# USP Guidances on Environmental Control including related USP, FDA, EMEA & PDA Activities

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# Operators & Contamination

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- **Hank Avallone – 1988**

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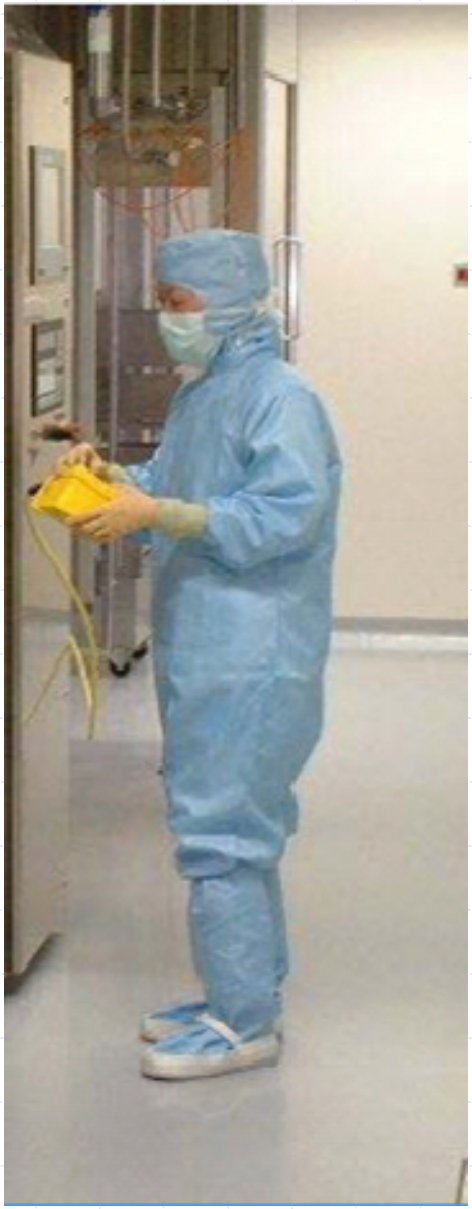


# Aseptic Cleanroom - ~1970 practices

# USP Activities

# <1116> Microbiological Control

- Presents an entirely new perspective on environmental control relying on incident rates rather than action / alert levels.
- Reflects the uncertainty in microbial recovery especially in the cleanest environments.
- Makes a clear distinction between environments for aseptic and other cleanroom applications (to be covered in a separate chapter). The new chapter may be patterned after <1116>.

# Old School Micro "Requirements"

Microbiological cleanliness levels 'In Operation' cfu/$m^3$

| | EU Annex 1 | '04 FDA | USP 1116 |
|---|---|---|---|
| **Aseptic core** | **A <1** | **<1** | **<3** |
| **Aseptic processing area** | **B <10** | **n/s** | **<20** |
| **Controlled processing area** | **C <100** | **<10** | **<100** |
| **Controlled support area** | **D <200** | **<100** | **n/s** |

- The critical values are essentially identical.

# A New Reality?

- "It is not possible to maintain a manufacturing environment that is sterile.
- In any environment where human operators are present microbial contamination is inevitable.
- Best clean room environment design and operating practices cannot prevent the shedding of microorganisms into the environment by human operators
- Thus, an expectation of zero contamination at all locations during every aseptic processing operation is technically wrong and unrealistic."

# Relationship to ISO 14644 series

- The design and construction of clean rooms and controlled environments are covered in ISO 14644.
- ISO 14644 stipulates the total particulate counts required for a clean environment to meet the defined air quality classifications.
- USP accepts this standard verbatim.

# Limitations of Microbial Monitoring

- "Monitoring can not identify and quantify all microbial contaminants present."
- "Microbiological monitoring of a clean room is technically a semi-quantitative exercise, given the limitations in sampling equipment."
- "Lack of precision of counting methods and limited sample volumes mean that environment monitoring is incapable of providing quantitative information regarding sterility assurance."

# What Monitoring Can Do

- "The real value of a microbiological monitoring program lies in its ability to confirm consistent, high quality environmental conditions at all times.
- Monitoring programs can detect changes in the contamination recovery rate that may be indicative of changes in the state-of-control within the environment."

# Monitoring Frequencies

**Table 2. Suggested Frequency of Sampling for Aseptic Processing Areas**

| Sampling Area | Frequency of Sampling |
|---|---|
| ISO Class 5 or better room | Each operating shift (if a Class 5 rated hood is used only for control of non- viable particulate, microbiological testing is not required. |
| Isolator systems: | |
| Active air sampling | Once per day; |
| Surface monitoring | At the end of each campaign |
| Aseptic Processing area adjacent to ISO Class 5 (e.g. Class 7) | Each operating shift |
| Other support areas in aseptic Processing (ISO Class 8) | Twice/week |
| Other less critical support areas in aseptic processing (ISO Class 8) | Once/week |

# <1116> Incidence Rates

**Table 3 Recommended Contamination Incident Rates**

| Grade | Active air sample | Settle Plate (9cm) 4hr exposure | Contact Plate or Swab | Glove or Garment |
|---|---|---|---|---|
| Isolator (ISO 5 or better) | <0.1% | <0.1% | <0.1% | <0.1% |
| ISO 5 | <1% | <1% | <1% | <1% |
| ISO 6 | <3% | <3% | <3% | <3% |
| ISO 7 | <5% | <5% | <5% | <5% |
| ISO 8 | <10% | <10% | <10% | <10% |

# Incidence Rates (continued)

- "NOTE: Contamination recovery rates should be based upon actual monitoring data and should be re-tabulated monthly. Action levels should be based upon actual empirical process capability. When contamination recovery rates are observed that exceed the recommendations in the table or are greater than established process capability corrective actions should be taken."

# Incidence Rates (continued)

- "Corrective actions may include but are not limited to:
  1. Revision of the sanitization program including selection of anti-microbial agents, application methods, and frequencies.
  2. Increased surveillance of personnel practices by supervisory staff; this may include written critiques of aseptic methods and techniques used by personnel.
  3. Review of microbiological sampling methods and techniques.
  4. When higher than typical glove and garment contamination recovery levels are observed additional training on gowning practices may be indicated."

