106TPDA04024

衛生福利部食品藥物管理署委辦計畫

「推動新興生醫產品GMP評鑑符合性計畫」

新興生醫產品 GMP 訓練活動(5)、(6)

日期：民國 106 年 8 月 28 日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講 師 資 料

Minh Tran/ Head of Single Use Sales Development, Merck, Asia Pacific

Michael Payne/Principal Technical Consultant, Technology Management, Merck, Asia Pacific

時 間 表

時 間	內 容	講 師
8:30-9:00	報 到	
9:00-9:10	長 官 致 詞	TFDA 風管組代表
9:10-10:30	➢ Considerations Of Single Use Systems As a Manufacturing Process Template	Minh Tran
10:30-10:50	休 息	
10:50-12:10	➢ Fundamentals of Aseptic Processes, Microbiological Control and Environmental Monitoring	Michael Payne
12:10-13:10	午 餐	
13:10-14:10	➢ Biological Process Validation – with Reference to Qualifying Sterile Operations(I)	Michael Payne
14:10-14:30	休 息	
14:30-15:30	➢ Biological Process Validation – with Reference to Qualifying Sterile Operations(II)	Michael Payne
15:30-16:00	交 流 討 論	TFDA 風管組代表 及講師
16:00-16:30	課 後 測 驗	

目　　錄

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CONSIDERATIONS OF SINGLE USE SYSTEMS AS A MANUFACTURING PROCESS TEMPLATE

Minh Tran
Head of Single Use Sales Development– APAC
Process Solutions – Merck Life Science
August 28th, 2017
Minh.Tran@merckgroup.com
LinkedIn

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AGENDA

1. Introduction- My background
2. Drivers of single use systems
3. Process and operational risks in bioprocessing
4. Managing and reducing contamination risks
5. Film technologies used in bag making
6. How are SU assemblies manufactured?
7. Examples of single use applications
8. E&L validation considerations
9. Implementation and Summary

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Minh Tran

Head of Single Use Sales Development – Asia Pacific

• Bachelor of Science, Microbiology and Cellular Biology, from the University of Washington, in Seattle, WA USA in 1991. Graduate of Project Management Institute (PMI). Joined Millipore in 2009.

• 23+ years of experience in biotechnology industry with functions in Quality Control, Process Development, and Clinical to Commercial Manufacturing.

• Worked as a Principal Process Engineer in Cell Science and Technology at Amgen Washington for 5 years responsible for process scale-up and optimization. Performed technology and process transfers between clinical and commercial CMO and Amgen facilities.

• Implemented SU manufacturing technologies for key projects and unit operations globally from consultation on facility design, SU technologies, and implementation.

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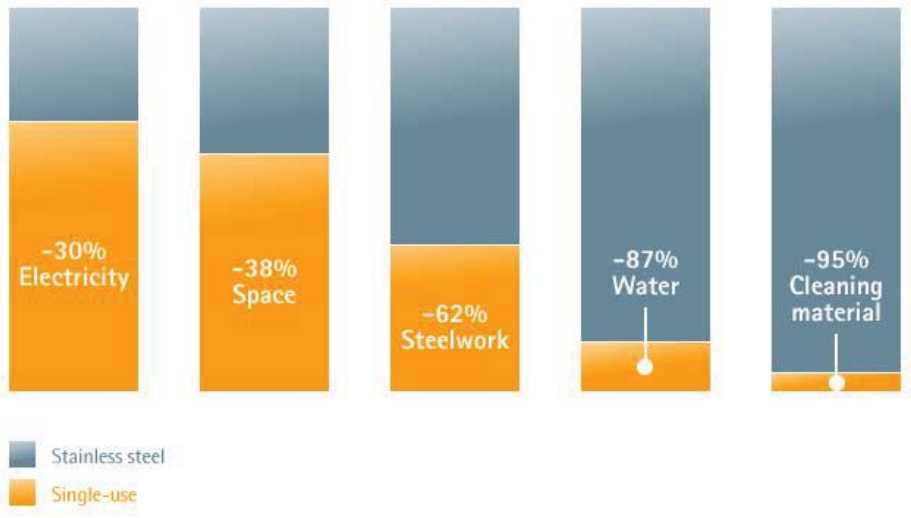
Drivers of single use systems



* Reference: Sinclair, A.; Leveen, et al.; The Environmental Impact of Disposable Technologies, The Biopharm International Guide, November 2008; Base of the analysis: Typical mAb process at 3 x 2000 L scale

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Process and operational risks in bioprocessing

Ensuring product safety with multi-layers of control and single use technologies

Eliminating Risks

Preventing Risks

Monitoring and controlling

BIOPHARMACEUTICAL MANUFACTURING

Upstream Processing & Operations

Downstream Processing & Operations

Final Filtration and Filling

$

In-process Testing & Monitoring

Solution Preparation and Storage

- SU Mix Systems and Bioreactors
- Solution filtration assemblies
- Sterile connection / reconnection
- Self-Deploying Storage Bags

Purification and Filling

- SU Chrom / TFF / Virus Systems
- Product filtration assemblies
- Sterile connection / reconnection
- Product pools / Filtration / Filling

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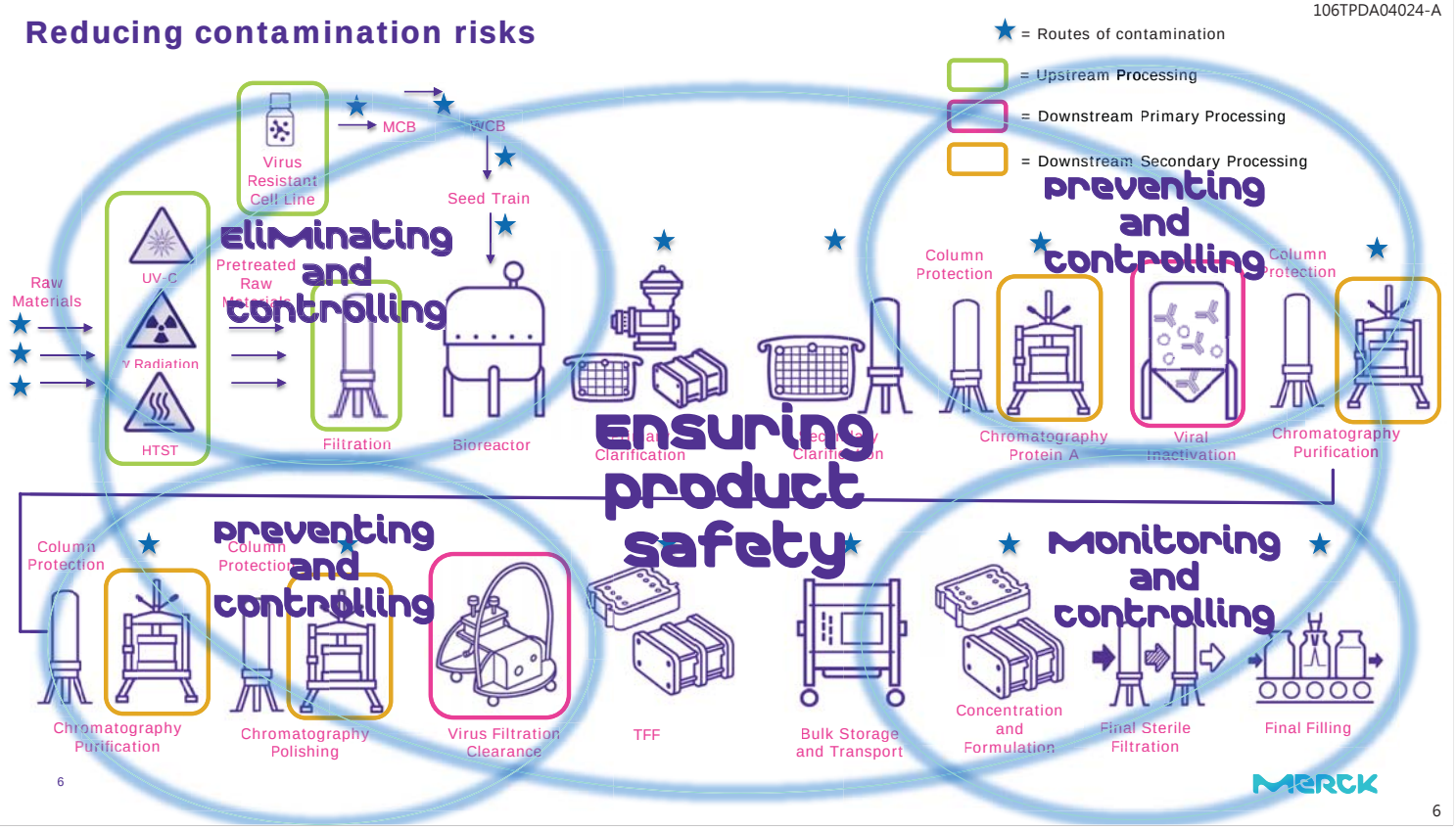
Reducing contamination risks



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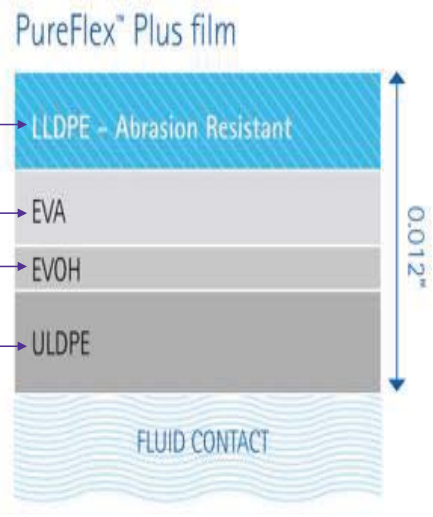
FILM TECHNOLOGIES USED IN BAG MAKING

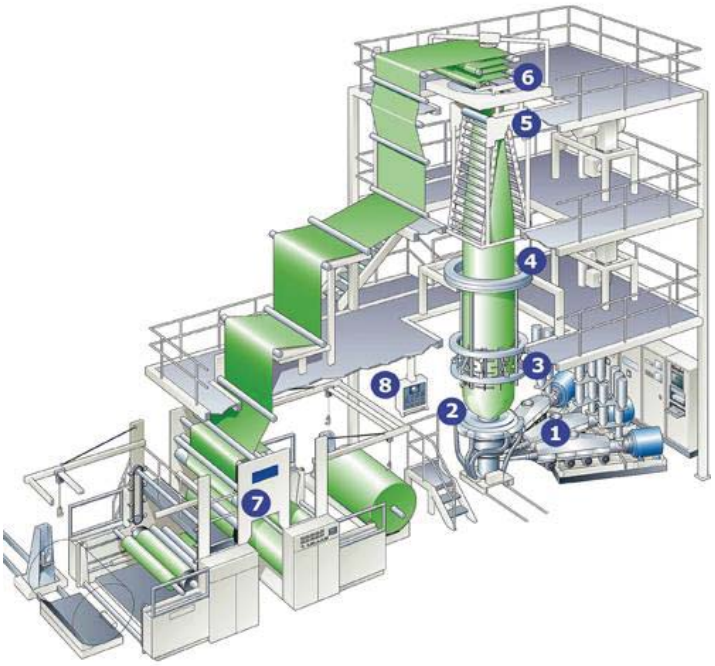
Film technologies used for bag making

- Increase abrasion resistance of film during manufacturing and use
- Increase flexibility of the film membrane
- Gas barrier layer to prevent moisture, CO2, and O2 from transitioning across the film membrane
- Product contact layer using clean simple resins with low E&L profiles

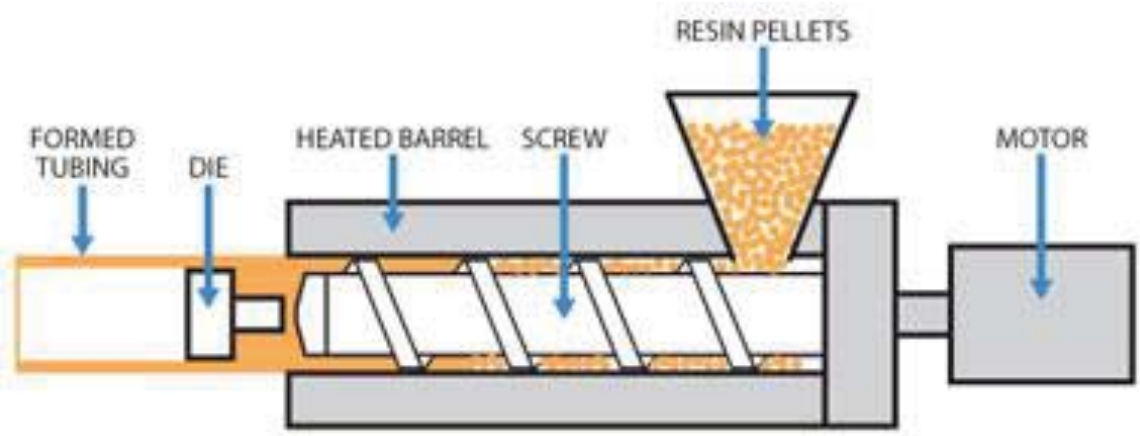


- Films need to provide process robustness and resistance to leak formation
- Good packaging of assemblies and handling of bag assemblies are critical
- If possible use one film from beginning to end of process to reduce E&L validation scope

Blown Film Process



Extrusion Process



Extruders

Importance of film validation

PHYSICAL DATA
(Post gamma irradiation at ≈ 45 kGy)

Properties	Tests	Average Values
Tensile Strength	ASTM® D882	2700 psi (18.6 MPa)
Elongation	ASTM D882	570%
Yield Strength	ASTM D882	1360 psi (9.4 MPa)
Secant Modulus	ASTM D882	37 ksi (255 MPa)
Toughness	ASTM D882	9100 in.-lbf/in.^{3} (63 MJ/m^3)
Seam Strength	ASTM D882	18 Lbf/in. (32 N/cm)
O_2 Transmission Rate	ASTM F1307 at 23 °C	0.063 cc/100 in.^{2}/24 hrs (0.98 cc/m^2/24 hrs)
CO_2 Transmission Rate	ASTM F2476 at 23 °C	0.13 cc/100 in.^{2}/24 hrs (2.02 g/m^2/24 hrs)
MVTR	ASTM F1249 at 23 °C	0.034 g/100 in.^{2}/24 hrs (0.53 g/m^2/24 hrs)
Haze	ASTM D1003	23%
Glass Transition Temperature	ASTM D5026	-14.8 °F (-26 °C)
Film Thickness	ASTM D374	0.01 in. (0.25 mm)
Operating Temperature Range*		-112 to 140 °F (-80 to 60 °C)

BIOCOMPATIBILITY DATA
(Post gamma irradiation at ≈ 45 kGy)

Properties	Tests	
USP Class VI	USP <88>	passed
Cytotoxicity	USP <87>	passed
Bacterial Endotoxin	USP <85>	passed
Heavy Metals	USP <661>	passed
Buffering Capacity	USP <661>	passed
Non-volatile Residuals	USP <661>	passed
Residue on Ignition	USP <661>	passed
Hemolysis	ISO 10993-4	passed
Appearance	EP 3.2.2.1	passed
Acidity and Alkalinity	EP 3.2.2.1	passed
Absorbance	EP 3.2.2.1	passed
Reducing Substances	EP 3.2.2.1	passed
Transparency	EP 3.2.2.1	passed
Particulate Matter	USP <788>	passed

* Freezing requires the film to be supported. Note: These are average data for PureFlex film.

HOW ARE SINGLE USE ASSEMBLIES MANUFACTURED?

Where are SU assemblies manufactured?

Material flow of components

Qualified material is received

- Shipping clerk verifies that the Packing Slip matches the Purchase Order
- Inspects the material for shipping damage
- Labels the material with part number, lot number, acceptance criteria

Material is picked

- Work Order is generated for released job, listing the catalog number, part numbers, part lot number, and location of material
- Outer bag removed, wiped down and passed through into the Class 100k clean room.

Material is kitted

- In the Class 100k clean room, material is measured, placed on cart with all components to complete order.
- Once kitting complete, cart is moved to Class 10K clean room.

[√] DTS [ ] VRO [ ] Quarantine

Part number:

Lot Number:

[ ] DTS [√] VRO [ ] Quarantine

Part number:

Lot Number:

QC Accept

Part number:

Lot Number:

Making of bag containers

1) Film cutting

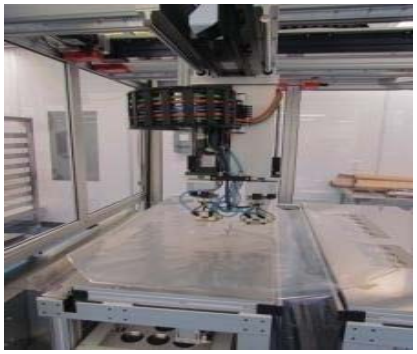
- Film material is cut on the Automated Flash Cutters

3) Film Bonding

- Film bonding to make bag container

2) Port Sealing

- Ports are added to location on film



Making of assemblies

Assembly

- Tubing, filters, connectors added
- Procedures and drawings specify configurations

Assembly Integrity Test

- Gold 100% via pressure decay
- Silver Cert - 3 samples are taken one from the beginning, middle and end

In-process Inspection

- Each unit is inspected by QC, verify that all the components are present and visually acceptable
- Random samples are taken and measured to verify that the tubing length and bag dimensions met spec.

Units are double bagged and labeled

In-process Inspection

- Each unit is inspected by QC to verify the product is labeled correctly, visually acceptable.

Material is passed through the final product pass through.

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Post-Clean Room Process Flow

Material is boxed

- Certificates of Quality are attached and enclosed

QA Release prior to sterilization

- Reviews all production and QC batch record
- Verifies product and box labeling
- Certificate of Quality are present

Daily shipments to gamma sterilizer

- SU Products return to warehouse
- Held in quarantine pending release by QA

QA Release after sterilization

- Verify gamma irradiation information
- Gold Certificate of Quality
  - Endotoxin Testing
  - Particle Testing
- **Final release of product into inventory for shipping to customers**

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Examples of single use technologies

Assemblies

Easy to use single-use assemblies for media/buffer filtration and storage to formulation and final filtration

Single Use Mixers

Easy to use mixing systems with single-use process containers from 10 to 3000 L

Sterile Connectors

Truly sterile-to-sterile connectivity

Sterile disconnection

Securely crimp and cut single-use assembly into two sterile fluid paths

Steamable Connectors

Integrating stainless steel with disposable assemblies

Single Use Bioreactors

Single-use stirred-tank bioreactor 3L to 2000L

Polyethylene Drums

Drums to contain single-use assemblies

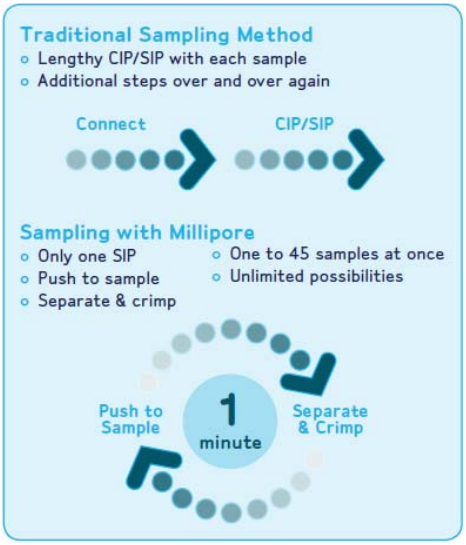
Stainless Steel Bins

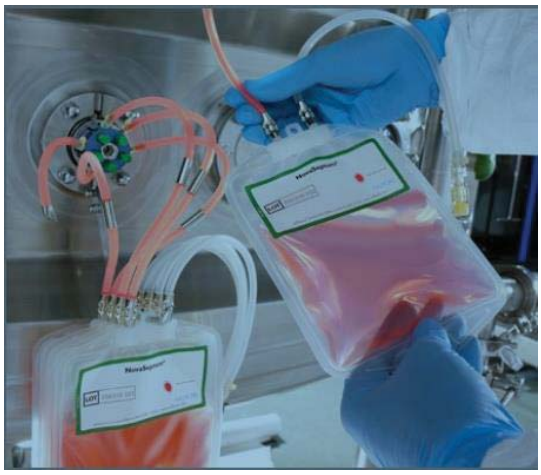
Convenient handling and flawless bag positioning

Self deploying from 200L to 3500L

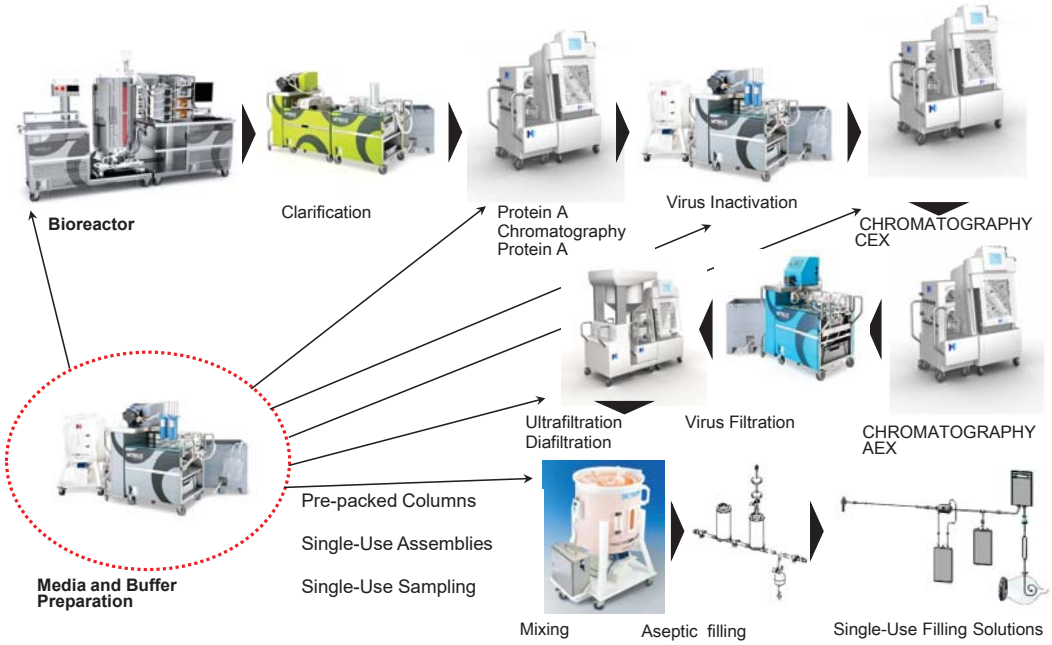
Sampling System

Increase sampling productivity, while reducing set-up, cleaning and flushing time





