Why Drugs Cost So Much…

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See….

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 14 February 2008

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

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 freeze-dried vials	November 2005 to December 2007
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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

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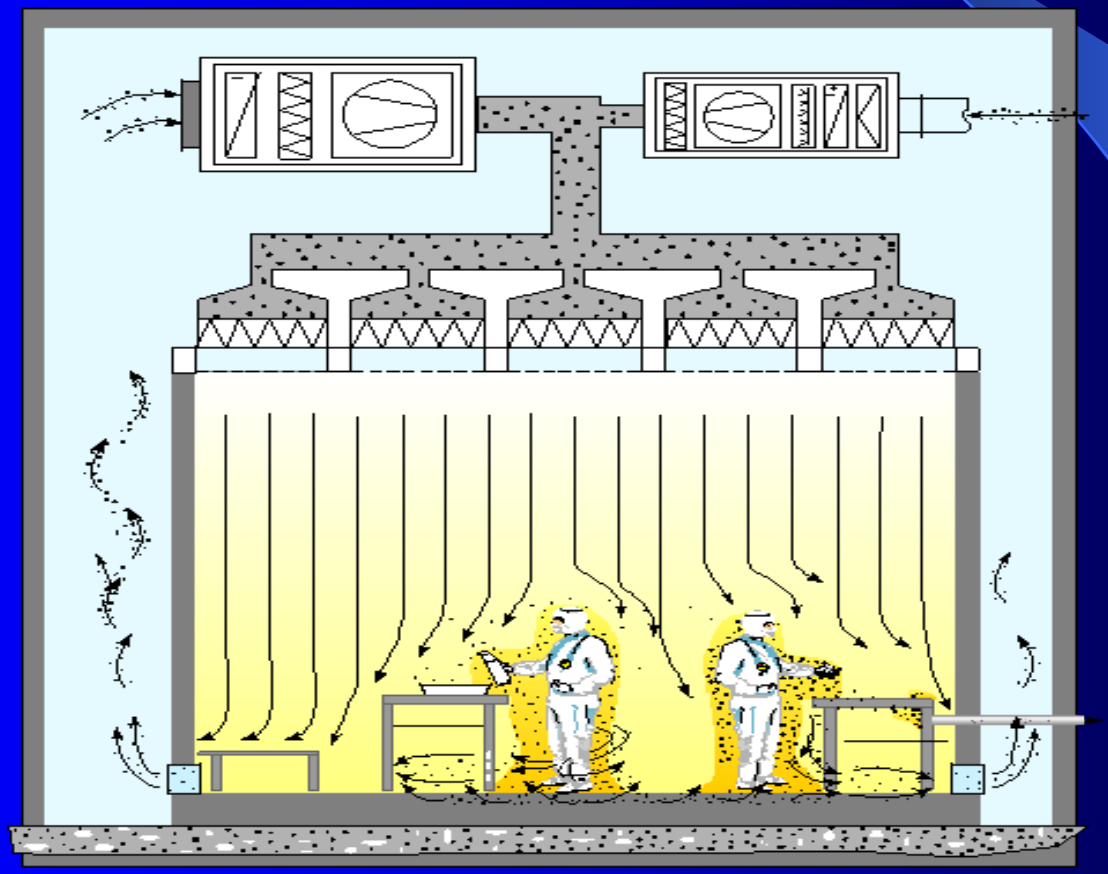
First Work Location (now referred to as "First Air")

