Aseptic Processing of Biological Products: Current Regulatory Issues

"Facing the Challenges of Drug Product and Device Development & Manufacturing"

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Scope

- Laws, regulations and guidance
  - Basis for application review and site inspection for sterility assurance
- Integrated review and inspection
  - Role of sub offices in the Office of Pharmaceutical Quality (OPQ)
- Overview of microbiology quality assessment of BLAs
  - Drug product
- Conclusions

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

- Federal Food, Drug, and Cosmetic (FD&C) Act (1938, 1962, 1997, 2007)
  - Interprets that “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
- Both the PHS and FD&C Acts require that biological products must be manufactured under CGMP as described in 21 CFR 210 and 211 and 600-680

Applicable Regulations for Sterile Product (211s)

- 211.111 Time limitations on production.
  - Addresses processing and hold time limits.
- 211.113 Control of microbiological contamination
  - Addresses the validation of aseptic and sterilization processes
- 211.94 Drug product containers and closures
  - Addresses container closure integrity, depyrogenation/sterilization of containers, closures and sterile product contact equipment
- 211.167 Special testing requirements
  - Addresses microbial testing requirements
- 211.137 Expiration dating
  - Addresses post reconstitution storage requirements

Guidance for Sterile Drugs

- Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (Nov. 1994)
  - This guidance clarifies the type of information that should be submitted in applications to the FDA in support of sterile drug applications manufactured using aseptic processing methods.
- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, 2004
  - Provides guidance on how to comply with CGMP regulations
  - Use in conjunction with other compliance programs and guidance
- Container Closure System Integrity Testing *in lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products, 2008
- Established Conditions: Reportable CMC Changes for Approved Drug and Biologics Products, 2015 draft

Pharmaceutical CGMP for the 21st Century - A Risk Based Approach

- Initiative launched in 2002 to modernize FDA's regulation of pharmaceutical quality of drugs
  - Role of current good manufacturing practices as an important tool for improving overall quality
  - To ensure that "the product review program and the inspection program operate in a coordinated and synergistic manner."
  - Intended to encourage the adoption of modern and innovative manufacturing technologies
  - Overarching philosophy is:
    - ***Quality should be built into the product, and testing alone cannot be relied on to ensure product quality*.**

