Sterile Environments and Cleaning Validation Inspections, Warning Letters, and Trends with US FDA

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Goal of this talk

Understanding FDA expectations to better defend your process

Current Situation – Industry Perspective

- ***What are the most typical observations or focus areas with respect to Cleaning Validation you are seeing in the industry over the past year?***
  - "The basics"
  - "Most programs do not hold up to cursory review much less in-depth one"
  - "Trend for inspectors wanting to expand the scope of CV"
  - "inspection more focused on data integrity then any of the science or studies, seems to be the buzz these days"
  - "Observations tied to equipment exteriors, rooms and floors"
  - "Insufficient testing to support carryover limits"
  - "Data integrity issues"

Agenda Topics

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- What the FDA expects
- Discuss current Cleaning Validation Trends
- Discuss current Critical/Sterile Environment Trends

FDA Valid

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Drugs

- High Purity Water Systems (7/93)
- Lyophilization of Parenterals (7/93)
- Microbiological Pharmaceutical Quality Control Labs (7/93)
- Pharmaceutical Quality Control Labs (7/93)
- Validation of Cleaning Processes (7/93)
- Dosage Form Drug Manufacturers cGMPs (10/93)
- Oral Solid Dosage Forms Pre/Post Approval Issues (1/94)
- Sterile Drug Substance Manufacturers (7/94)
- Topical Drug Products (7/94)
- Oral Solutions and Suspensions (8/94)

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What the FDA Expects

Guide to Inspections Validation of Cleaning Processes, 1993

- Written procedures detailing the cleaning process
- Cleaning process residues also removed
- Written Validation procedures to address:
  - Who is responsible for performing and approving?
  - Acceptance criteria
  - Re-validation timeline
- Validation protocols to address:
  - Sampling procedures
  - Analytical methods
- Follow protocols and document results (data)
- Final Validation report
- **Times 3?!**

Barr Decision: 1993

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U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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Drugs

Home › Drugs › Development & Approval Process (Drugs) › Manufacturing

- Development & Approval Process (Drugs)
- Manufacturing
- Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations
- Positron Emission Tomography (PET)
- Questions and Answers on Current Good Manufacturing Practices (CGMP) for Drugs
- Current Good Manufacturing Practices for Drugs: Reports, Guidances and Additional Information

Court decision strengthens FDA's regulatory power

FDA Consumer, Sept. 1993 by Dixie Farley

In a landmark regulatory action initiated by FDA, a federal court in New Jersey ordered a major generic drug manufacturer to recall millions of its tablets and other drug products. The court found these products had failed to meet quality requirements.

FDA initiated the action under the Federal Food, Drug, and Cosmetic Act. To take such items off the market in the past, either the involved firm voluntarily recalled the products, or FDA requested courts to order seizure by U.S. marshals --provided the agency could find the products. Now, with this precedent-setting decision, FDA can ask the court to order the responsible firms to recall.

After a long hearing at which five industry experts, an FDA investigator, and several company employees testified, Judge Alfred M. Wolin, U.S. District Judge for the District of New Jersey, issued a 79-page opinion last February in the case of Barr Laboratories, Inc., of Northvale, N.J., and Pomona, N.Y.

The recalled drugs are various analgesics and antibiotics. Listed with the numbers of their recalled batches in parentheses, the products are: * aspirin with codeine 325/60-milligram tablets (1C280DY) * erythromycin delayed-release 250-mg capsules (1F584EV) * erythromycin ethylsuccinate 400-mg tablets (OB259FA) * erythromycin ethylsuccinate and sulfisoxazole acetyl for oral suspension, 200 mg/600 mg (1H445DQ, 1I445EF) * erythromycin stearate 240-mg tablets (O1013FQ) * erythromycin stearate 500-mg tablets (2A219HJ) * hydrocodone bitartrate with APAP 5 mg/500-mg tablets (1D325CL) * meperidine HCl 50-mg tablets (OB381AO, OB381AT, OB381AW, OB381AV).

The court also ordered Barr to stop distributing 24 of its products that had a history of manufacturing deficiencies until the firm validated their manufacturing processes. Barr must demonstrate to the satisfaction of FDA and the court that these processes

produce a study to validate that the firm's regular cleaning procedures actually clean its milling machine * identify the cleaning agents used in all its cleaning validation studies

In addition, Barr must immediately put into place a wide range of manufacturing and drug-testing controls and explain any gaps in its validation testing. For example, it must: * document the reason for excluding a batch from testing * investigate the reasons for a failed batch before resampling it for testing again * produce a study to validate that the firm's regular cleaning procedures actually clean its milling machine * identify the cleaning agents used in all its cleaning validation studies * record individual test results, not just averages * base product release on all results, not just averages.

failure to validate test methods and manufacturing processes, including cleaning processes

On behalf of FDA, the U.S. Attorney's Office had filed suit against Barr and some of its officers on June 12, 1992, to stop the company from manufacturing and distributing drugs FDA alleged to be substandard. FDA also sued to obtain a court-ordered

Why a sound cleaning program is important

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- Cleaning shows an Auditor a lot about a facility
  - Quality mindset – How site makes decisions under manufacturing schedule stress (first patient in)
  - How they investigate deviations
  - Do they understand the process?

"For example, your firm does not have data to demonstrate your cleaning processes for non-dedicated manufacturing equipment and utensils are adequate".

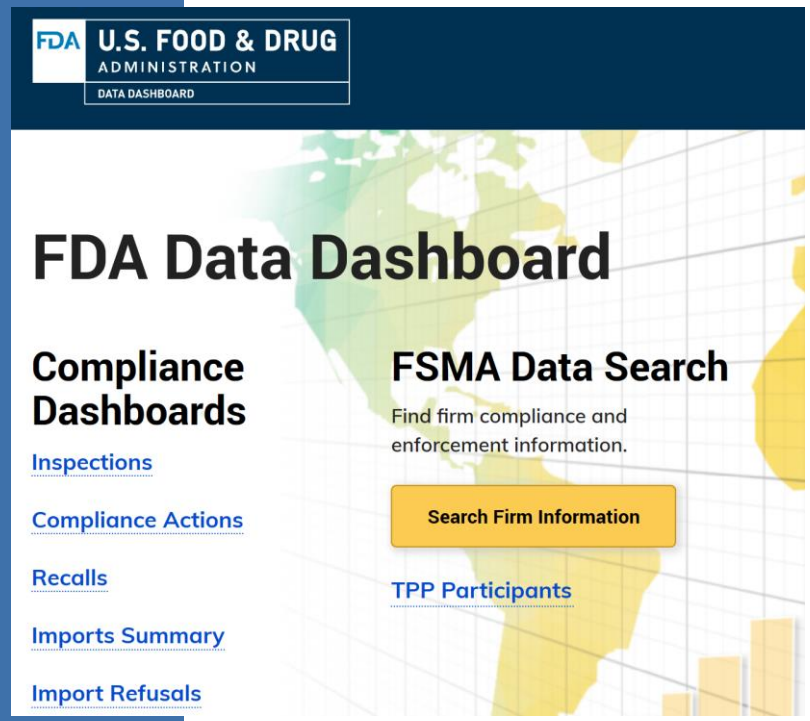
"There is not sufficient documentation to determine the effectiveness of your cleaning agent used".

"You have not established an adequate rationale, including determining whether this product is the most difficult product to clean".

Freedom of Information Act Reading Room

- Warning Letters and Form 483 observations available to public

https://www.fda.gov/about-fda/office-regulatory-affairs/ora-foia-electronic-reading-room



Why do they make the data available?

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- They believe the information will:
  - Help industry improve Quality by sharing common observations from inspections
  - Identify possible areas of emerging concern
  - Possibly help firms avoid receiving Warning Letters

Inspection References

- This page includes information provided to FDA investigators and inspectors to assist them in their daily activities
  - https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references
  - Compliance manuals:
    - **Compliance Program Guidance Manual (CPGM)** – instructions to FDA personnel for evaluation of industry compliance
    - **FDA Compliance Policy Guides (CPG)** – policy and regulatory guidance for FDA staff
    - **Investigations Operations Manual (IOM)** – procedure manual for FDA personnel performing inspections
    - **Foreign Inspections** – procedures for FDA personnel performing inspections abroad
      - **https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/foreign-inspections**

Compliance Program Guidance Manual (CPGM)

- Instructions to FDA personnel for evaluation of industry compliance
- Program 7356.002 Drug Quality Assurance
  - **Set of 6 systems to inspect:**
    - Quality system
    - Facility and Equipment systems
    - Materials Systems
      - Measures to control products, gas, water, inventory
    - Production Systems
    - Packaging/Labeling
    - Laboratory

