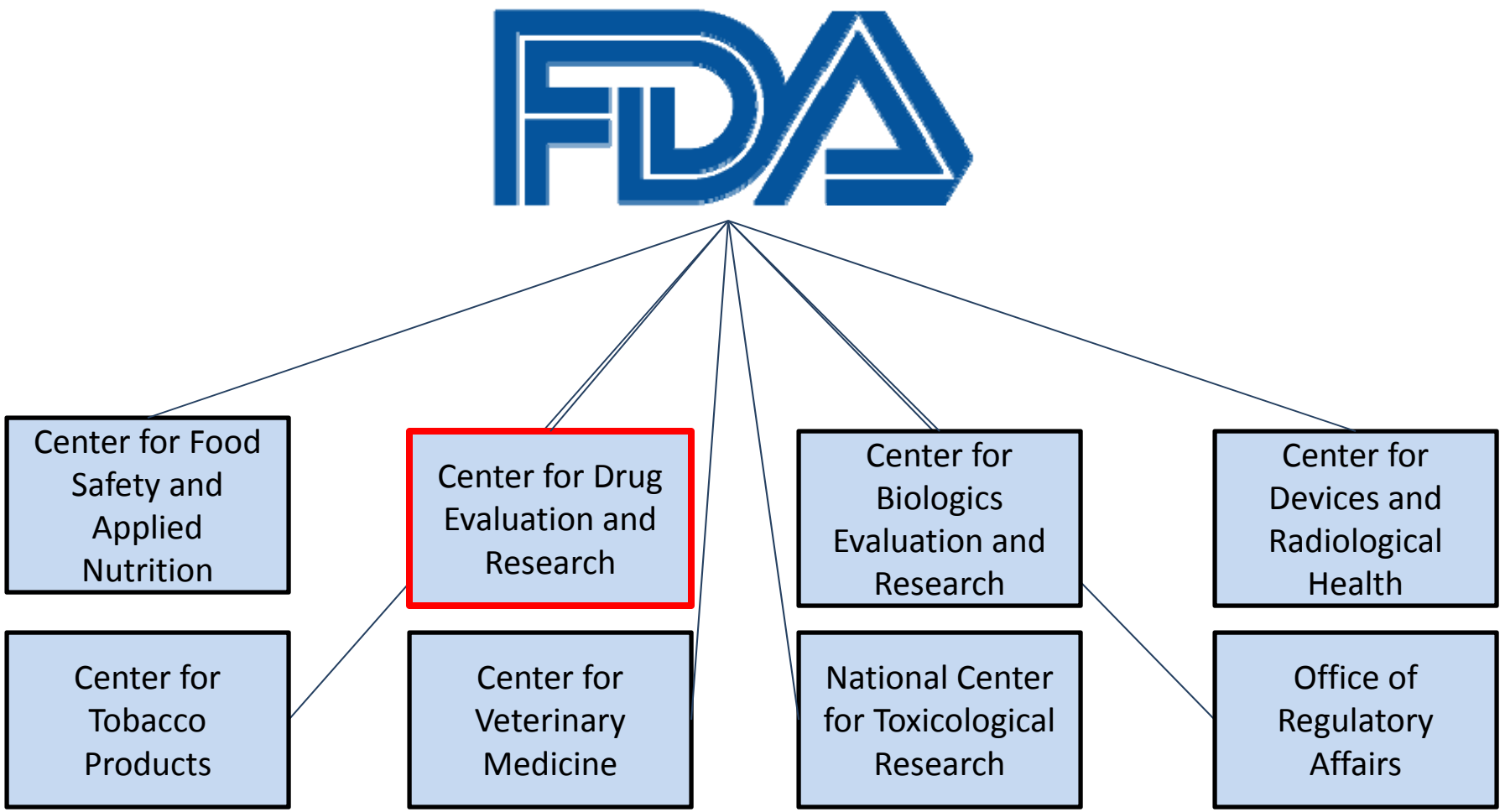
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