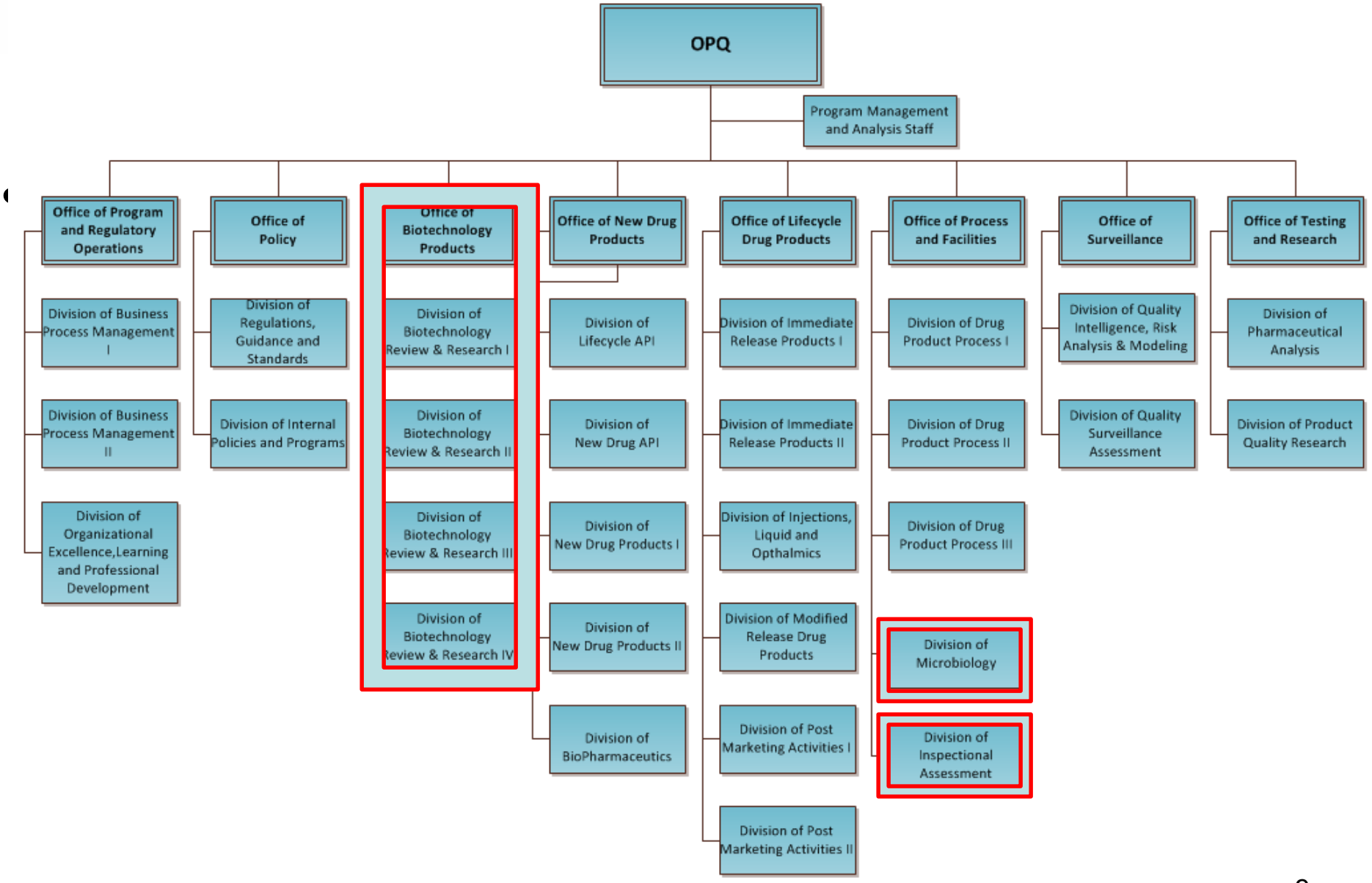
Modernization for the Desired State: Integration of Functions

- Industry
  - R&D and Production need to be integrated
  - Modern quality systems are needed domestically and internationally
- FDA
  - CMC and CGMP Programs need to be integrated

- Will lead to Industry and Regulator synergy to advance to the “desired” state

Office of Pharmaceutical Quality (OPQ)

- In 2014 Dr. Woodcock announced the establishment of a new organizational structure in CDER –
  - Establishment of the Office of Pharmaceutical Quality, a new superoffice that creates a single unit in CDER dedicated to product quality
    - All quality oversight activities occur in OPQ
    - "One quality voice"
      - A uniform drug quality program across all sites of manufacture and across all drug product areas – new drugs, generic drugs and over-the-counter drugs
  - Re-alignment of preapproval and surveillance inspection activities from the office of Compliance to OPQ
  - New organization implemented in January 2015
  - Michael Kopcha, Ph.D. R.Ph. OPQ Director


OPQ
Program Management and Analysis Staff
Office of Program and Regulatory Operations
Division of Business Process Management I
Division of Business Process Management II
Division of Organizational Excellence,Learning and Professional Development
Office of Policy
Division of Regulations, Guidance and Standards
Division of Internal Policies and Programs
Office of Biotechnology Products
Division of Biotechnology Review & Research I
Division of Biotechnology Review & Research II
Division of Biotechnology Review & Research III
Division of Biotechnology Review & Research IV
Office of New Drug Products
Division of Lifecycle API
Division of New Drug API
Division of New Drug Products I
Division of New Drug Products II
Division of BioPharmaceutics
Office of Lifecycle Drug Products
Division of Immediate Release Products I
Division of Immediate Release Products II
Division of Injections, Liquid and Opthalmics
Division of Modified Release Drug Products
Division of Post Marketing Activities I
Division of Post Marketing Activities II
Office of Process and Facilities
Division of Drug Product Process I
Division of Drug Product Process II
Division of Drug Product Process III
Division of Microbiology
Division of Inspectional Assessment
Office of Surveillance
Division of Quality Intelligence, Risk Analysis & Modeling
Division of Quality Surveillance Assessment
Office of Testing and Research
Division of Pharmaceutical Analysis
Division of Product Quality Research