7348.809A	Radioactive Drug Research Committee (PDF - 142KB)
7346.832	Pre-Approval Inspections/Investigations (PDF - 385KB)
7346.843	Post-Approval Audit Inspections (PDF - 152KB)
7352.002	Unapproved New Drugs (Marketed, Human, Prescription Drugs only) (PDF - 52KB) [HTML version]
7352.004	In Vitro Methods Development and Validation for Generic Drugs (Not available online)
7353.001	Postmarketing Adverse Drug Experience (PADE) Reporting Inspections
7356.002	Drug Manufacturing Inspections (PDF - 160KB)
7356.002A	Sterile Drug Process Inspections (PDF - 292KB)
7356.002B	Drug Repackers and Relabelers (PDF - 182KB)
7356.002C	Radioactive Drugs (PDF - 180KB)
7356.002E	Compressed Medical Gases (PDF - 239KB)
7356.002F	Active Pharmaceutical Ingredients (PDF - 150 KB)
7356.002M	Inspections of Licensed Biological Therapeutic Drug Products (PDF - 93KB) [HTML version]

Investigations Operations Manual (IOM)

- Procedure for FDA personnel performing inspections - https://www.fda.gov/media/76769/download
- Section 5.4.5 – Equipment and Utensils
  - Arrive before processing begins – evaluate conditions and practices not otherwise observable before plant start-up.
    - Assess adequacy of clean-up
    - Where and how equipment is stored while not in use
    - Assess if personnel sanitize hands and equipment before beginning work
    - Examine all equipment and utensils to determine the following:
      - Design, materials of construction, maintenance, suitability and ease of cleaning
      - Open inspection ports to check inside/notice if inspection ports have been painted over or permanently sealed
      - Determine if equipment is cleaned prior to each use and the method of cleaning

Agencies Focusing on Cleaning Validation

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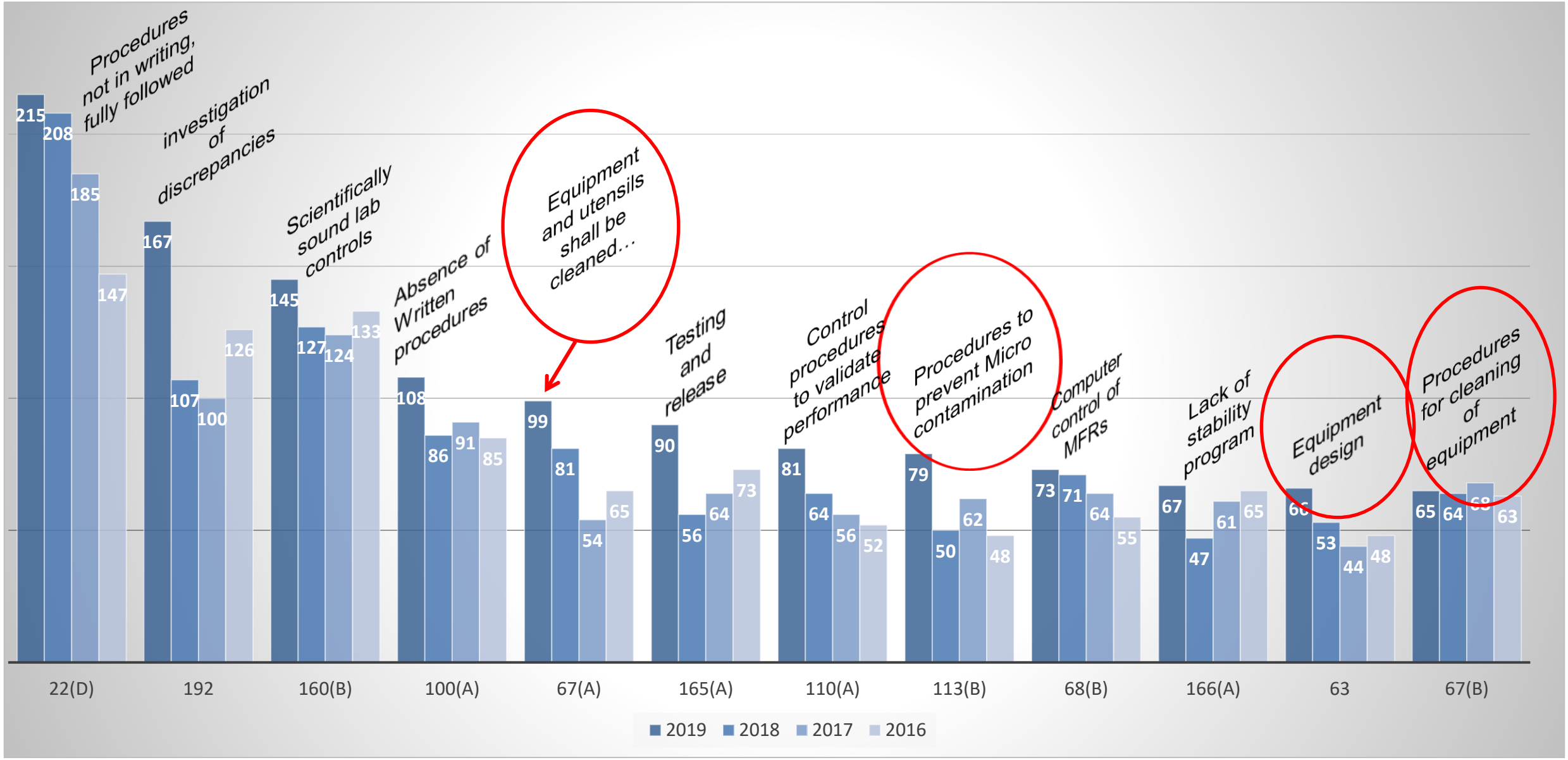
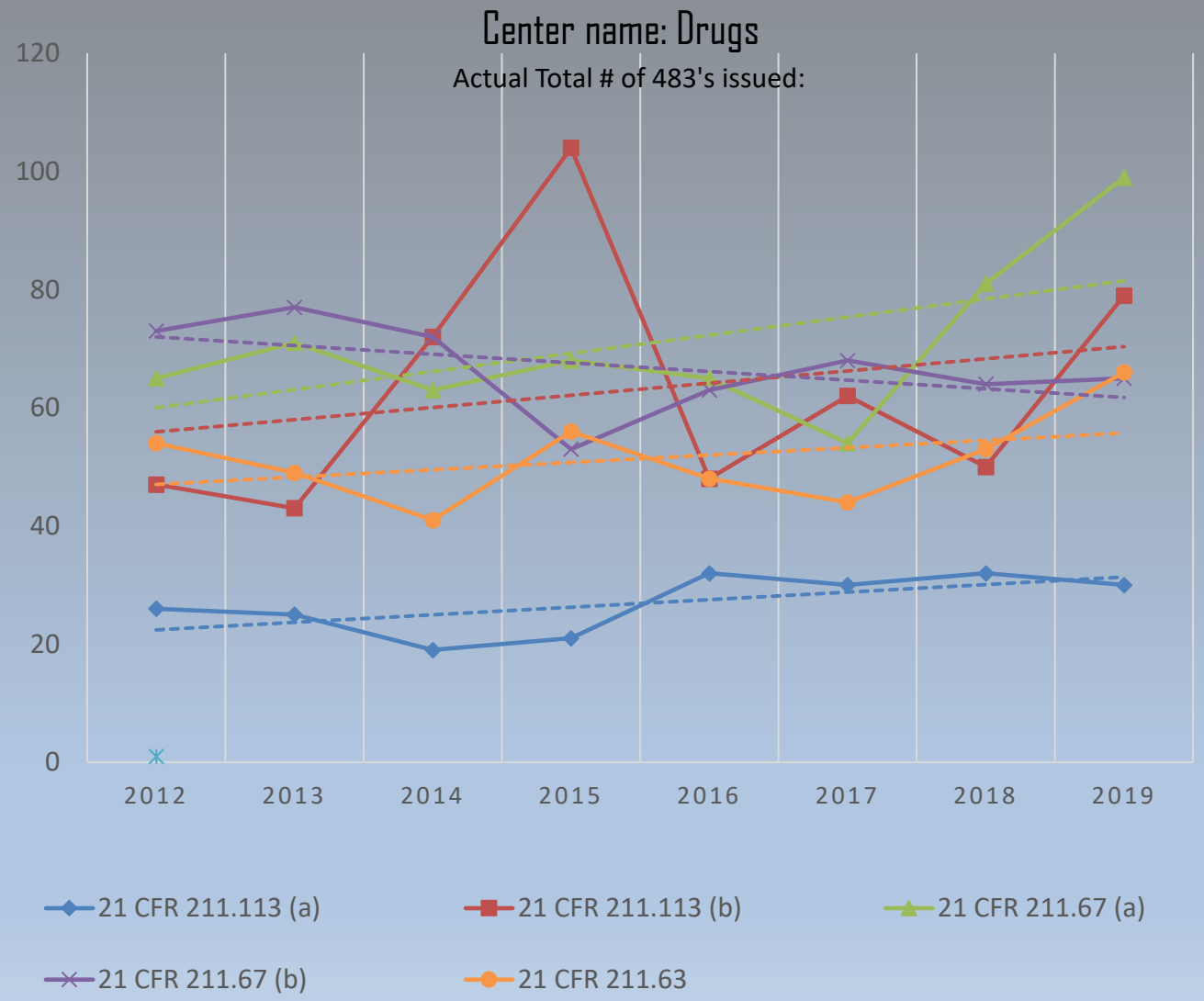
- **~10%** of all observations (483's) related to cleaning validation and documentation (drug products only)