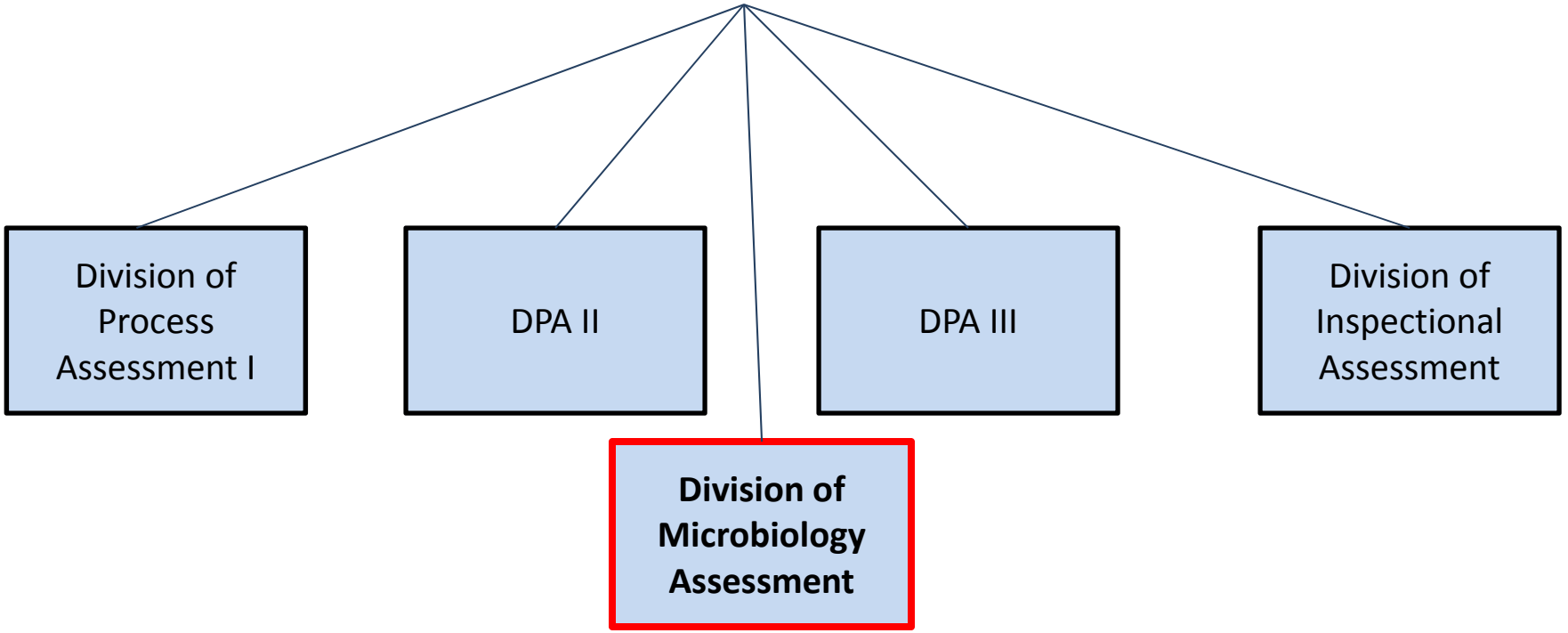
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Presentation Outline