Integrated Product Review and Inspection

- Team approach
  - The same product quality and micro quality reviewers participate on inspections of manufacturing sites in pre-approval inspections
    - Focus is on product specific aspects
  - Additional participants on inspection include members of the Division of Inspectional Assessment (DIA)
    - focus on the qualification of the facility and equipment and CGMPs
  - The approach is intended to provide a comprehensive oversight of the facility, process and product
    - Provides a basis for product quality lifecycle oversight

Microbiology Quality Oversight

- Quality microbiologists in OPQ assess the adequacy of the
  - microbial process controls,
  - sterility assurance supporting validation studies, and
  - microbial product quality attributes (sterility, endotoxins, bioburden, container closure integrity, antimicrobial effectiveness)
- Both drug substance and drug product sections of a BLA are assessed from a microbiology quality perspective
- Quality oversight includes an assessment of information and data in a BLA and an evaluation of a facility and process

Microbiology Drug Product Quality Review of a BLA: Scope

- Process description including facility design, equipment and fill line (RABS, isolator, open clean room)
- Microbial attributes
- Bulk thaw, formulation, mixing, diluting and hold conditions
- Sterilizing filtration
- Depyrogention and sterilization of components
- SIP of equipment in direct contact with sterile product and of lyophilizers

Microbiology DrugProduct Quality Review of a BLA: Scope (cont.)

- Media fill program
- Environmental monitoring
- Lyophilization as part of the aseptic processing
- In-process and release testing (sterility, endotoxins, container-closure integrity)
- Stability (container-closure integrity)
- Shipping validation
- Expiration of reconstituted drug product

Drug Product Quality Issues

General

In-process microbial control deficiencies

- Bulk thaw and pooling conditions not adequately described and monitored
  - Pooling steps should be well controlled and monitored for bioburden and endotoxins
- Bioburden limits not established or not in-line with current standards
  - In-process limits should be consistent with process capabilities and industry standards
- No in-process monitoring of endotoxins

Hold conditions: common deficiencies

- Hold conditions not adequately supported by data
  - Time limits for processing steps should be in place and include:
    - Supporting microbial data for hold steps longer than 24 hours
    - Bioburden and endotoxins should be monitored at the end of a hold step and prior to filtration
  - Sterile holds (post sterile filtration) should be supported by sterilization validation data and/or simulated during media fills

Sterilization validation of container/closure/components: deficiencies

- Autoclave sterilization validation studies not completed or three initial or requalification studies not submitted
  - Deficiencies related to loads (minimum and maximum), lack of information on biological indicators (BIs) (BI type [spore strips ampoules, etc.], population number, D-value and expiry date), inappropriate use of rapid BIs
- Missing LOA to reference DMF or LOA that reference Master Files from other centers (CBER, CDRH)
- Relevant DMFs are not updated with relevant validation data

Depyrogenation: examples of deficiencies

- Performance parameters for routine production and validation not described or not submitted
- Summary validation data not submitted
- Missing LOA to reference DMF
- Relevant DMF not updated with relevant validation data

Media fill program: common deficiencies

- Maximum hold times not validated
- Insufficient detail and justifications regarding the media fill conditions (e.g., line speed, number of vials filled, inspected, rejected or discarded and incubated)
- Missing summaries of environmental monitoring data during media fills
- Growth promotion studies incomplete
- Contaminating microorganisms not identified
- No plans for actions to be taken following a media fill failure