Top FDA form 483 observations (21 CFR 211) for FY2019



Information from FDA website: https://www.fda.gov/ICECI/Inspections/ucm250720.htm

Cleaning Validation 483 trends



21 CFR 211.113 Control of microbiological contamination:
(a) "'Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile are not [established] [written] [followed]. Specifically,"
(b) "'Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include [adequate] validation of the sterilization process. Specifically,"

21 CFR 211.67 Equipment cleaning and maintenance:
(a) "'Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product. Specifically,"
(b) "Written procedures are not [established] [followed] for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product. Specifically," **and**
"'Written procedures for cleaning and maintenance fail to include [assignment of responsibility] [maintenance and cleaning schedules] [description in sufficient detail of methods, equipment and materials used] [description in sufficient detail of the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance] [instructions for removal or obliteration of previous batch identification] [instructions for protection of clean equipment from contamination prior to use] [parameters relevant to the operation]. Specifically, "

21 CFR 211.63 Equipment design, size, and location:
"Equipment used in the manufacture, processing, packing or holding of drug products is not [of appropriate design] [of adequate size] [suitably located] to facilitate operations for its [intended use] [cleaning and maintenance]. Specifically,"

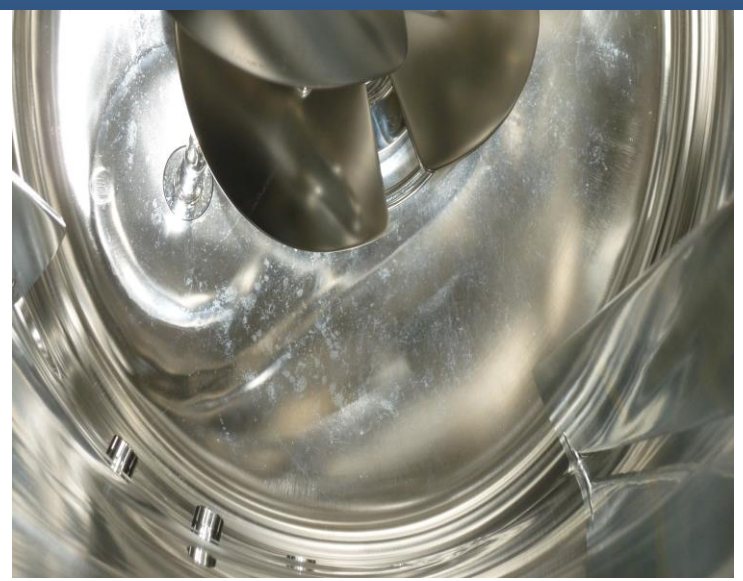
Source: http://www.fda.gov/ICECI/Inspections/ucm250720.htm

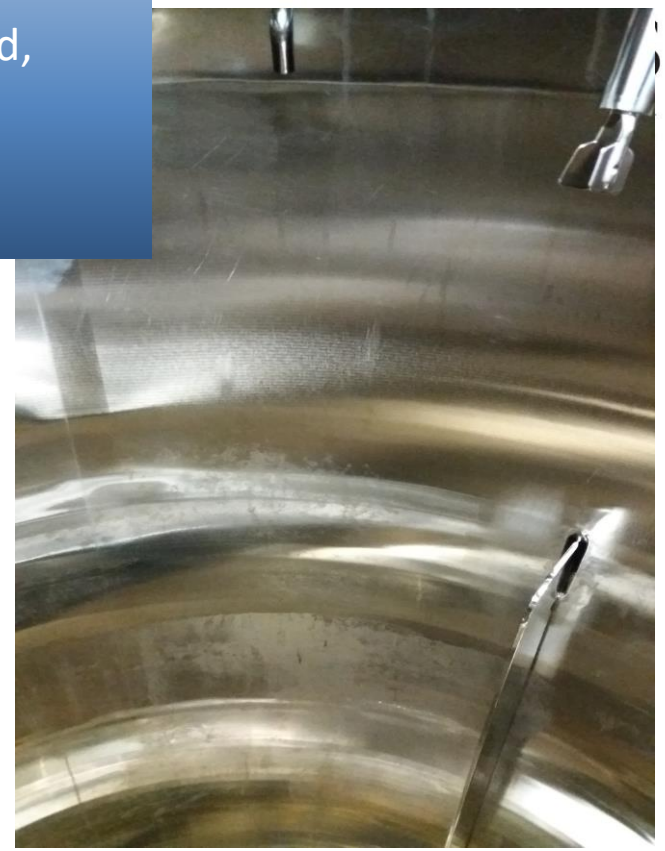
FDA trends 2019

- Over 2,000 observations were issued by FDA's Office of Regulatory Affairs in 2019 across the four FDA regulated industries: Drug, Device, Biologics, and Veterinary.
- Regulations haven't changed!
  - FDA uses computerized systems (turbo 483) allowing more risk based, better focused inspections on industry trends
  - Top citation: Procedures not in writing, fully followed
  - 1 – 4 all pertained to procedures, controls and investigations
  - Procedures for sterile drug product (prevent contamination of drug product) WAS trending down
    - 2018 #12 from **#8 with 62 citations in 2017 and 79 in 2019 (#8)**
  - **67(a) Equipment and utensils not cleaned, maintained moved from #12 in 2017 to #5 in 2018 & 2019**

Understanding your process

- **Manual cleaning not an option per EH&S**
  - Ladder to get into the reactor, person can get harmed,
  - Entry can damage Brx
  - Process time consuming
  - Requires a total of 3 persons to clean





WHAT WE KNOW:

BIOREACTOR RUNS FOR 14 DAYS, ANTIFOAM IS USED

BIOREACTOR CURRENTLY TAKES 8 HOURS TO CLEAN USING NAOH AND 10% CITRIC ACID.

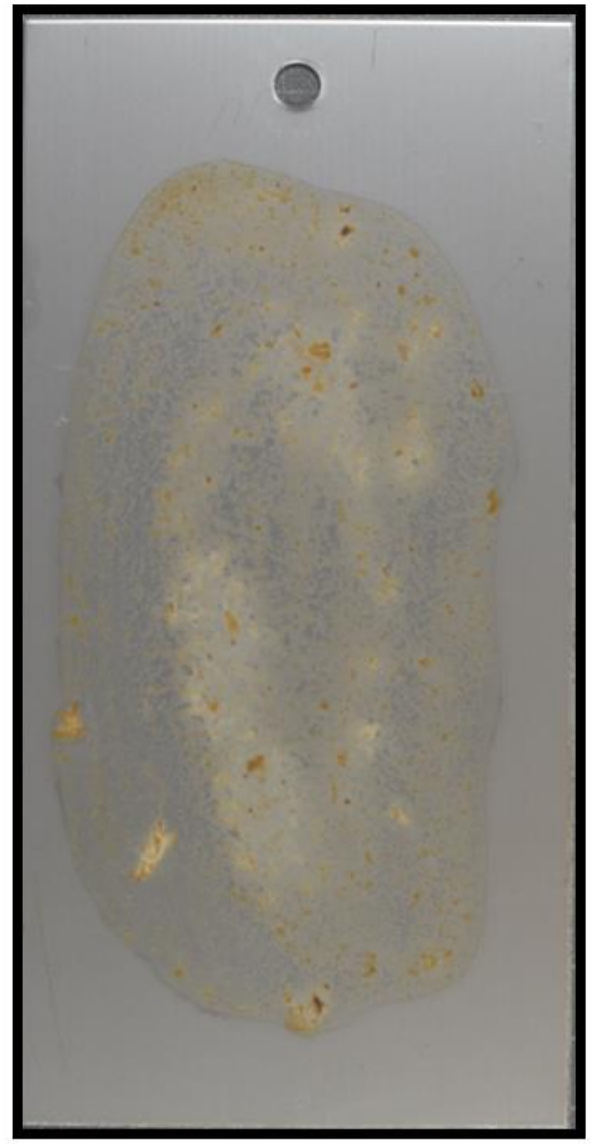
TANK IS NOT VISUALLY CLEAN AFTER CLEANING PROCESS

RESIDUE IS REMOVED BY WIPING, HOWEVER, NOT ALLOWED DUE TO CONFINED SPACE CONCERNS

Understand your process

Coated stainless steel coupons with cell culture residue for 14 days (heated) and then air-dried at ambient temperature for 16 hours

Cleaning Agent	Temperature	Time
1% Formulated Alkaline detergent	25°C	15 minutes



Cleaning process design is so much more……

- Key elements to be considered in design
  - Equipment to be cleaned
    - Design
    - MOCs (and condition)
  - Soils to be removed
    - Type
    - Amount
  - Manufacturing conditions
  - Cleaning methods
  - Cleaning mechanisms
  - Cleaning parameters
  - Cleaning agents