- Overview of the Division of Microbiology Assessment
- Overview of the sterility assurance application review
- Common sterility assurance review issues

Division of Microbiology Assessment (DMA)

- All terminally sterilized and aseptically processed sterile drug product applications
  - NDAs, ANDAs, BLAs, INDs and some DMFs
- Some nonsterile drug product applications
  - INDs, NDAs, and ANDAs
- Meeting packages
- Controlled correspondence
- Consults regarding sterility assurance and microbiological issues from other FDA offices (i.e., Office of Compliance)
- Inspections
  - PAIs, PLIs and in some cases surveillance inspections (as SMEs)
- Policy work inside and outside of FDA

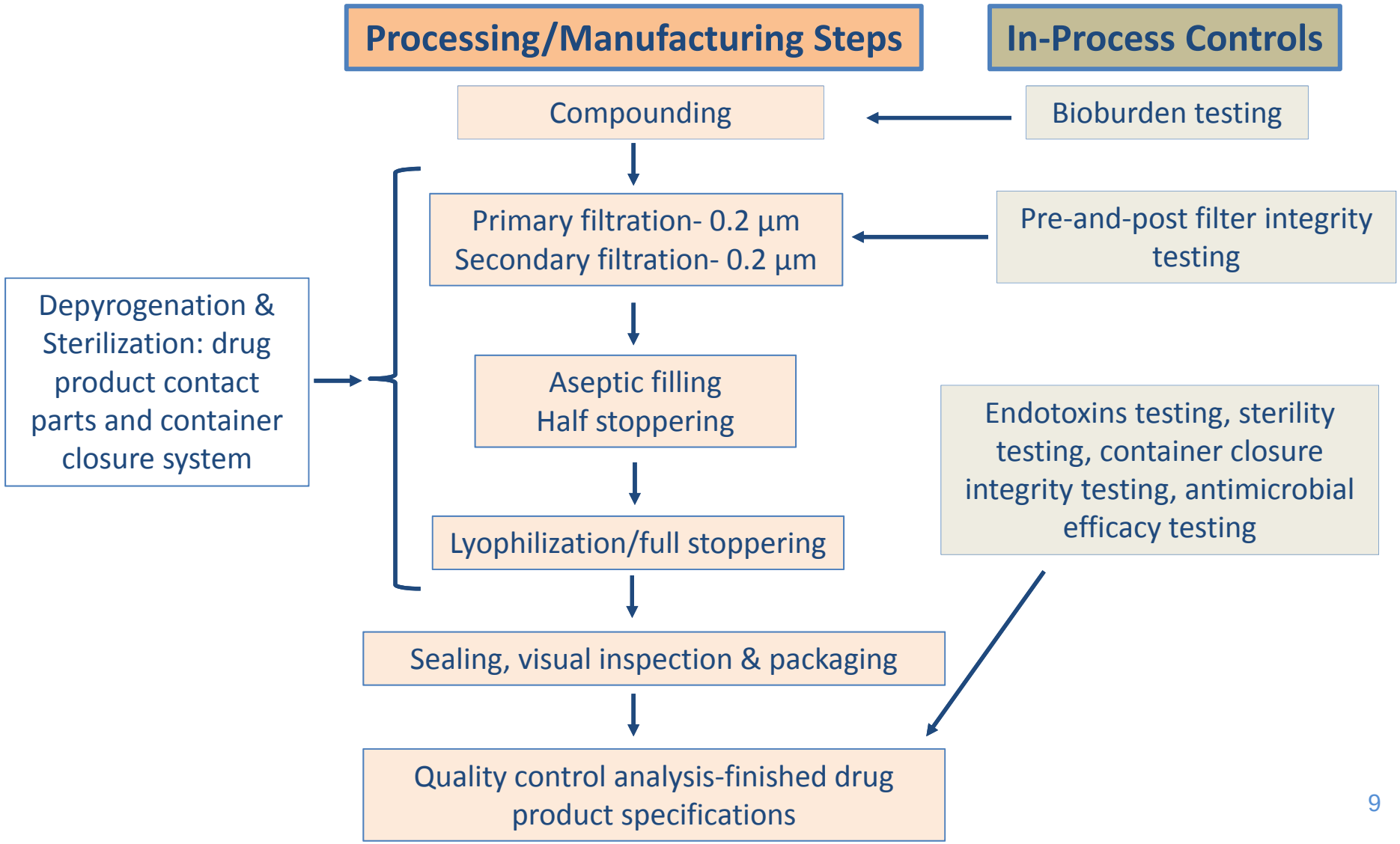
Drug product application review is based on…

- Patient safety
- Science based assessment
- Risk-based assessment
  - Low, medium or **high risk** (sterile drug products)
- Safe and quality drug products for the American public

Sterility assurance application review: frequently used documents

- Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994)
- Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing practice (2004)
- USP<71>, USP<51>, USP<85>, USP<61/62> and USP<1111>
- ANSI/AAMI/ISO 11138-1:2017, 11138-2:2017 and 11138-3:2017
- Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A (R2) Stability Testing of New Drug Substances and Products, Section 2.2.7
- *PDA Technical Report #26*

Sterility assurance review overview: aseptically processed sterile drug products



A/NDA sterility assurance review covers…

- **In-Process**
  - Environmental monitoring
  - Bioburden
  - Water
- **Validation**
  - Container closure integrity testing
  - Antimicrobial effectiveness testing
  - Hold time studies
  - Filter validation studies
  - Sterilization studies
  - Media fills
  - Post-reconstitution/Post-dilution studies
- **Finished Product**
  - Endotoxin and sterility

Sterility assurance review

- **In-process and validation studies**
  - Bioburden testing
  - Container closure integrity testing
  - Hold time studies
  - Filter validation studies
  - Sterilization studies: biological indicators
  - Media fills
  - Post-reconstitution/Post-dilution studies
  - Sterilization validation studies: moist heat, ethylene oxide, gamma irradiation, etc.
  - Antimicrobial effectiveness testing

Review issue: *Bulk bioburden*

Case study 1: Bulk bioburden

- "The bulk drug solution is filtered through two 0.2 µm filters. Bioburden monitoring/sampling is performed as part of the in-processing testing."