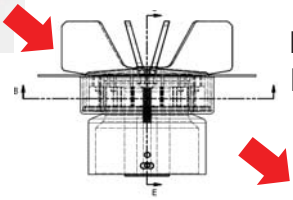
Examples of a Single Use Manufacturing Template



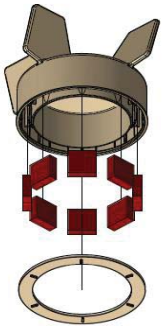
SINGLE USE MIXING

Design Evolution of the mixing technologies

Started with our own NovAseptic technology



Leveraged our existing SU knowledge



Sourced standard readily available magnets which provide a higher coupling force

Yielding faster and more efficient mixing in a SU format

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Powder Bags for Mixing Systems

Filling station and funnel

Hoist and MIX support plate

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Powder Bags for Mixing Systems

Sizes: 5, 10, 15, 25 kg

Features:

- Butterfly valve for metered addition
- 4” TC connection
- Screw cap for long term storage
- Wash down bladder (optional)
- Integrates with MIX 100, 200, 500, 1000 MIX bag TC port

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Mixing and Storage

Mixers: 10L to 3000L

Storage Bags: 2D: 50mL to 50L

3D: 200L to 3500L

Most important considerations for mixing are:

- Robust mixing
- Scalable platform
- Product recovery
- Easy to use

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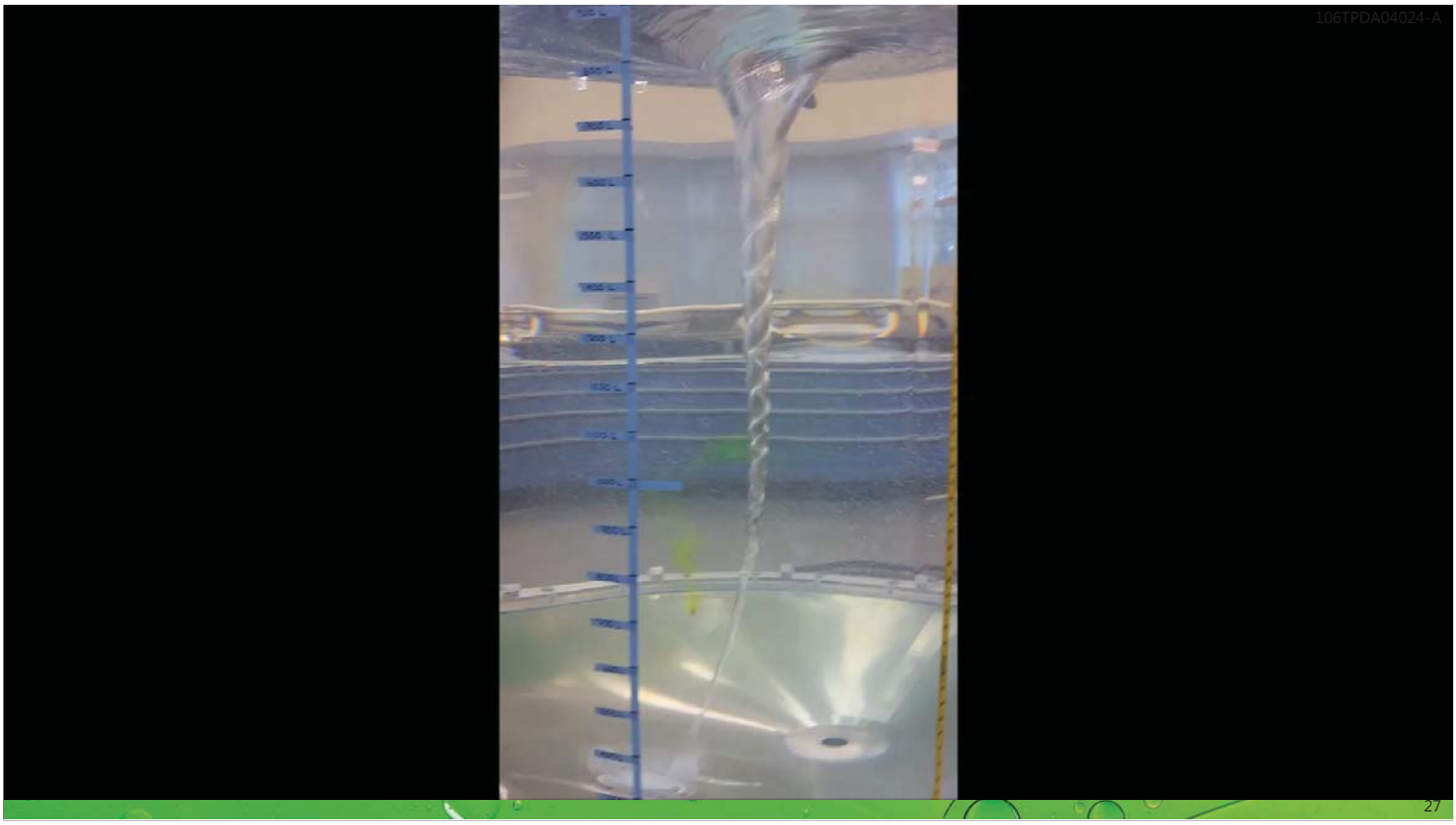
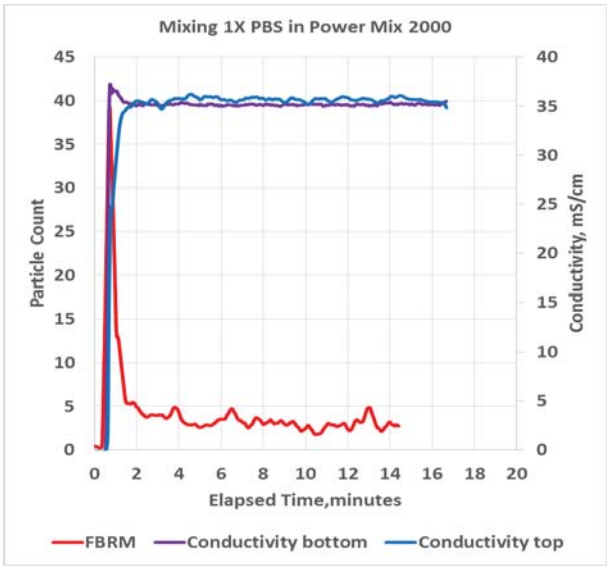
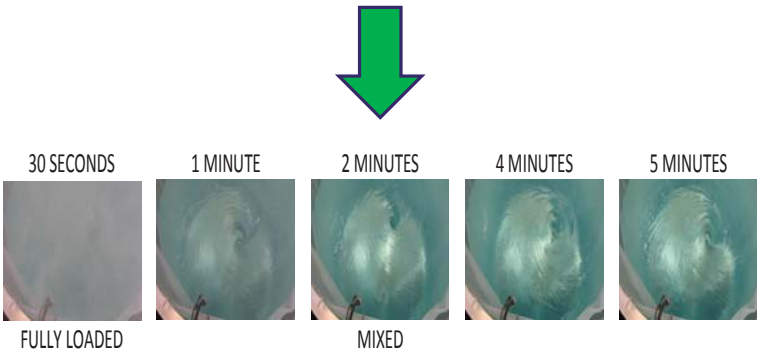


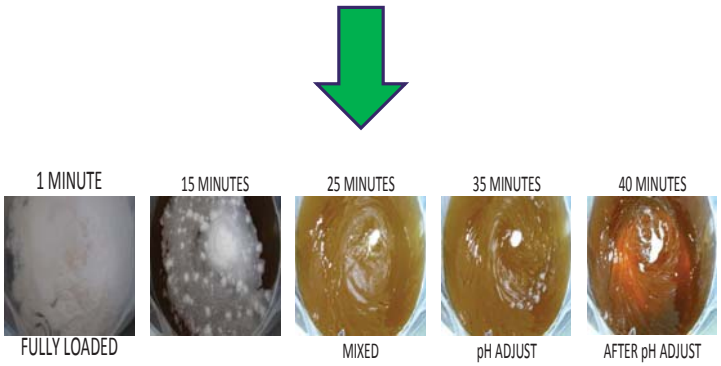
Applications Work
Demonstration of Efficient Mixing of Typical Buffer

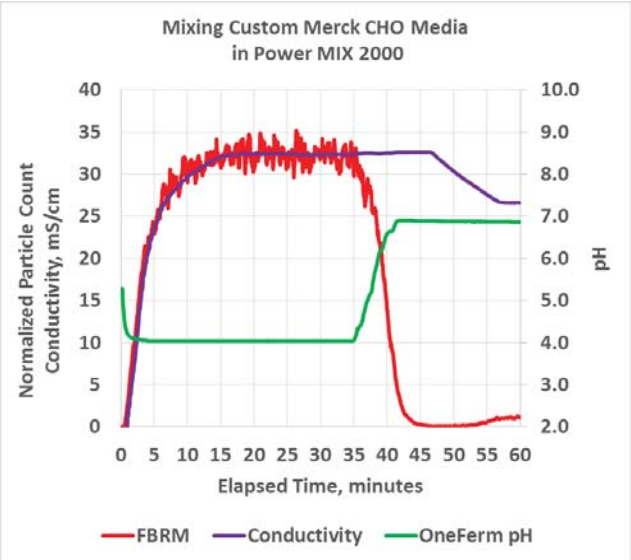


Buffer



Applications Work
Demonstration of Efficient Mixing of Typical Media Powder





Media

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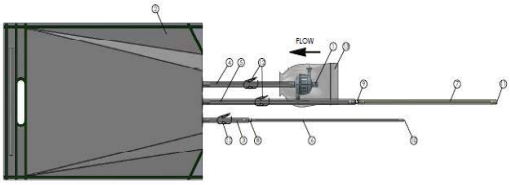
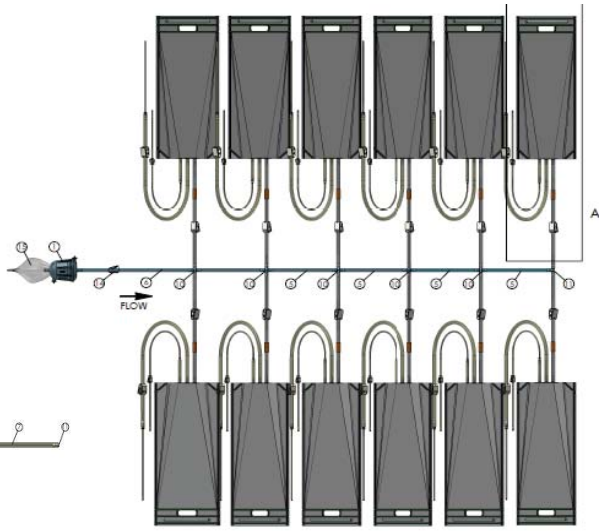
EXAMPLES OF SINGLE USE APPLICATIONS

Media / Buffer filtration

Type 1: Sample bags
50 - 100 - 250 - 1000ml

Type 2: Pillow bags
5 - 10 – 20 – 50 Liter





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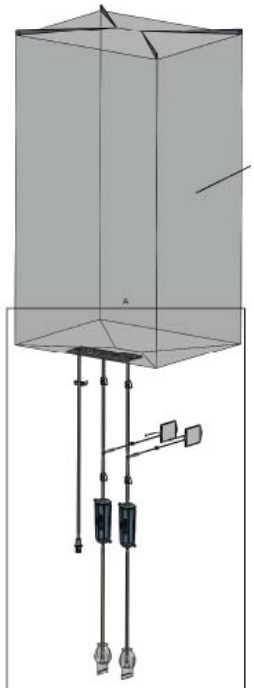
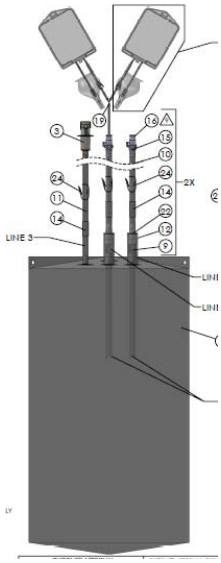
Film: 3D Bags:

Type 1: Cylindrical
- **50 L**
- **100 L**
- **200 L**

Type 2: Cubical
- **200**
- **500**
- **1000**
- **1500**
- **2000**
- **3000**
- **3500**





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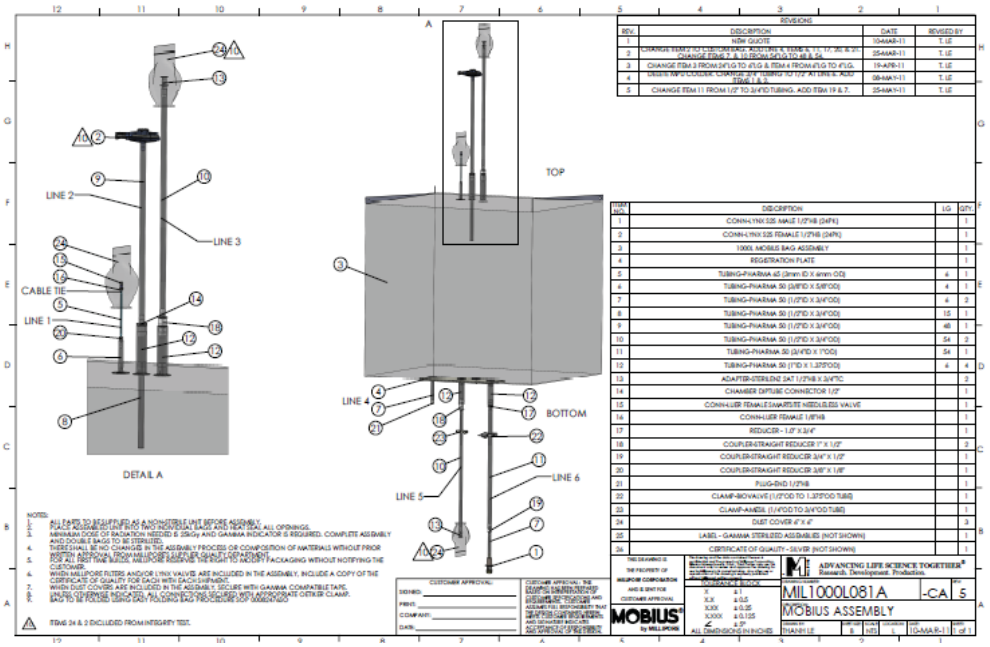
Intermediate 1000L bag with recirculation loop



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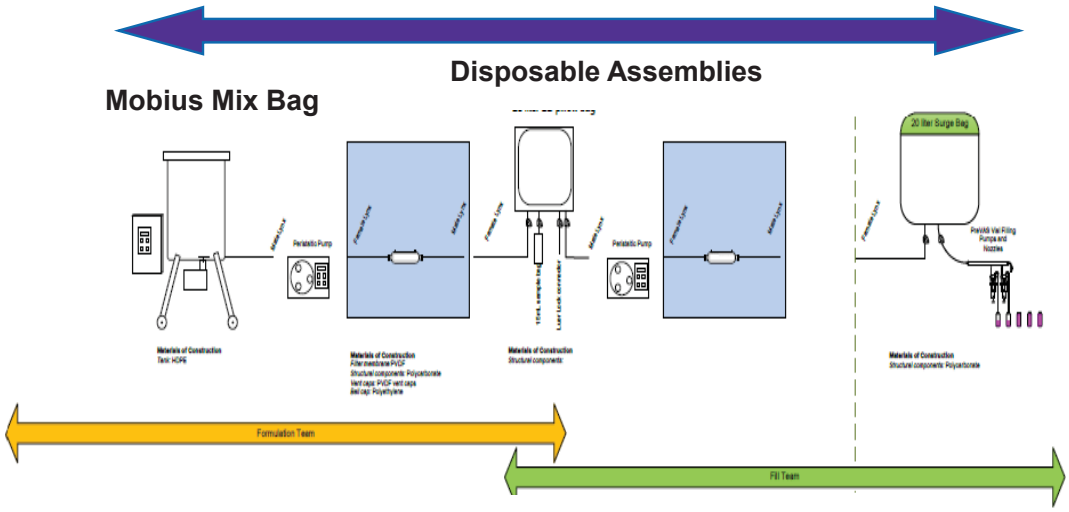
Formulation and Fill Finish



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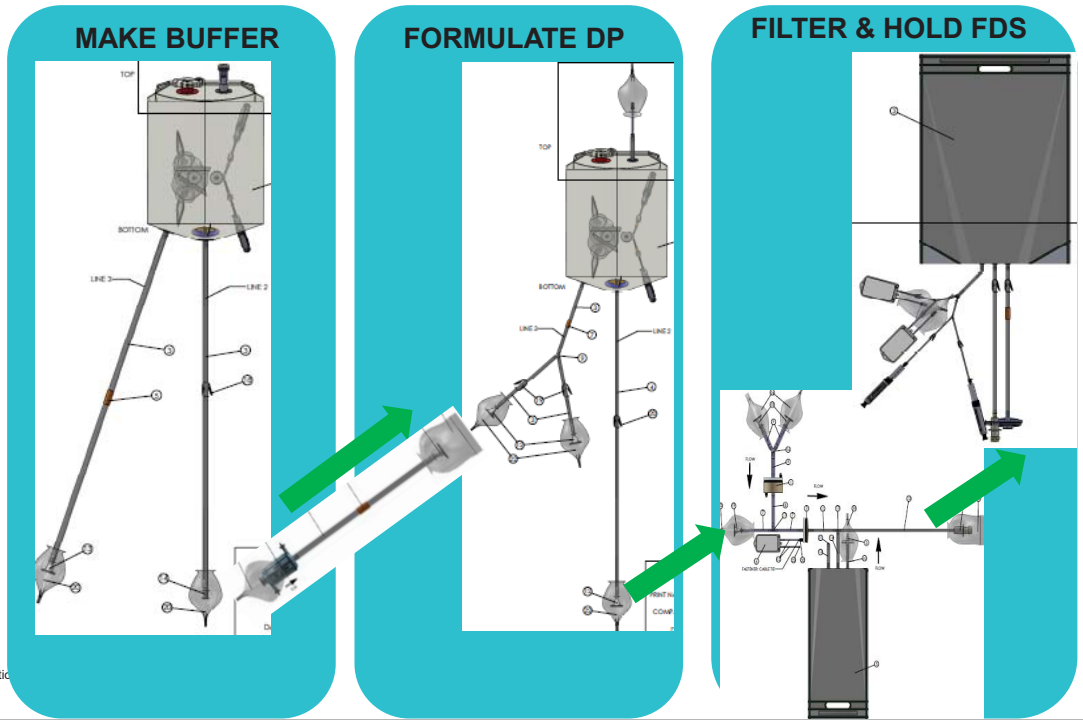
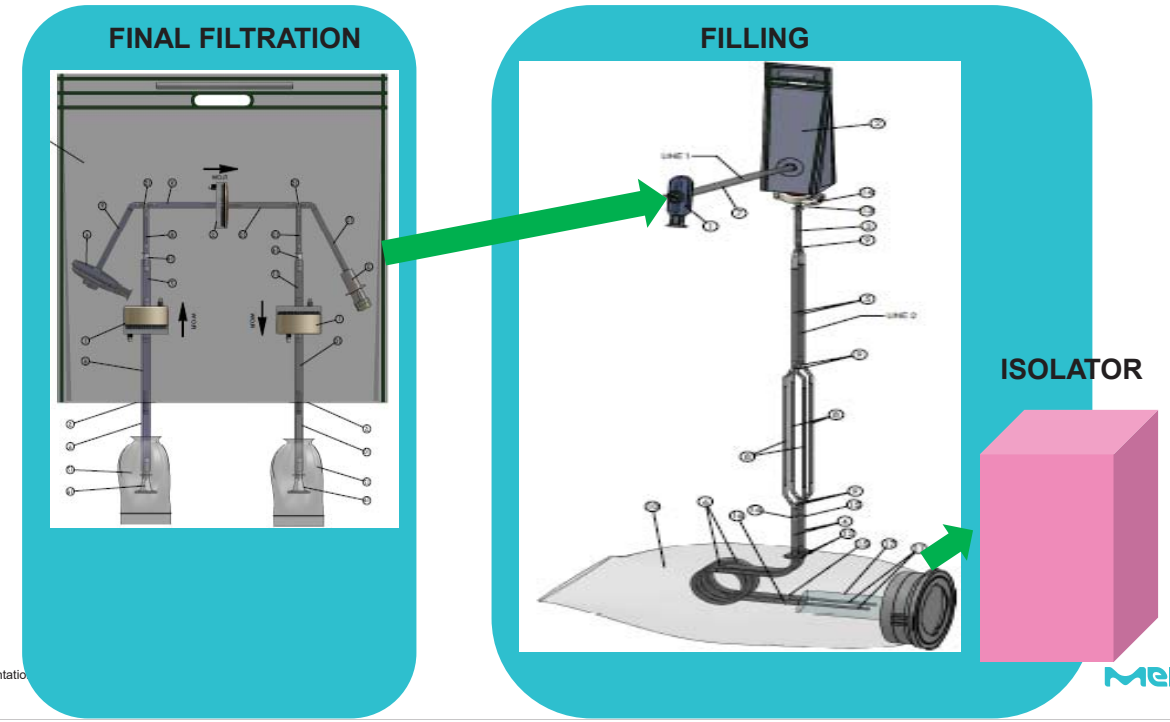
Formulation and sterile transfer



Final Filtration



E&L VALIDATION CONSIDERATIONS

How to approach assemblies & components qualification

SUS Supplier

Process and Manufacturing
Product and Patient Knowledge
Internal Procedure and Controls
Risk Tolerence
Past Experience

Material/Component Knowledge
Assembly Qualification and Design
Manufacturing and Controls
Assembly handling best practices
Regulatory framework & industry trends knowledge
Experience across many customer processes

Collaboration is key to success

Extractables and Leachables

Extractables

- Extracted from plastic or elastomeric materials in solvents under aggressive conditions.
- Determined under “worst-case” conditions (Model Stream approach)

Leachables

- Compounds that leach from the plastic or elastomeric materials into actual drug product under normal use conditions.
- Determined with the product under normal processing/storage conditions

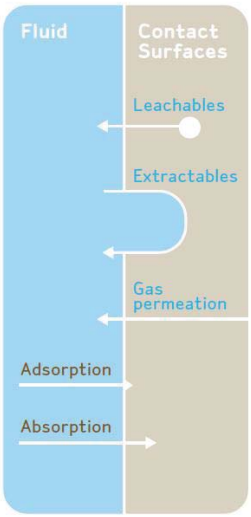


Figure 1. Possible interactions between fluid and its contact surfaces

Extractables & Leachables Testing Have Different Goals...