PDADMAC: *Charged polymer induced cell debris coagulation*

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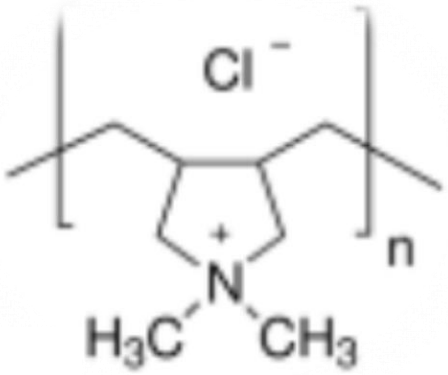

mAbs

MAbs. 2015 Mar-Apr; 7(2): 413–427.
Published online 2015 Feb 23. doi: 10.1080/19420862.2015.1007824
PMCID: PMC4622464
PMID: 25706650

PDADMAC flocculation of Chinese hamster ovary cells: Enabling a centrifuge-less harvest process for monoclonal antibodies

Thomas McNerney,[1,*] Anne Thomas,[1] Anna Senczuk,[1] Krista Petty,[2] Xiaoyang Zhao,[2] Rob Piper,[1] Juliane Carvalho,[3] Matthew Hammond,[4] Satin Sawant,[5] and Jeanine Bussiere[5]

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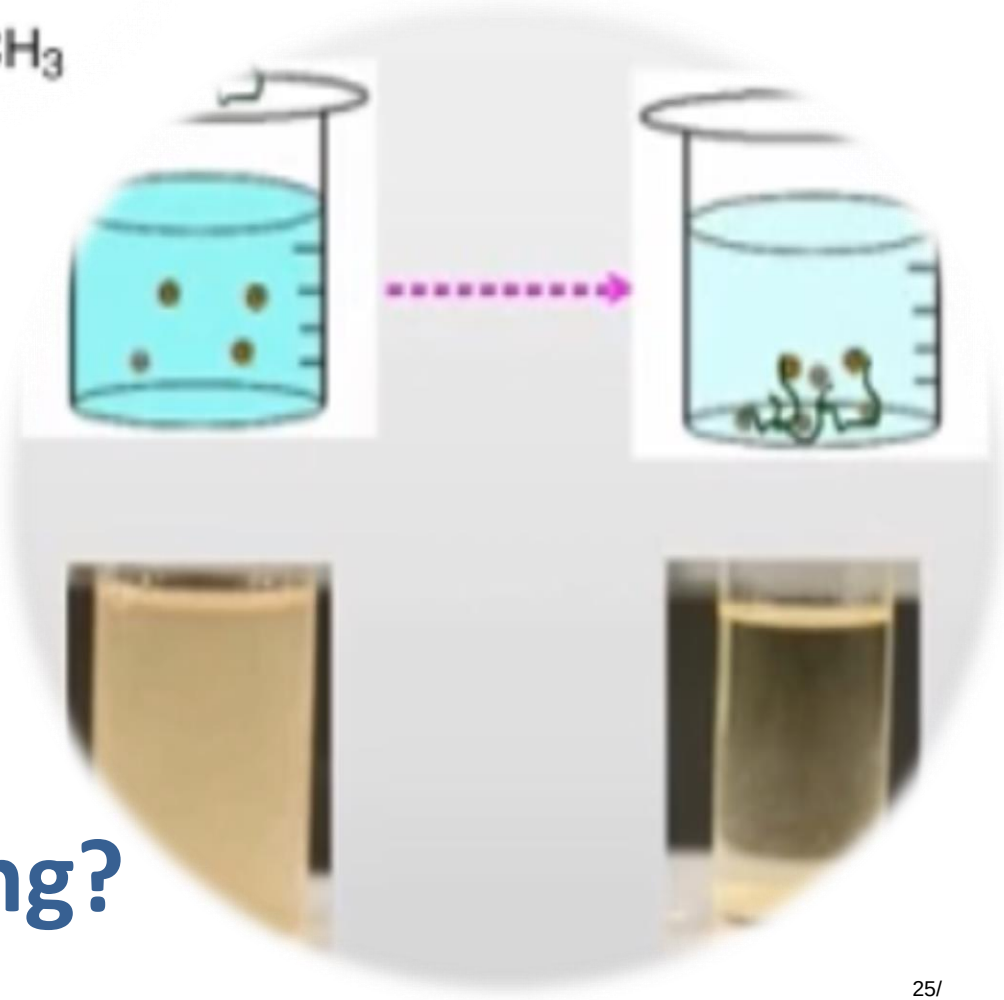
Abstract Go to:

High titer (>10 g/L) monoclonal antibody (mAb) cell culture processes are typically achieved by maintaining high viable cell densities over longer culture durations. A corresponding increase in the solids and sub-micron cellular debris particle levels are also observed. This higher burden of solids (≥15%) and



What else are you cleaning?

Cleaning improvment

Update June 2018

Conclusion after 3 runs:

- The new recipe meet all cleaning acceptance

validation R1

2% Formulated Alkaline Detergent +
2% Oxidative Detergent Booster

-25 %
- 2000 L / CIP

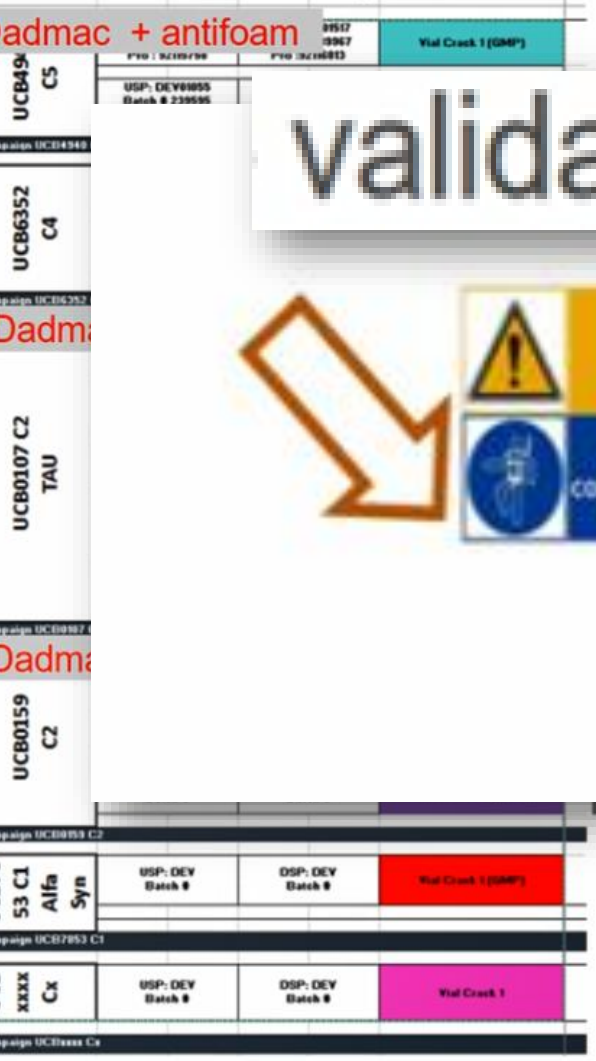
- 29 %
- 2,2 h / CIP

- 85 %
- 2.905 EUR / CIP

-25 %
- 2000 L / CIP

- 29 %
- 2,2 h / CIP

- 85 %
- 2.905 EUR / CIP



Routine for CIP100 recipe

Occupy Space with consistency: take accountability for trying new ideas/approaches that are aligned with our purpose, strategy and values

Derive actionable solutions based on true insights rather than assumptions/opinions

Current Situation

- Confusion in setting limits
  - EMA published Guidance on HBEL's 01 Jun 15 (EudraLex – Volume 4 – GMS guidelines
  - Q&A followed 19 Apr18

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 April 2018
EMA/CHMP/CVMP/SWP/246844/2018
Committee for Medicinal Products for Veterinary Use (CVMP)
Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on implementation of risk-based prevention of cross-contamination in production and 'Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'
(EMA/CHMP/CVMP/SWP/169430/2012)

Q1. Are Health-Based Exposure Limits (HBELs) required for all medicinal products?

A: Yes, HBELs should be established for all medicinal products.

The toxicological or pharmacological data, on which the HBEL calculation relies, requires periodical re-assessment throughout a product's lifecycle.