# Significant Excursions

- "Excursions beyond approximately 15 CFU recovered from a single sample, whether airborne, surface or personnel should happen very infrequently in aseptic processing environments. However, when such occurrences do occur they may be indicative of a significant loss of control, particularly when they occur within the ISO 5 critical zone in close proximity to product and components. Therefore, any excursion $\geq$15 CFU should be the subject of a careful and thorough investigation."

# <1072> Disinfectants And Antiseptics

- Antiseptic—An agent that inhibits or destroys microorganisms on living tissue including skin, oral cavities, and open wounds.
- Chemical Disinfectant—A chemical agent used on inanimate surfaces and objects to destroy infectious fungi, viruses, and bacteria, but not necessarily their spores.
- Cleaning Agent—An agent for the removal from facility and equipment surfaces of product residues that may inactivate sanitizing agents or harbor microorganisms.
- Disinfectant—A chemical or physical agent that destroys or removes vegetative forms of harmful microorganisms when applied to a surface.
- Sanitizing Agent—An agent for reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses, and bacteria.
- Sporicidal Agent—An agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.
- Sterilant—An agent that destroys all forms of microbial life including fungi, viruses, and all forms of bacteria and their spores. Sterilants are liquid or vapor-phase agents.

# Disinfection Targets

| Type of Microorganisms | Examples |
|---|---|
| Bacterial spores | *Bacillus subtilis* and *Clostridium sporogenes* |
| Mycobacteria | *Mycobacterium tuberculosis* |
| Nonlipid-coated viruses | Poliovirus and rhinovirus |
| Fungal spores and vegetative molds and yeast | *Trichophyton, Cryptococcus,* and *Candida* spp. |
| Vegetative bacteria | *Pseudomonas aeruginosa, Staphylococcus aureus,* and s*almonella* spp. |
| Lipid-coated viruses | Herpes simplex virus, hepatitis B virus, and human immunodeficiency virus |

# Classifying Disinfectants

| | | |
|---|---|---|
| **Aldehydes** | **Sporicidal agent** | **2% Glutaraldehyde** |
| **Alcohols** | **General purpose disinfectant, antiseptic, antiviral agent** | **70% Isopropyl alcohol, 70% ethanol** |
| **Chlorine and Sodium hypochlorite** | **Sporicidal agent** | **0.5% Sodium hypochlorite** |
| **Phenolics** | **General purpose disinfectant** | **500 µg per g Chlorocresol, 500 µg per g chloroxylenol** |
| **Ozone** | **Sporicidal agent** | **8% Gas by weight** |
| **Hydrogen peroxide** | **Vapor phase sterilant, liquid sporicidal agent, antiseptic** | **4 µg per g $H_2O_2$vapor, 10%–25% solution, 3% solution** |
| **Substituted diguanides** | **Antiseptic agent** | **0.5% Chlorhexidine gluconate** |
| **Peracetic acid** | **Liquid sterilant, vapor phase sterilant** | **0.2% Peracetic acid, 1 µg per g peracetic acid** |
| **Ethylene oxide** | **Vapor-phase sterilant** | **600 µg per g Ethylene oxide** |
| **Quaternary ammonium compounds** | **General purpose disinfectant, antiseptic** | **Dependent on Application Benzalkonium chloride** |
| **β-Propiolactone** | **Sporicidal agent** | **β-Propiolactone** |

# Disinfectant Effectiveness

- "The effectiveness of a disinfectant depends on its intrinsic biocidal activity, the concentration of the disinfectant, the contact time, the nature of the surface disinfected, the hardness of water used to dilute the disinfectant, the amount of organic materials present on the surface, and the type and the number of microorganisms present."

# Resistance to Disinfectants?

- "The development of microbial resistance to disinfectants is less likely to occur at relevant levels, as disinfectants are more powerful biocidal agents than antibiotics. In addition, they are normally applied in high concentrations against low populations of microorganisms usually not growing actively, so the selective pressure for the development of resistance is less profound."

# Disinfectant Rotation

- "The rotation of an effective disinfectant with a sporicide is encouraged. It is prudent to augment the daily use of a bactericidal disinfectant with weekly (or monthly) use of a sporicidal agent. The daily application of sporicidal agents is not generally favored because of their tendency to corrode equipment and because of the potential safety issues with chronic operator exposure."

# Control of Environments - 1

- Development of a chapter on Microbiological Control & Monitoring of Non-Aseptic Processing Environments <1111> has been discussed by USP MSA.
- There were significant problems right from the onset.
  - Operational intentions vary much more widely than in aseptic processing.
  - No widely accepted standards for the various facility designs. Significant differences in approach for the same product types are in current use.
  - Thus, there is no clear path forward derivable from existing aseptic environmental standards.

