Sterile Drug Products Produced by Aseptic Processing - CGMPs

Midwest FDC Conference
November 4 2005

Susan Bruederle, Investigator
FDA / ORA / Central Region
Chicago District / Hinsdale IL

FDA's Guidance for Industry

- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
- http://www.fda.gov/cder/guidance/5882fnl.pdf
- Authors = CDER, CBER, ORA
- Published as Final in September 2004

FDA's Guidance for Industry

- FDA's "Current Thinking"
  - Does not bind FDA or public
  - Recommendations unless specific regulatory requirements cited
  - "Should" = suggested, not required
  - Alternate approach acceptable, if
    - Satisfies the statute or regulation
    - Firm can discuss with FDA staff

FDA's Guidance for Industry

- Extremely Brief History
  - Concept Paper (2002)
    - Advisory Committee Meeting
    - PQRI Aseptic Processing Working Group
  - Draft (2003)
    - Industry / Individual Comments
    - Workgroup Review of Public Comments
  - Final (2004)

FDA's Guidance for Industry

- Intention of document
  - Help firms meet the requirements in FDA's CGMP regs when manufacturing sterile drug and biologic products using aseptic processing
  - Replaces, update and clarifies 1987 guidance document

Table of Contents

21 CFR 211 References

- Each section preceded by black box that includes the 21 CFR 211 References

Today's Topics

- Highlight Important Issues
  - Highlighting in mine (not agency)
- Discuss in More Detail
  - Personnel
  - Process Simulation (media fills)
  - Environmental Monitoring

Sections I - III

- Introduction
- Background
- Scope

Section IV

Buildings & Facilities

- Section Covers
  - Air Quality
    - Non-Viable Particles
    - Air Velocity
    - Air Pattern Analysis
  - Clean Air Separation
    - Pressure Differentials
    - Air Change Rates

Section IV

Buildings & Facilities

- Section Covers Cont'd
  - Air Filtration (HEPA Filters)
    - Leak Testing
    - Monitoring Velocity
  - Design Issues

Section IV

Air Classifications

- Non-Viable particles in cubic meter
- Micro is 1 per cubic meter (normally should be 0)
- EU / USP designations are different

Section IV

Air Quality

- Air Pattern Analysis
  - In situ analysis
  - Conducted at critical areas
  - Demonstrate unidirectional airflow and sweeping action over and away from product under dynamic conditions
  - Include interventions and equipment design
  - Documented
    - Video
    - Written conclusions

Section IV

Air Filtration

- Air Filtration
  - Should include periodic monitoring of filter attributes such as uniformity of velocity across the filter and relative to adjacent filters
  - Measured at 6 inches from the filter face and a defined distance close to the work surface
  - **Measurements should correlate to the velocity range established at the time of the in situ air pattern analysis studies**

Section V

Personnel

- Well designed system minimizes personnel interventions
- Personnel should not have to enter the critical (Class 100) area

Section V

Personnel Training

- Topics
  - Aseptic technique
  - Cleanroom behavior
  - Hygiene
  - Gowning
  - Patient safety hazards posed by a non-sterile drug product
  - SOPs covering aseptic manufacturing

Section V

Aseptic Techniques

- Contact sterile materials only with sterile instruments
  - Gloves DO NOT remain sterile
  - Personnel should not directly contact critical surfaces with any part of gown or glove
- Move slowly & deliberately

Section V

Aseptic Techniques

- Keep entire body out of path of unidirectional airflow
- Approach necessary manipulation in a manner that does not compromise sterility of product
- Maintain proper gown control

Section V

Aseptic Gowning Certification

- Assess by testing after gowning
  - Micro surface sampling after gowning
- Initial certification
- Periodic assessment
  - Annual normally okay

Section V

Routine Personnel Monitoring

- Gloves = every day or for each lot
- Appropriate sampling frequency for gowns
- More comprehensive for operators involved in labor intensive operations
- Sanitizing just prior to sampling is not appropriate
- Investigate if exceed limits or adverse trend

Section VI

Components, Containers / Closures

- Discusses different types and suitable methods of sterilization
- Discusses inspection of containers
  - Any damaged or defective unit should be detected and removed during inspection
  - Any defects or results outside of the specs (in-process or finished product) shall be investigated

Sections VII & VIII

Endotoxin Control & Time Limits

- See Guidance Document (very short)
- Adequate cleaning, drying & storage of equipment will control bioburden and prevent endotoxin load

Section IX

Validation of Aseptic Processing & Sterilization

- Section Covers:
  - Process Simulation
  - Filtration Efficacy
  - Sterilization of Equipment, Containers and Closures

Section IX

Process Simulations (Media Fills)

- 21 CFR 211.113(b) requires validation of sterilization processes, including aseptic assembly

Section IX

Process Simulations

- Study Design
  - Guide includes long list of what to include IF APPLICABLE
  - Same vigilance for media fills as for production
  - Media fills should not be used to justify bad practices