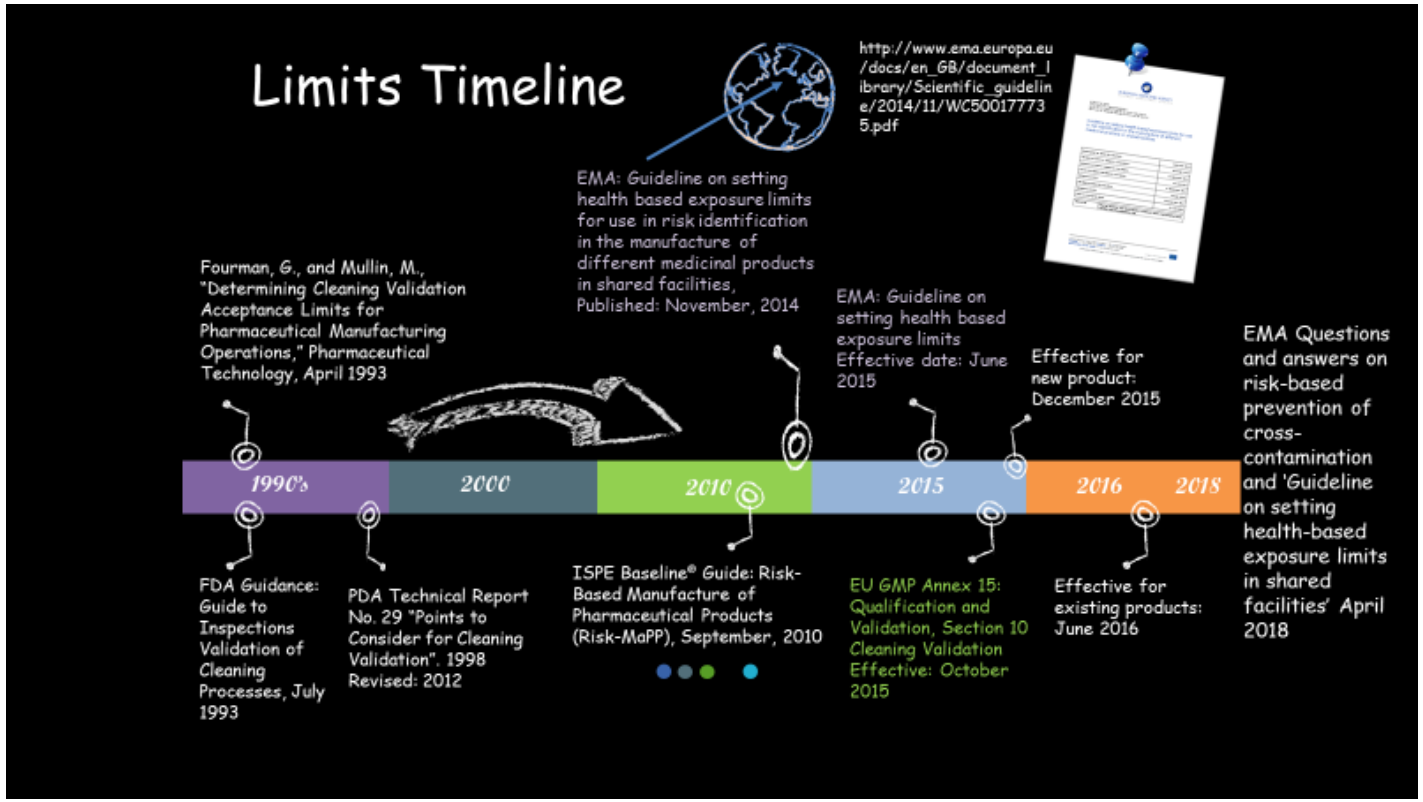
Q2. Is there a framework that could be used to define the significance of the Health-Based Exposure Limit (HBEL) such that there can be broad guidance on the extent of Quality Risk Management (QRM) and control measures required?

A: Firstly, it should be recognised that hazard varies on a continuum scale and that there are no firm cut off points, risk should be controlled on a proportionate basis. However, as a broad hypothetical model the following figure could be considered to show the increasing level of hazard (red being highest hazard) presented by products and there should be a commensurate increase in the level of control to prevent potential cross contamination in a shared facility. Actual HBEL values should be used in QRM studies to determine the actual controls required.

Increasing hazard

Health Based Exposure Limit (HBEL) - PDE

>10000 µg/day | 10000 µg/day | 1000 µg/day | 100 µg/day | 10 µg/day | <10 µg/day



PIC/S and WHO Recent Documents

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- **PIC/S 01 Jun 2020**: *Inspection of HBEL Assessments and Use in Quality Risk Management*
  – Aide Memoire
- **PIC/S 01 Jun 2020**: *Q&A on implementation of risk-based prevention of cross-contamination in production and 'guideline on setting HBEL's for use in risk identification in the manufacture of different medicinal products in shared facilities*
- **WHO draft May 2020**: *Points to consider on the different approaches – including HBEL – to establish carryover limits in CV for ID of contamination risks when manufacturing in shared facilities*

Industry perspective

- ***If acceptance limits were discussed, what was the stance of EMA, FDA, etc? Did they require calculation of PDE and establishing a lower process capability number or alert type of limit?***
  - "Agency personnel, for the most part, do not understand PDE concept either"
  - "Agency fine seeing multiple limits then using lowest, also fine with process capability"
  - "Alert limits were discussed with emphasis on lowering these if data supported"
  - "Discussion on what actions would need to be addressed if a trend of alerts were noticed since they are not technically action limits that were exceeded"

Calculation of ADE/PDE Value

- Per ISPE Baseline®Guide: Risk-Based MaPP
  - ADE should not be seen as a “limit”
    - Initial acceptance criteria are limits safe for the patient
  - Use as a reference point for determining level of risk
  - Establish Process Control Limits based on PD Studies
    - Tighter inner control limits (MOR’s & PAR’s)
    - Calculated per statistical analysis of CV data and monitoring data
- ADE limit alone may not be acceptable as carryover, though considered safe
  - Flavor, smell, product quality, etc.
  - Default to visually clean

$$Cpk = \frac{USL - \mu}{3\sigma}$$

Where:
Cpk = Capability index
USL = Upper Specification Limit
μ = average of the measurements
σ = standard deviation of the measurements

Setting Limits

- Determine PDE/ADE value – this becomes your PAR
- Collect data for pre-determined amount of time
- Use data to set MOR or process capability limit
- Have plan in place for when MOR is exceeded
  - For example: investigate and comment for isolated incident, formal investigation into trend.
- Some have set %’s and assigned Alert/Action limits, others have pushed back on FDA

Cleanroom control global trends

- Annex 1 revision
- Rotation
- Rinsing program

New Draft Annex 1 – PIC/S and EU finally arrives! (Almost…..)

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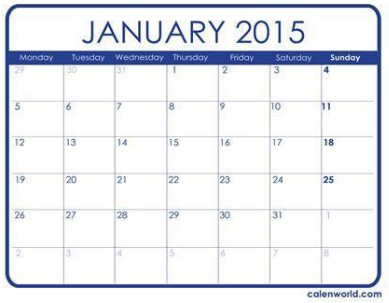

- Update was announced in January 2015
- Reasons for revision:
  - ICH Q9 (QRM) and Q10 (Pharma QS) not included in 2007 version
  - Advances in sterile manufacturing since 2007
  - Historical ambiguity in 2007 document
  - Annex 1 scope to encompass use beyond sterile manufacturing


EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

Brussels, 25 November 2008 (rev.)

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 simulations, 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.

New Draft Annex 1 – PIC/S and EU finally arrives! (*Almost……*)

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New Annex 1 not a revision, it is a rewrite:

- 269 clauses – compared with 127 in the 2007 version
- 100 new clauses with no direct link to an existing clause (not considering sub-clauses and expanded content
- 14 clauses from previous revision not included in new version
- At least 70 clauses from the previous revision which may have some impact on manufacturers

Annex 1 new topics:

- Process water systems
  - requirement to sample from the worst-case sample point each time water is used for manufacturing
- Aseptic operator qualification
- Single use technologies (interaction between product and surface, pre-use integrity testing, compromised packaging)
- Critical utilities
- Closed manufacturing systems (sterility, integrity, background environment)
- Material airlocks (MALs)
  - Materials transferred into area should be on an authorized list. If not on the list, should be an exception

New Draft Annex 1 – PIC/S and EU finally arrives! (*Almost……*)

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New Annex 1 provides greater detail (almost too much):

- Additional requirements for cleanroom classification
  - Requirement for higher number of samples and volume for aseptic processing rooms and adjacent areas
- Airlock alarms – previously allowed for interlocking, visual, or audible
  - Grade A now requires interlocks, also describes time delay
- Trending of Environmental Monitoring data
  - Increasing numbers of action or alert limit breaches
  - Consecutive alerts
  - Isolated events which may have a common cause (i.e. after a preventive maintenance)
- Cleanroom clothing type
  - Dedicated socks worn before entry to change rooms for grade C and B
- Personnel allowed in the Aseptic Processing Area based on QRM (Quality risk management)

Draft Annex 1: Disinfection – 2007 versus 20XX

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in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the