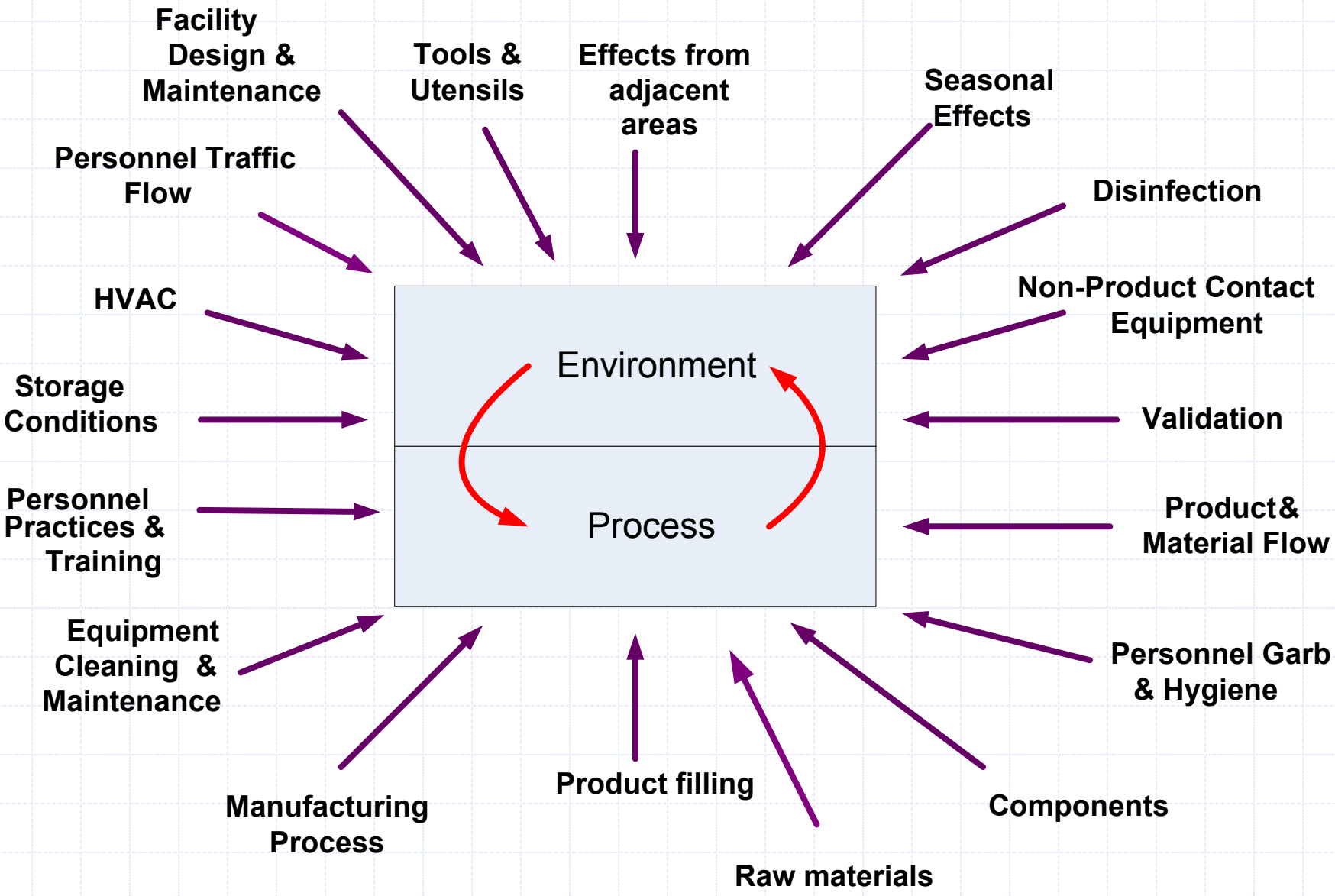
# Control of Environments - 2

- We think we know what we don't want:
  - Singular standards force fit onto every possible processing environment.
  - Monitoring (or worse yet limits) without recognition of the need for related controls.
  - Incompatibility with <61> with respect to product expectations.
  - Something that resembles the current <1116>, Annex 1 or other aseptic schemes
  - An approach that fails to address non-classified operations as well.

# <61>/<62> Microbial Limits

| Dosage Form | TAMC cfu/g or mL | TCYMC cfu/g or mL | Absence of Specified Organism Requirement (1 g or mL) |
|---|---|---|---|
| Tablets and capsules | 1000 | 100 | *E. coli; Salmonella* spp. (Containing unprocessed animal, plant or mineral ingredients) |
| Oral liquids | 100 | 10 | E. coli |
| Rectal products | 1000 | 100 | - |
| Topical and nasal products | 100 | 10 | *S. aureus; P. aeruginosa* |
| Vaginal products | 100 | 10 | *S. aureus; P. aeruginosa; C. albicans* |
| Inhalants | 100 | 10 | *S. aureus; P. aeruginosa*<br>*Bile-tolerant Gram-negative bacteria* |

# Monitoring Non-Sterile Processes



# The Next Step for <1111>

- Define the appropriate operational controls necessary to ensure an appropriate level of microbial control over non-sterile processes.
- Give due consideration to location in the overall process , purification steps in the process, route of administration, water activity, etc.
- Result – a workable approach, but surely not one size fit's all.

# <1211> Completed Activities

- Eliminated the entire discussion of sterility testing at the conclusion of the chapter. The only content in USP relative to sterility tests will be in the harmonized <71>.
- Eliminated the older radiation sterilization guidance & directed reader to ISO standards.
- Sets the stage for future changes.

# <1211> Discussion Points

- Future chapter will address sterilization at a more basic level as an introduction only section.
- Follow with individual chapters on each sterilization method aligning each with the relevant BI chapters.
- Separate gas & vapor sterilization chapter.
- New chapter on liquid / chemical sterilization
- Develop Aseptic Processing as a stand alone chapter.
- Update references throughout.

# <1211> Sterilization

- Broader definition for overkill sterilization method.
- Definitions for BB/BI and bioburden sterilization methods
- Clarification of the role of the biological indicator in sterilization validation.
- Clarify understanding of PNSU, SAL and risk to patient.

# <1211> Sterilization

- Introduction to Sterilization
- Sterilization Validation Approaches
  - Overkill
  - Bioburden / Biological Indicator (terminal / lab media)
  - Bioburden (primarily for radiation)
- Sterility Assurance
  - SAL / PNSU ≠ Media Fill Test contamination rate
- Sterilization Process Control
  - Validation
  - Routine Operation
  - Physical & Microbiological Data
  - Chemical Indicators & Integrators

# <1229X> sub Chapter Breakouts

| Process | Introduction | BI <55>, <1035> | Parametric <1222> |
|---|---|---|---|
| Steam Porous loads | X | X | N/A |
| Steam Non-Porous loads (Terminal/Lab) | X | X | X |
| Dry heat Sterilization | X | X | ? |
| Dry Heat Depyrogenation | X | ? | ? |
| Gamma Ray Sterilization | X | ? | X |
| Electron Beam Sterilization | X | ? | X |
| X-ray Sterilization | X | ? | ? |
| Gas Sterilization | X | X | X |
| Vapor Sterilization | X | ? | ? |
| Chemical Sterilization | X | ? | N/A |
| Filtration | X | ? | N/A |