▪**Extractables Studies**:

To identify and quantify as many compounds as possible that have **the potential** to become leachables

▪**Leachables Studies**:

To identify and quantify as many compounds as possible that migrate from the filtration process or storage systems into the actual drug product

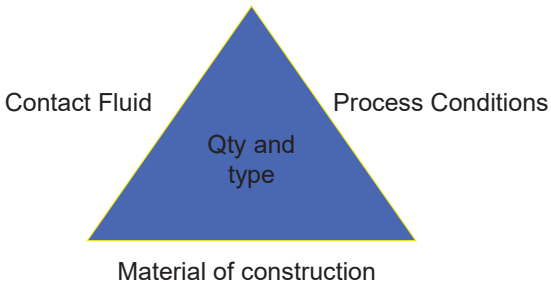
▪ **Leachables evaluation starts with a well defined extractables study.**

What are Extractable and Leachable Substances?

Oligomers
PVDF, PP, PE
Etc.

Additives and degredants
Antioxidants, UV stabilizers,
Slip agents, etc.

Residual Solvents



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MM Step-wise Approach Validation of SUS

1: Risk assessment / Criticality

2: Extractable Evaluation

3: Toxicity risk assessment / Patient Safety

4: Leachables or additional Testing

5: Assess Risk / Patient Safety

Supplier / end-user collaboration

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Setting up a V&Q strategy

- Collaborative FMEA analysis / Risk assessment based approach
  - Effectively mitigate potential risks
  - Ensure Regulatory approval
  - Avoid any delay, ….

- Global Validation Master Plan (VMP)
- Specific validation activities, studies and testing

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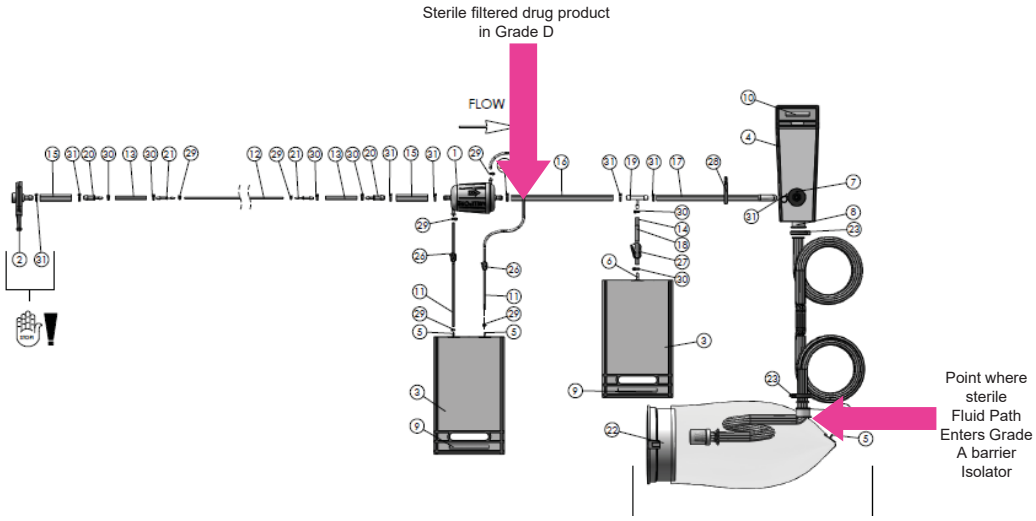
Case Study #1: V&Q of xx Final Fill Assembly



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Solution

Collaborative FMEA Analysis

Change Controls Assessment

Packaging Testing | Shelf Life | Sterilization Validation

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Solution

Qualification/Validation

- FMEA (process & Design & Changes/modifications)
  - Design (Component selection, use of assemblies at customer site)
  - Process (Manufacturing, Gamma Sterilization, Shipping)
  - Changes (Effect of changes on performed validation studies)
- High Sensitivity Integrity Test (Correlated to 30µm pore size)
  - Correlation to 30µm pore size using Aerosol testing
  - Qualification of HSIT test parameters
  - Pressure Decay test at higher pressure
- Packaging Validation (Complaint with ISTA 2A)
  - ISTA 2A test (vibration, drop, compression)
  - Bubble emision test (outer packaging bag)
  - Verification of Integrity after 2 years (Standard IT and HSIT)
- Shelf Life Validation
  - Using accelerated aging at 55 degC simulating 2 years shelf life
  - Verification of Integrity after 2 years (Standard IT and HSIT)

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Solution

Qualification/Validation

- Sterility Validation
  - 30x SUA Bioburden Test,
  - 10x Sterility Test Verification dose ISO11137-2,
  - 6x Bioburden LaCalhene bag using spore strips
- Correlation to MM‘s Quarterly Dose Audit
  - Component correlation to Monster Assembly
- Training
  - Design and components
  - Documentation: Drawing, Certificate Of Quality, Certificate Of Processing
  - Product Labels
  - Unpacking, Inspection, Installation
  - Operation
  - Removal
  - Operator Certification

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Outcome

“The inspectors concluded the inspection of our new manufacturing facility with no critical and no major observations while congratulating us for our accomplishments….
The inspectors acknowledged the thoughtful approach towards new technology, design, and the depth of qualification.
This is truly the success of our partnership!
We are happy to look forward to the next chapters of disposable usage in fill/ finish together with you! “
Email: C M, xxx Head

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SUMMARY

Keys for practical implementation of single use systems

1. ELIMINATION, PREVENTION, MONITORING, and CONTROLLING are keys to overall product safety
2. Key drivers for implementation of single use systems:
   - Eliminate high costs of cleaning cycles and validation
   - Quick change over time of equipment
   - Gain competitive edge and flexibility
3. Must start with facility conceptual design strong focus on daily operations and processing
4. Training and support by supplier is critical part of successful implementation of a single use template

CONCLUSION

- Many SUS readily available and thorough considerations needed
- Customers and vendors MUST work together from design to implementation to ensure success
- SUS must meet the processing and regulatory needs
- Vendors capable of validation support needed for regulatory compliant and product approval
- Qualified manufacturing process and application experts to help

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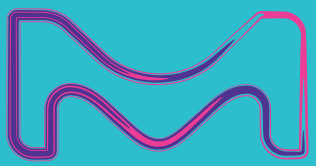
FUNDAMENTALS OF MICROBIOLOGICAL CONTROL AND ENVIRONMENTAL MONITORING FOR BIOPHARMACEUTICAL PROCESSES



Michael Payne
Merck Millipore

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Impact of microbiological contamination

Routes of contamination in the process

Risk Assessment and Mitigation Strategies

Filter locations and microbiological concerns

Questions asked during FDA & WHO inspections

Environmental monitoring

Microbiological control

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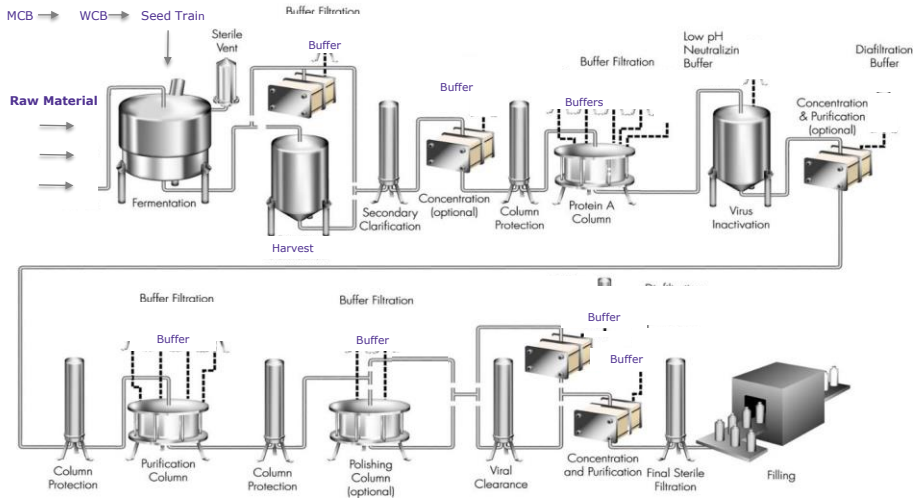
Overview of Generic Biological Manufacturing Process



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In-Process Contamination
Biologics

30	1-6	1-10
Percent	Months	Million Euro
*Average percent of process deviations caused by contamination**	*Length of time to complete an investigation*	*Average operations cost of microbial contamination*

Impact:
Interruption of patient product supply, delays in clinical development, batch loss, consent decrees, requalification studies, financial losses

*Sources Langer 2013, Wiebe 2014

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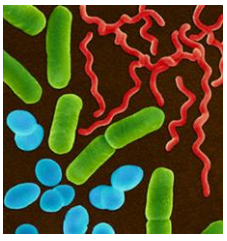
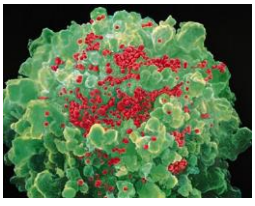
Contaminants of Concern in Biologics

Adventitious Agents

Microorganisms that have been unintentionally introduced into the manufacturing process of a biological product:

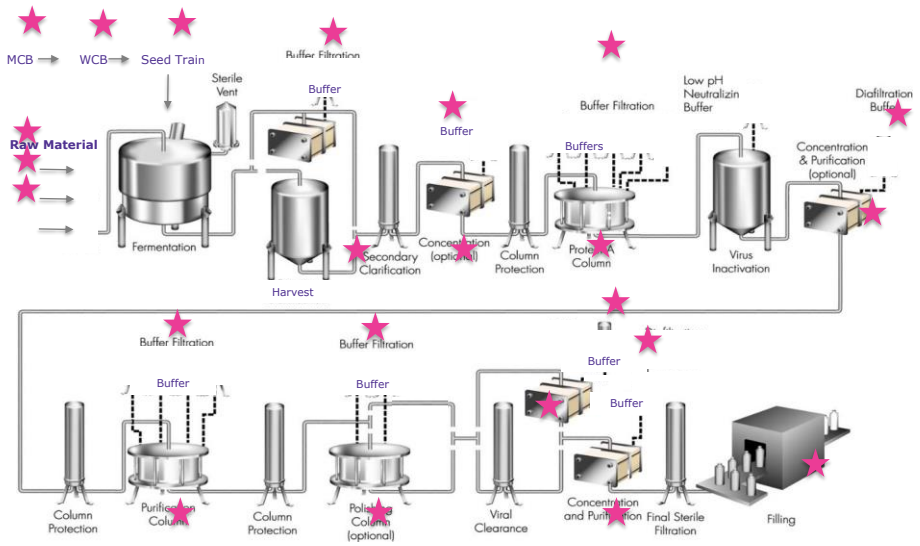
- Bacteria
- Fungi
- TSE Agents
- Virus





HIV infecting a human T cell

Routes of Contamination



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Key Points

Routes of Contamination

Many routes for microbial contamination

- Increased awareness of virus, mycoplasma, and *Leptospira* contamination in upstream processes

Intensive risk assessments could have prevented many of these contaminations

Raw Materials are a significant cause of contamination

Downstream contamination is often the result of:

- Improper cleaning or sanitization
- Suboptimal system design

Leverage supplier expertise during process development

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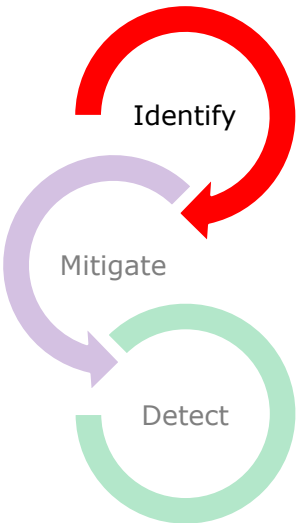
Risk Assessment: Identify



Assess extent of risk, ability to detect, and frequency of occurrence

Identify


Facility


Equipment

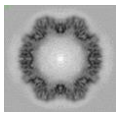

Process

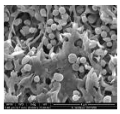

Materials

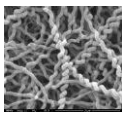

Utilities


Personnel

Each source is a potential entry point for microbial contamination


Minute virus of mice (MVM)
~18-24 nm


Acholeplasma laidlawii
< 0.2 µm


Leptospira species
0.4 µm x >>5 µm


Bacillus species
1 µm x 4 µm

Case Studies of Microbial Contamination in Biologic Product Manufacturing
Suvarna, K., Lolas, A., Hughes, P., Friedman, R. Biotechnology Manufacturing Team, Division of Manufacturing and Product Quality, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration

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Process Flow Raw Materials

Each step may introduce microbes into the process

- Handling
- Transport of materials in the facility
- Testing
- Sampling
- Transfer into different packaging
- Storage conditions
- Weighing
- Sieving
- Crushing
- Sifting
- Water transfer (cleaning, compounding)
- Compounding
- Mixing
- Hold times
- Dispensing
- Sampling
- Room Cleaning
- Equipment Cleaning
- Personnel Hygiene

How do I assess the risk of these parameters?

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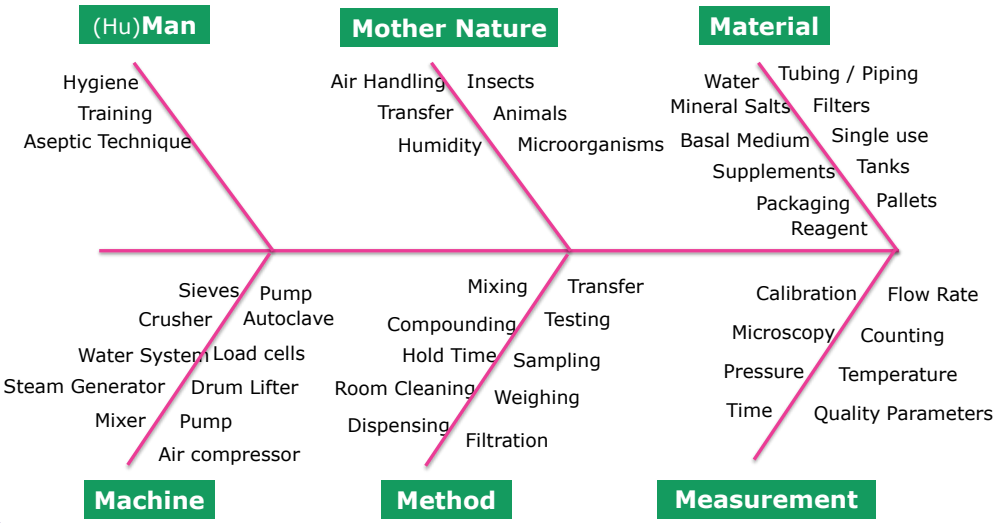
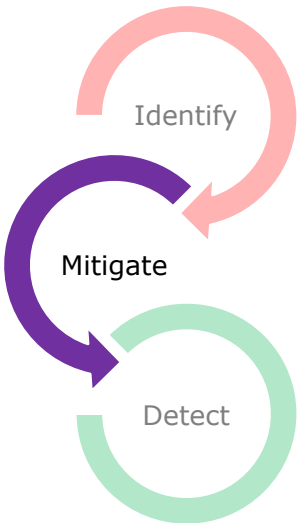
What process inputs could introduce contamination

Example: Cause and Effect Diagram – the 6 "M"s



Risk Assessment: Mitigate

Eliminate source or reduce likelihood of occurrence



Prevent Human Contamination

Strategies for prevention, mitigation and detection

Prevention

- Remove people from the environment

Mitigation

When people have to be in the environment

- Wear cleanroom attire
- Work in cleanrooms
- Properly trained personnel

Detection

- Viable air sampling
- Surface monitoring
- Personnel monitoring

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Prevent Raw Material Contamination

Raw Material Selection

Prevent

- Remove animal derived components
  - Caution! Serum-free does not mean mycoplasma free
  - Consider chemical free
- Recombinant alternatives to serum
  - r-Insulin, r-Transferrin & r-albumin
- Select raw material quality grade
  - Pharmaceutical grade versus analytical grade
- Audit vendor

Mitigate

- Pre-treat components
  - Choose treatments effective for viral and bacterial reduction

Detect

- Screen raw material with rapid tests
  - Caution! Sample sizes versus kG to tons of material

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Key Points
Mitigate

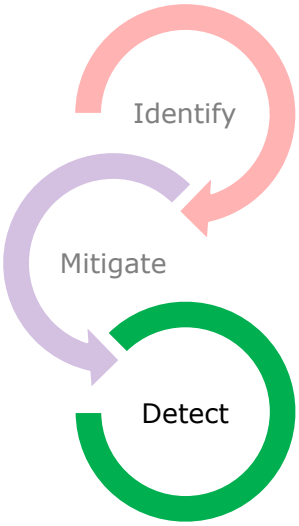
Prevention
- Best option wherever possible

Containment
- Personnel Control
- Single Use Technologies

Raw Material Selection
- Vendor qualification
- Pre-treatment

Downstream Processing
- Viral Clearance
- Filtration
- Sanitization, cleaning and storage

Risk Assessment: Detect



Determine location, frequency, and limits of detection

Sterile or virus-free is only as good as the detection method used

Microbiological Detection

Classical Methods

Most developed in the 19th century

- Microscopy
- Growth-based methods

Benefits

- Easy to implement
- Easy to qualify
- Larger sample volumes possible

Limitations

- No universal medium or growth conditions
- Only detect those microbes capable of replicating in the chosen test medium under the specified conditions
- Can take days to weeks for a result

Rapid Methods

Developed over the past 30 years but slow adoption rate

- qPCR
- TMA
- Microcolony growth detection

Benefits

- Rapid results
- Higher sensitivity for equal volume compared to classical methods

Limitations

- More extensive validation
- Higher expertise required
- False positives doesn't distinguish viable cells
- Small sample size
- Often destructive
  - Split samples needed for identification

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Limits of Detection

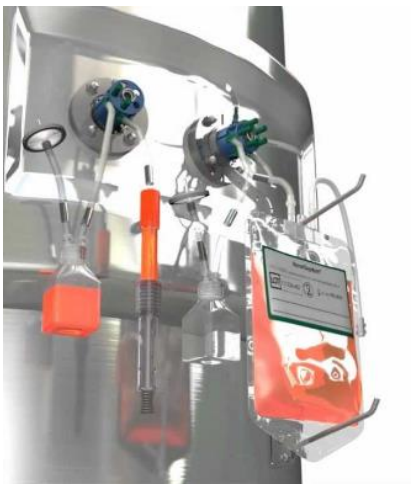
Sampling Volumes

Sampling

- Vessel Liters to 10,000+ Liters
- Sample Volume
  - Less than 1 Liter

Assay

- Removed from sample volume
- Milliliter to microliter



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Limits of Detection

Sampling

Assume a 1 L sample from a 10,000 L Bioreactor
Assay requires a 1 mL sample for testing

CFU per Liter	10	1,000	10,000
CFU per mL	0.01	1	100
Probability an organism will **NOT** be detected in the sample	**0.99**	**0.9**	**0.37**

Assay Sensitivity

LOD PCR for *Leptospira:* 100 CFU (equivalent)
LOD PCR for Mycoplasma: 1-10 CFU (equivalent)
LOD by light microscopy @ 400 x: 10^5 to 10^6 cells
LOD $TCID_{50}$: 15 to 10^4 $TCID_{50}$/mL

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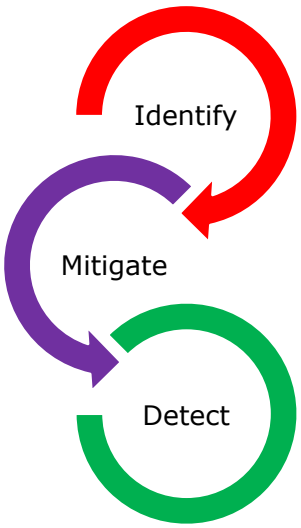
Risk Assessment to Prevent Contamination



Assess extent of risk, ability to detect , and frequency of occurrence

Eliminate source or reduce likelihood of occurrence

Determine location frequency, and limit of detection

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Routes of contamination in the process

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Microbiological control

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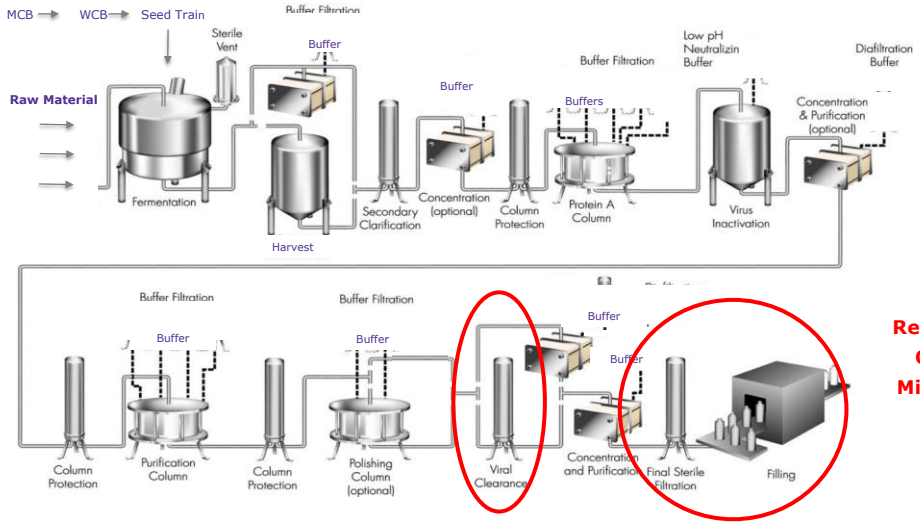