Sanitation

effective, cleaning to remove surface contamination must be performed first)., More than one type of disinfecting agent should be employed, and should include the periodic use of a sporicidal agent. Disinfectants should be shown to be effective for the duration of their in use

on which they are utilized. Monitoring should be undertaken regularly in order to show the effectiveness of the disinfection program and to detect the development of resistant and/or spore forming strains. Cleaning programs should be effective in the removal of disinfectant residues.

should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

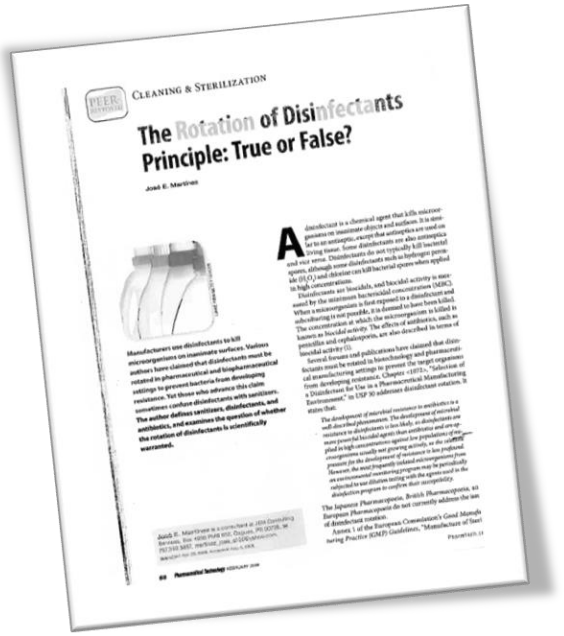
63. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

5.34 Fumigation or vapour disinfection of clean areas such as Vapour Hydrogen Peroxide (VHP) may be useful for reducing microbiological contamination in inaccessible places.

Rotation

Alternation of antimicrobial actives

- Two disinfectants in sequence, regular rotation, with sporicidal agent as needed
- One disinfectant daily, with sporicidal weekly or monthly



CLEANING & STERILIZATION

The Rotation of Disinfectants Principle: True or False?

Rotation

Recent scientific discussion on need for rotating disinfectants

- Bacteria resistance?

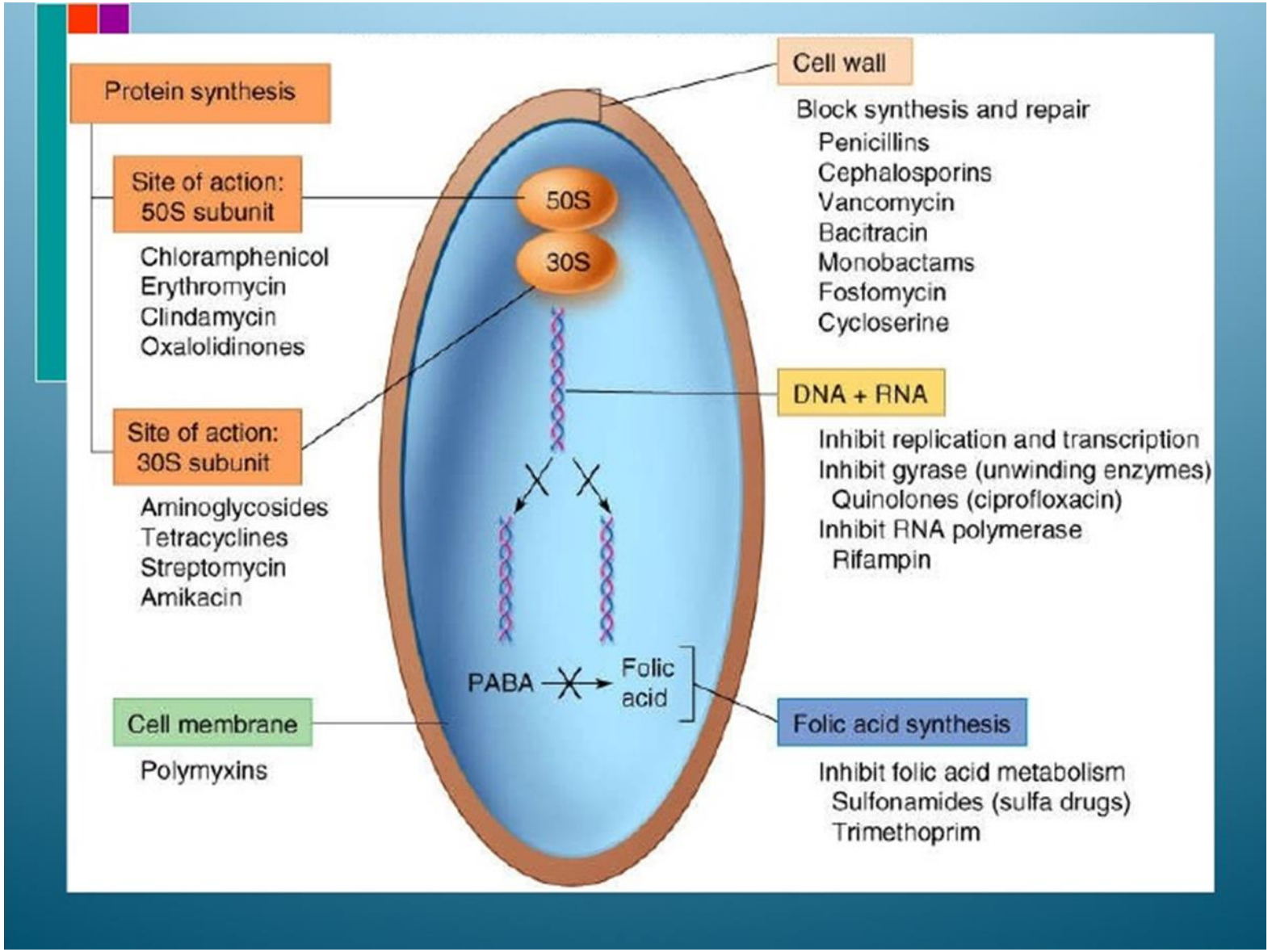
Chemical disinfectants

- have a higher biocidal activity and bacterial populations are generally very low in cleanrooms.

Persistent bacterial populations due to:

- Ineffective cleaning methods
- Disinfectant cannot reach the bacteria
- Misuse of disinfectant

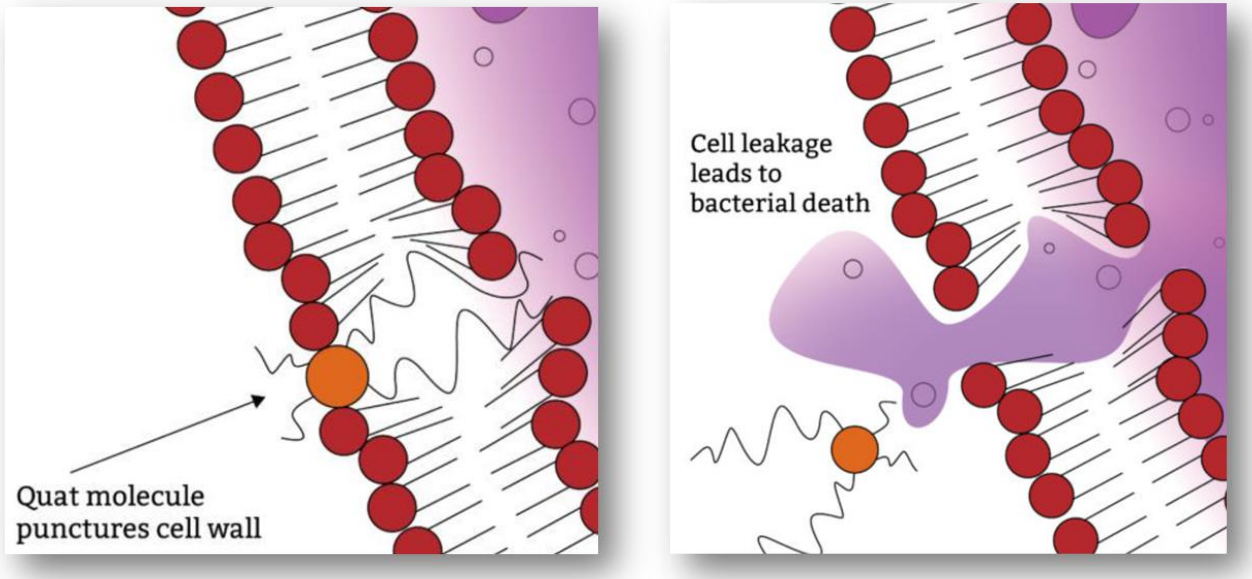
Antibiotic Action Sites



How Disinfectants work

Disinfectants have three mechanisms of action or ways that they affect or kill an organism

- Cross-linking, coagulating, clumping
- Structure and function disruption
- Oxidation



- Chlorine – Oxidizing proteins, lipids, and carbohydrates
- Peroxide compounds – Oxidizes cell membrane and protein coat on spore causing them to collapse exposing core to lethal disinfectant
- Phenols – penetrates and disrupts proper functioning of the cell wall

Rotation - MICROBIAL RESISTANCE TO DISINFECTANTS?

