Division of Microbiology Assessment:
Who we are, what we do and our recommendations to industry

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Division Director (Acting)
Division of Microbiology Assessment
Office of Process & Facilities
Office of Pharmaceutical Quality
Center for Drug Evaluation & Research
U.S. Food & Drug Administration

Regulatory Education for Industry (REdI):
Generic Drug Forum
April 13-14, 2016

Office of Pharmaceutical Quality (OPQ)

- 2014 CDER Director announces establishment of OPQ
  - New super-office to create a single CDER unit dedicated to quality
  - All quality oversight activities occur in OPQ
  - "One quality voice"
    - A uniform drug quality program across all sites of manufacture and all drug product areas – new, generic & over-the-counter drugs
- January 2015 - OPQ stand-up
- Michael Kopcha, Ph.D., R.Ph., OPQ Director

"One Quality Voice"

One Quality Voice for Drugs:
OPQ will centralize quality drug review — creating one quality voice by integrating quality review, quality evaluation, and inspection across the product lifecycle.

One Quality Voice for Patients:
OPQ will assure that quality medicines are available for the American public.

One Quality Voice for Industry:
OPQ will establish consistent quality standards and clear expectations for industry.

One Quality Voice for Health Care Professionals:
OPQ will anticipate quality problems before they develop and help prevent drug shortages.

One Quality Voice for Health Care Purchasers:
OPQ will emphasize quality metrics.

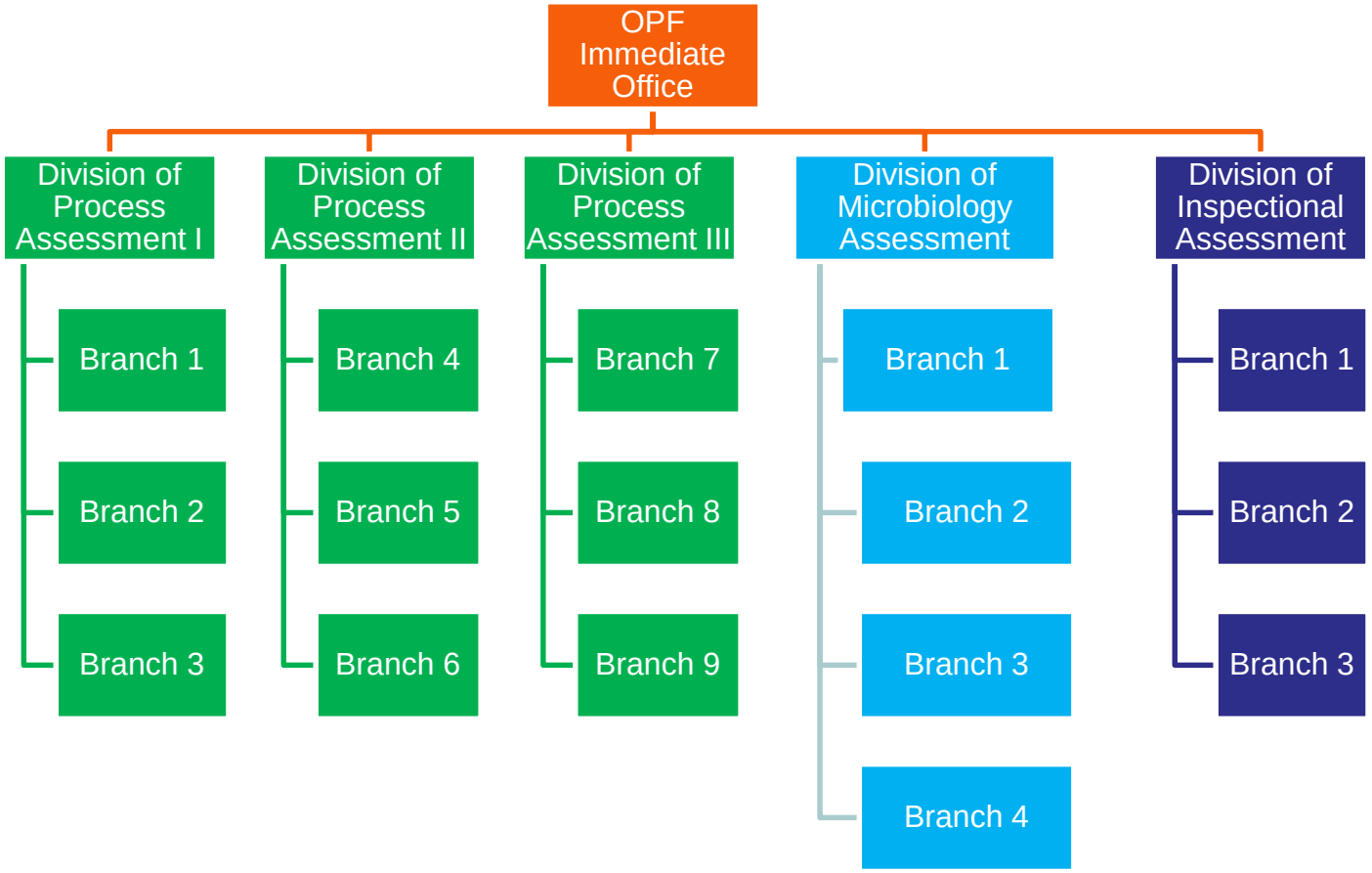
OPQ Integrated Quality Assessment

- **Team approach**
  - Includes all disciplines involved in the review and inspection of the application & facility
  - Provides holistic oversight of the facility, process and product
  - Team oversight by ATL & RBPM
  - Risk-based assessment and one quality voice