# < 1229X> possible content??

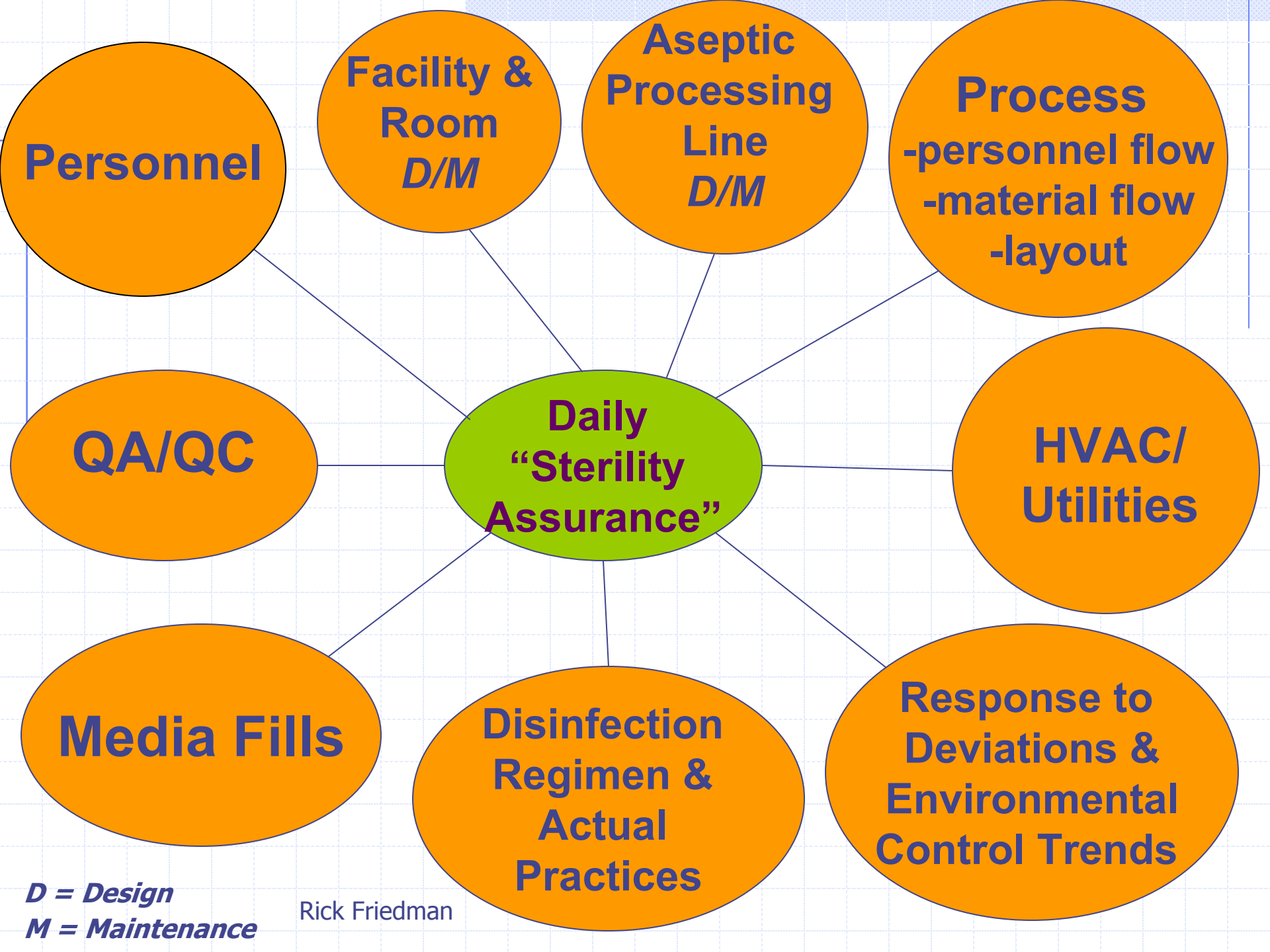
- Disinfection /Sanitization of Cleanrooms / RABS & Isolators?
  - <1072> Disinfection & Sanitization
  - High level Decontamination for RABS
  - Isolator Decontamination
- Combination Sterilization Methods?
- Validation of New Methods?

# What else is on the MSA Horizon?

- **<1021> Design and Validation of Isolator Systems for Use in Aseptic Processing**
- **<XXXX> Microbial Sampling Time Limits**
- **<XXXX> Design and Validation of RAB Systems for Use in Aseptic Processing**