Regulatory and Compliance Microbiological FOCUS

MICROBIOLOGICAL RISK HAMMOCK

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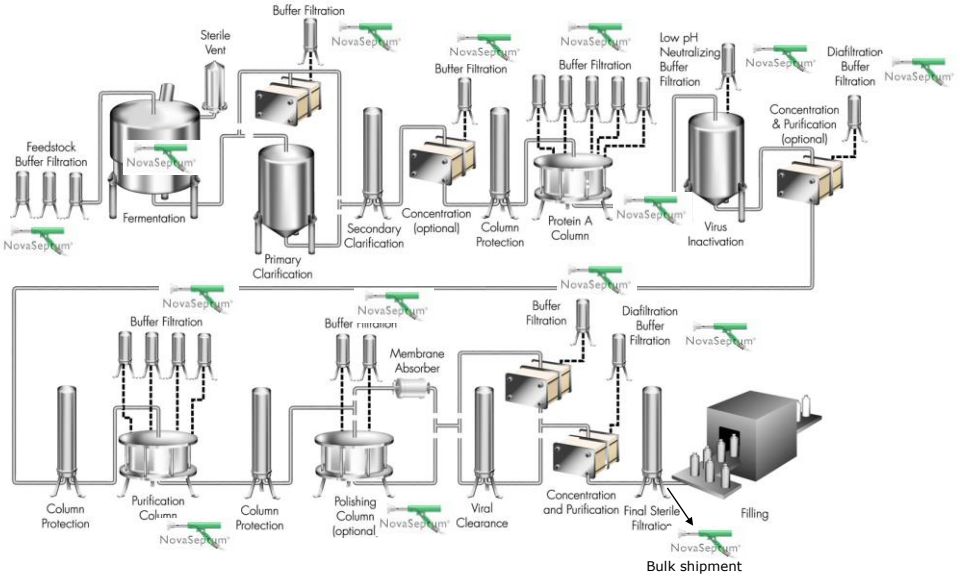
Sampling Locations



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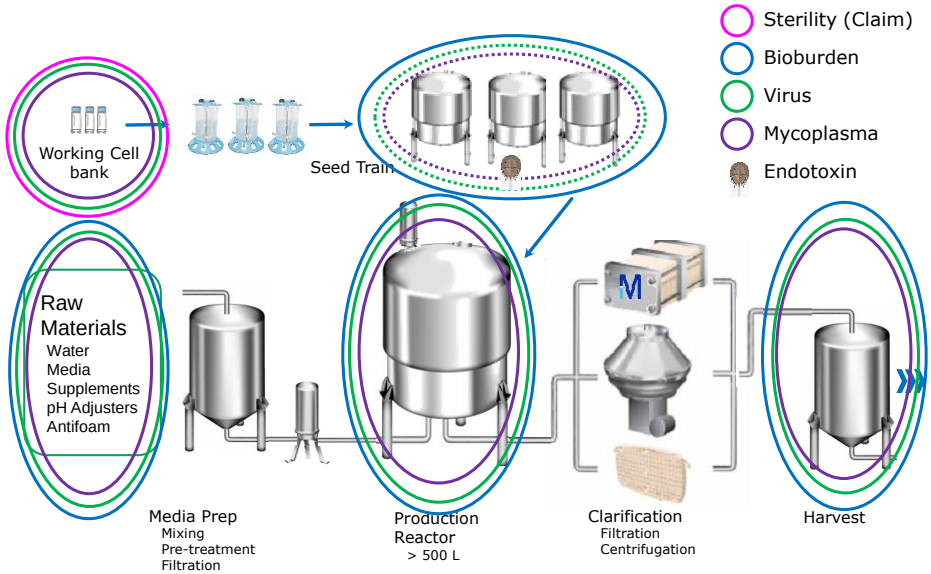
Biopharmaceutical Process
Upstream

For illustrative purposes. Regulatory requirements, industry guidance and previous data will factor into a microbiological sampling plan.



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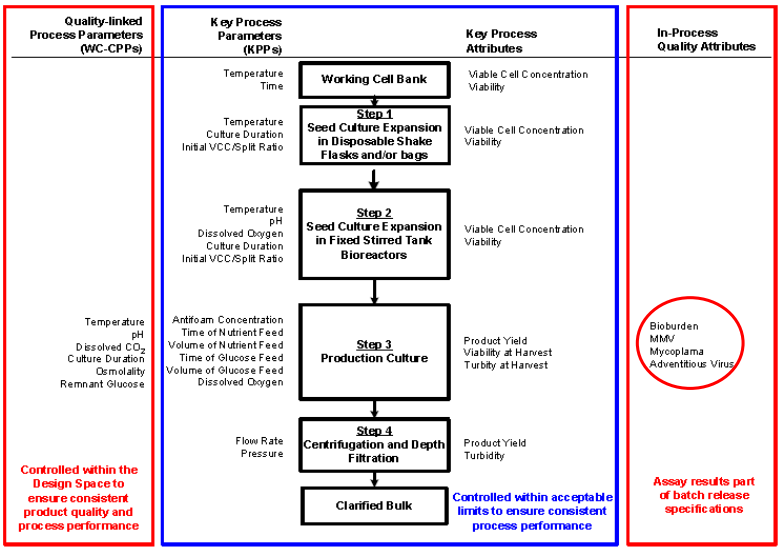
Control Strategy for Upstream Processes



From A-Mab

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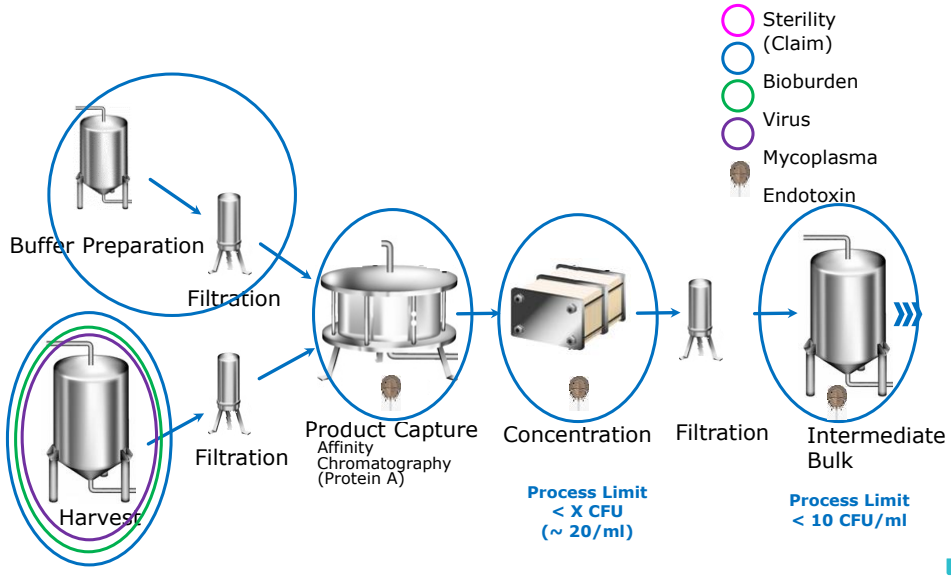
Biopharmaceutical Process

Downstream Purification (1)

For illustrative purposes. Regulatory requirements, industry guidance and previous data will factor into a microbiological sampling plan.



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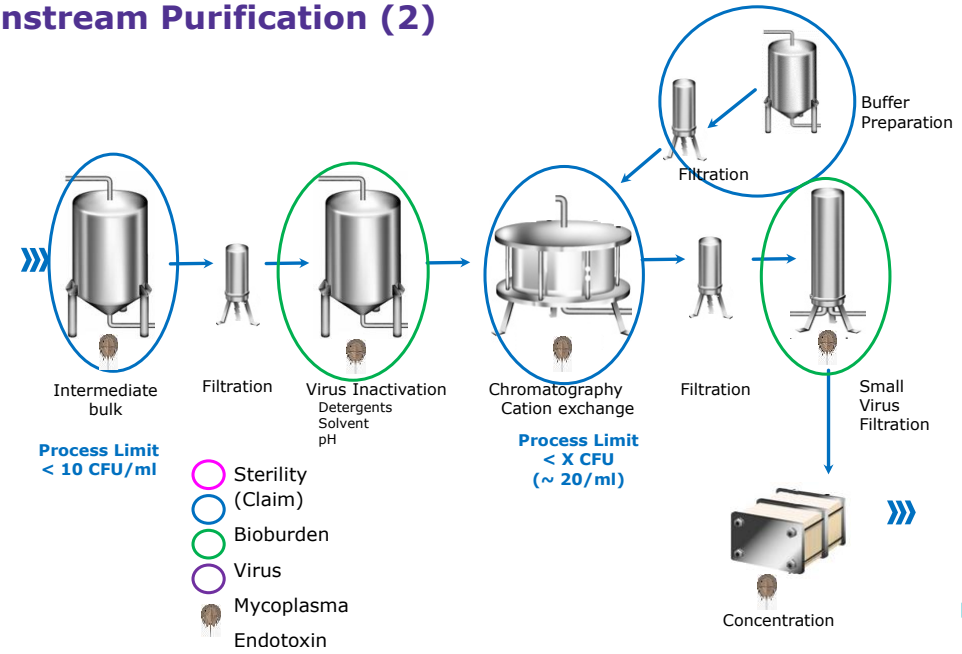
Biopharmaceutical Process

Downstream Purification (2)

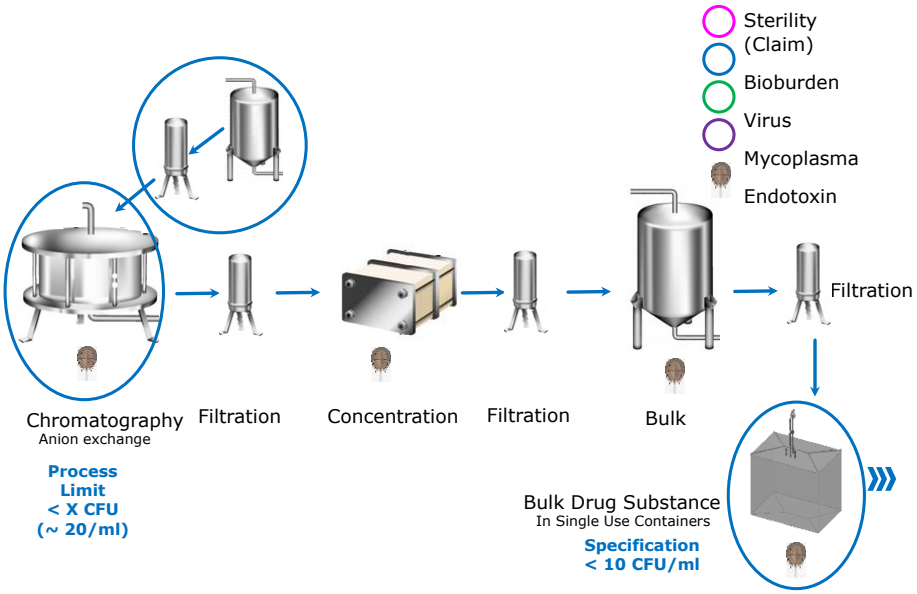
For illustrative purposes. Regulatory requirements, industry guidance and previous data will factor into a microbiological sampling plan.



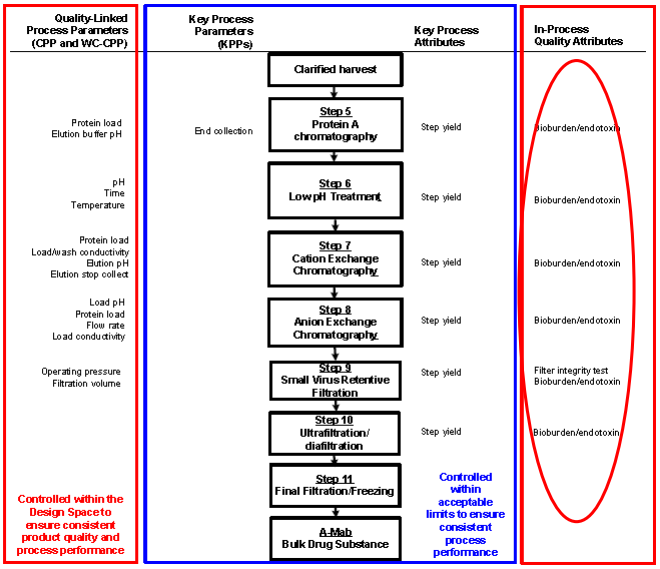
Biopharmaceutical Process

Downstream Purification (3)

For illustrative purposes. Regulatory requirements, industry guidance and previous data will factor into a microbiological sampling plan.



Control Strategy for Downstream Processes



From A-Mab

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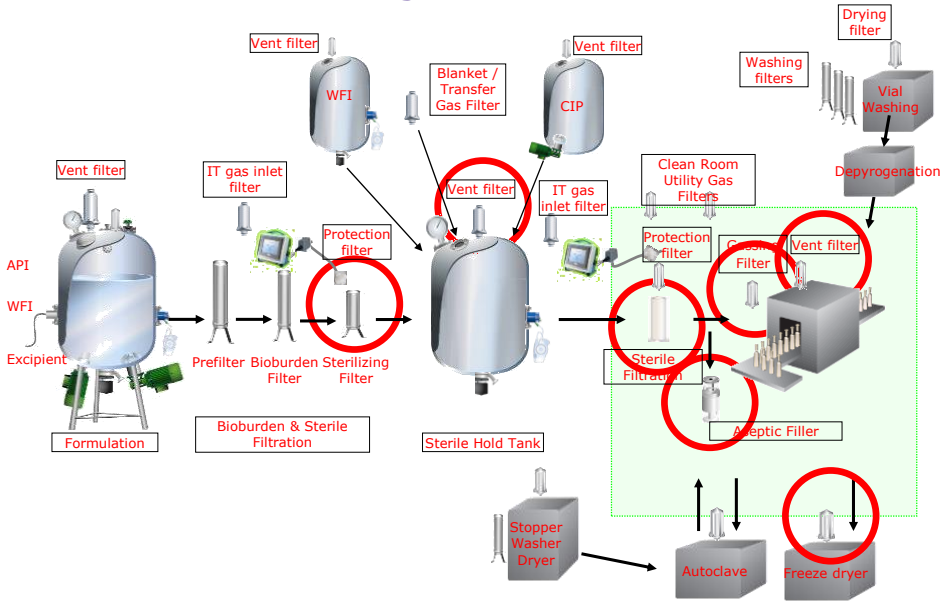
Filters in the Formulation / Filling Suite



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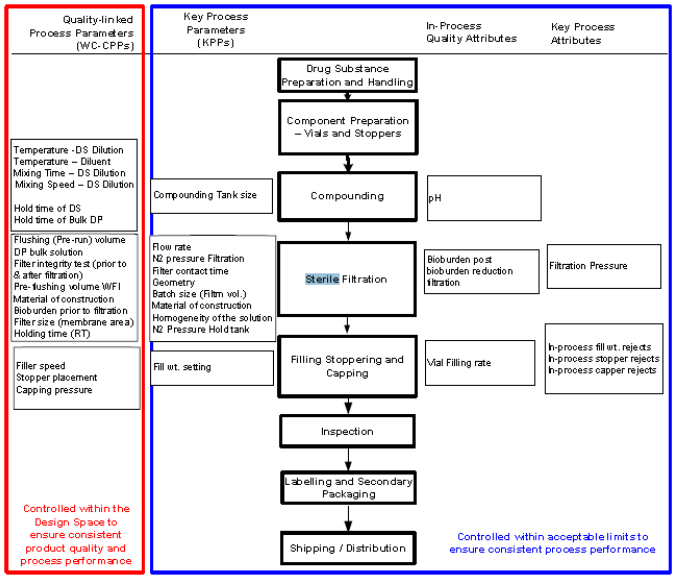
Control Strategy for Drug Product Processes



From A-Mab

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FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL

PROGRAM 7356.002A

CHAPTER 56 - DRUG QUALITY ASSURANCE

SUBJECT: STERILE DRUG PROCESS INSPECTIONS	IMPLEMENTATION DATE: November 5, 2012 COMPLETION DATE: November 5, 2015

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry codes 54, 56 and 60-66 inclusive	Domestic / Foreign Inspections: 56002A (Full Inspection) 56002I (Abbreviated Inspection) Related PACs 56002 56002C 56002M

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SAMPLE COLLECTION

Collect *documentary or physical* samples, including 'in-process samples where possible, to document any suspected adulteration and misbranding problems encountered during the inspection.
If microbiological contamination is suspected, document where possible the conditions which could contribute microbiological contamination to the product *both by collecting records and physical samples taken aseptically at points where such contamination might occur, such as from the WFI system.
Products found positive on initial sterility testing should also be considered for sampling.

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Examples of Questions during FDA Sterile Drug Inspections - 1

35. Does the firm have a written monitoring program for classified areas that included a scientifically sound sampling schedule that describes sampling locations, their relation to the working level, and frequency? Describe the basis for the sampling program.

36. Are both viable and non-viable particulate samplings performed in all classified areas during production?

37. Report the frequency of viable sampling using "active" sampling methods for:

a. exposed product areas

b. filling areas

c. surrounding areas

38. Report the limits used, length of sampling period, and if sampling is done during production or at rest.

39. Report the type of viable sampling equipment use (STA, Centrifugal sampler, etc.)

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Examples of Questions during FDA Sterile Drug Inspections - 2

40. Does the firm have data on the ability of these samplers to recover organisms without deleterious effect on survivability such as through impact or dessication of organisms or media?

41. Report the actual volume of air sampled per location.

42. Are settling plates used? Describe the length of exposure period; sampling frequency; location (including proximity to critical operations); microbial limits.

43. Are recovered microorganisms routinely identified? To what level (genus, species)?

44. Are the culture media used in the viable monitoring program shown to be capable of detecting molds and yeasts as well as bacteria by means of growth promotion tests? Is anaerobic monitoring performed?

45. What media are used?

46. Are deactivators (e.g., penicillinase) use for antibiotics or other bacteriocidal/bacteriostatic substances? Has the firm shown that these are effective? (Are records available? Are calculations correct?)

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Examples of Questions during FDA Sterile Drug Inspections – 3

47. What incubation periods are used and at what temperature?
48. How often is non-viable particulate sampling performed in classified areas:
a. exposed product areas
b. filling areas
c. surrounding areas
49. What sampling device is used? What volume of air is sampled?
50. How many samples are collected per location? Are results averaged?
51. When was sampling equipment last calibrated?
52. Were environmental sampling results within specifications during the manufacture of the batches of the selected drug product? (Describe any deviations and firm's response.)
53. How often is monitoring performed on filling room personnel?
54. What are the firm's alert and action limits for personnel monitoring?
55. What type of monitoring is done?

Examples of Questions during FDA Sterile Drug Inspections - 4

56. Does the firm have written procedures for the monitoring of product contact surfaces?
57. What type of contact surface monitoring devices are used (RODAC, swabs, etc.)?
245. Briefly describe the aseptic filling processes from preparation of bulk liquid product to filling and sealing of final dosage form, including the environmental monitoring performed in critical areas during actual production (e.g., how are Class 100 conditions maintained., where are the sampling sites; is bioburden testing performed on the bulk product?)
246. Review monitoring data for several representative months of production, including the period during which batches of the selected drug product were prepared. Were results within specifications? If not, what was the firm's response?
268. Are microorganisms from positive vials identified according to genus?
269. Are such microorganisms correlated to those found during environmental monitoring?

WHO Guide for inspection of manufacturers of biological products

Is there bioburden monitoring of starting, raw, and in-process materials before sterilization?

Are alert and action limits established for environmental monitoring, and are effective measures taken when limits are exceeded?

Is there monitoring of air for microbes?

Is there monitoring of air for particulates?

Is there monitoring of surfaces for microbes?

Is there monitoring of compressed gas for microbes?

Is there monitoring of compressed gas for particulates?

Is there monitoring of water for microbes and endotoxins?

Is there a defined schedule for environmental monitoring? Is it appropriate to each stage of the production process? Do the records indicate the schedule is followed?