Office of Pharmaceutical Quality

- Office of Program and Regulatory Operations
- Office of Policy for Pharmaceutical Quality
- Office of Testing and Research
- Office of New Drug Products
- Office of Biotechnology Products
- Office of Lifecycle Products
- Office of Process and Facilities
- Office of Surveillance

Office of Process and Facilities



OPF Mission Statement

OPF assures that quality pharmaceuticals are consistently manufactured over the product lifecycle

OPF Product Quality Microbiology

- Risk-based analysis of:
  - Manufacturing process/techniques
    - sterility assurance supporting validation studies
  - Microbial process controls
  - Finished product quality attributes
    - sterility, endotoxins, bioburden, container closure integrity, antimicrobial effectiveness
  - Both Drug Substance & Product
  - Application & Facility

OPF Product Quality Microbiology

- Risk-based analysis to:
  - Focus on impact on patient safety
  - Limit potential harmful effects of microorganisms on drug product

DMA Benefits

- Harmonization on microbiology-related policy
- Centralization for CDER product quality microbiology-related policy development and response to inquiries
- Flexibility of resources
- Staff professional development and cross-training

Division of Microbiology Assessment

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Branches I-III
(small molecules)

- Legacy OPS/IO (NDMS) & OGD Division of Microbiology
- Assessment of:
  - NDAs (originals & supplements)
  - ANDAs (originals & supplements)
  - INDs
  - DMFs
  - Meeting packages

Branch IV
(large molecule)

- Portion of legacy OC/BMAB staff
- Assessment of:
  - BLAs (originals & supplements)
  - INDs
  - DMFs
  - Consults from other centers (e.g., CBER, CDRH, CVM)
  - Meeting Packages
- Inspections
  - Typically lead PAI/PLI inspections for BLA drug substance
  - Participate as SMEs on other BLA inspections

Additional DMA Activities

- Subject matter experts for emerging issues:
  - Drug shortage & recall activities
  - Facility issues
  - Drug issues (focus on potential contamination concerns)
- Participation in policy development
  - With both internal & external organizations
    (e.g., FDA, PDA, USP, AAMI, GPhA, etc.)

Additional DMA Activities (2)

- Collaboration/Outreach with scientific organizations
- Training

Recommendations for Industry

Sterilizing Filtration

- Increase in the use of pre-sterilized, commercially available filling/filtration trains.
- Pre-packaged and pre-sterilized sterilizing filter, tubing, large flexible bag, etc.

Sterilizing Filtration

- **Recommendation**:
  - Clearly mention the use of this in application
    - Reference DMF if necessary
  - Clearly indicate responsible party for sterilization of system
  - Provide results from bacterial retention studies
- **Why?:**
  - Avoid deficiencies concerning the content of equipment loads or equipment included in SIP validations
  - Not captured by ‘worst case’ loads

Drug Master Files

- DMFs tend to cause confusion and potentially decrease review and application approval efficiency

Drug Master Files

- **Recommendation:**
  - Clearly indicate where appropriate validation information can be found
    (e.g., LOAs with vol./pg. # of relevant information)
  - Electronic DMF submissions
  - If possible, provide information in application
- **Why?:**
  - Avoid deficiencies concerning absent or confusing validation data
  - Increase review efficiency and speed approval process

Reconstitution/Dilution Storage

- Applications missing assessment of microbiological quality following product penetration

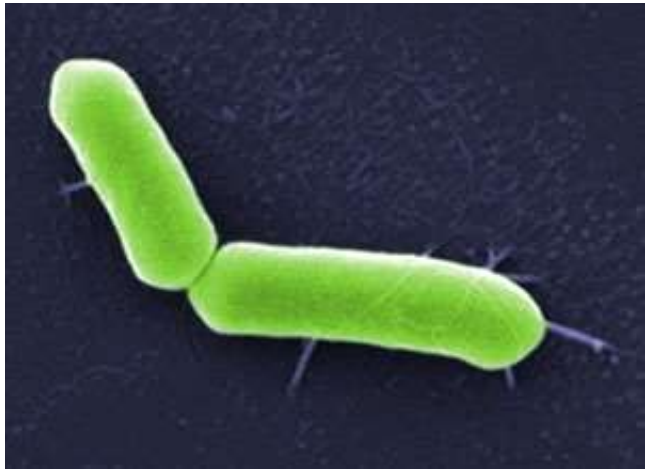
- Post-reconstitution or dilution

Reconstitution/Dilution Storage

- **Recommendation:**
  - Provide risk assessment data to support the proposed post-penetration holding parameters per product labeling
  - 'Adapted' USP<51> Antimicrobial Effectiveness Testing
- **Why?:**
  - Understanding of the risk associated with product labeling with regard to in-use stability and/or diluent compatibility claims