NOT ACCEPTABLE

Case study 1: Bulk bioburden

- **Issues:** Sampling point(s)/manufacturing step(s) and bioburden limit(s).

- **Agency's recommendation/expectation:**
  - Bioburden sampling prior to any filtration step
  - Bioburden sampling points/manufacturing steps should be clearly described.
  - Bioburden limit should be established

Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing practice (2004)

Review issue: *Container closure integrity testing (CCIT)*

Case study 2: CCIT

- "CCIT is performed by microbial immersion. The units are submerged in a microbial solution for 24 hours. Units are incubated and then visually assessed for microbial growth."

NOT ACCEPTABLE

Case study 2: CCIT

- **Issue:** Lack of pressure and/or vacuum and no description for the positive controls

- **Agency recommendation/expectation:**
  - Studies with the use of pressure and/or vacuum are conducted.
  - Adequate description of the positive controls used.

USP<1207>

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Review issue: *Hold times*

Case study 3: Hold times

- "The bulk drug solution is filtered immediately after compounding; therefore, there are no specifications for hold times during manufacturing. The total manufacturing duration for the drug product is NMT 30 hours."

NOT ACCEPTABLE

Case study 3: Hold times

- **Issue:** No description for the proposed maximum aseptic processing times during manufacturing.

- **Agency recommendation/expectation:**
  - Specifications concerning any holding periods between compounding and filling (lyophilization) should be established, provided and supported by scientific studies.

Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994)

21 CFR 211.111- Time limitations on production

Review issue: *Filter validation*

Case study 4: Filter validation

"Filter validation studies were performed for multiple drug products ranging from pH 2 to pH 12. Therefore, the drug product is well bracketed in terms of excipients, pH and concentration."

NOT ACCEPTABLE

Case study 4: Filter validation

- **Issue:** Bracketed approach with different drug products.

- **Agency recommendation/expectation:**
  - The same drug product
  - Different concentration/potency
  - Scientific explanation/justification

PDA Technical Report #26

Review issue: *Biological indicators*

Case study 5: Biological indicators

- "All BIs used during the validation studies were incubated at 55-60°C for 24-48 hours."

NOT ACCEPTABLE

Case study 5: Biological indicators

- **Issue:** Incubation time

- **Agency recommendation/expectation:**
  - 7 day incubation period

ANSI 11138-1:2006/(R)2010/2017

USP<55>

Review issue: *Media fills*

Case study 6: Media fills

- "Three media fill runs were conducted using an aseptic filtration time of 2 hours and a fill duration of 10 hours. Worst-case conditions were used since planned and unplanned interventions were performed. The proposed aseptic filtration time is 6 hours and the duration of fill is NMT 20 hours."

NOT ACCEPTABLE

Case study 6: Media Fill

- **Issue:** Validation of aseptic processing steps

- **Agency recommendation/expectation:**
  - "Media fill simulations should closely simulate aseptic manufacturing operations."
  - "The duration of media fill run should take appropriate consideration of the actual duration of the actual aseptic processing operation."

Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994)

Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing practice (2004)

Review issue: *Post-reconstitution/Post-dilution studies*

Case study 7: Post-reconstitution/Post-dilution studies

- "The drug product is to be reconstituted with sterile WFI, 0.9% sodium chloride or bacteriostatic WFI, prior to administration. The reconstituted product is stable for 3 days at room temperature or 7 days under refrigeration. Chemical stability studies are included to support the stability during the storage conditions."

NOT ACCEPTABLE

Case study 7: Post-reconstitution/Post-dilution studies

- **Issue:** No microbiological studies

- **Agency recommendation/expectation:**
  - Microbiological studies to support storage conditions if:
    - Stored at >4 hours at RT and/or >24 hours refrigerated

Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A (R2) Stability Testing of New Drug Substances and Products, Section 2.2.7

In summary

- Sterility assurance review process is a risk based assessment based on:
  - Different regulatory documents, technical reviews, scientific standards, product quality microbiology experts, compliance of regulatory requirements, etc.
  - Subject matter experts in microbiology and sterility assurance issues.

GOAL: Assure that quality drug products are available for the American public.

Thank You!

Contact Information

Yeissa Chabrier-Roselló, Ph.D.

240-402-8603

Yeissa.ChabrierRosello@fda.hhs.gov

Additional Inquiries:

CDER-OPQ-Inquiries@fda.hhs.gov


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