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cGMP Sterilizing Filtration Systems Over the Past 20 Years

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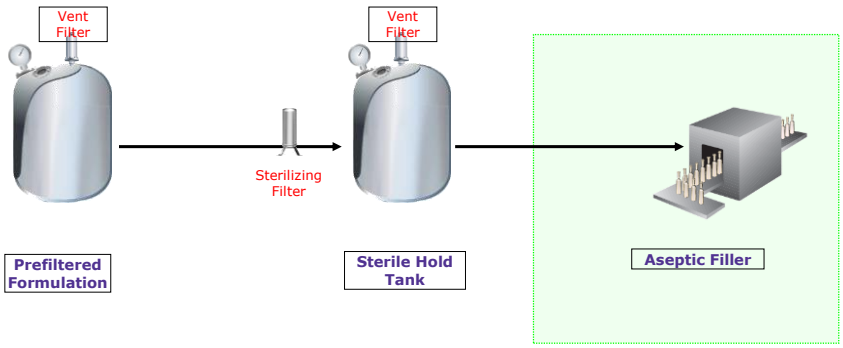
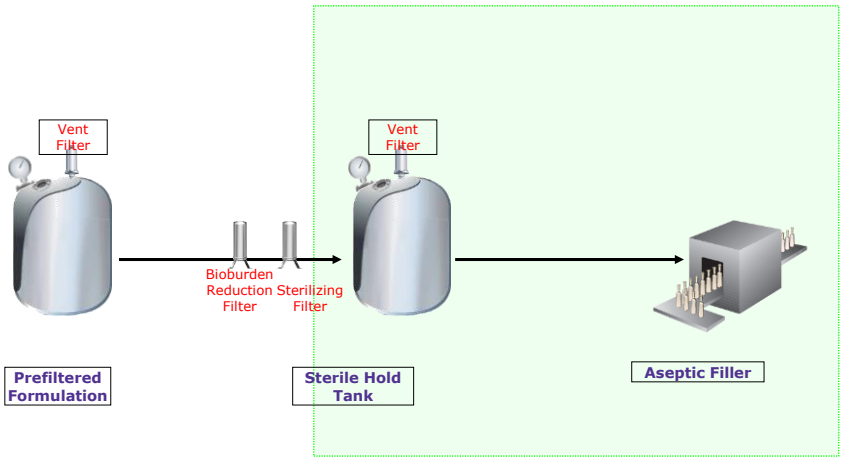
Generic Sterile Formulation / Filling Suite
- Traditional style sterile filtration system

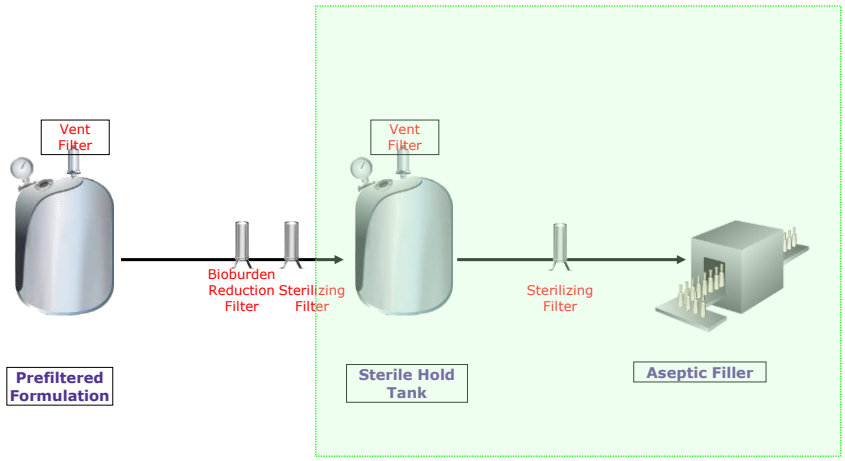


Generic Sterile Formulation / Filling Suite
Traditional style sterile filtration system *with bioburden reduction filter*



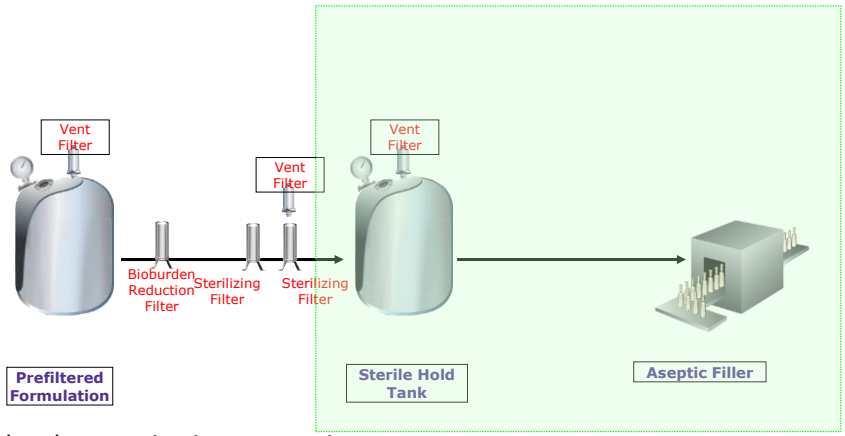
Monitor bioburden for each batch, state maximum value or if value is >10 CFU/100ml, use a bioburden reduction filter

Generic Sterile Formulation / Filling Suite
Traditional style sterile filtration system with bioburden reduction filter and EMA compliant



Bioburden monitoring as previous
Use a second microorganism retentive filter as close as possible to the final use

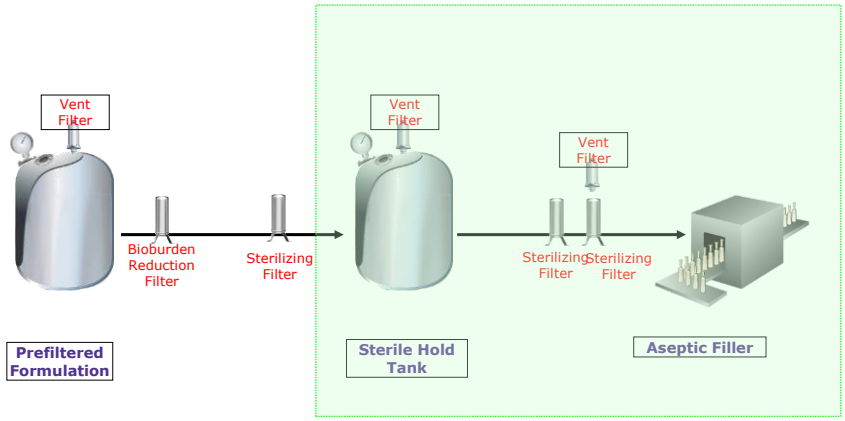
Generic Sterile Formulation / Filling Suite
Traditional style sterile filtration system with bioburden reduction filter and FDA compliant for "at risk" product (redundant final filtration system)



Bioburden monitoring as previous
Justify use of a sterilizing filter and a second sterilizing filter not being as close as possible to the final use and operation of sterilizing filter in Grade C

Generic Sterile Formulation / Filling Suite

Traditional style sterile filtration system with bioburden reduction filter and EMA compliant and FDA compliant for "at risk" product (redundant final filtration system) at POU



Bioburden monitoring as previous
Use a sterilizing filter and a second sterilizing filter as close as possible to the final use

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PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 032-2
8 January 2010

RECOMMENDATION

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

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4.5 Bioburden monitoring. Comment on Section 80 – 1

80. The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products.

The contribution to bioburden of the various raw materials and packaging materials together with the manufacturing processes prior to the sterilisation step should be understood and controlled.
A monitoring and control strategy including periodic monitoring and trending of bioburden prior to any bioburden reduction step should be established and justified on the basis of process risks.
Volumes sampled should be justified and take account of the expected level of contamination

The bioburden should at least be determined for the product prior to the final sterilization step.

Acceptance criteria for bioburden must be based on the sterilising step, a sterility assurance level of 10-6 must be met. The results of the bioburden assays must be present before release (unless an overkill cycle is used for terminal sterilisation).

A risk assessment should be performed in order to determine the need for endotoxin studies. When needed, endotoxins should be determined also for the units of product that were filled the last.

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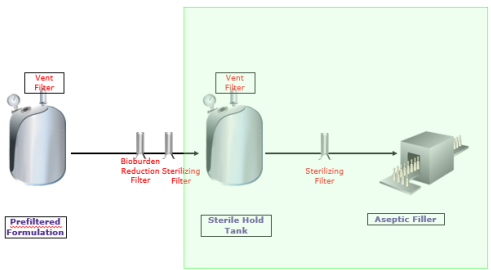
4.5 Bioburden monitoring
Comment on Section 80 - 2

Aseptic operations: For sterile filtration, filter efficacy studies must be taken into account when determining the acceptance criteria for the bioburden prior to filtration.

This means that if two subsequent filtration steps are used, product has to be sampled prior to the last filtration step, if technically possible, e.g. first filtration into bulk tank, second filtration immediately prior to filling.

However, if a system of two filters with redundancy is used (the second filter is used for security, if one fails the required SAL is still achieved), sampling should be performed upstream of these filters in order not to compromise the filtration step.

The company has to justify its approach
if sampling is done before the first filtration step.



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Impact of microbiological contamination

Routes of contamination in the process

Risk Assessment and Mitigation Strategies

Filter locations and microbiological concerns

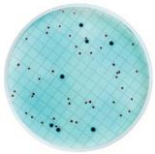
Questions asked during FDA & WHO inspections

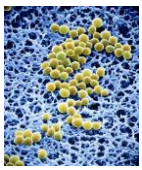
Environmental monitoring

Microbiological control

Introduction to the application

Application: **Bioburden** testing in liquid san
Indirect & individual **Enumerat**
Micro-organisms **colony** counti

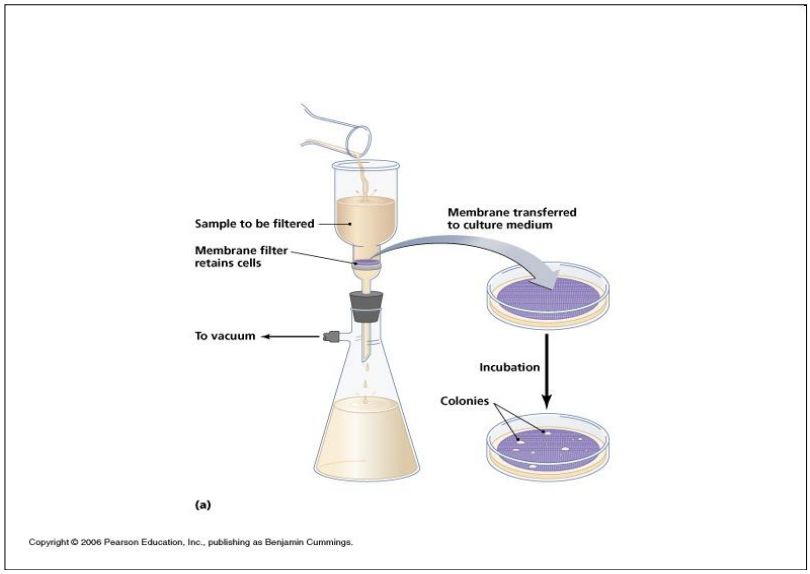




Technology: Membrane filtration

Samples: Pharmaceutical water types
Process water
Final products

Technology overview: membrane filtration



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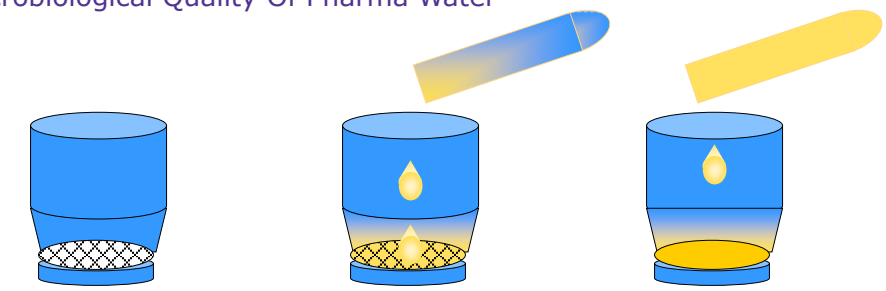
Microbiological Quality Of Pharma Water



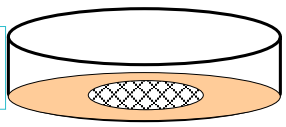
Sterile Filter in funnel

Add Sample

RINSE

Transfer membrane on media

Incubate



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Membrane filtration positioning

Membrane Filtration

Advantages

- Rinse away inhibitory or preservatives agents
- Sample concentration :
  - high volume sample can be filtered, not aliquot
  - Statistically more valid
  - More sensitive: 1 CFU/volume

Limitations

- Non filterable samples
- High solids may plug membrane

Direct Inoculation

Advantages

- Fast, Easy
  - Wide selection of media
  - Non-filterable samples

Limitations

- Limited sample size: lower sensitivity
- Small Colonies
- Inhibition issues

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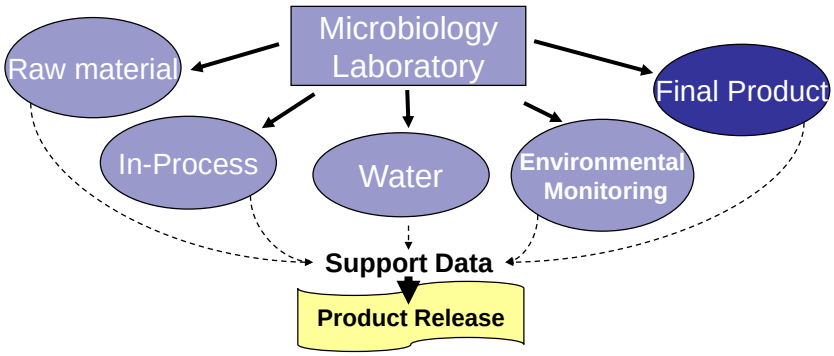
QC testing in microbiological laboratory



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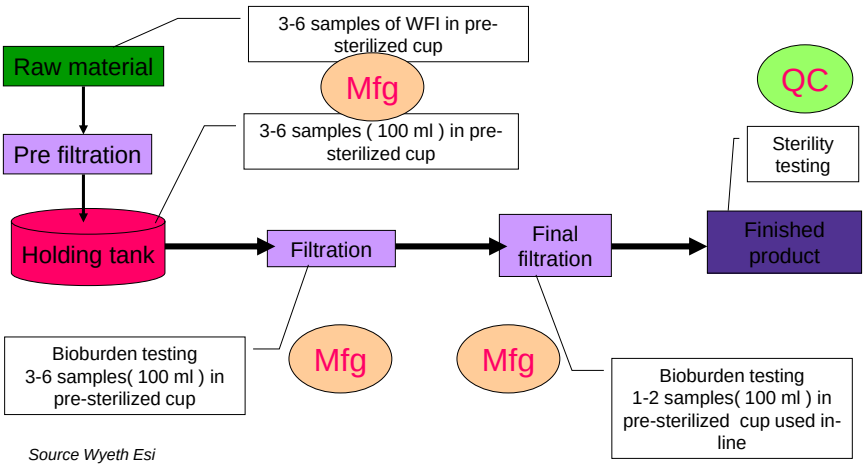
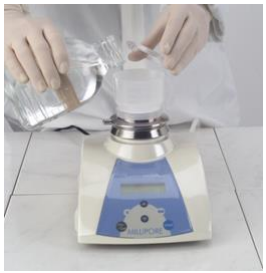
Generic workflow



Source Wyeth Esi

Technology



Filtration step

Transfer on Media

Funnel Removal

Filtration unit based on a membrane welded under sterile funnel that brakes-off after the membrane is adapted to a media cassette.

Technology

Incubation step

Result

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Water testing & Pharmacopeia

Microbial Specifications

- ► EP:"... using at least 200 ml of water for injections (WFI)..."
- ► Total count: action level tolerated for value < 10 CFUs/100 ml (EP & USP)
- ► Media : PCA (USP), R2A (EP)
- ► Free of pathogenic & source of endotoxin (Pseudomonas, gram negative)

250mL Funnel

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High Quality water

FDA, Guide to inspections of High Purity Water Systems

"“...for Water for Injection, it is expected that they be essentially sterile. Since sampling frequently is performed in non-sterile areas and is not truly aseptic, occasional low level counts due to sampling errors may occur...”

WFI is considered as sterile. Meaning that any contaminants or positive results should be regarded as an important watch out for the production (critical impact if customer has false positive due to sampling or QC test failure).

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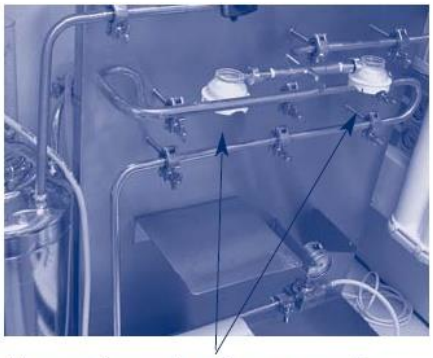
On-line Samplers & sampling valve



on-line filtration samplers

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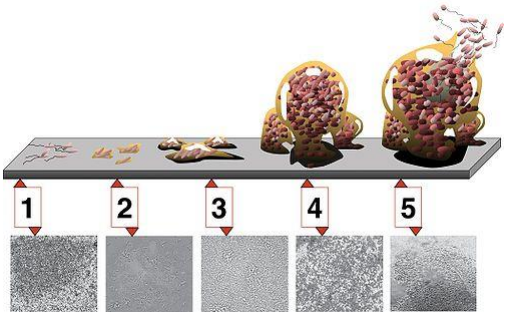
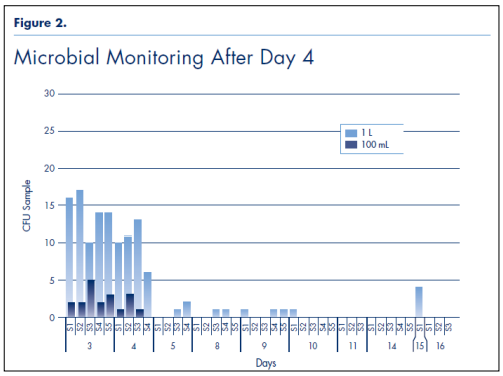
Biofilms



Salmonella enterica



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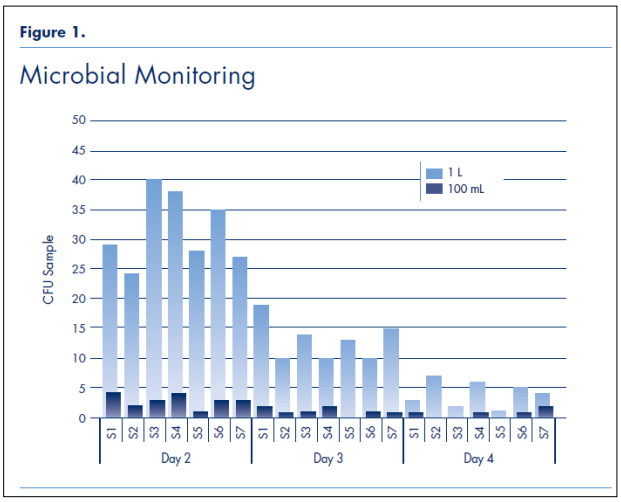
Sampling volume



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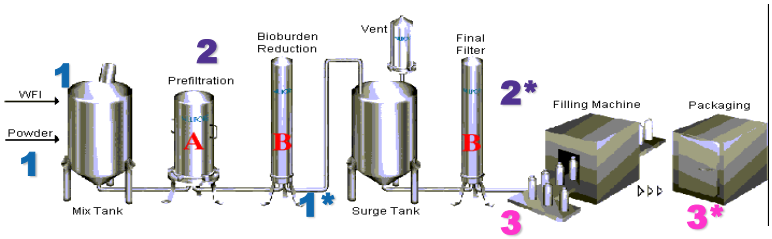
Microbiological Monitoring Synergies



1	Bioburden/Microbial Limits Test of Raw Materials
1*	Bioburden/Microbial Limits of Inprocess Samples
2	Environmental Monitoring of Clean Rooms
2*	Environmental Monitoring of Equipment
3	Sterility Testing of Components (container)
3*	Sterility Test of Final Product

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Impact of microbiological contamination

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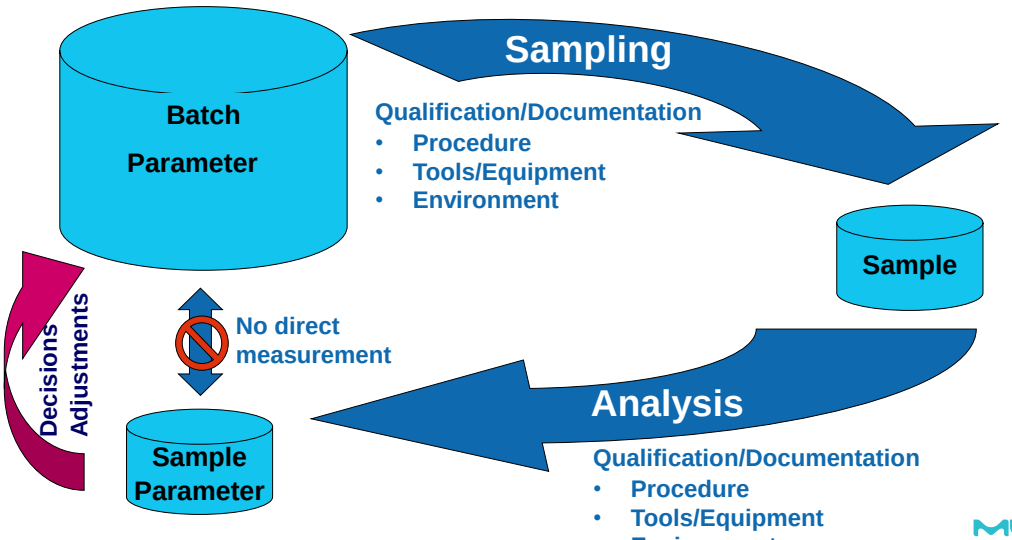
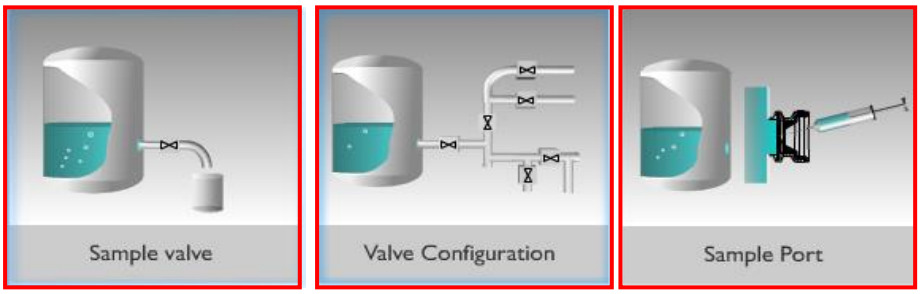
Sampling – A Difficult Process



Common sampling methods



Some Current Sampling Methods

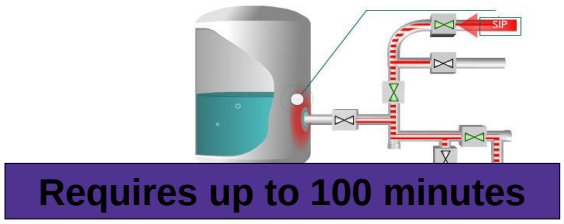
Steam on Sampling – Using Glass bottles

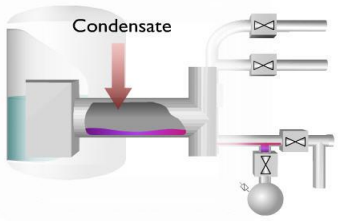
Challenges:

- CIP/SIP between samples
- Heat-up tank wall
- Condensation Issues
- Inconsistent
- Not Representative
- Low Sampling Frequency
- Slow (Assembly)

Advantages:

- Flexible, multiple samples, compatibility





Some Current Sampling Methods

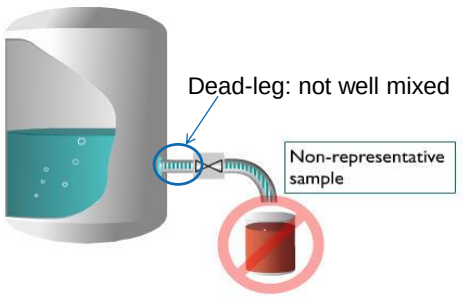
Using a Sample Valve

Challenges:

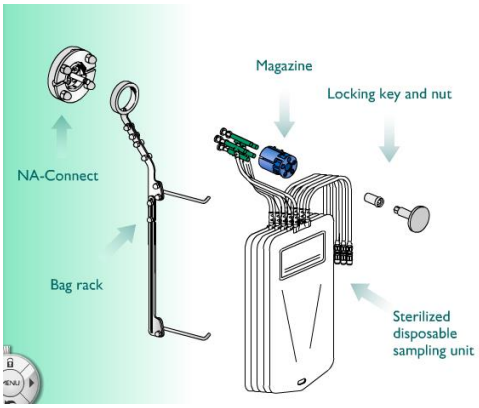
- Dead leg
- Pre-flush Needed
- Contamination Risk
- Difficult to Sterilize
- Not Representative

Advantages:

- Flexible, multiple samples



Set up



Step 1: Assemble sample units and attach to tank

Step 2: Perform CIP/SIP

Begin Sampling

Step 3:

- Press the trigger to sample
- Needle punctures the silicone diaphragm
- Release the trigger when sampling is complete

Step 4:
Seal and Separate

Step 5
Ready for Testing

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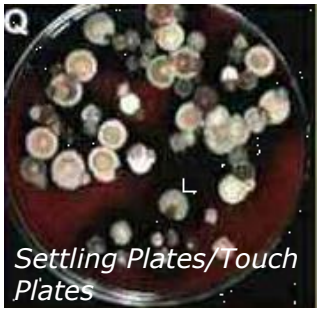
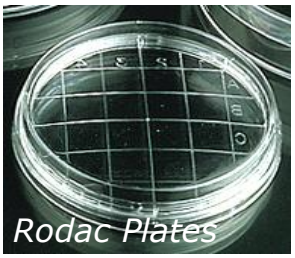
Environmental Testing -Surfaces and Personnel





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Environmental Monitoring Expectations

What it is

- 2000 -"Gives the best chance of detecting TRENDS that would cause product sterility problems." Friedman, PDA Scientific Conference on EM and Aseptic Processing
- 2002 - Establishes if the Aseptic Processing Environment is in a Sustained State of Particulate Control. comments on Aseptic Processing Guidelines Feb.2002

What it is not

- Quantitative assessment of the precise microbial population in the environment.
- A Sterility Test.

