Parenteral Drug Association

Current Issues: Aseptic Processing

RMJ Current Aseptic July 2013Australia.pptx

Connecting People, Science and Regulation®

Introduction

Richard M. Johnson
Member, PDA for 24 years
President & CEO since 2009

- Ladies and Gentlemen, I am happy to be here with you.

Overview

- Aseptic processing involves the interaction of a number of different processes, all of which must be designed, executed and controlled in order to yield sterile products.
- Current Issues
  - High regulatory scrutiny
  - Manual Aseptic Operations

HIGH REGULATORY SCRUTINY

US FDA Guidance

- "Guideline on Sterile Drug Products Produced by Aseptic Processing," Center for Drugs and Biologics and Office of Regulatory Affairs, Food and Drug Administration, Sept. 2004.
  - Includes tightened media fill criteria
  - „Clarifies" controversial environmental monitoring issues
  - Includes annex for Advanced Aseptic Processing.

EU Directive

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Annex 1
Manufacture of Sterile Medicinal Products
(corrected version)

Document History	
Previous version dated 30 May 2003, in operation since	September 2003
Revision to align classification table of clean rooms, to include guidance on media simultations, bioburden monitoring and capping of vials	November 2005 to December 2007
Date for coming into operation and superseding	01 March 2009[1]

Please note correction on the implementation of provisions for capping of vials!

[1] Note: Provisions on capping of vials should be implemented by 01 March 2010.

PI 032-2
8 January 2010

GMP ANNEX 1 REVISION 2008, INTERPRETATION OF MOST IMPORTANT CHANGES FOR THE MANUFACTURE OF STERILE MEDICINAL PRODUCTS

In order to assure a harmonised conduct of inspections, with respect to the 2008 revision of GMP Annex 1 [2], this document summarises the interpretations which an inspector of the competent regulatory authority should adopt when performing an inspection of a manufacturer of sterile medicinal products.

This document reflects the most important changes and also addresses the feedback from industry concerning the GMP Annex 1 Revision. It is not meant to address all changes within the Revision.

Top 10 FDA Domestic Inspection Citations October 2010 - October 2012

CFR Section	Description	Number of Times Cited
211.22(d)	Procedures not in writing/fully followed	356
211.100(a)	Absence of written procedures	241
211.160(b)	Scientifically sound laboratory controls	239
211.192	Investigations of discrepancies/failures	234
211.110(a)	Control procedures to monitor and validate performance	158
211.67(b)	Written procedures not established/followed	155
211.25(a)	Training - operations, GMPs, written procedures	152
211.100b)	SOPs not followed/documented	149
211.67(a)	Cleaning /sanitizing /maintenance	144
211.165(a)	Testing and release for distribution	134

Areas of FDA Interest

- Aseptic Processing
- CMOs/Knowledge Transfer
- Drug Shortages
- Environmental Monitoring
- Failure Investigations
- Metrics for Quality
- Particulates/Visual Inspection
- Sterilization
- Training

Specific FDA Observations

- **FDA observation requiring a European firm performing aseptic processing of sterile drug products to incubate media-filled test units for 14 days @ 20-25°C followed by another 14 days @ 30-35°C.**
- *Are there legitimate reasons for such a requirement? If so, what are they?*

Specific FDA Observations

- **Sterility Test – There was not sufficient evidence to invalidate the sterility test, but retesting of additional samples was allowed and the product lot was released for distribution to the marketplace**
- ***Bacillus circulans* was recovered from the sterility testing suite several times, but was not used for growth promotion testing of sterility test media**

Environmental Monitoring Excursions

- "The root cause analysis and conclusions regarding the environmental monitoring out of specification is inadequate in that it fails to address historical trends for the recovery of the microorganisms isolated in the production environment across all sampling points, especially those located in critical areas"

Environmental Monitoring - Identification

- "Identification of environmental microbial isolates which do not meet or exceed the firm's action or alert levels are only identified on a monthly basis. This identification frequency does not enable the firm to have a sufficient understanding of the normal microbial flora that could be present in the firm's production area"

Sterility Test Failure Investigations

- "Failure investigations and corrective actions are inadequate for sterility failures. Not all data gathered were documented for root cause/risk analysis and/or the conclusions provided are inadequately supported by data. As a result, lots were released at risk, adequate corrective/ preventive actions were not taken and additional product sterility failures occurred."