# FDA Activities

# RABs – circa 2000

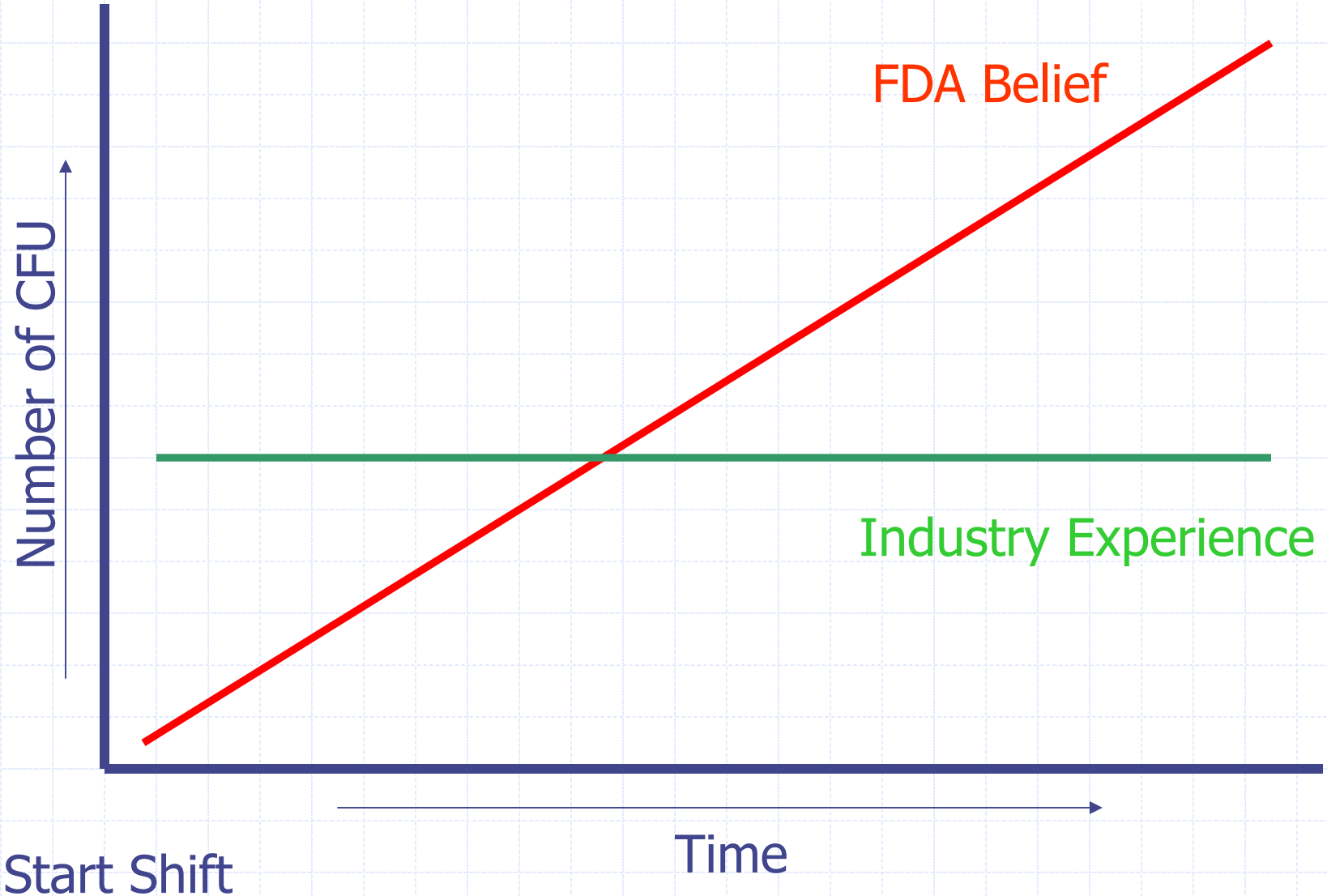

Personnel
Facility & Room D/M
Aseptic Processing Line D/M
Process -personnel flow -material flow -layout
QA/QC
Daily "Sterility Assurance"
HVAC/ Utilities
Media Fills
Disinfection Regimen & Actual Practices
Response to Deviations & Environmental Control Trends
D = Design
M = Maintenance
Rick Friedman

# FDA Pressures on Industry

- **"No microorganisms detected in Class 100"**
- **"Product contact surfaces must be sterile"**
- **"Media fills shall have no contamination"**

- **These conditions are considered normal performance and any deviation from them should be reacted to by the firm.**

# Aseptic EM Results & Time



# Proposed CGMP Revisions - 1

- "Paragraph (b) of § 211.113 *Control of microbiological contamination* - Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes."

# Proposed CGMP Revisions - 1

- This goes well beyond what industry believes is possible with respect to aseptic processing.
- Aseptic processing simulations can only demonstrate the capabilities of the process at a point in time, they cannot provide affirmation of a low contamination rate over an extended period.
- Media fills don't validate anything!
- A contamination rate is not an SAL or PNSU.

# Proposed CGMP Revisions - 2

- "Paragraph (c) of § 211.94 *Drug product containers and closures* – "Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated."

# Proposed CGMP Revisions - 2

- A blanket provision mandating depyrogenation of components based upon the nature of the drug does not recognize the inherently non-pyrogenic nature of many polymeric materials. It would be more appropriate to give consideration to the component materials rather than solely upon the drug product for which they are intended. This would eliminate requirements for depyrogenation of polymeric materials that are never in contact with aqueous materials and thus do not require depyrogenation prior to use.

# Container-Closure Integrity

- New FDA guidance issued February 2008 states that the advantages of using container and closure system integrity tests *in lieu* of sterility tests include:
  - Such alternate methods may detect a breach of the container and/or closure system prior to product contamination
  - Some of the alternate methods used to evaluate container and closure integrity can conserve samples that may be used for other stability tests.
  - Alternative test methods may require less time than sterility test methods which require at least seven days incubation.
  - The potential for false positive results may be reduced with some alternative test methods when compared to sterility tests.
- Recommended tests include: validated physical or chemical container and closure system integrity methods such as bubble tests, pressure/vacuum decay, trace-gas permeation/leak tests, dye penetration tests, seal force or electrical conductivity and capacitance tests.

# Informal FDA Endotoxin Initiative

- FDA has rejected recent INDs and NDA's for ophthalmic and topical products where the firm has not provided for endotoxin control.
- There has been no formal announcement, it is being implemented piece meal!
- This actually impacts all products a firm makes because of the difficulties in management of a dual control system.
- Implications are for increased controls for water systems, equipment cleaning, raw materials, packaging, etc.

# EMEA Activities

# Isolator Filling Line – circa 1988

# Federal Standard 209E - 1992

| Class Name ** | | Class limits | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.1 m | | 0.2 m | | 0.3 m | | 0.5 m | | 5 m | |
| | | Volume units | | Volume units | | Volume units | | Volume units | | Volume units | |
| SI | English*** | ($m^3$) | ($ft^3$) | ($m^3$) | ($ft^3$) | ($m^3$) | ($ft^3$) | ($m^3$) | ($ft^3$) | ($m^3$) | ($ft^3$) |
| M1 | | 350 | 9.91 | 75.7 | 2.14 | 30.9 | 0.875 | 10.0 | 0.283 | – | – |
| M1.5 | 1 | 1,240 | 35.0 | 265 | 7.50 | 106 | 3.00 | 11.0 | 1.00 | – | – |
| M2 | | 3,500 | 99.1 | 757 | 21.4 | 309 | 8.75 | 100 | 2.83 | – | – |
| M2.5 | 10 | 12,400 | 350 | 2,650 | 75.0 | 1,060 | 30.0 | 353 | 10.0 | – | – |
| M3 | | 35,000 | 991 | 7,570 | 214 | 3,090 | 87.5 | 1,000 | 28.3 | – | – |
| M3.5 | 100 | - | - | 26,500 | 750 | 10,600 | 300 | 3,530 | 100 | – | – |
| M4 | | - | - | 75,700 | 2,140 | 30,900 | 875 | 10,000 | 283 | 247 | 7.00 |
| M4.5 | 1,000 | - | - | - | - | - | - | 35,300 | 1,000 | 618 | 17.5 |
| M5 | | - | - | - | - | - | - | 100,000 | 2,830 | 2,470 | 70.0 |
| M5.5 | 10,000 | - | - | - | - | - | - | 353,000 | 10,000 | 6,180 | 175 |
| M6 | | - | - | - | - | - | - | 1000,000 | 28,300 | 24,700 | 700 |
| M6.5 | 100,000 | - | - | - | - | - | - | 3530,000 | 100000 | 61,800 | 1,750 |
| M7 | | - | - | - | - | - | - | 10000000 | 283000 | | |