Shipping: examples of deficiencies

- Missing shipping validation studies
- Inadequate description of shipping conditions
  - Criteria for shipping duration and temperature
  - Shipping lanes, minimum and maximum allowable temperatures (including durations of allowable excursions)
  - Temperature mapping and monitoring during drug product shipment
  - Effect of shipping on container closure integrity of syringes (plunger movement)

Endotoxins: examples of deficiencies

- Endotoxin method not identified
- Qualification report and data not submitted
- Low endotoxin recovery not assessed and/or protocol and report not submitted

Rabbit Pyrogen Test: examples of deficiencies

- Missing:
  - Rabbit pyrogen testing not conducted on three lots and/or report not submitted
  - Justification for the administered dose based on the maximum dose of drug product per day per kg of body weight of a human
  - Number of rabbits used for testing each lot
  - Data on the temperature rise in rabbits compared to the baseline temperature

Specific Review Examples

Container closure integrity

Sterile filtration

Post-reconstitution storage

FDA 1994 Guidance: Container-closure Integrity

- "The ability of the container-closure system to maintain the integrity of its microbial barrier, and hence, the sterility of a drug product throughout its shelf-life, should be demonstrated…….sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container-closure system. Documentation of the sensitivity of the container-closure integrity test should be provided."

FDA 2008 Guidance on Container-closure Integrity

- "Sterility tests are not recommended as a component of a stability program for confirming the continued sterility throughout a product's shelf-life or dating period. Alternative methods may be more reliable…"
- Alternatives to sterility testing …might include any properly validated physical or chemical container and closure system integrity test ….or microbiological container and closure system integrity tests (e.g., microbial challenge or immersion tests)."

FDA 2008 Guidance on Container-closure Integrity (cont.)

- "A test method is adequately validated if it has been proven through scientifically accepted studies to be capable of detecting a breach in container and closure system integrity;
- "An appropriate container and closure system integrity test should be conducted annually and at expiration or as otherwise required by applicable regulations."

Container-closure integrity test (CCIT): common deficiencies

- CCIT not included in the stability program
- Inadequate qualification of the container closure system for integrity
  - Inadequate description of the CCIT methods
    - Sensitivity of method not known or described
    - Lack of positive and negative controls
    - Inadequate microbial or dye ingress challenge conditions in the microbial ingress test
- Vial capping parameters not described
  - Worst case capping parameters not validated
- CCI of syringes
  - Shipping of syringes

Example 1: Container-closure integrity test with an inadequate positive control

- Issue:
  - An applicant used positive controls with a large defect size:
- The applicant was sent the following information request:
  - The system suitability controls for container closure integrity testing of syringes and pens are prepared with a relatively large defect size (removing the needle shield). System suitability controls with a smaller defect size should be used for routine testing. The study performed by [XXXYY contract lab] showed that the method is capable of detecting 5, 10, and 30 micron defects.
- Resolution:
  - The applicant committed in a post-marketing commitment (PMC) to implementing a system suitability control with a smaller defect size ($\leq$ 20 microns).

Example 2: Container-closure integrity test with an inadequate positive control

- Issue:
  - A applicant proposed to use a CCIT capable of detecting defects as small as 160 micron.
    - The defective positive control used during method validation was a container prepared with a 160 micron defect.
  - Current CCIT methods are capable of detecting leaks $\leq$ 20 microns.
    - Use of positive controls with defects $\leq$ 20 microns is standard industry practice for method validation and routine CCIT.
    - The FDA requested that the sponsor confirm that the dye ingress method is capable of detecting leaks $\leq$ 20 microns.
- Resolution
    - The sponsor agreed to revise the CCIT methods and to include a positive control with a $\leq$ 20 micron defect based on the results of the validation study.

Example 3: Container-closure integrity test 483 observation on inspection

- The methylene blue dye penetration test used to evaluate drug product XYZ container closure integrity is inadequate. Specifically, the procedure […] for dye penetration test for drug product samples does not require reconstituting the lyophilized cake with water after challenging the vials in methylene dye solution. Any leakage in areas that are not clearly visible (e.g., under the stopper) may not be detected.