Sterility Test Failure Investigations

- "Failure to notify FDA regarding sterility failures that could potentially impact product released to the marketplace. Four sterility test failures occurred for product *ABCED* from June 2010 thru August 2012. The definitive root causes for these failures were not determined. Those failing lots were rejected, but product lots filled on the same line since have been distributed to the U.S. Market"

Process Simulation Runs – Media Fills

- "The failure investigation report indicates that since XXYY there have been no turbid [contaminated with viable microbes] vials found for media fills performed on Filling Line #AA. The report failed to mention that one turbid vial was found for the media fill run conducted on 10 January 2012, which was conducted for the lyo pathway"

Media Fill Test Unit Inspection

- "The operators performing visual inspection of incubated media filled bottles have not received adequate training on visual inspection of media filled units"
- "In addition, the operating instructions are not sufficient to ensure that the examination is capable of detecting turbid units"

Aseptic Processing – Disinfection Practices

- "The environment surrounding Filling Line XY is congested with racks holding material to be used for other filling operations on the same day. The amount of material in the filling suite does not allow for easy cleaning and disinfection"
- "Disinfectant efficacy challenge studies do not use 'in-house' isolates in addition to standard strains [e.g. ATCC]"

Environmental Monitoring Oversights

- "Employees reported as 'sweating' during set up operations for the filling line were only monitored on their gloves; no gown surfaces were monitored"
- "The employee that performed an adjustment to the stopper feed on the aseptic filling line was not properly monitored, i.e., no samples were taken from gown surfaces"

WL Citation

- Your aseptic processing room was not adequately constructed to meet design specifications.
- You do not have justification that adequate active air sampling locations … during aseptic filling operations. You also have not [done] post-filling microbial surface monitoring of critical surfaces.

WL Citation

- There is no documentary evidence of in-situ air pattern analysis (e.g., smoke studies)…monitoring differential pressures within the aseptic processing areas is not sufficient…no procedures for the qualification of operators who conduct operations within the aseptic processing areas.
- Investigators observed poor aseptic technique for manufacturing and quality control microbiology personnel working inside the aseptic fill suite and core
- There is no assurance that manufacturing employees' sterile garments and gloves remain sterile after lying on the bench in the gowning room

WL Citation

- Operators did not follow SOP requirements pertaining to interventions into the Class 100 (ISO 5) zone.
- Your firm failed to design and perform an adequate aseptic process simulation (i.e., media fill) based upon the same controls used for routine production.

EU GMP Deviations: *From* R. Guinet (AFFSA)

at PDA Parenteral Conference in Berlin 2010

- **<u>MAJOR</u> The plunger stoppers provided by XX are radio-sterilised by gamma irradiation between 12 kGy and 25 kGy by a sub-contractant. The validations shown were made in 2000 and there is no guaranty that all the stoppers in the load were correctly sterilised (GMP LD 12.9, LD 12.10, LD 1.98, LD 1.99).**

EU GMP Deviations: *From* R. Guinet (AFFSAPS)

at PDA Parenteral Conference in Berlin 2010

- **MAJOR. This site receives the primary components, syringes and plunger stoppers sterilised and RTU after released by the head quarter. The QA of this site has not verified that the sterilisation conditions of the syringes by Ethylene Oxide and radio-sterilisation of the stoppers by the supplier and its subcontractants have been correctly validated following the requirements of the EP and EU GMP (BPF LD 1.83, LD 1.104, LD 12.9).**

EU GMP Deviations: *From* R. Guinet (AFFSAPS)

at PDA Parenteral Conference in Berlin 2010

- **It is not possible to verify routinely at the point of use that the ready-to-use sterilised syringes provided by the supplier in nets wrapped in bags remain sterile without any invisible micro-leak in the containers like, for instance, it is possible for the stoppers provided in bags sealed under vacuum (GMP Annex 1.81).**

Recall of Products

- Amgen Initiates Voluntary Nationwide Recall of Certain Lots Of Epogen® And Procrit® (Epoetin Alfa) (Sept. 24, 2010) The product that is being recalled may contain extremely thin glass flakes (lamellae) that are barely visible in most cases.