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Significance of Environmental Monitoring

Humans constantly shed both viable and non-viable particles

- Skin Cells: Average human sheds 10,000,000 skin cells/day
- Clothing and body hair fibers: Sitting still generates 100,000 particles/min

Non-viable particles and fibers can transport native microbes to surfaces and products

Estimated ratio of Non viable particles to Viable Particles

- 1500 : 1
- 400,000 viable particles in this room in 30 minutes!

Environmental Monitoring tests for <u>Viable</u> particles in air & on surfaces including personnel

Personnel are the greatest risk in Aseptic Processing

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Key Elements of an EM Program

Proper Selection of Sampling Sites

- Where is product most at risk

Verify Testing Methodology

- Growth and Recovery
- Assumptions of hazards and risks-static versus dynamic

Establish Action and Alert Level

- Based on historical & validation data & regulatory recommendations
- Identification of Contaminant
- Maintain trend data

Documentation

- Training, Validation and Investigation

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Where to Sample - Site Selection

Sites having greater opportunity for contributing bioburden to the product

- FDA Guideline, facility design, validation data

Sites most prone to microbial proliferation

- Historical data
- Most difficult areas to clean or sanitize identified in PQ

Statistical design (Calculations Standard 209E)

- Air Monitoring based on surface area calculation
- **A / $(N_c)^{0.5}$** or **A/25**, whichever is less

Not always practical at the most critical location

- Risk of contamination during sampling

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Examples of Sampling Sites (PDA No. 13)

System	Site
Surface (Equipment)	Filling line, Control panels, Tanks
Surface (Facility)	Floors, Handles, Walls, Curtains, Doors , Drains
Laminar Air Flow (Hood)	Near high activity areas
Environmental Air	Close to vents, Filling and Work Areas
Personnel	Gown, Finger impressions

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Minimum Recommended Monitoring Frequencies

	Grade A	Grade B	Grade C
Non viable particles	Each shift	Each shift	Monthly
Viable Particles	Each shift	Each shift	Weekly
Settle Plates	1 plate/hr	Each shift	Not recommended
Contact Plates	Daily	Weekly	Monthly
Swabs	Daily	Weekly	Monthly
Personnel	Each shift	Each shift	Not recommended

USP <1116> Microbiological evaluation of clean rooms,
EU GMP Annex I , Draft Aseptic Processing Guidelines

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Isolators are Not Exempt

VHP residuals can inhibit microbial growth

Isolator interior considered a critical zone

PDA Technical Reports offer guidance:
Frequency:
once/shift for isolator
weekly for isolator support area

Viable Limits :
0.1 cfu/ft^3 for isolator
5.0 cfu/ ft^3 for isolator support area

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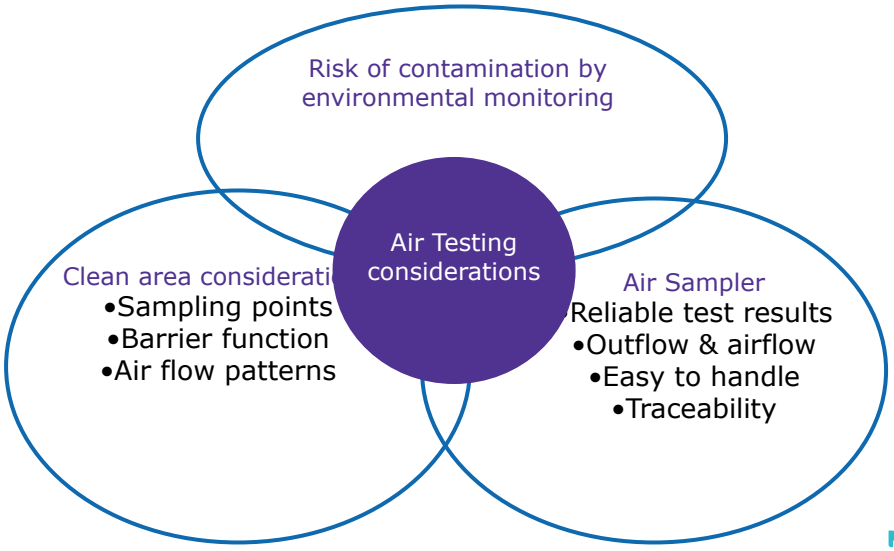
Air testing



Viable Air Monitoring Testing Methods

Passive

Gravitational settling

Active

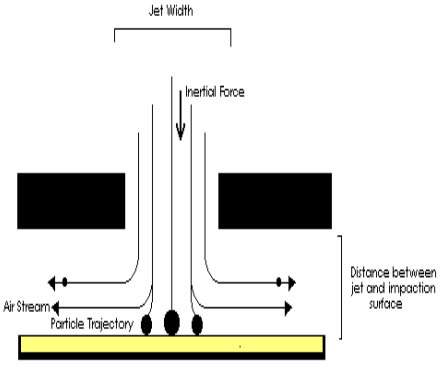
Inertial Impaction

Centrifugal Impaction

Liquid Impingement

Size Exclusion

Electrostatic Deposition



Air Samplers for Isolators

- Inertial Impaction Methodology
- Fast (1 m^3 in < 7 minutes)
- ~1000 holes minimizes overlapping colonies
- Device features: portable, programmable sample volume, & time delay
- Isokinetic Sampling in Isolator
- Enhanced media for recovery in presence of VHP residuals
- Validation Protocols & on-site validation

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Specifications for Viable Counts

Cleanroom Class		USP 25		EU GMP	FDA 1987	
SI	US	cfu/m^3	cfu/ft^3	cfu/m^3	cfu/m^3	cfu/ft^3
M 3.5	100	<3	<0.1	<1 (A) 10 (B)	≤ 3	≤ 0.1
M 5.5	10,000	<20	<0.5	100	N/A	N/A
M 6.5	100,000	<100	<0.25	200	≤ 88	≤ 2.5

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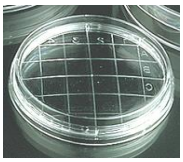
Surface Testing



Sample Sites
Equipment-
Sites of operator contact:connections, handles, consoles
Product risk: plugs, bowls
Equipment used in maintenance, monitoring, cleaning facilities
Difficult to clean crevices and corners

Personnel
Gowns (neck and torso) & Gloves
Glove are considered a critical area - especially in isolators

Methods
Contact plates
Swabs
Rinse

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Operation Limits for Surfaces

	Surface Cfu / 55mm contact plate *	
	US	EU dynamic
Grade A Class 100	3	<1
Grade B Class 10,000	5 10 (floor)	5
Grade C Class 100,000	_	25
Grade D	_	50

USP <1116> & EU GMP Annex 1

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Limits for Personnel

	Personnel Gloves Cfu / contact plate		*Personnel Gown Cfu / contact plate*	
	US	EU dynamic	US	EU dynamic
Class 100/A	3	<1	5	_
Class 10,000/B	10	5	20	_
Class 100,000/C	_	_	_	_

USP <1116> & EU GMP Annex 1

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Trend Analysis of Data

EM Data is measurement of process performance

- No automatic batch rejection if limits exceeded

Alert Level

- Background "noise" or occasional excursions
- Aseptic areas are not sterile, counts are expected
- If a trend is detected investigations should be initiated

Action Level

- Indicative of process drifting out of control
- All breeches require thorough investigation with organism ID
- Corrective actions established and implemented

483's over past 18 months suggest customers

- Fail to investigate OOS Environmental Data

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Example of Historical Environmental Monitoring Approach

Air - Conduct Viable and Non-Viable Testing - from

- Center of the room

Surfaces - Viable - from

- Center of each wall
- Floor - corner of each room, center of room

What is the justification for this choice of locations?

Comparison with Risk Based Approach to Environmental Monitoring

- Use MBWA approach (management by walking around) in each room/area if possible
- Review personnel flow
- Review material flow
- Identify potential sample site locations based on activity risk
- Assess likelihood of process contamination
- Focus on open processes
- Don’t forget closed processes - People likely largest contributors of room contamination if closed process
- Check for liquids or possible presence of water
- Review potential contamination from other pharmaceutical products
- Don’t be driven by the number of sample locations – focus on identifying and reducing the number of potential contamination sources

Use Advice from PDA TR13 *Fundamentals of an Environmental* Monitoring *Program*

Factors to consider in selecting sites for routine surveillance are:

- At which sites would microbial contamination most likely have an adverse effect on product quality?
- What sites would most likely demonstrate heaviest microbial proliferation during actual production?
- What sites would represent the most inaccessible or difficult areas to clean, sanitize, or disinfect?
- What activities in the area contribute to the spread of contamination?
- Would the act of sampling at a given site disturb the environment sufficiently to cause erroneous data to be collected or contaminate product?

WHO Advice on Environmental Monitoring Limits and Frequency for Vaccines

Table 4. WHO recommended limits for microorganisms during operation[4]

Grade	Air sample (CFU/m^3)	90 mm diameter settle plates (CFU/4hours)	55 mm diameter contact plates (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	-

Table 5. Microorganism *in-operation (dynamic)* routine monitoring frequencies

Classification	Volumetric(2)	Settle plate(2)	Contact plate	Glove print
Grade A (filling operations)[1]	Once per shift	Once per shift	Once per shift	Once per shift
Grade B	Daily	Daily	Daily	Daily
Grade C	Weekly	Weekly	Weekly	N/A
Grade D	Monthly	Monthly	N/A	N/A
UDAF in B	Once per shift	Once per shift	Once per shift	Once per shift
UDAF in C	Weekly	Weekly	Weekly	Weekly
UDAF in D	Monthly	Monthly	Monthly	N/A

USP <1116> Advice for Environmental Monitoring Sampling Plan and Locations

Table 2. Suggested Frequency of Sampling for Aseptic Processing Areas[a]

Sampling Area/Location	Frequency of Sampling
Clean Room/RABS	
Critical zone (ISO 5 or better)	
Active air sampling	Each operational shift
Surface monitoring	At the end of the operation
Aseptic area adjacent critical zone	
All sampling	Each operating shift
Other nonadjacent aseptic areas	
All sampling	Once per day
Isolators	
Critical zone (ISO 5 or better)	
Active air sampling	Once p day
Surface monitoring	At the end of the campaign
Nonaseptic areas surrounding the isolator	
All sampling	Once per month

US FDA ORA & CDER Environmental Monitoring Recommendations for Sampling

1. Swab the frequently utilized surfaces within the controlled work station such as:

   Center of work surface, Fingertips & sleeves of Isolator gloves , Storage bins inside work station, Shelving inside work station or any other stationary items, Equipment control panels including on/off switches of LFH/BSC, Flexible plastic curtains used to separate multiple workstations

2. Swab corner crevices inside the HEPA Filtered work station.

3. Swab the handle, squeeze trigger and nozzle of any bottle kept in the clean room or work station used for spraying (i.e., 70% alcohol, disinfectant solutions, etc.).

4. Swab the underside of the chair in front of the work station. Specifically, on the front bottom rim where personnel would hold to pull up the chair.

5. Swab tables or benches within the controlled room where product container(s) or post sterilized product may be held outside of the HEPA filtered workstation.

6. Swab the air in-take grid on each of the HEPA filtered work stations. Usually located on top of the unit holding the course filters.

US FDA ORA & CDER Environmental Monitoring Recommendations for Sampling

7. Swab the exhaust (return) grid for the room air handling system that is connected to the facility air supply where the product manufacturing or compounding occurs.
8. Swab the light switch and door knob or handles leading into and out of the clean room.
9. Swab any cardboard boxes, handles of plastic containers, tools (crimpers) or scissors, key pads on weighing scales or computers kept in the cleanrooms.
10. Swab the exterior cuffs of the used lab coats worn by personnel during manufacturing or compounding. They may be hanging in the entry (ante) gowning room.
11. Swab the bottom horizontal window sill within the clean room.
12. Swab any area under open or dislodged ceiling panels.
13. Sample areas of discoloration, stains or water and oil droplets.
14. Use your discretion to swab any other high risk surface locations.

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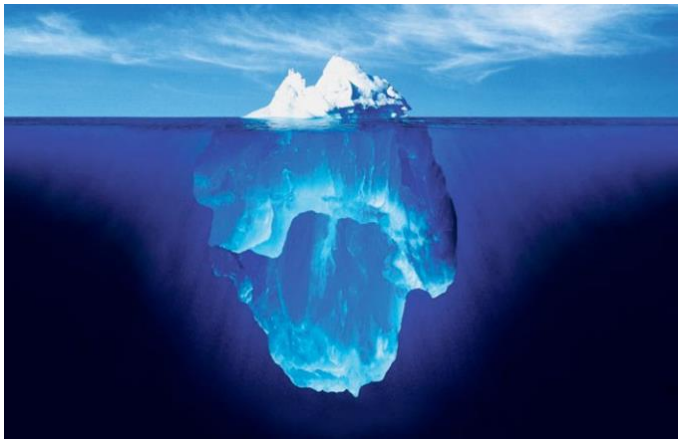
Thank You for your Attention!
May we be of Further Assistance?



michael.payne@merckgroup.com

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Some Key References

• ISO 14644-1 “Cleanrooms and Associated Controlled Environments - Part 1: Classification of Air Cleanliness”, 1999

•USP 1116 “Microbiological Control and Monitoring of Aseptic Processing Environments”

•USP 1115 “ Bioburden Control of Nonsterile Drug Substances and Products”

•FDA Aseptic Processing Guideline

•EU Annex 1

•Japan Aseptic Processing Guide and JP

•AAMI TIR 52 – Environmental Monitoring for the Manufacture of Terminally Sterilized Healthcare Products – Medical Device

PDA Technical Report 13

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Process Validation for Biological Processes - Qualification of Sterile Operations

Michael Payne
Principal Technical Consultant
Merck Millipore

106TPDA04024-C

Objectives

- Define quality by design (QbD) and Quality Risk Management (QRM)
- Define the levels of filtration in simple and complex operations
- Show QbD approach in critical filtration
- Show a design space approach for sterile liquid and gas filtration
- Use a qualification approach to critical filtration
- Identify key vendor and user responsibilities
- Examine operations in the sterile core for aseptic filling
- Compare single, serial and redundant approaches to sterile filtration

US Regulators Vision of the Future

"The Desired State: A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."

Janet Woodcock; Oct 2005

How do we Achieve the Desired State?

Three Key Concepts

- ✓ Quality by design and the design space concept — ICH Q8
- ✓ Quality Risk Management — ICH Q9
- ✓ Robust Quality Systems — ICH Q10

106TPDA04024-C

Key Regulatory Concerns

Efficacy / Strength	Does the qualified filtration process result in product / residues that interfere with final product strength or efficacy?
Identity & Purity	Does the qualified filtration process result in product / residues that interfere with final product purity?
Safety	Does the qualified filtration process result in product / residues that are toxic to the patient?

Important consideration –
How may this filtration activity affect the pharmaceutical company's quality or product / risk assessment process

What is Process Validation?

EMA

"The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes."

EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, 27 February 2014

US FDA

"collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."

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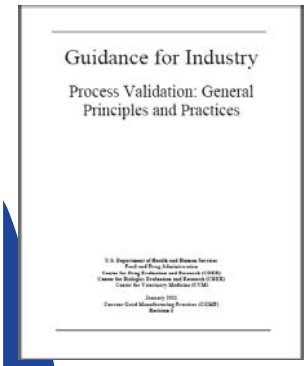
US FDA – Process Validation Guidance
January 2011


Guidance for Industry

Process Validation: General Principles and Practices

Activities over the lifecycle of the product and process.

Stage 1 – Process Design:
defined based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification:
determines if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification:
assurance gained during routine production that the process remains in a state of control.

Note – does not apply to sterilization processes – these are covered in Aseptic Processing Guidance for Industry: Sterile Drugs Produced by Aseptic Processing

Process Validation is a Lifecycle Approach

Product Lifecycle Validation Sequence

Process mapping	Qualification of sanitisation and sterilisation	Parts, components hold studies	Environmental monitoring
Risk assessment	Filter validation	Gowning and personnel qualification	Sterility testing
Identify, eliminate, reduce, mitigate, accept interventions	Smoke studies	Facility and equipment qualification	Evaluation of interventions
Procedures	Training	Aseptic process simulations	Re-assessment
	Monitoring		

IRISH MEDICINES BOARD

Aseptic Process Validation - *IMB GMP Information Seminar, 27 September 2012*

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Some Key Process Validation Questions

Do I have confidence in my manufacturing process? Or, more specifically, what scientific evidence assures me that my process is capable of consistently delivering quality product?

How do I demonstrate that my process works as intended?

How do I know my process remains in control?

Process Validation A Lifecycle Approach
Grace E. McNally
Senior Policy Advisor U.S. Food and Drug Administration, CDER
May 6, 2011

Challenge – Aseptic Processing of Biological Products

106TPDA04024-C

What is Aseptic Processing?

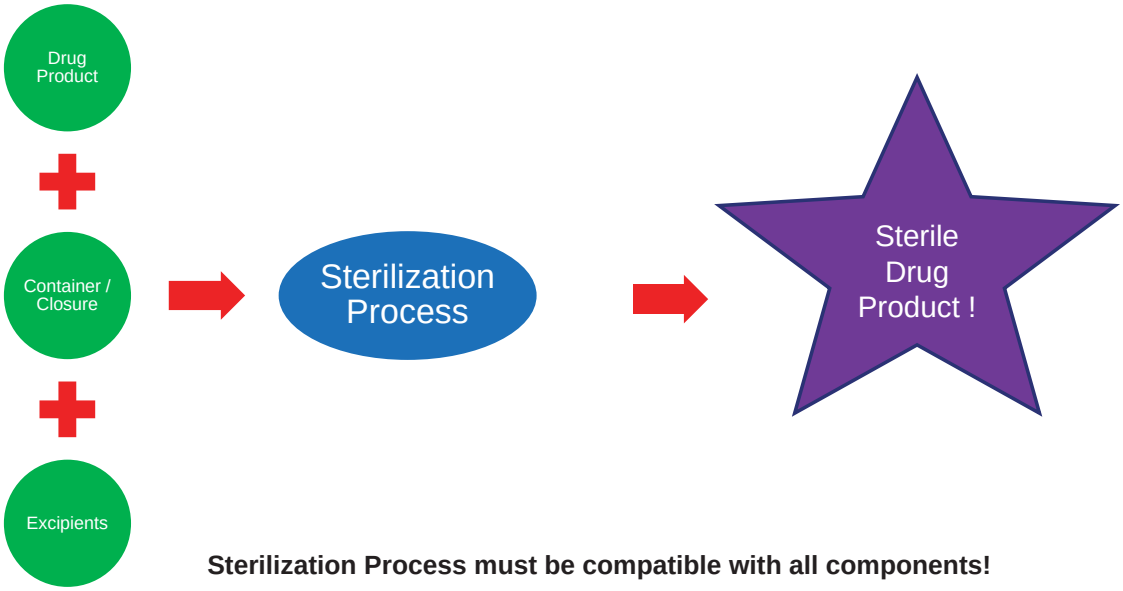
"Sterile drug manufacturers should have a keen awareness of the public health implications of distributing a nonsterile product. Poor CGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient."
FDA Guidance "Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice" 2004.