Section IX

Process Simulation

- Frequency
  - Initially: enough to show consistency
    - Recommend 3 consecutive runs
  - Routine: semi-annual for each processing line (2 times per year)
  - Represent each shift and shift change
  - All personnel at least once a year
    - Includes technicians and mechanics
  - After investigation of media fill failure

Section IV

Process Simulation

- Duration of run
  - The time it takes to incorporate manipulations and interventions
  - Represent the duration of the commercial operations

Section IX

Process Simulation

- Interventions
  - Routinely simulate common interventions
  - Periodically simulate interventions that occur rarely
- Manual Filling / Manual Manipulations
  - Duration should be no less than the length of the actual operations

Section IX

Process Simulation

- Lyophilization
  - Unsealed vials exposed to partial evacuation of chamber
  - Do not freeze media
  - Maintain aerobic state
    - Do not use nitrogen to break vacuum

Section IX

Process Simulation

- Size of Run
  - Sufficient to accurately simulate activities that are representative of the manufacturing process

Section IX

Process Simulation

- Size of Run
  - 5000 – 10,000 (generally acceptable starting point)
  - If commercial lot is less than 5000
    - Media fill should equal max batch size
  - If commercial process in manual
    - Approach the full size of the batch

Section IX

Process Simulation

- Line Speed
  - Address full range
  - Each evaluate a single speed
  - Justify speed chosen
    - High speed = more interventions
    - Low speed = prolonged exposure

Section IX

Process Simulation

- Media
  - Soybean casein digest should be used
  - Anaerobic media should be considered under special circumstances
  - Growth Promotion
    - Gram+, Gram-, yeasts, molds
    - Represent production isolates
  - Inoculate with less then 100 cfu

Section IX

Process Simulation

- Incubation
  - 14 days
  - NEVER out of range of 20-35ºC
  - Plus or minus 2.5ºC of target temp
  - Incubate all integral vials
    - Vials with cosmetic defects should be incubated

Section IX

Process Simulation

- Examination
  - Use clear vial (identical) if amber vials used for commercial production
  - Examine by trained personnel
  - If QC lab personnel do not do, there should be QC oversight throughout exam
  - Any unit found to be damaged should be included in the data
    - Fully justify if not included

Section IX

Process Simulation

- Intervention Vials
  - Vials removed because of interventions do not have to be incubated if written procedures & documentation for routine production adequately describes what vials should be cleared from line

Section IX

Process Simulation

- Vial Accountability
  - Appropriate criteria for yield and accountability
  - Full accounting and description of units rejected and not incubated

Section IX

Process Simulation

- Interpretation
  - THERE IS NO ACCEPTABLE CONTAMINATION RATE !!!!!
  - Any contamination is indicative of a potential sterility assurance problem

Section IX

Process Simulation

- Recommended criteria
  - Less than 5000 vials
    - 1 or more positive vials is cause for revalidation
  - 5000-10000
    - 1 positive should be investigated, including "consideration" of repeat media fill
    - 2 or more considered cause for revalidation following investigation

Section IX

Process Simulation

- Recommended Criteria
  - Over 10,000 units
    - 1 positive unit should be investigate
    - 2 are considered cause for revalidation following investigation
  - Any size run
    - Intermittent incidents can be indicative of a low level contamination problem that should be investigated

Section IX

Process Simulation

- A media fill should be aborted only under circumstances in which written procedures require commercial lots to be equally handled

Section X

Laboratory Controls

- Environmental Monitoring
- Micro Media & Identification
- Prefiltration Bioburden
- Alternate Micro Test Methods
- Particle Monitoring

Section X

Environmental Monitoring

- *"One of the most important laboratory controls is the environmental monitoring program"*
- Include
  - Well-defined written program
  - Scientifically sound methods
  - Monitoring of critical surfaces

Section X

Environmental Monitoring

- Important Issues
  - Establishing Levels (Limits)
  - Trending
    - Consecutive growth at same site is only one type of trend
    - Trend also means increased incidence
    - Remedial action in response to adverse trends
  - Positive samples do not mean lot must be rejected

Section X

Environmental Monitoring

- Disinfection Efficacy
  - Disinfectant must be sterilized before bringing into cleanroom
  - Many disinfectant are not effective against spores

Section X

Environmental Monitoring

- Methods of Monitoring
  - Surface (touch plates, swabs, contact plates)
  - Active Air Monitoring
  - Passive Air Monitoring (settling plates)

Section X

Environmental Monitoring

- Micro Media
  - Should be validated as capable of detecting fungi as well as bacteria
  - Incubated at appropriate conditions of time and temperature
  - Total aerobic bacterial count
    - 30-35ºC for 48-72 hours
  - Total combined yeast and mold count
    - 20-25ºC for 5 – 7 days

Section XI - Sterility Testing

- Topic for another day
- See Guidance Document

Section XII
Batch Record Review

- Read Document
  - Says interventions should be documented
  - Environmental data reviewed prior to batch release, but does not have to be in batch record.

Appendices

1. Isolator Technology
2. Blow Fill Seal Technology
3. Processing Prior to Filling and Sealing Operations

Additional Info

- References
- Relevant Guidance Documents
- Glossary