EU GMP Deviations: *From* R. Guinet (AFFSAPS)

at PDA Parenteral Conference in Berlin 2010

- **The filling and closure process of the syringes in the new syringe filling line of building XX was not initially validated for integrity (Annex 1.88/1.117).**
- **Samples of each batch of filled syringes and vials in buildings XX and XX are not checked during the process for integrity according to appropriate procedures, since only dimensional and positional parameters are checked during the process (Annex 1.88/1.117).**

EU GMP Deviations: *From* R. Guinet (AFFSAPS)

at PDA Parenteral Conference in Berlin 2010

- **CRITICAL The detection of glass particles in freeze-dried vials of injectables was not considered critical and no investigation was conducted in production. Thus, batches were released with important rejection rates for glass particles after human visual inspection. This visual inspection was considered perfect for the detection of glass particles in freeze-dried products without any specific validation.**

Regulatory Diligence

- Requirements can be explicit or implicit
- Constantly changing
- Monitor-stay current-anticipate

MANUAL ASEPTIC PROCESSING

What makes MAP special?

Image courtesy of inventionmachine.com

- Manual aseptic processing (MAP) operations differ from automated operations
- These differences pose unique operational and evaluation challenges
- These challenges must be considered thoroughly when designing the evaluation procedure or protocol for the MAP operation

What makes MAP special?

MAP involves a human operator performing, at a minimum, the container and/or closure movements

MAP relies heavily on individual operators' basic understanding of microbiology proficiency

Personnel must be individually qualified

People - the Usual Suspects!

The greatest sources of microbial contamination during MAP are operational personnel and their activities.

Image courtesy of Cleanroom Technology

People - the Usual Suspects!

Human performance deviations or failures are linked to:

- Complex aseptic processing tasks
- The continuous span of time during which an operator carries out repetitive aseptic activities
- The expected rate of activity
- Change in personnel

Goal of Aseptic Processing Evaluation

Prevent the contamination of sterile materials during their processing

- Demonstrate that aseptic processing can be achieved and maintained successfully under the specified operational configuration, activities, and conditions
- Same goals for manual or automated aseptic operations and for small-scale or large scale operations

Manual Aseptic Process Evaluation

Adequate evaluation of MAP requires accountability for human factors in the

- Design of MAP
  - Design of APS program

Image courtesy of www.spaceforhealth.nhs.uk

APS: A means for establishing the capability of an aseptic process as performed using a growth medium