Aseptic Processing

Asepsis is the practice to reduce or eliminate contaminants (such as bacteria, viruses, fungi, and parasites) from entering the operative field in surgery or medicine to prevent infection. Ideally, a field is "sterile" — free of contaminants — a situation that is difficult to attain. However, the goal is elimination of infection, not sterility. *http://en.wikipedia.org/wiki/Asepsis*

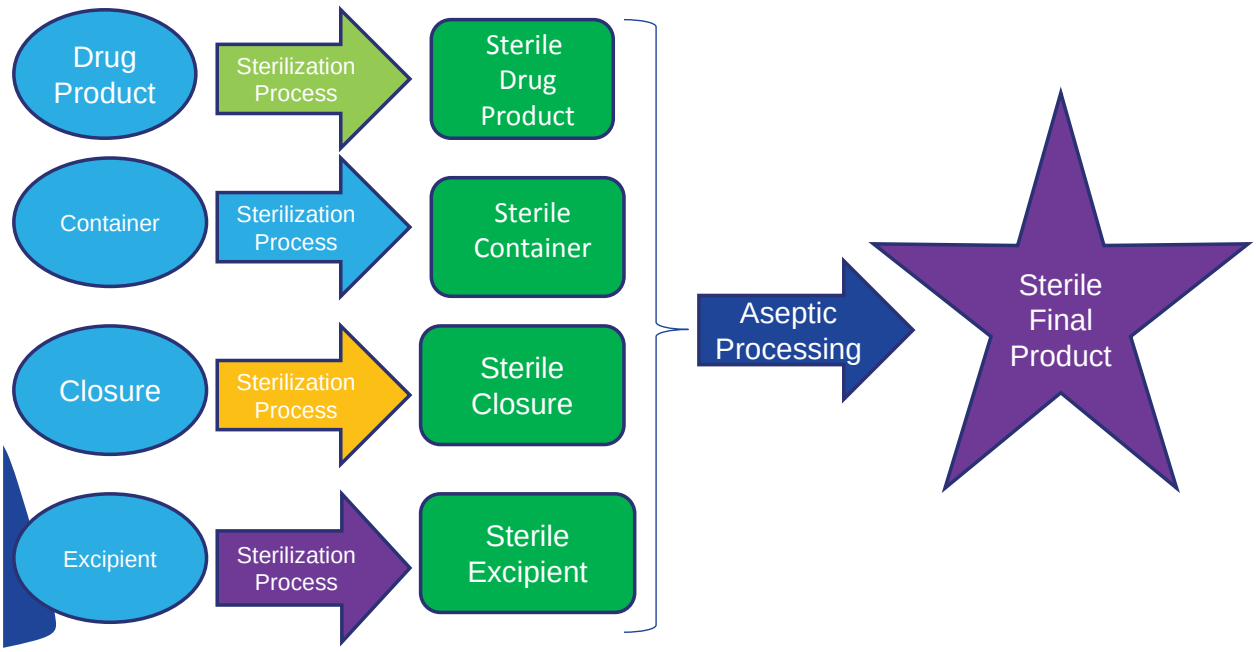
Asepsis- " A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbiological contamination of the exposed sterile product"
Guidance for industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice. USFDA, September 2004

Terminal Sterilization



Sterilization Process must be compatible with all components!

Aseptic Processing



Can use multiple sterilization processes each optimized for the individual component

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Quality by Design (QbD)

Quality by design (QbD)

Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

ICH Topic Q8 Annex. Pharmaceutical Development.

Steps in QbD

- Define your product (**& impurity**) profile and what the product should do
- Define your CQAs (critical quality attributes) for the product and critical in process steps
- Define process element (CPPs (critical process parameters and control points)
- Determine operating ranges to consistently yield acceptable product & process.
- Define your design space and operate in a controlled way within it

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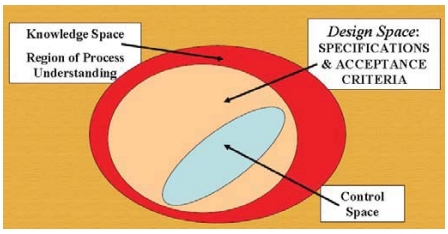
Today's Focus – Critical Filter Design Space

Design Space

- Defined as: "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." ICH Q8(R2), http://www.fda.gov/downloads/Drugs/Guidances/ucm073507.pdf
- Demonstrated range of all process parameters where process meets the CQAs
- Consists of Knowledge space, design space and control space

Challenges

- Characterize CPPs to assess their impact on CQAs
- Build application model: Empirical (DOEs) or physical laws
- Accommodate scaling and variability



"Implementation of Quality by Design". J.F. Haury, Amgen 2006
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm118776.pdf

Overall picture of quality by design

Product & process design and development

Define desired product performance upfront; identify product CQAs → Design formulation and process to meet product CQAs

Continually monitor and update process to assure consistent quality ↔ Identify and control sources of variability in material and process ↔ Understand impact of material attributes and process parameters on product CQAs

Risk assessment and risk control

Implementing Quality by Design - Helen N. Winkle, FDA, Sept 2007

When Should QbD Considerations Occur?

As early as possible!!

Pre-Clinical → Phase I → Phase II → Phase III

	Small Scale	Pilot scale	Manufacturing Scale
Manufacturing			
Analysis	Validated Safety Testing	Validated Safety, Identity, Purity, impurities	Fully Validated In-process and Release Tests

RISK ↔ QUALITY

Why is QbD Important for Critical Filtration & Aseptic Processing?

- It defines the process and product parameters in which the filter will need to work to produce sterile filtrate
- It is the first part of a critical filter duty statement (a.k.a. “Fit for Use” or “Fit for Purpose” or “Filter URS”)
- It is proof that the pharmaceutical company meets cGMP requirements (“documented scientific evidence”)
- It provides documented scientific evidence of risk assurance
- It is an expected part of the pharmaceutical company’s approach to critical processes that affect the key regulatory concerns

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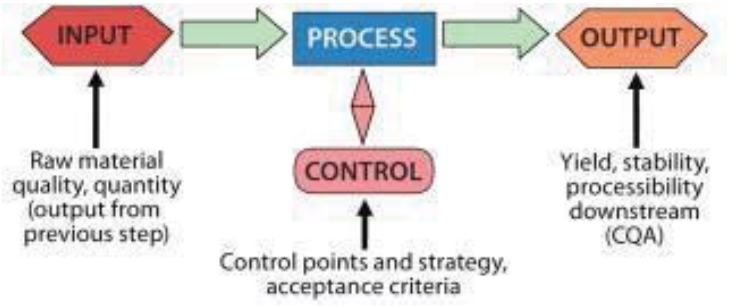
Why can Critical Final Filtration QbD be Easy?

Link raw material attributes & process parameters to CQAs



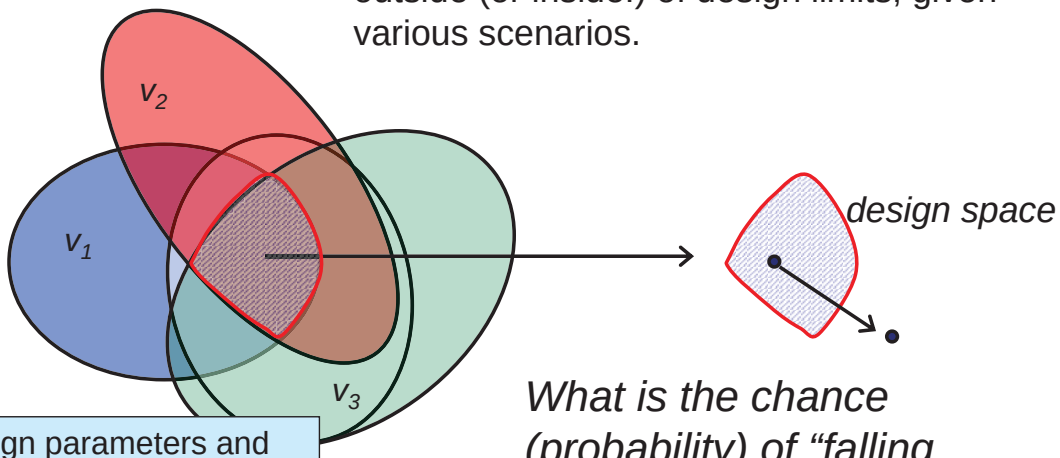
In many cases of final sterilizing liquid & gas filtration

Input material quality attributes = Output material attributes

Source: How QbD and the FDA Process Validation Guidance Affect Product Development and Operations, Part 1, Peter H. Calcott, (November 2011), Bioprocess International (http://www.bioprocessintl.com/analytical/downstream-validation/how-qbd-and-the-fda-process-validation-guidance-affect-product-development-and-operations-part-1-323457/

QRM and the Production Design Space

Risk analysts estimate probabilities of being outside (or inside!) of design limits, given various scenarios.



Design parameters and their intersection in a "design space" concept

What is the chance (probability) of "falling outside" of the design space per unit time?

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Critical Filtration Operations in Biopharmaceuticals

Simplify the Filtration Process with Filter Categories

Recommended that filters are reviewed site-wide and divided into 3 categories

Critical

- The filter directly affects product quality
  - Examples: vent filter on a sterile hold vessel, sterile liquid filter, viral filter

Moderately critical

- The filter indirectly affects product quality
  - Examples: vent filter in a grade C area, bioburden reduction filter

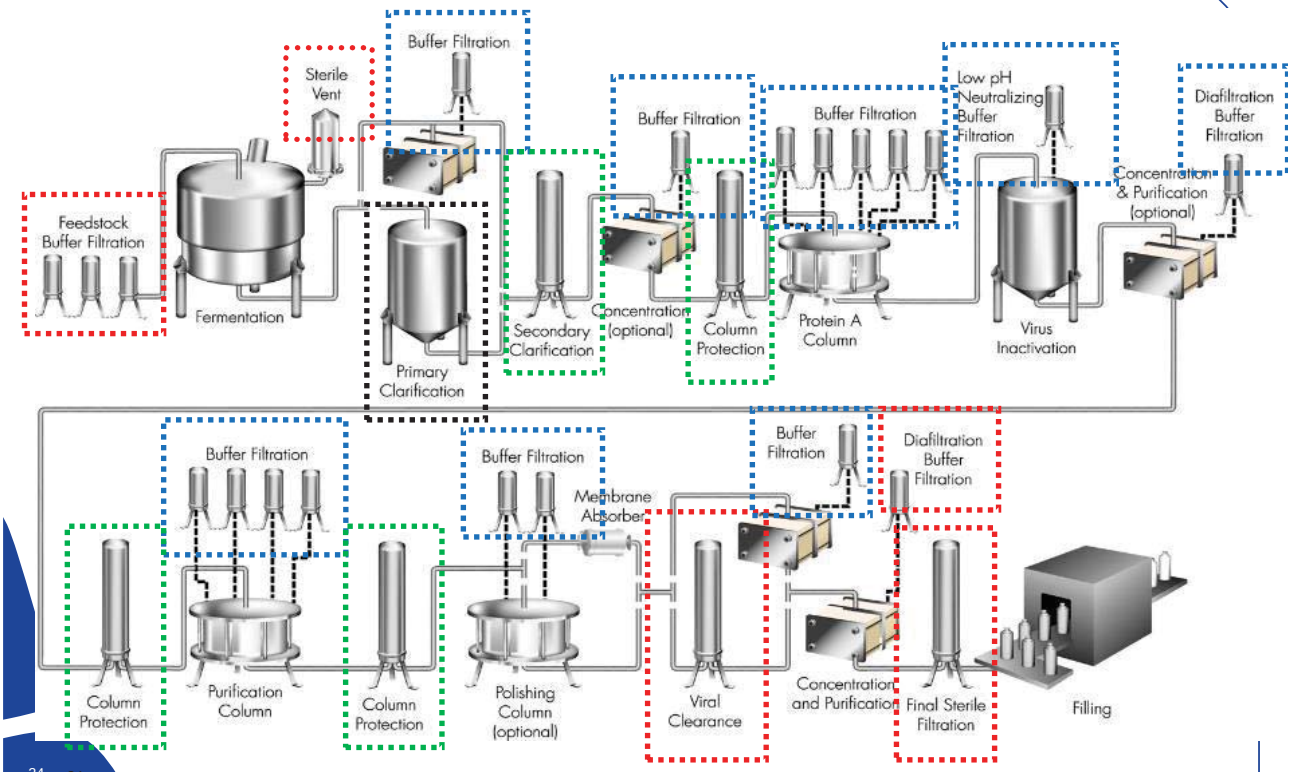
Service

- The filter does not affect product quality
  - Examples: distribution gas filter, water prefilter

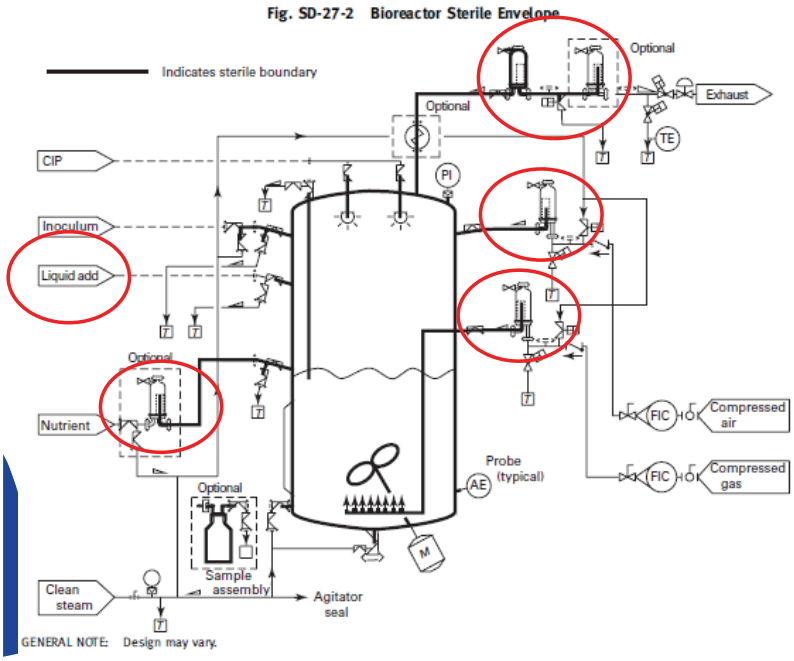
Uses definitions from PDA Technical Reports 26 (liquid filters) & 40 (gas filters), and ISPE Baseline Guide to Commissioning and Qualification

Filters in a Generic Biological Process

Filter groups come from their location, and classification in the process, not the regulations, guidelines or filter label. Key output is process/product risk



Critical Filters Around the Bioreactor / Fermenter



- Service filters not shown
- Clarifying, prefilters not shown
- Critical gas filters
  - Overlay, sparge, exhaust
- Critical liquid filters
  - Media, additives
- For redundant or serial filters, furthest away defines sterile boundary

From ASME BPE-2009 Bioprocessing Equipment

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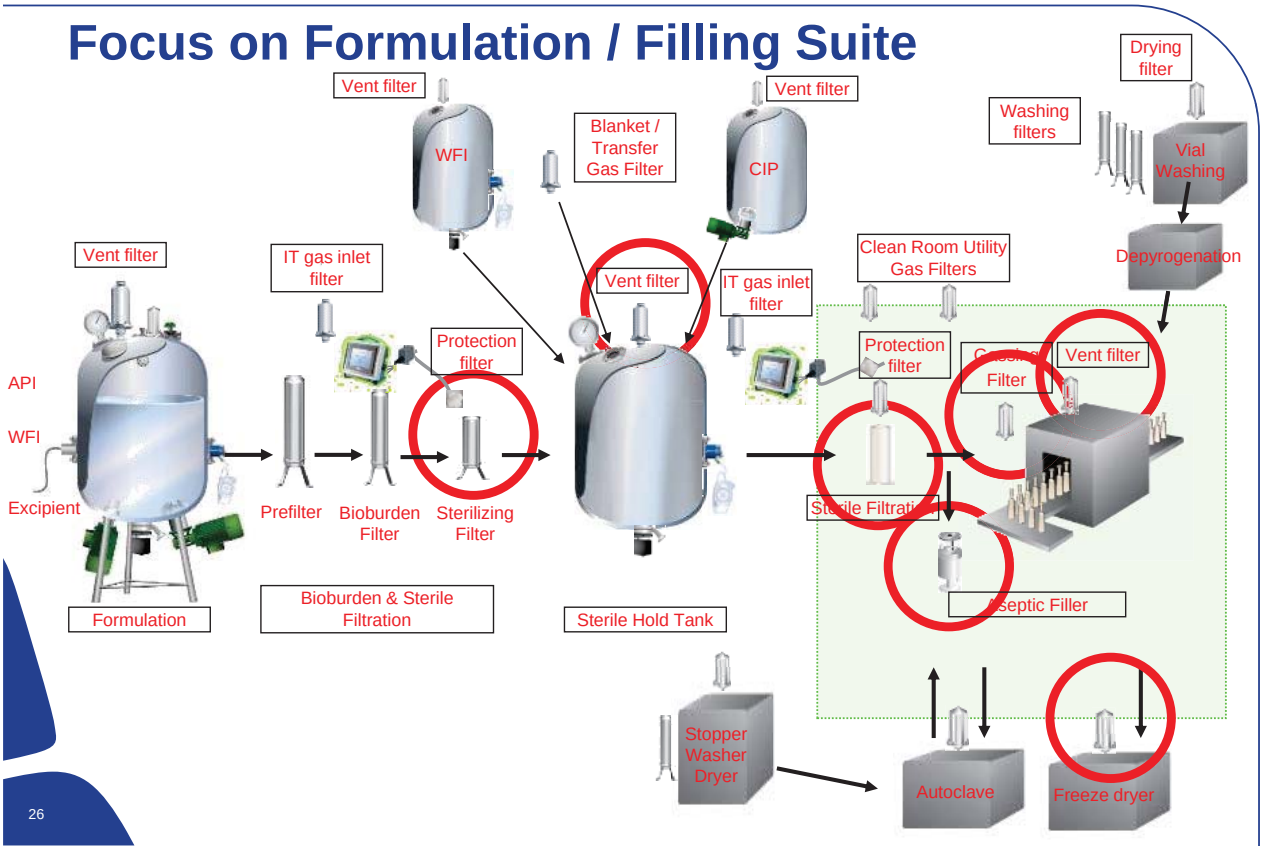
Focus on Formulation / Filling Suite



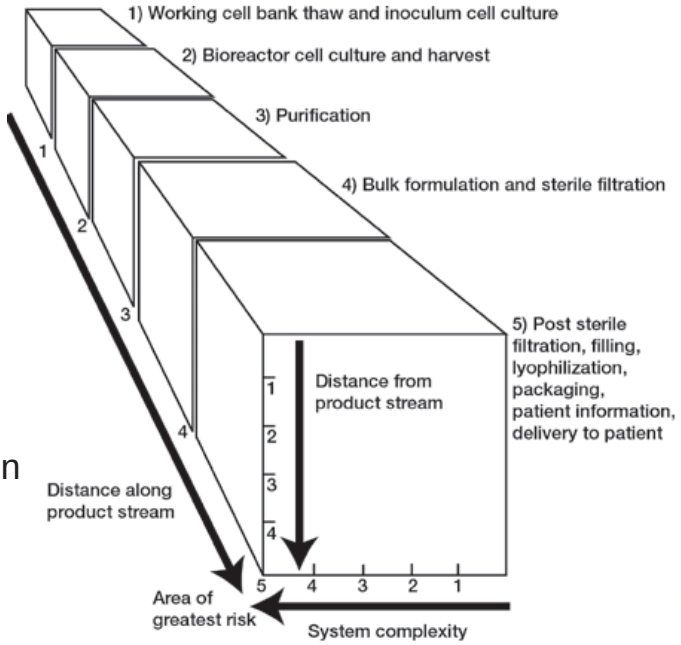
3D System Risk Assessment Tool

Considers

- a system‘s distance from the process stream
- its location along the process stream
- the system‘s complexity

Highest score is highest risk

This tool is mainly used to assign risk level to an overall complex system



From IVT Autumn 2008, pp70-76, J Oliver Baxter Bioscience

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Examples of Sterilizing Filtration Risk

Risk = process location x operation complexity x product contact

Bioreactor liquid media filter

Risk = 1 x 2 x 2 — 4

Bioreactor Gas Filter

Risk = 1 x 3 x 2 — 6

Sterile hold tank gas filter

Risk = 4 x 2 x **5** — 40

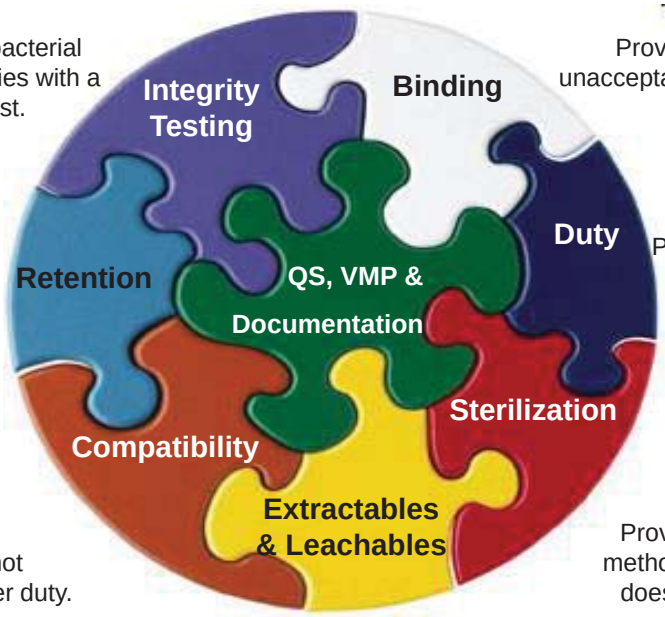
Final POU liquid filter

Risk = 5 x 4 x 5 — 100

NB: Severity, use time, process condition, defect detection, economics not considered

8 Elements of Sterile Filtration Qualification

Represent “worst case” process conditions, process fluid, filter performance and microbiological challenge



Prove the filter’s bacterial retention capabilities with a non-destructive test.