# EU Annex 1 Particle Limits - 1995

| | at rest (b) | | in operation | |
|---|---|---|---|---|
| Grade | maximum permitted number of particles/$m^3$ equal to or above | | | |
| | 0.5 µm | 5 µm | 0.5 µm | 5 µm |
| A | 3 500 | 0 | 3 500 | 0 |
| B (a) | 3 500 | 0 | 350 000 | 2 000 |
| C (a) | 350 000 | 2 000 | 3 500 000 | 20000 |
| D (a) | 3 500 000 | 20 000 | not defined (c) | not defined (c) |

**There's a belief by the authors (EU Inspectors) that microorganisms can "ride" on large particles.**

# EU Annex 1 Particle Limits - 2002

| | at rest *(b)* | | in operation *(b)* | |
|---|---|---|---|---|
| Grade | maximum permitted number of particles/$m^3$ equal to or above *(a)* | | | |
| | 0,5 µm *(d)* | 5 µm | 0,5 µm *(d)* | 5 µm |
| A | 3 500 | *1 (e)* | 3 500 | *1 (e)* |
| B *(c)* | 3 500 | *1 (e)* | 350 000 | 2 000 |
| C *(c)* | 350 000 | 2 000 | 3 500 000 | 20 000 |
| D *(c)* | 3 500 000 | 20 000 | not defined *(f)* | not defined *(f)* |

(e) ***It is expected to get these areas completely free from particles sized equal or greater than 5µm. As it is impossible to demonstrate absence of particles with any statistical significance the limits are set to 1 particle / m3. During the clean room qualification it should be shown that the areas could be maintained within the defined limits.***

**Better, but really no difference.**

# Annex 1 Particle Limits (05 draft)

| | at rest | | in operation | |
|---|---|---|---|---|
| Grade | Maximum permitted number of particles/$m^3$ equal to or above | | | |
| | 0.5 µm | 5.0µm | 0.5 µm | 5.0µm |
| A | 3 500 | 1* | 3 500 | 1* |
| B | 3 500 | 1* | 350 000 | 2 000 |
| C | 350 000 | 2 000 | 3 5000 000 | 20 000 |
| D | 3 500 000 | 20 000 | Not defined | Not defined |

** The maximum permitted number of particles at <5.0µm is established at 1/$m^3$ but for reasons related to false counts associated with electronic noise, stray light, etc. the limit of 20/$m^3$ could be considered.*

**No meaningful difference as interference has to be proven. It might not be interference.**

# Annex 1 Particle Limits 2008

| | Maximum permitted number of particles per $m^3$ equal to or greater than the tabulated size | | | |
|---|---|---|---|---|
| | At rest | | In operation | |
| Grade | 0.5 µm | 5.0µm | 0.5 µm | 5.0µm |
| A | 3 520 | 20 | 3 520 | 20 |
| B | 3 520 | 29 | 352 000 | 2 900 |
| C | 352 000 | 2 900 | 3 520 000 | 29 000 |
| D | 3 520 000 | 29 000 | Not defined | Not defined |

For classification purposes in Grade A zones, a minimum sample volume of $1m^3$ should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥5.0 µm. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes. For Grade C (at rest & in operation) the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.

# EN / ISO 14644-1

Table 1 Selected airborne particulate cleanliness classes for cleanrooms and clean zones

| ISO classification number (N) | Maximum concentration limits (particles/$m^3$ of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with 3.2) | | | | | |
|---|---|---|---|---|---|---|
| | 0,1 µm | 0,2 µm | 0,3 µm | 0,5 µm | 1 µm | 5 µm |
| ISO Class 1 | 10 | 2 | | | | |
| ISO Class 2 | 100 | 24 | 10 | 4 | | |
| ISO Class 3 | 1 000 | 237 | 102 | 35 | 8 | |
| ISO Class 4 | 10 000 | 2 370 | 1 020 | 352 | 83 | |
| ISO Class 5 | 100 000 | 23 700 | 10 200 | 3 520 | 832 | 29 |
| ISO Class 6 | 1 000 000 | 237 000 | 102 000 | 35 200 | 8 320 | 293 |
| ISO Class 7 | | | | 352 000 | 83 200 | 2 930 |
| ISO Class 8 | | | | 3 520 000 | 832 000 | 29 300 |
| ISO Class 9 | | | | 35 200 000 | 8 320 000 | 293 000 |

NOTE: Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level.

# EU Annex 1 Surface Limits

| | Recommended limits for microbial contamination (a) | | | |
|---|---|---|---|---|
| Grade | air sample cfu/m³ | settle plates (diam. 9 0 mm), cfu/4 hours (b) | contact plates (diam. 55 mm), cfu/plate | glove print 5 fingers cfu/glove |
| A | < 1 | < 1 | < 1 | < 1 |
| B | 10 | 5 | 5 | 5 |
| C | 100 | 50 | 25 | – |
| D | 200 | 100 | 50 | – |

# EU Annex 1 – 2008 Crimping

- "120 - Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped."

# Some of the Current Problems

- Annex 1 requires averaging of micro data; FDA mandates response to individual excursions.
- FDA/EMEA suggest microbial resistance to sanitizers is possible.
- Use same media fill criteria, but no clarity for large fills.
- Mandated temperature and pressure control for autoclaves.
- Sterility test samples to be associated with interventions.