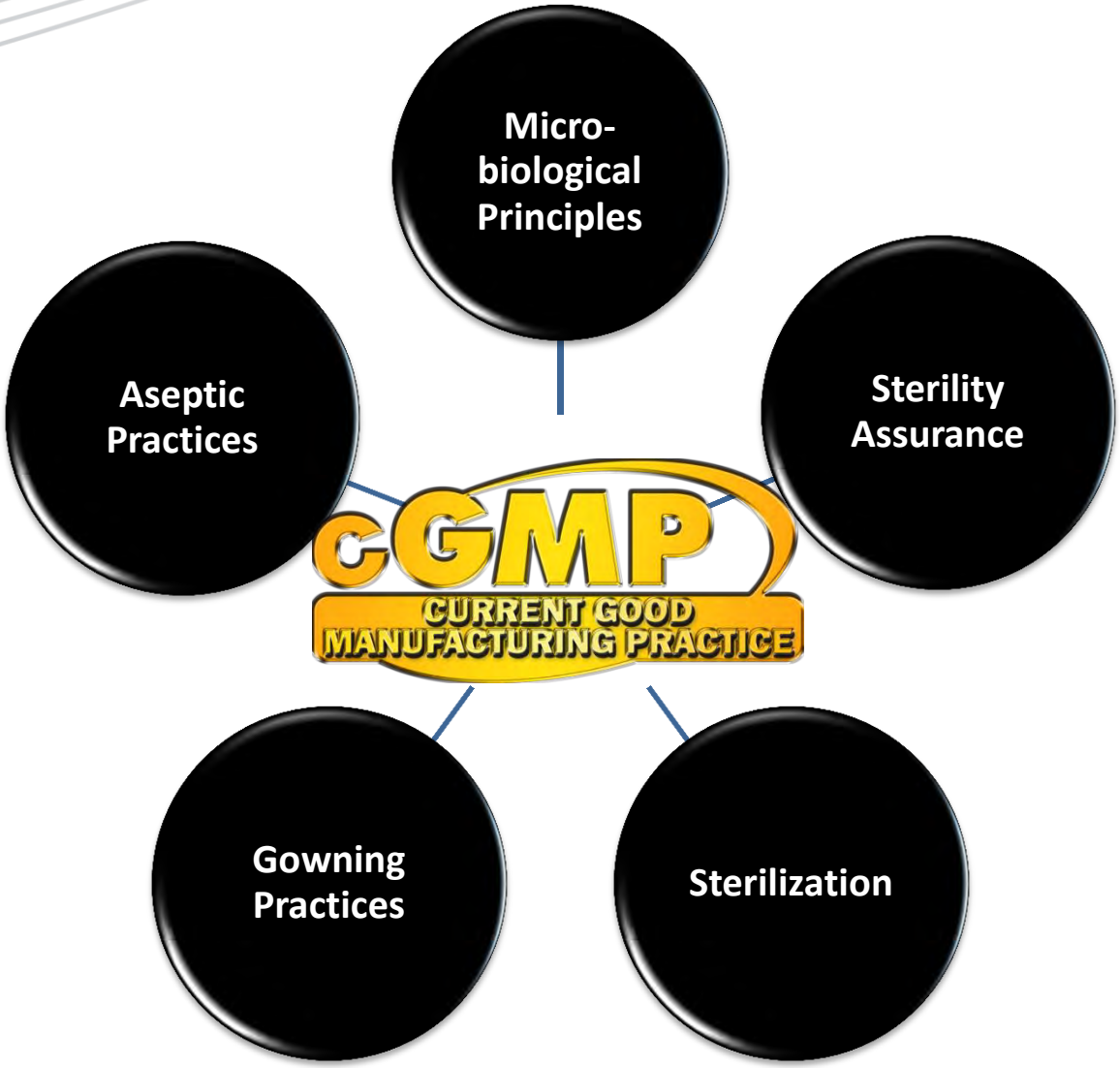
Personnel Training & Qualification

People are the most critical operational variable in manual aseptic processing

Therefore personnel training and qualification becomes critical to success

Photo courtesy of *www.uthsc.edu*

Elements of Training Requirements



Knowledge Alone is Insufficient

Operators must be able to:

- ✓ Apply classroom learning to real world
- ✓ Excel in aseptic gowning, assembly and technique
- ✓ Consistently perform without contamination

Risk Management

MAP frequently involves greater risks than automated aseptic processes.

A risk-based quality management system is necessary.

"Quality risk management can be an effective method of identifying and reducing aseptic processing risk, thus improving the assurance of sterility, endotoxin control, and subsequent patient safety." (*PDA Technical Report 44)*

Useful PDA Technical Reports

PDA Technical Report 22, Revised 2011 Process Simulation for Aseptically Filled Products

PDA Technical Report 36, Current Practices in the Validation of Aseptic Processing - 2001

PDA Technical Report No. 62 (TR 62) Recommended Practices for Manual Aseptic Processes

Useful Websites (1)

- **Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition (Dec 2009)**
  http://www.cdc.gov/biosafety/publications/bmbl5/index.htm
- **European Pharmacopoeia (*Ph. Eur.*) 2.6.1, Sterility**
  http://www.tailingood.com/uploads/2009_5_14182924.pdf
- **2004 FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice**
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070342.pdf

Useful Websites (2)

- **EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 1 Manufacture of Sterile Medicinal Products** http://tern-quay.com/Orange_Guide/Annexs/EU-GMP-Vol4_Annex1.pdf

- **Pharmaceutical Inspection Co-operation Scheme (PIC/S) Publications**

  list http://www.picscheme.org/publication.php

  document downloads http://www.picscheme.org/publication.php?id=8

  - Validation of Aseptic Processes PI007-6
  - Isolators Used for Aseptic Processing and Sterility Testing PI014-33
  - Technical Interpretation of Revised Annex 1 to PIC/S GMP Guide PI037-1
  - PIC/S Guide to Good Practices for the Preparation of Medicinal Products In Healthcare Establishments PE010-3

Recap

- Aseptic Processing is complex
- Compliance requires constant vigilance for
  - Design
  - Operation
  - Monitoring
- Regulatory expectations / industry standards constantly changing

PDA Contact Info:

PDA USA Member Relations:
4350 East West Hwy. Suite 200, Bethesda, MD USA
info@pda.org or 301-656-5900

PDA Europe Member Relations:
Adalbertstr. 9, 16548 Glienicke / Berlin, Germany
Tel: +49 33056 2377-0 or -10 or Fax: +49 33056 2377-77 or -15
info-europe@pda.org

Speaker's Contact Information:
Richard M. Johnson, President, PDA
Johnson@pda.org