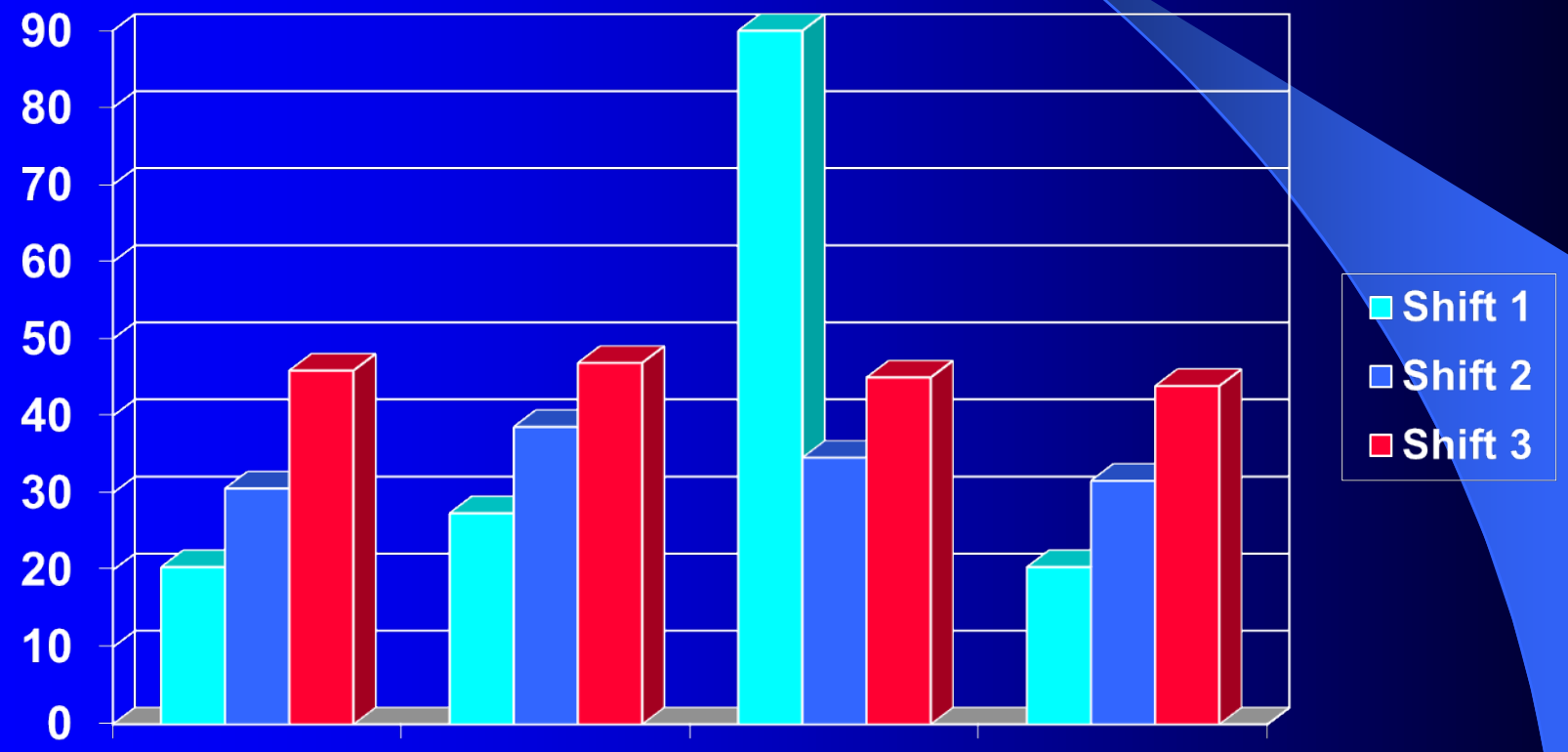
- "The work location first in the path of the (HEPA-)filtered air."

  [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



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Case Study No. 1—*B. subtilis* spores in 70% IPA, final conc = 2.3 x 10^2/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 x 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 x 10^5/mL—used for sanitizing sterilized commodities into the pass-through of the Filling Room; *B. licheniformis* ~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 x 10^4; 9 x 10^6 *B. subtilis spores inoculated on underside if each FD shelf; B. licheniformis 2 x 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

  $\geq$ 2Contaminated Units—Re-validate
- Re-validate?
- Hummmmm….

Rotation of Disinfectants?

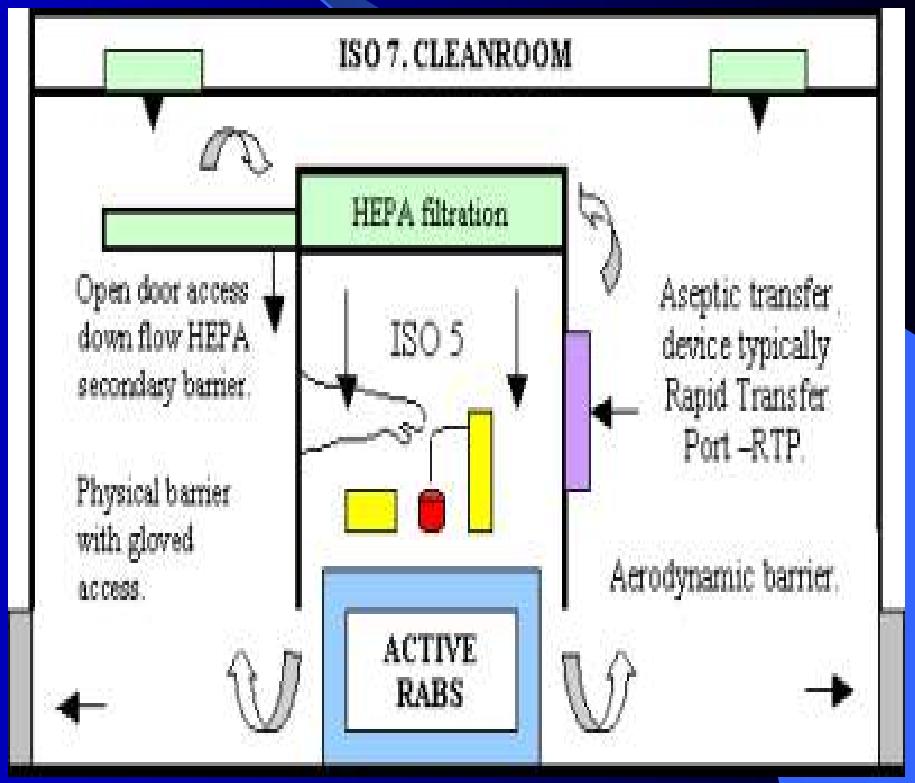
- Sales pitch 20-25 years ago: High pH and low pH Phenols
- USP <1072> brought some sanity to disinfectant rotation
- Microorganisms only mutate when they are replicating
- New Sporicidal? Low conc. Silver products

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



Valentine's Day, 2008

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Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11

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 is 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

NECC

- 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

NECC 483 (20 NOV 2012)

- 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

NECC 483 (20 NOV 2012)

- 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

What's This Got to Do with US?

- 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_2O_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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