# Isolator Filling Line – circa 2005

# An Overview of Revisions to PDA's TR #22 --- PROCESS SIMULATION FOR ASEPTICALLY FILLED PRODUCTS

# What We Set Out to Do

- Inclusion of risk management concepts.
- Update / clarify coverage of interventions.
- Address personnel participation in a meaningful and coherent fashion.
- Maintain the clarity of prior version.
- Outline the process alternatives more fully.
- Include accountability discussion.
- Clarify application to aseptic steps in the drug compounding process.
- Outline execution practice in greater detail.
- Maintain consistency with regulatory guidance (especially FDA's 2004 AP guide).

# Some Important Points

- APS demonstrates capability, does not determine an SAL.
- Interventions are either:
  - Inherent – a integral part of the process
  - Corrective – performed to fix problems
- Interventions must be the focus of the discussion, because contamination is largely associated with them.
- Aseptic process simulation, is not just media filling.

# The purpose of a simulation is to:

- Demonstrate as part of an overall process validation approach, the capability of the aseptic process to produce sterile drug products.
- Evaluate proficiency of aseptic processing personnel.
- Comply with current Good Manufacturing Practice requirements.
- Confirm the appropriateness of operating practices used in support of aseptic processing.

# APS as Capability Demonstration

- "Aseptic processing relies heavily on personnel, equipment features, and procedures that in combination serve to exclude microorganisms from sterile products. These elements of aseptic processing cannot be as rigorously controlled as a sterilization process can. And thus the outcome of an aseptic process is more variable. The APS is only a demonstration of the capability of the process to produce sterile products aseptically."

# Process Simulation for Dosage Forms

- This section is largely unchanged with the exception of expanded content on aseptic compounding steps in sterile product manufacturing. Coverage is provided on:
  - Solutions
  - Suspensions
  - Creams, Ointments, & Emulsions
  - Lyophilized Products
  - Powder Formulations

# Aseptic Compounding

- Solution formulations aseptic steps may be limited to set-up, sampling, and in-situ filter integrity testing.
- Suspensions, ointments and other non-filterable formulations may require a substantial number of aseptic steps.
- Processes requiring the addition of sterile powders should employ an acceptable placebo material in containers identical to those utilized in the process being evaluated.
- Blending, milling and subdivision process performed at sterile powder fill sites require similar attention.

# Elements of Aseptic Process Simulation

- Reorganized in sequential fashion
- New sections on
  - Interventions (brief coverage, more elsewhere)
  - Pre-incubation inspection
  - Accountability
  - Campaign operations
- Minor changes in other sections including: duration, media selection, inert gassing, & post-incubation inspection.

# Interventions

- The human operator is by far the greatest source of microbial contamination during an aseptic process.
- To demonstrate aseptic processing capability, process simulations should include all the inherent (part of the process) and corrective (problem resolution) activities that occur during an aseptic filling process.
- An entire section devoted to intervention related issues was added.

# Interventions & Risk

- In evaluating aseptic processing we must be fixated on the need to avoid interventions, and where they are unavoidable to minimize their impact as much as possible.
- *Inherent interventions* are activities that are integral parts of the aseptic process and every batch.
- *Corrective interventions* are activities that rectify problems and may not be a part of every batch.

# Types of Interventions

## Inherent

- Line set-up
- Replenishment of components
- Weight / volume checks / adjustments
- Environmental monitoring
- Breaks, lunch

## Corrective

- Stopper jams
- Broken / fallen glass
- Defective seals on containers
- Liquid leaks
- Other mechanical failures requiring manual correction

# Inherent Interventions

- An intervention that is an integral part of the aseptic process required for either set-up, routine operation and/or monitoring, e.g., aseptic assembly, container replenishment, environmental sampling, etc. Inherent interventions are required by batch record, procedure, or work instruction for the execution of the aseptic process.

# Corrective Interventions

- An intervention that is performed to correct or adjust an aseptic process during its execution. These may not occur with the same frequency (or at all) in the aseptic process. Examples include such activities as: clearing component miss-feed, stopping leaks, adjusting sensors, and replacing equipment components. Corrective measures should be taken to reduce their extent and frequency.

# Interventions - 2

- Identifying interventions
  - Inherent
  - Corrective
- Intervention procedures for both in detail.
- Study design to include interventions at the appropriate level.
- Frequency in APS should approximate routine operations.
- Handling of intervention containers.

# Personnel Qualification - 1

- Personnel successfully meet the firm's gowning certification requirements.
- They should have completed all relevant training, including but not limited to GMP training, procedure training, gowning training, clean room practices training, and specific clean room operation, function and relevant intervention procedure training.
- New section in this draft addresses personnel in greater detail.

# Personnel Qualification - 2

- "They should demonstrate their proficiency in aseptic technique by successfully performing a qualification test entailing manual media manipulation.

or

- They should participate in a successful aseptic process simulation run in which they perform the same function(s) to the extent that they will perform it during actual production."
- Set-up and other complex interventions are excluded from this qualification.

# Acceptance Criteria

- Simulate the process as closely as possible.
- Methodology and limits must be justifiable and documented.
- The methodology should confirm a low process simulation contamination rate, and the selected limit must be routinely achievable.
- Any positive unit is significant, regardless of run size, and should result in a thorough, documented investigation.
- Process simulation contamination rates approaching zero should be achievable using automated production lines in well designed aseptic processing facilities, blow-fill-seal and form-fill-seal and in isolator-based systems.
- Recurring positive units in successive process simulations indicate a problem and should be investigated and resolved even when the acceptance criteria are met for each individual simulation.

# New Appendixes

- Appendix 2 – Media Preparation and Sterilization –
  - Outlines alternatives for execution.
  - Allows for variation from process.
  - APS does not validate process filtration.
- Appendix 3 - Aseptic Process Simulation Execution Sequence
  - Outline for sequencing APS activities.