Specific Review Examples

Container closure integrity

Sterile filtration

Post-reconstitution storage

1994 Guidance: Drug Product Solution Filtration

- "The specific bulk drug product solution filtration processes….should be described. A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter on the product formulation should be described."

Sterilizing filter validation: common deficiencies

- Missing information and data:
  - No information or insufficient information on bubble point determination
  - Filter pre-use and post-use integrity testing not described or results from validation lots not included
  - Refiltration conditions not described
- Microbial retention studies
  - Report not included in the application
  - Microbial retention test parameters do not support the production parameters
    - Production conditions for critical operating parameters are not supported by the scaled-down validation studies (flow rate, filter surface area, product exposure time, temperature, etc.)

Example 1: Inadequate sterilizing filter validation study

- Issue:
  - A filter validation study for microbial retentivity was conducted using a *B. diminuta* cells in water because the drug product formulation was bactericidal to the challenge microorganism.
  - An information request (IR) was sent to the applicant:

Example 1: Inadequate sterilizing filter validation study (cont.)

- IR to the applicant:
  - The microbial retention study was done with purified water as a surrogate solution for the drug product. Perform a repeat microbial retention study for the sterilizing filter using a suitable surrogate solution. Product attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, a reduced exposure time approach may be appropriate.

Example 2: Uncertainty regarding post-use filter integrity testing

- Issue:
  - An applicant proposed to use water as a wetting agent for post-use filter integrity testing
    - Filter must be rinsed to remove the drug product prior to testing
    - Uncertainty regarding the filter flush process to remove product
- Resolution:
  - The applicant was requested to confirm that the flush volume used adequately removed the drug product from the filter with a PMC
- PMC:
  - Validate the filter flush volume for the sterilizing filter. The flush volume should be validated by either measuring the amount of product in the flush or by repeatedly flushing with a specified volume until a stable bubble point is reached for the integrity test….update the BLA file accordingly.

Example 3: Inadequate microbial retention studies for sterilizing filters

- Issue:
  - An applicant validated a 6 hour time limit for the sterilizing filtration step but proposed a 12 hour time limit for the sterilizing filtration step
- Resolution:
  - The filtration time has been limited to 6 hours until an additional microbial retention study is performed to validate a 12 hour time limit for sterilizing filtration.
- PMC:
    - Perform a microbial retention study to support the proposed 12 hour time limit for sterilizing filtration. Limit the validated time for sterilizing filtration to 6 hours until the 12 hour time limit has been approved by the Agency.

Specific Review Examples

Container closure integrity

Sterile filtration

Post-reconstitution storage

Post-reconstitution storage

- Lyophilized products have to be reconstituted prior to administration, as directed in the label
- Proposed post-reconstitution storage time must be supported by microbial challenge studies to demonstrate that the product does not support microbial growth under the proposed storage conditions

Post-reconstitution storage studies

- To support a post-reconstitution storage, challenge studies should be conducted using a panel of microorganism provided in the USP<51> Antimicrobial Effectiveness Testing plus typical skin flora or species associated with hospital-borne infections
    - Challenge levels should be less than 100 CFU/mL.
    - Temperature(s) described in the proposed product's labeling should be tested.
    - Test should be conducted for twice the recommended storage period and use the label-recommended diluent.
    - No increase from the initial counts is defined as less than 0.5 $\log_{10}$ unit higher than the initial inoculum.