CURRENT USP 42 <1072> DISINFECTANTS AND ANTISEPTICS

"The development of microbial resistance to disinfectants is less likely to occur…, as disinfectants are more powerful biocidal agents than antibiotics".

"…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".

"…frequently isolated microorganisms ….may be periodically subjected to use-dilution testing with the agents used in the disinfection program to confirm their susceptibility, as there are real differences among different species in resistance to the lethal effects of different sanitizers".

Rotation - MICROBIAL RESISTANCE TO DISINFECTANTS?

EudraLex annex 1 (2008)

"61. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. **Where disinfectants are used, more than one type should be employed.** *Monitoring should be undertaken regularly in order to detect the development of resistant strains.*»

PIC/S WHO

JP guidance on aseptic manufacturing (2006)

(3) **If selected disinfectants might have inferior efficacy against microorganisms isolated** from the environment, the efficacy should be **reevaluated** and the **replacement** with **or alternate use of different disinfectants** should be considered and implemented, as appropriate.

(4) If **environmental monitoring data indicate** or suggest the presence of **spore-forming bacteria or fungi,** suitable **sporicides** or **fungicides** should be **selected for disinfection**."

FDA guidance on aseptic manufacturing (2004)

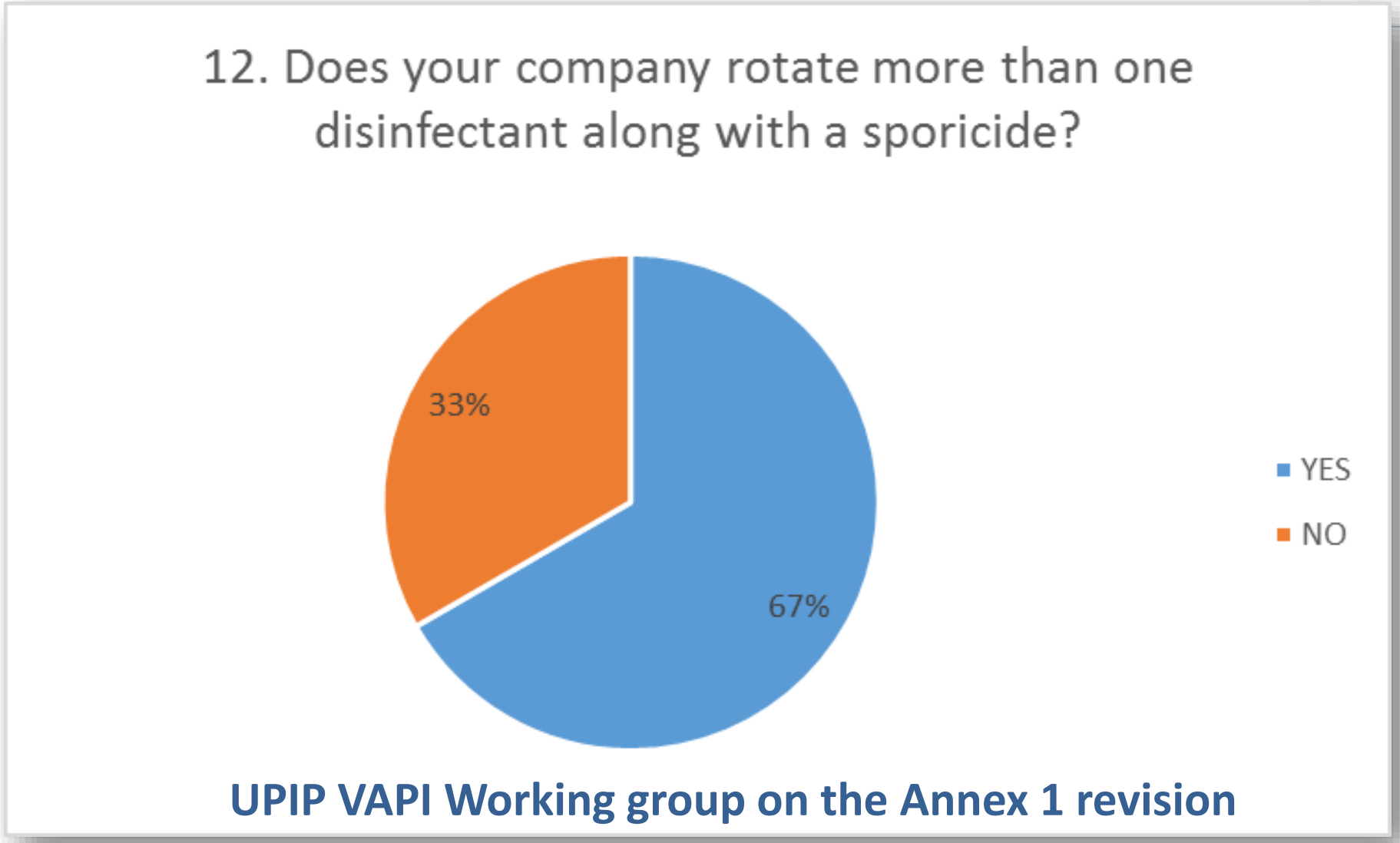
"…. Routinely used disinfectants should be effective against the normal microbial vegetative flora recovered from the facility….." and "…Therefore, ***a sound disinfectant program also includes a sporicidal agent,*** *used according to a written schedule and* ***when environmental data suggest the presence of spore forming organisms.****"*

PDA TR70 cleaning and disinfection (2015)

"The antimicrobial agents typically employed in cleanrooms continue to be effective because they have **numerous effects on a number of aspects of cellular physiology**. That means multiple mutations would be required in a short period of time (ex. 5 minutes) with exposure to low numbers of cells typically found in a cleanroom to overcome their detrimental effects. As such, **resistance of a cell to agents used in a disinfection process would be highly unlikely** given the environmental conditions and low cell number."

Given this knowledge, the pharmaceutical and biotechnology **industries have moved away from the rotation of two disinfecting agents.** This formerly common practice led to high residue levels and subordinate efficacy performance. Today most firms use a system whereby a **disinfectant is rotated with a sporicidal to more effectively reduce the bioburden** levels. The rotation of a disinfectant with a sporicide is **superior to the use of rotations of multiple disinfectants.**"

Rotation



Source: Working group Annex 1 - 19 answers received

Future requirements for disinfectant rotation

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- More than one type of disinfecting agent should be employed and should include the periodic use of a sporicidal agent

- Disinfectants should be shown to be effective for the duration of their in-use shelf-life taking into consideration appropriate contact time and the manner in and surfaces in which they are utilized

- Monitoring should be undertaken regularly in order to show the effectiveness of the disinfection program and to detect the development of resistant and/or spore forming strains.

- Cleaning programs should be effective in the removal of disinfectant residues.

RINSING

CLEANING TO REMOVE DISINFECTANT RESIDUES

Regulatory and GMP Expectations

STERIS Life Sciences

- Parenteral Drug Association (PDA) Technical Report 70, Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities
  - Mentions residue removal as important for inspection readiness
  - Discusses types of cleaning agents
  - Defines what is meant by “cleaning” and necessary
  - Describes how to assess frequency
  - Section concerning reducing corrosion and deterioration of surfaces

Why Residues are a concern

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Efficacy concerns:

- Residues inhibiting Biocides
- Do residues support harbor microbial growth?
- Do residues inhibit preceding actives

Mean Log Reduction of *B. subtilis* using dried phenolic residues and sporicidal agent solution

Minutes, Post Inoculation	2.5	5	10
Mean Log Reduction: Sporicidal agent + Water	0.94	2.94	> 4.02
Mean Log Reduction: Sporicidal agent + low pH phenolic disinfectant	1.22	> 4.04	> 4.02
Mean Log Reduction: Sporicidal agent + high pH phenolic disinfectant	1.75	> 4.04	> 4.02

Functional Issues:

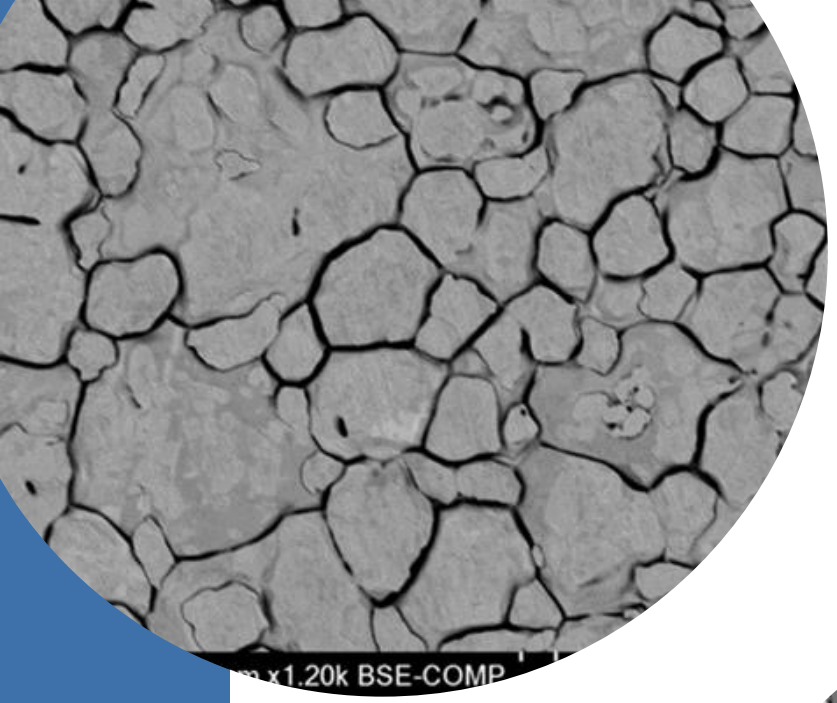
- Sticky or opaque surfaces due to residues

