Why Drugs Cost So Much...

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**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

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Why Drugs Cost So Much...

- Media Fill Challenges at PDA & ATI
- 2004 FDA Aseptic Guideline
- Rotation of Disinfectants?
- To RABs or Not to RABs?
- Annex 1
- Current Microbiological Regulatory Issues
- The Future Impact
EVERYTHING YOU ALWAYS WANTED TO ATTEMPT IN AN ASEPTIC ENVIRONMENT BUT WERE AFRAID TO DO

John M. Lindsay
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First Work Location (now referred to as “First Air”)

“The work location first in the path of the (HEPA-)filtered air.”

[NASA Standards for Clean Rooms and Work Stations for the Microbially Controlled Environment, NHB 5340.2, Aug. 1967]
“First Air”
Media Fill Challenge Test Data
Published:

Environmental Monitoring
Volume 2
Edited by Jeanne Moldenhauer
Available from PDA Press
Case Study No. 1—*B. subtilis* spores in 70% IPA, final conc = 2.3 x 10²/mL—used for sanitizing hands in Filling Room

- Morning & Afternoon Media Fill: 0/1849 + vials
- EM
  - Viable air: 0/14 + samples
  - Surfaces: Positive recovery from 1 entry door, 1 set-up cart and 1 floor sample all other samples (55) were 0
  - Personnel: B.s. from 11/60 FIP’s—6 were Action Levels; 1 TNTC B.s. from a chest 2 other Action Levels
Case Study No. 2—*B. subtilis* spores in 70% IPA, final conc = ~$10^4$/0.1mL—>inoculated stopper bowl; ~$10^4$/mL *B. licheniformis* in 70% IPA used to Sanitize Operator Gloves

- Morning Media Fill: 0/783 + vials; vials incubated upright
- EM
  - Viable air: 1/11 + samples (Alert Level)
  - Surfaces: 0/24 samples positive
  - Personnel: 19/58 + FIP samples (4 Actions, 6 Alerts); 10/27 + gown samples (1 Action Level)
Case Study No. 2—*B. subtilis* spores in 70% IPA, final conc = ~$10^4$/0.1mL—>inoculated stopper bowl; ~$10^4$/mL *B. licheniformis* in 70% IPA used to Sanitize Operator Gloves

- **Afternoon Media Fill**: 2/799 + vials (*B. subtilis*); vials incubated inverted

- **EM**
  - Viable air: 1/15 + samples
  - Surfaces: 1 positive floor sample (1 CFU); others-- 0/24 samples positive, including stopper bowl
  - Personnel: 1/50 + FIP samples (Alert); 8/33 + gown samples (2 Action Levels)
Case Study No. 3—*B. subtilis* spores in 70% IPA, final conc = $1.3 \times 10^5$/mL—used for sanitizing sterilized commodities into the pass-through of the Filling Room

- Morning Media Fill: 6/637 + vials; *B. subtilis*
- EM
  - Viable air: 2/12 + samples (One Alert Level)
  - Surfaces: 11/25 samples positive (6 Action Levels)
  - Personnel: 20/32 + FIP samples (17 Actions, 2 Alerts); 18/40 + gown samples (5 Action Levels, 3 Alert Levels)
Case Study No. 3—*B. subtilis* spores in 70% IPA, final conc = $1.3 \times 10^5$/mL—used for sanitizing sterilized commodities into the pass-through of the Filling Room; *B. licheniformis* $\sim 10^{-6}$ on Fill Needle

- Afternoon Media Fill: 1/789 + vials (*B. subtilis*)
- EM
  - Viable air: 0/12 + samples
  - Surfaces: 12/25 + samples; mostly *B. subtilis*; filling needle was TNTC *B. licheniformis*
  - Personnel: 23/38 + FIP samples (most were *B. subtilis*), 18 Actions; 13/52 + gown samples, 3 Action Levels
Case Study No. 4—*B. pumilus* spores in 70% IPA, final conc. $2.5 \times 10^4$; $9 \times 10^6$ *B. subtilis* spores inoculated on underside of each FD shelf; *B. licheniformis* $2 \times 10^7$ swabbed onto crimper.

- 0/2575 + vials; all vials incubated inverted
- Viable air: 6/31 + samples (2 Action Levels)
- Surfaces: 23/55 + samples (13 Action Levels)
- Personnel: 44/96 + FIPs (23 Actions); 16/71 + gown samples (2 Actions)
What this Data Does NOT Demonstrate

- There must be 10,000 CFUs on a stopper bowl surface before a product or media may become contaminated.
Case Study No. 15 (Nov. 2006) -- Area cleaned & sanitized as validated; all commodities sterilized as routinely done; media fills performed wearing lab coats, hair nets, booties & sterile gloves

- 0/2057 media filled vials contaminated
- Viable air: 6/22 air samples +, PT--G (+) cocci; Staging rack--G(+) cocci, 1 Bacillus
- Surface samples: 26/108 samples positive; 3 Bac (floor & inside Lyo 2)
- Personnel Monitoring: 21/142 FIP’s--4 Action & Levels; Gowns: 88/88--74 Action Excursions
What this Data Does NOT Demonstrate

- Sterile cleanroom gowns are unnecessary for filling product.
CONCLUSIONS

1. The level of environmental contamination (Cleanroom Creep) can impact the sterility assurance of the product being filled. Percent positive EM samples more significant than a single Action Level excursion.
CONCLUSIONS

2. Good aseptic technique can reduce the risk of product contamination even in the presence of a contaminated environment.
CONCLUSIONS

3. Personnel are the main vectors of contamination in the aseptic filling facility, unless a contaminated aerosol is created.
CONCLUSIONS

4. A contaminated media fill unit is a major event. In modern cleanrooms with basic facility design, including HEPA-filtered air, and a knowledge of good aseptic techniques, including “First Air,” a positive media-filled vial or product filled vial should NEVER occur.
CONCLUSIONS

5. Any positive media-filled unit, regardless of the number of vials filled, should be investigated thoroughly. If a reasonable assignable cause is not determined the result should be considered a failure.
FDA Aseptic Guideline

- PQRI Aseptic Processing Committee
- Media Fill Acceptance Criteria:
  1 Contaminated Unit—Investigate
  ≥ 2 Contaminated Units—Re-validate
- Re-validate?
- Hummmmm...
Rotation of Disinfectants?