Example: Post-Reconstitution storage not supported by data

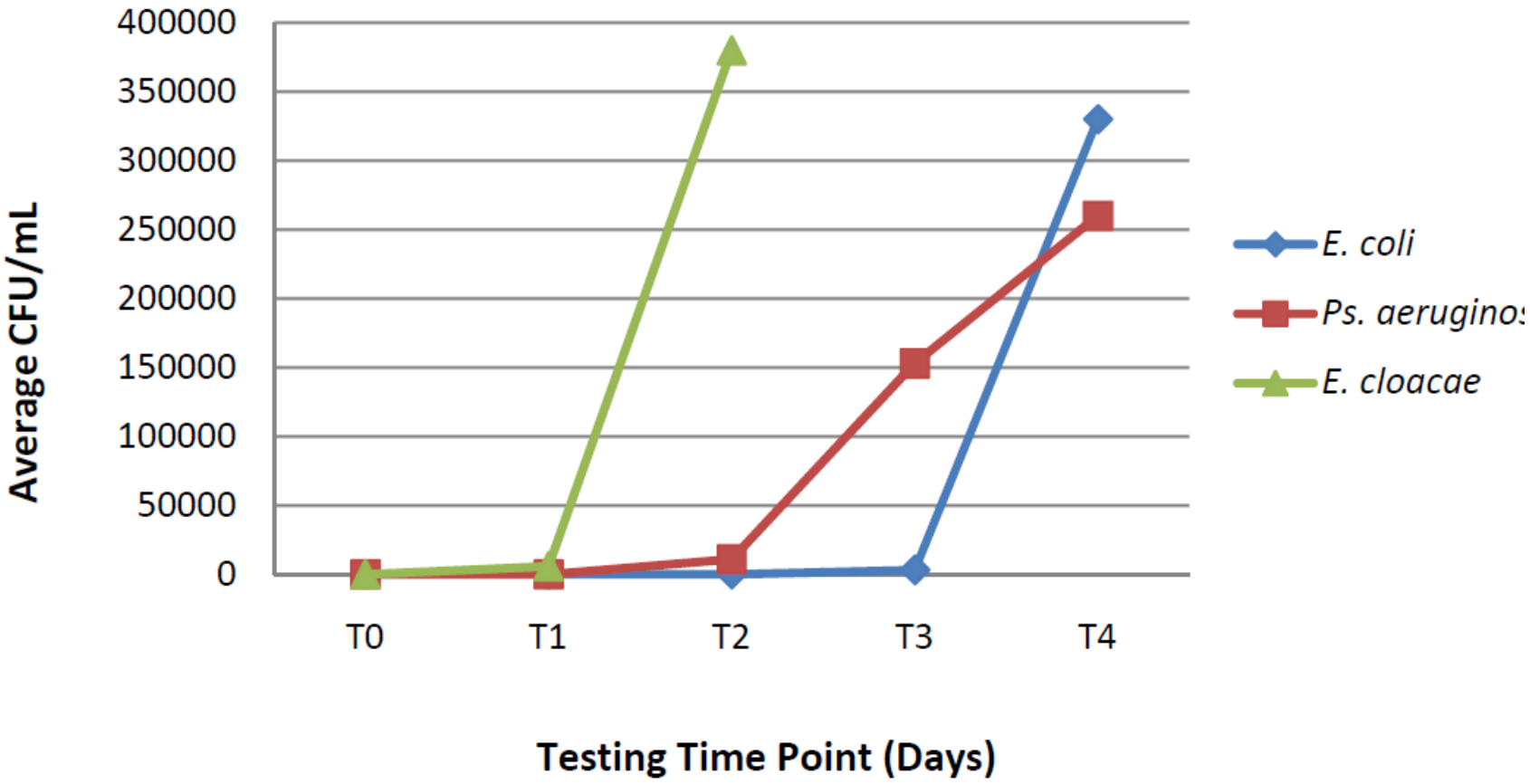
- The draft label proposed that lyophilized product in vials be reconstituted with SWFI, further diluted with 0.9% NaCl in infusion bags, and then stored at room temperature (23- 27˚C) or 2-8˚C.
  - The proposed storage conditions in the label were not supported by microbial challenge data.