Aesthetic Issues:

- Surfaces do not look “clean”

Safety Issues:

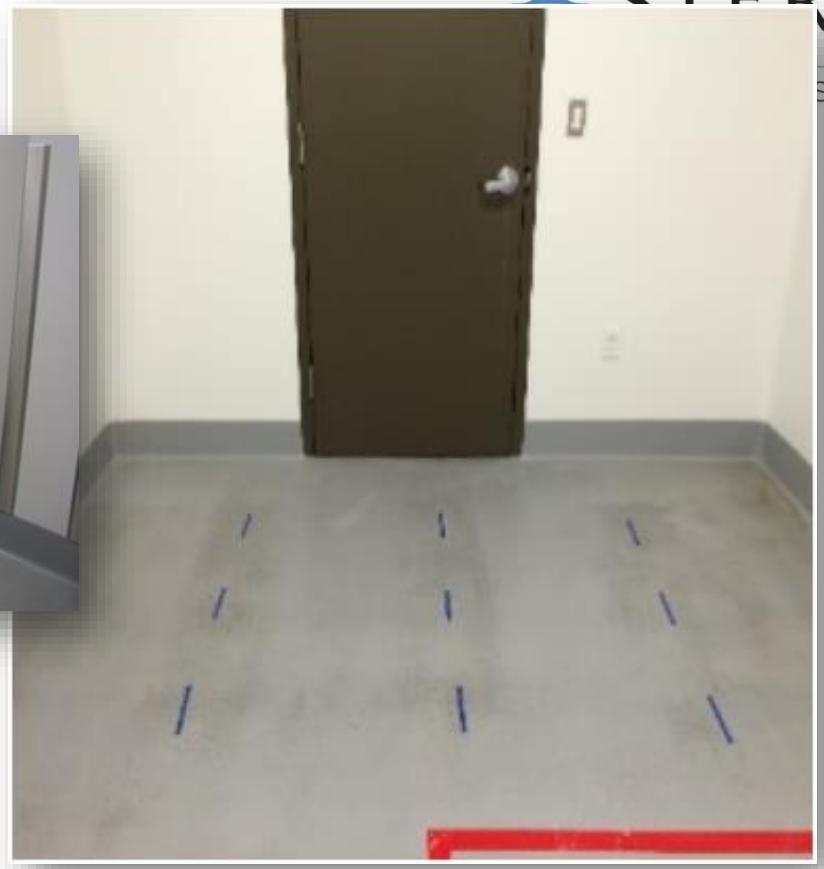
- Transfer (direct and indirect) from surfaces to manufactured drug products or medical devices
- Personnel safety (slippery, tacky, sticky, etc.)



Where does the residue come from?

- Compatibility issues
  - Different agents in rotation program
  - Surface substrates
    - Corrosion – attack of the impurities in the metal by chemical agents
    - Staining
- Poor cleaning practices
- Drug product/process spills

Residue removal trial



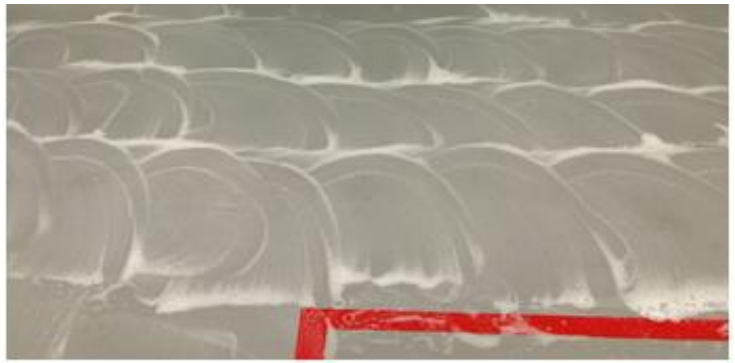
Desco Quartz Epoxy flooring system in an ISO 8 gowning room marked off in a grid pattern for in-situ testing. Two-year-old floors are disinfected daily with phenolics and once per month application of sporicidal agent one time per month without rinsing.

Desco flooring after residue removal trial using:

- *WFI (lane 1),*
- *Sterile oxidative detergent (lane 2)*
- *Sterile neutral detergent (lane 3)*

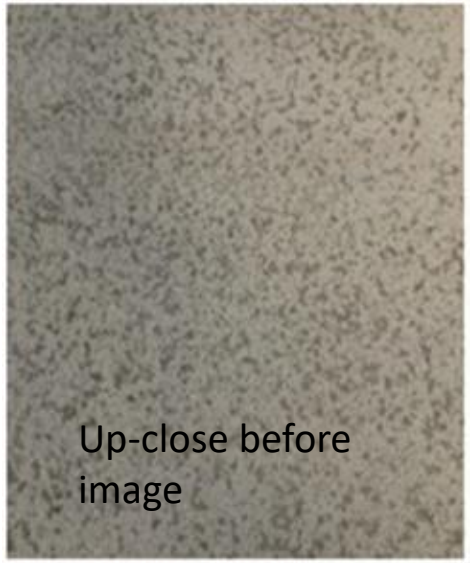
Residue removal trial

Control – random sampling					
Before Cleaning			**After Cleaning**		
EM Sample ID	Results cfu/plate	Microbial Isolates	EM Sample ID	Results cfu/plate	Microbial Isolates
1D1	2	*M. luteus*	1D2	<1	N/A
2D1	4	*S. cohnii*	2D2	<1	N/A
3D1	10	*Bacillus (Solibacillus) isronensis*	3D2	2	*B. megaterium*



Application of sterile detergent

Desco flooring after residue removal trial using sterile neutral detergent and rinse



Residue removal – Microbial removal

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WFI results					
Before Cleaning			After Cleaning		
EM Sample ID	Results cfu/plate	Microbial Isolates	EM Sample ID	Results cfu/plate	Microbial Isolates
1A1	<1	N/A	1A2	5	*M. luteus* *S. epidermidis*
2A1	3	*B. subtilis* *S. sarprohyticus*	2A2	6	*S. epidermidis*
3A1	5	*B. subtilis*	3A2	5	*Paenibacillus lentus*

Sterile oxidative detergent					
Before Cleaning			After Cleaning		
EM Sample ID	Results cfu/plate	Microbial Isolates	EM Sample ID	Results cfu/plate	Microbial Isolates
1B1	10	*B. arybhattai*	1B2	3	*O. kimchi*
2B1	13	*M. luteus*	2B2	4	*B. amyloliquefaciens*
3B1	19	*D. cinnamea* *S. cohnii*	3B2	6	*S. epidermidis*

Sterile neutral detergent					
Before Cleaning			After Cleaning		
EM Sample ID	Results cfu/plate	Microbial Isolates	EM Sample ID	Results cfu/plate	Microbial Isolates
1C1	10	*B. licheniformis*	1C2	9	*B. marisflavi*
2C1	19	*B. subtilis*	2C2	<1	N/A
3C1	7	*O. kimchi* *B. amyloliquefaciens*	3C2	9	*Sporosarcina soli*

Program Recommendations

How often to clean???

- Environmental cleaning frequency determined by:
  - ISO Classification of area
  - Application technique
  - Activity level in area or use
  - Environmental monitoring feedback
  - Type of process being performed & equipment used
  - Substrates
  - Visual observation

Contamination Control Program Recommendation

STERIS Life Sciences

For clean rooms we still recommend

- Disinfectant Rotation
    - Phenols or Quats on monthly basis (never a phenol and a quat)
- Sterilant use routinely based on environmental data
- Rinsing on a routine basis
    - Not necessarily daily, but SOPs should include weekly/monthly rinsing with IPA or water
- Evaluate cleanability of heavy residues

Summary: How can you ensure your program is audit ready?

- Know what you are cleaning – understand your process
- Understand how changes to the cleaning process impact the cleaning efficacy – review changes/plans
- Ensure procedures are robust and data is accurate
- Have a plan in place for incorporation of Health Based Limits

Sterile Environments and Cleaning Validation Inspections, Warning Letters, and Trends with US FDA

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Thank you for your time!