# Risk & Aseptic Processing

# RABs Filling Line– circa 2002

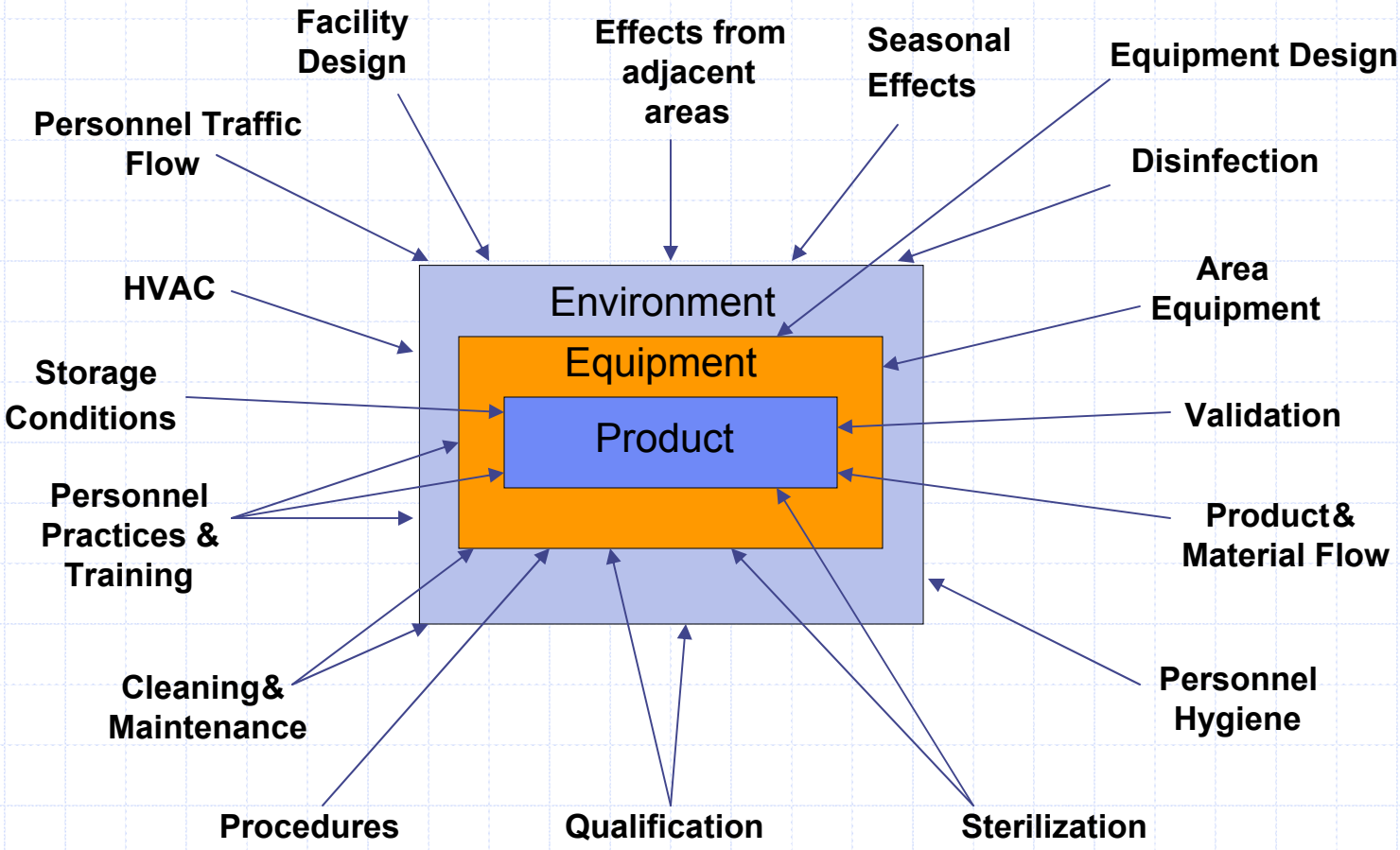
# How do you evaluate risk?

- How many of you exceeded the speed limit on the way here?
- How many of you talked on the cell phone while driving this week?
- How many of you have ever jumped out of a perfectly good airplane?
- How many of you currently purchase raw materials from China?
- How many of you have recently received an injection of a aseptically filled sterile product?

# Risk in Aseptic Processing

- There are 2 distinct elements of risk associated with aseptic processing
  - Risk Mitigation – consideration of contamination potential during the design of facilities, selection of equipment, definition of procedures and operation of the process itself
  - Risk Assessment / Analysis – efforts to quantify the risks resulting from the prior decisions.
- Risk mitigation is of far greater importance, because it can serve to improve the process. Done properly meaningful reduction in contamination can result.

# Product & Process Influences - Sterile Products




Adapted from Leonard Mestrandrea

# Risk Assessment Models

- Bill Whyte – University of Glasgow
  - Deposition based model of microbes from air into containers.
- Lilly / Ed Tidswell
  - Environmental monitoring based model using Monte Carlo simulation of contamination.
- Akers- Agalloco Method
  - Intervention / technology based model ignoring environmental uncertainties.
- PDA Risk Aseptic Risk Monograph
  - Summarizes prior efforts
- Globally regulators speak of risk-based compliance but have provided little insight into how this is to be accomplished in an aseptic processing context.

# Conclusion

# The Proper View of Interventions

- **Interventions always mean increased risk to the patient.**
- **There is no truly safe intervention.**
- **The ‘perfect’ intervention is the one that doesn’t happen!**

# Technology Focus

- Recognition that personnel are the contamination source of concern has led to designs that exclude them
- The approaches usually rely on means to:
  - separate them from the environment
  - limit their interaction with sterile materials
  - remove them entirely from the environment
  - some combination of the above
- Cutting edge concepts are increasingly available that employ one or more features to reduce microbial contamination potential in aseptic processing.

# Steps towards Personnel Removal

- Separation of Personnel
  - Flexible Barrier Systems
  - Rigid Barrier Systems
  - RABS (restricted access barrier systems)
- Limiting Human Involvement
  - Blow-fill-seal
  - Robotics
  - Advanced machine designs
- Remove Personnel From the Environment
  - Closed Isolators
  - Open Isolators

# PostScript

- The challenge in aseptic processing is always personnel:
  - As a source of microbial and particle contamination.
  - As a brake on the implementation of improved technology.


Walter Kelly, 1971