Example study results

Growth of microorganisms (CFU/mL) in an infusion solution at 20-25˚C

Time point (Days)		T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_8
Microorganisms	*E. coli*	54	52	59	$3.3x10^3$	$3.3x10^5$			
	Ps. aeruginosa	51	53	$1.1x10^4$	$1.5x10^5$	$2.6x10^5$			
	E. Cloacae	74	$6.0x10^3$	$3.8x10^5$					
	S. aureus	62	51	40	29	12	9	6	0
	M. luteus	44	38	16	6	4	1	1	0
	C. albicans	32	38	30	20	15	12	13	8
Un-inoculated bag control		N/A	0	0	0	0	0	0	0

Growth at 20-25˚C



More study results from the challenge studies

Growth of *E. cloacae* (CFU/mL) in an infusion solution at 20-25˚C

Time point (hours)	T_0	$T_{6\ hr}$	$T_{12\ hr}$	$T_{18\ hr}$	$T_{24\ hr}$	$T_{48\ hr}$
E. cloacae	56	67	152	$8.6x10^2$	$5.7x10^3$	$4.1\ x10^5$
Un-inoculated test bag control	N/A	0	0	0	0	0
Fluid A Control	0	0	0	0	0	0
0.9% Saline Control	0	0	0	0	0	0

Study results from challenge and storage at 2-8˚C

Growth of microorganisms (CFU/mL) in an infusion solution

Time point (Days)		T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_8	T_{10}	T_{12}	T_{14}	T_{16}
Microorganisms	*E. coli*	63	52	54	51	51	45	46	51	37	32	25	32
	Ps. aeruginosa	58	49	39	27	19	15	8	5	1	0	0	0
	E. cloacae	70	69	57	77	68	61	57	82	46	49	44	44
	S. aureus	52	51	53	53	59	52	55	41	51	44	50	58
	M. luteus	38	36	38	43	34	35	42	40	35	32	42	38
	C. albicans	41	34	44	23	18	15	8	6	5	8	4	7
Un-inoculated test bag control		N/A	0	0	0	0	0	0	0	0	0	0	0
Fluid A Control		0	0	0	0	0	0	0	0	0	0	0	0
0.9% Saline Control		0	0	0	0	0	0	0	0	0	0	0	0

Resolution: Post-reconstitution storage

- Lyophilized vials reconstituted with SWFI and further diluted with 0.9% NaCl IV bags could not be stored at RT
- Label was amended:
  - Store at 2-8˚C if not used immediately

Conclusions

Conclusions

- A complete BLA submission provides for an efficient and timely review
- An adequate BLA submission should contain the following microbiology product quality information and data:

Microbiology Product Quality Information in the Drug Product Section of a BLA

- Under 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:
  - Description of the manufacturing areas and fill line, including air classifications.
  - Description of the environmental and personnel monitoring programs.
  - Sterilization and depyrogenation process parameters for equipment and components that contact the sterile drug product, unless referenced in Drug Master Files.
  - Description of the sterilizing filter (supplier, membrane material, membrane surface area, etc.), the pressure limit or flow rate limit for sterilizing filtration, and the acceptance criterion for post-use integrity testing.
  - Parameters for filling, stoppering, and capping.
  - Processing and hold time limits, including the time limit for sterilizing filtration.

Microbiology Product Quality Information in the Drug Product Section of a BLA

- Protocols and reports with validation data under Section 3.2.P.3.5:
  - Bacterial filter retention study for the sterilizing filter.
  - Sterilization and depyrogenation of equipment and components that contact the sterile drug product.
  - In-process microbial controls and hold times.
  - Pre-bioburden reduction and pre-sterile filtration bioburden limits
  - Isolator decontamination, if applicable.
  - Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.
  - Summary of shipping validation studies and data.

Microbiology Product Quality Information in the Drug Product Section of a BLA

- Method validation information under 3.2.P.2.5 and 3.2.P.5:
  - Container closure integrity testing (3.2.P.2.5).
    - System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability.
  - Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate (3.2.P.5)
    - Recovery of endotoxin spiked in undiluted drug product by LAL methods
  - Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21CFR610.13(b) (3.2.P.5).

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