Biological Indicators in Validation/Qualification

- Misinterpretation of BI incubation time for DP manufacturing facilities
- 7 days vs 24 hours



BIs in Validation/Qualification

- USP <55>

  "Incubate each tube at the optimal recovery temperature specified by the manufacturer. Observe each inoculated medium-containing tube at appropriate intervals for a total of 7 days after inoculation."

- ISO 11138

  "An incubation period is commonly recognized to be 7 days for established sterilization processes, such as moist heat."


Center for Food Safety and Applied Nutrition
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Center for Tobacco Products
Center for Veterinary Medicine
National Center for Toxicological Research
Office of Regulatory Affairs

Guidance for Industry and FDA Staff

Biological Indicator (BI) Premarket Notification [510(k)] Submissions

1. Introduction

FDA regulates biological indicators (BI) intended to monitor sterilizers used in health care facilities as class II medical devices requiring premarket notification (510(k)). 21 CFR 880.2800(a). This guidance document provides information that will help manufacturers prepare 510(k)s for BIs used with conventional sterilization methods. FDA believes that providing this information will promote a consistent and efficient regulatory process.

Attachment II. Examples of Validation of Biological Indicator Incubation Time

These recommendations are appropriate for all biological indicators, self contained or on a strip, which are intended to accompany products being sterilized through a sterilization procedure and to monitor adequacy of sterilization.

The incubation period for BIs may be reduced from the standard seven or more days, provided that the validation studies demonstrate that the revised numbers of days of incubation are sufficient according to appropriate methodology.

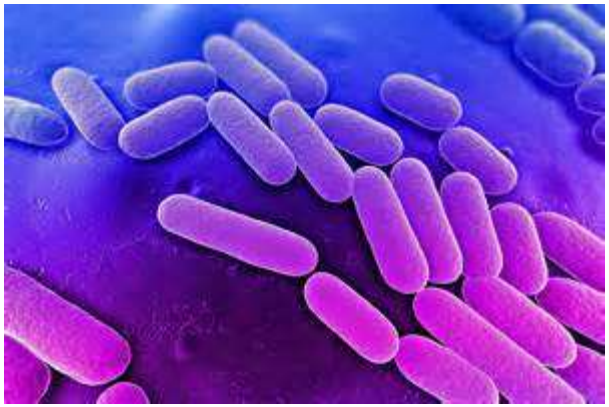
- Using the number of BIs that test positive on day 7 as the base of 100% grow out (denominator data), determine from the growth chart the number of BIs that have more than 97% of the base number of BIs (numerator) that test positive in each partial cycle for the proposed incubation time to be acceptable.

BI for Validation/Qualification

- **Recommendation:**
  - Incubate BIs for at least 7 days used in validation studies
- **Why?:**
  - Reduced incubation time clearance is for healthcare facilities – not drug product manufacturing sites.
    - The clearance for reduced time denotes that 97% of positive indicators show growth during the incubation period.
    - Is that acceptable for your facility?

Product Endotoxins Testing

- Pooling of samples, generally for small-volume parenterals (NMT 100 mL)



Product Endotoxins Testing

- **Recommendation:**
  - Pooling acceptable, NMT 3 units
  - MVD adjusted to proportional, lower value
  - "Adjusted MVD" = MVD / # samples pooled
- **Why?:**
  - Ensure test method's ability to overcome potential product-related interference or enhancement

References

- *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for*

  Human and Veterinary Drug Products

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf

- *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf

References (2)

- *Guidance for Industry: Container and Closure System Integrity Testing* in Lieu *of Sterility Testing as a Component of the Stability Protocol for Sterile Products – 2008*

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM146076/pdf

- *Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers - 2012*

  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314718.htm

References (3)

- *Guidance for Industry: Comparability Protocols – Chemistry, Manufacturing, and Controls Information – Draft 2/03*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070545.pdf

- *Guidance for Industry: Changes to an Approved NDA or ANDA – 2004*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf

- *Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards – 2013*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf

Technical Questions

- How to submit Control Correspondences

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM411478.pdf

- Mail to: GenericDrugs@FDA.HHS.Gov

General OPQ Inquires

- Mail to: CDER-OPQ-Inquiries@fda.hhs.gov

Summary

- OPQ/OPF's DMA performs product quality assessment of new, generic & biologic products
- Many reference documents available to describe application expectations
- OPQ Holistic assessment to ensure safe, quality products are available to consumers
  - Quality by Design

Contact Information

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Questions?

surveymonkey.com/r/GDF-D1S7