- Sales pitch 20-25 years ago: High pH and low pH Phenols
- USP <1072> brought some sanity to disinfectant rotation
- Microorganisms only mutate when they are replicating
- New Sporicidal? Low conc. Silver products
Isolators Are the Answer!!!
(25 Years Ago)

- Sterile!!!---Uh, NO!
- Easy to Validate---Uh, NO!
- Panacea for all our Aseptic Processing Issues---Uh, NO!
- RABs Systems—Cheaper and better answer?---Uh NO…
- Real Advantages---Perception---Ummmm
Isolator and RAB Systems

- Still required to use good aseptic technique
- “First Air” is still the fundamental principle of good aseptic technique in an isolator
- Personnel training is even more important
**Annex 1**

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1 Note: Provisions on capping of freeze-dried vials should be implemented by 01 March 2010.
Revision of Annex 1

The latest revision provides updated guidance on:

- Classification table for environmental cleanliness of cleanrooms and associated text
- Guidance on media simulations
- Guidance on capping freeze-dried vials
Why Monitor 5 micron particles?

- **High Risk Appetite:**
  - “As 5 micron counts are a good early diagnostic tool for detecting early failure of HVAC systems, machine failure or poor practices, then not monitoring them would indicate the company has a high risk appetite with regard to accepting the chance of
    - Rejected batches
    - Cleanroom failure…etc.
Editorial changes

- Laminar air flow becomes unidirectional airflow
- Clean room becomes cleanroom
Media Simulations

- Acceptance limits harmonized with FDA Guidance
Capping of Vials

- Covers both freeze-dried product and standard liquid or powder product vials
- Vials should be protected by Grade A conditions until the cap has been crimped.
- Why?
Capping of Vials

- Inspectors observed missing stoppers being replaced or being pushed home by hand in warehouse environments.
- RABs and isolators may be beneficial in assuring the required conditions and minimizing direct human interventions into the capping operation.
Airlocks

- Transitions between Unclassified to D, D to C, C to B
- Engineering Issues
Current Regulatory Activity

- NECC
- Other Compounding Pharmacies (Med Prep)
- Big Pharma Impact
The Role of Compounding Pharmacies

- Hospital Pharmacies generally provide formulated drug products for patients and doctors within their hospital.
- Large Compounding Pharmacies may provide formulated drug products to many hospitals and doctors.
- The oversight for Compounding Pharmacies is typically by state regulatory boards.
The Role of Compounding Pharmacies

“The intent is that a Licensed Pharmacist prepare a final dosage form for a specific patient with a valid prescription, using safe and approved ingredients using good manufacturing practices. The formulated drug product should not be a copy of a commercially-available drug.”

--Legislative Proposal from Congressman Edward Markey
Outbreak of fungal meningitis in patients administered steroid Methylprednisolone acetate

Distributed to practitioners in 23 states

Injected into 14,000 patients into the spine, knee, ankle or shoulder

Over 70 deaths and many people infected
Investigation Findings:

- 83 of 321 vials found greenish black foreign matter
- 17 more had a white filamentous material
- The firm’s only sterility sample was a single bulk sample—no growth
- FDA samples—50/50 contained a filamentous sample that had fungal features when examined microscopically
The firm manufactured product with non-sterile raw materials.

Bacteria and mold were recovered from EM samples from both cleanrooms, including recoveries from ISO5 horizontal LFHs.

The firm routinely turned air handlers off between 8:00 PM and 5:30 AM nightly.
NECC

- Closed by FDA Oct. 3, 2012
- 18,000 vials of the steroid and other products produced since the beginning of 2012 recalled
- Patients are still dealing with very painful treatment
- The overall prognosis is not good
...and the Beat Goes On...

- FDA blitz on Compounding Pharmacies began in February
- Since mid-February there have been 15 483’s issued to Compounding Pharmacies
- Last week a New Jersey Compounding Pharmacy shut down and has recalled 50 mL bags of Sterile Magnesium Sulfate because of visible mold
What’s This Got to Do with US?
What’s This Got to Do with US?

- Nov. 2011 a 483 was issued and in Feb. 2013 a CD was issued to a firm
- One of the findings: Numerous recoveries of mold in one of the aseptic suites—discovered the roof had leaked and replaced it; mold was still recovered!
- Facility was shut down until just recently
What’s This Got to Do with US?

Another Large Company’s 483s:
- 9 FDA Inspectors; 15 week long inspection
- The firm has failed to adequately control mold in manufacturing areas…Aug 2010 and Dec. 2012
- Failed to adequately investigate a mold in a MF
- 7/15 observations were due to EM or mold recoveries
Their response:

- Between Aug 2010 and Dec. 2012 a total of 945,151 EM samples were taken in A, B, C and unclassified areas.
- The total Mold Recovery rate = 0.02%.
- Action limit for mold to be 1 in A, B and C areas.
The Future

- Zero tolerance for mold
- Will require increased control measures:
  - H$_2$O$_2$ Wipes replacing traditional 70% IPA wipes
  - Enhanced access controls, e.g. Air Showers
  - Enhanced EM
  - More Air Locks???
And That’s Why Drugs Cost So Much!

Thank you…

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