Prove the filter does not unacceptably remove stream components.

Prove the filter removes bacteria from the stream compliant with ASTM 838-05 and regulations

Prove the filter meets all performance & duty requirements within product & process conditions.

Prove the stream does not adversely impact the filter duty.

Prove the sterilization method is effective and does not compromise the filter.

Identify, quantify, and assess impact of compounds that migrate from filter to process stream.

Prove the filter does not adversely affect the process stream

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Filter User Responsibilities

Define the operation space (requirements)

Establish filter/product compatibility

Audit vendor and contract laboratory

Validate test methods

Train & qualify operators

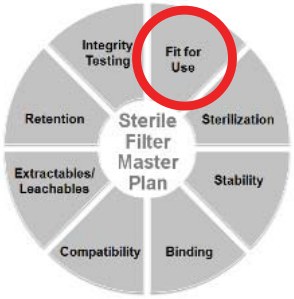
Validate filter sterilization

Validate equipment cleaning

Validate filtration process

Operate within manufacturer’s specifications
or within user documented and user defined conditions where quality attributes have no additional risk

Define Duty (fit for use) as part of QbD



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Sterilizing Filter Design Space

Process Attributes

Yield, time, pressure, temperature, flowrate, volume, sterilization method and conditions, pretreatment, integrity test

Product Attributes

pH, ionic strength, osmolarity, formulation, product concentrations (active, excipient, etc.), acceptable impurity levels

Microbiological Attributes

Species / Identity, concentration

Sterilizing Filter Operating Space

Feedstock

Volume

Contact Time

Flowrate

Pretreatment / Prefiltration

Inlet Pressure

Differential Pressure

Yield

Ease of Use / Handling

Sterilization Method

Integrity Test Method

Characteristics Required to be Maintained for Linear Scaling

Constants determined after a filter is selected

Feedstock

Pretreatment / Prefiltration

Contact Time

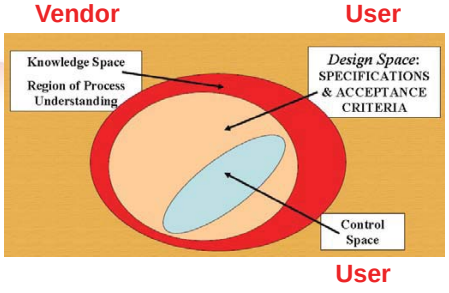
Pressures

Yield

Load (= Volume / Filter Area)

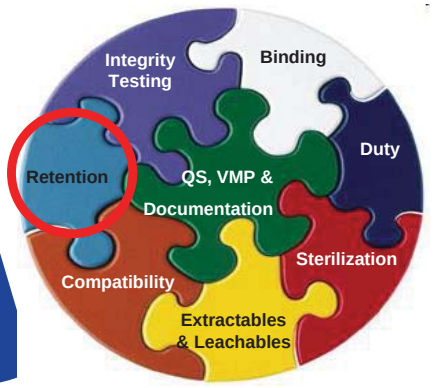
Flux (= Flowrate / Filter Area)

Filter Retention Testing – Showing how User & Vendor can Combine Strengths to Help Ensure QbD



Retention: What are the requirements

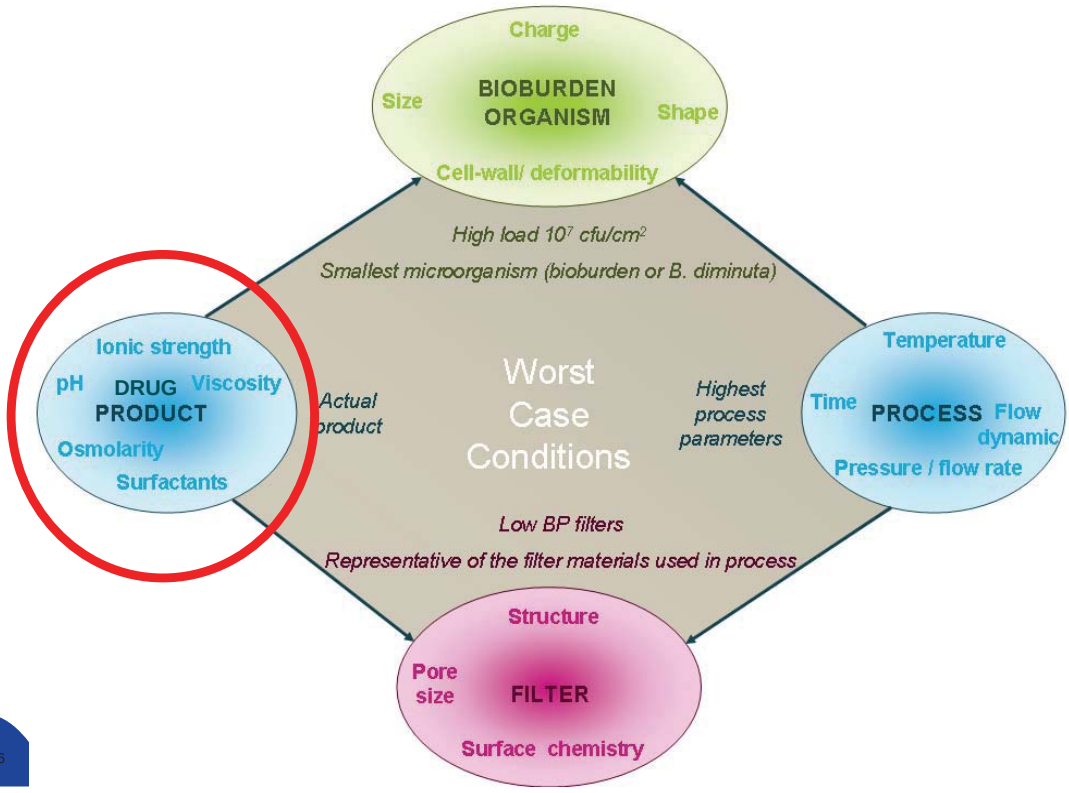
"All Sterilization Processes Should be Validated."
WHO Annex 6: Good Manufacturing Practices for Sterile Pharmaceutical Products section 5.4 page 273



"Whatever type of filter or combination of filters is used, validation should include microbiological challenges to simulate "worst case" production conditions. The selections of the microorganisms to perform the challenge test (e.g. P. diminuta) has to be justified. The nature of the product may affect the filter and so the validation should be performed in the presence of the product……"
PIC/S Guide for Inspectorates: Recommendation on the Validation of Aseptic Processes

A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product.
US FDA Guidance on Sterilization Validation

Defining the worst case conditions

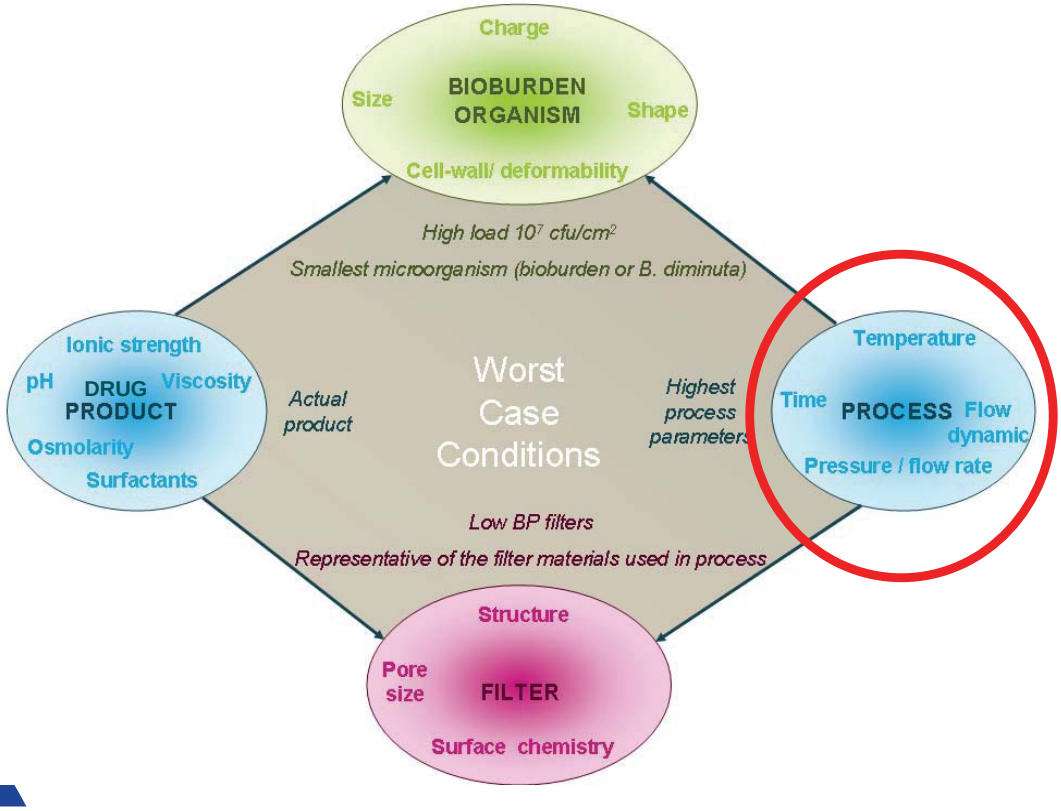


Product chemistry – Worst case conditions

	Main effect	Worst-case value
Osmolarity	Size of organism	Highest
Surface tension	Retention mechanism	Lowest
pH	Organism proliferation	5 - 9
	Filter compatibility	Highest
	Retention mechanism	Lowest & highest
Ionic strength	Retention mechanism	Lowest & highest
Viscosity	Retention mechanism	Highest

This becomes part of the design space consideration

Defining the worst case conditions



Process Parameters – Worst case conditions

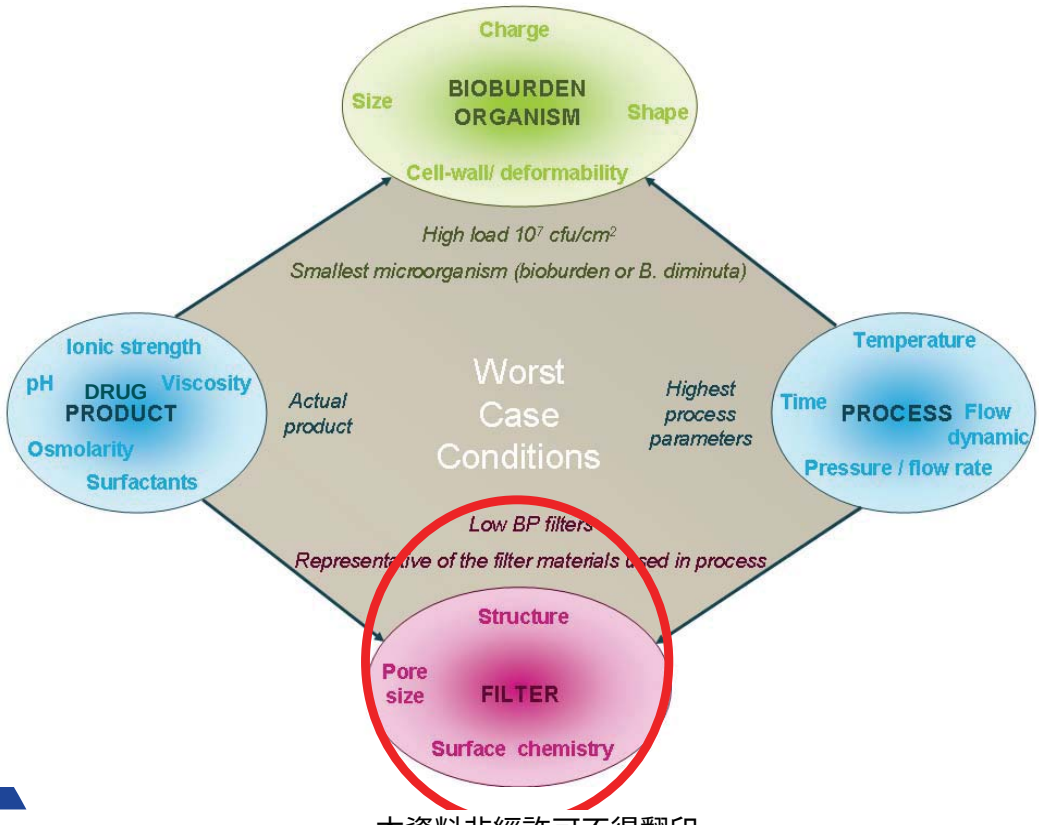
	Main effect	Worst-case
Pressure or Flow rate	Retention mechanism	Highest
Filtration time	Grow-through Bio-burden proliferation	Highest
Hydraulic shock	Blow-through	Highest
Temperature	Membrane compatibility Bio-burden proliferation	

→ In-line integrity testing

→Include any static holding time as well as non routine interventions & events

This becomes part of the design space consideration

Defining the worst case conditions



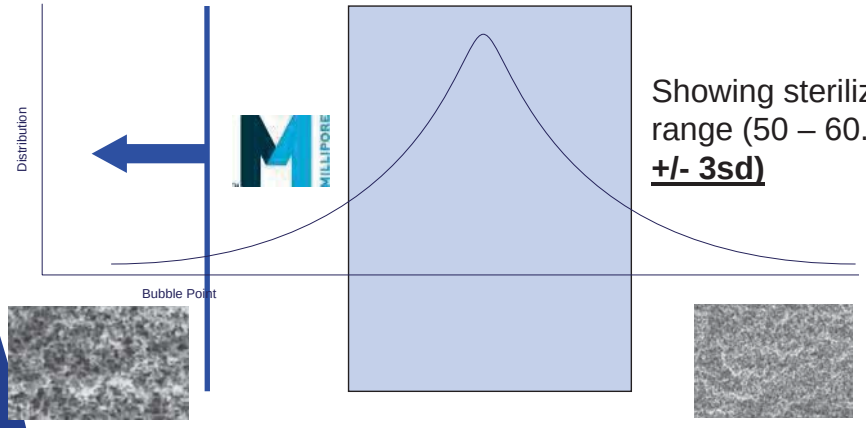
Filters - Worst Case Filters

Use of "Low" Bubble Point Filters

In general, FDA has stated that membranes within 10% of the minimum specification are adequate

"One test filter at or near (~10%) minimum B.P. (pre-challenge)." (Sweeney 2007 GPhA Fall Tech. Conference)

Worst-Case Selection Threshold



Showing sterilizing grade bubble point range (50 – 60.5 psi) and mean **(55.5 +/- 3sd)**

ISSUE – meeting FDA "recommendation" in this case is only mean bubble point. Retention test should show lowest expected bubble point otherwise sterilizing filter design space is compromised

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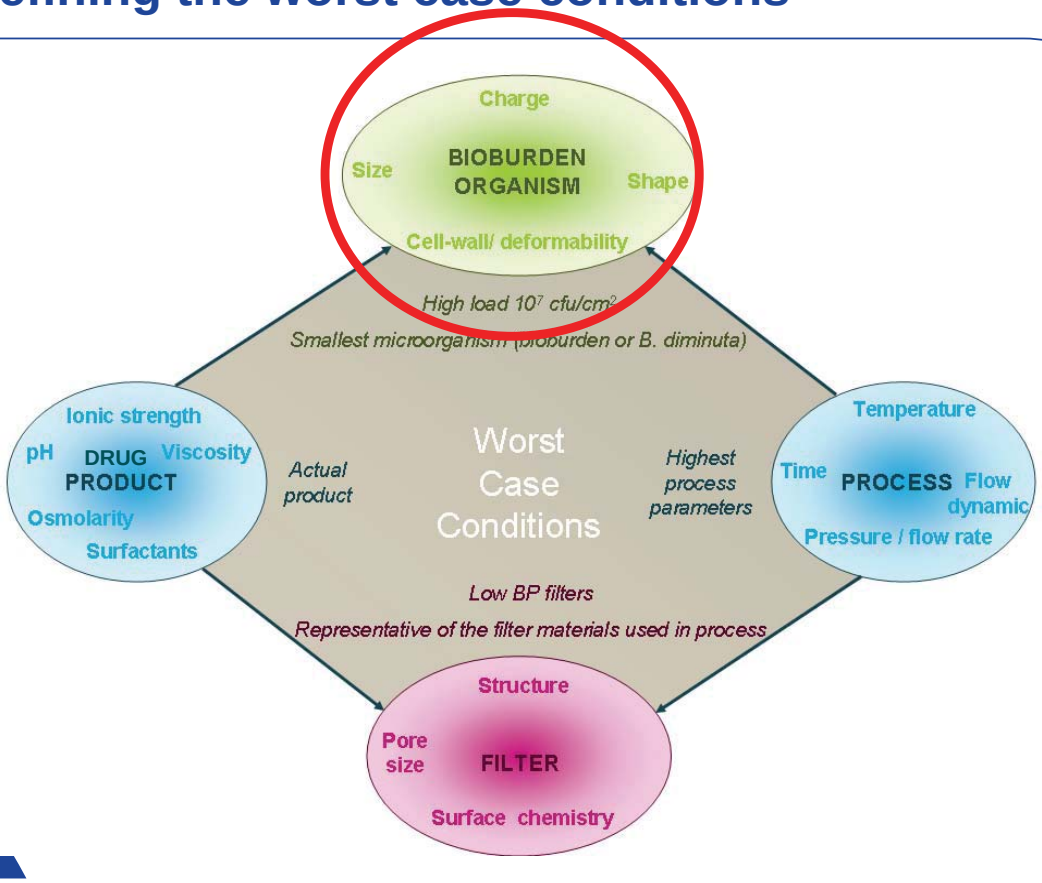
Defining the worst case conditions



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Challenge microorganism – worst case

B. diminuta & FDA Guideline

- *"B. diminuta* is the reference micro-organism ..."
- "... but one has to assure that actual bio-burden does not contain micro-organisms of a size and/or concentration that would reduce the targeted high level of filtrate sterility assurance"

More and more observations & comments from FDA & EMEA auditors

Know your bioburden - Review environmental monitoring program results to identify small water-borne organisms in the facility

Size organism in drug product and compare with B. diminuta

Use previously determined boundary conditions and process details to outline retention test conditions

Specified by filter user, included in test protocol by contract lab

This becomes part of the design space consideration

Hydrophilic Filter Qualification – TR26

Table 4.1-1 Qualification and Validation Recommendations

Criteria	Filter User	Filter Manufacturer	
	Device	Membrane Disc	Device
Bacteria retention in water or saline lactose broth (SLB) with integrity test correlation in water or solvent	-	Q, L	Q, L
Bacteria retention in product	V*	-	-
Chemical compatibility, effects on filter integrity	V	Q	Q
Extractables	V	Q	Q
Leachables	E	-	-
Sterilization method, effects on filter integrity	V	Q	Q
Integrity test (water or solvent)	V	Q, L	Q, L
Integrity test method selection (product)	V	-	-
Toxicity testing	-	Q	Q
Bacterial endotoxin	V	-	Q, L
Particulate matter	E	-	Q
Non-fiber release	E	-	Q
Total Organic Carbon (TOC) and conductivity	E	-	Q

N.B. Does not include filter modules process operating parameters (e.g. Size, connections, capacity, temperature, pressure, etc.)

L = Lot release criteria
Q = Qualification
V = Process-specific validation
V* = Can be performed in disc or device format
E = Evaluate the need for testing

Hydrophobic Filter Qualification – TR40

Tests Commonly Performed by Filter Users and the Filter Manufacturers—General Industry Practices

Criteria	Filter User	Filter Manufacturer	
	Filter Device	Membrane Disc	Device
Bacteria Retention/ Integrity Test Relationship Data	(E)	(Q)	(Q)
Integrity Test		(Q/R/L)	(Q/R/L)
Integrity Test Methodology and Selection	(E)	(R)	(R)
Microbial/Viral Retention (Liquid/Aerosol)	(E)	(Q/L)	(Q/L)
Compatibility/ Service Life	E/V	(Q/R)	(Q/R)
Toxicity Testing		(Q)	(Q)
Effects of Sterilization Methods on Filter Integrity	(E/V)	(Q)	(Q)

Note differences between hydrophilic and hydrophobic qualification recommendations

Q = Qualification Testing

V = Validation Testing—Process-Specific

E = Evaluate Applicability to Process

R = Recommendation for Validation

L = Filter Lot-Specific Release Criteria

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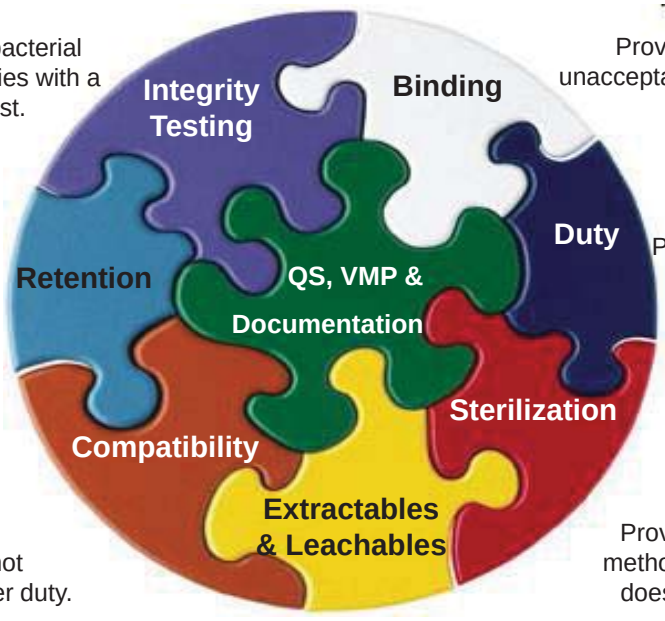
8 Elements of Sterile Filtration Qualification

Represent "worst case" process conditions, process fluid, filter performance and microbiological challenge



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Prove the stream does not adversely impact the filter duty.

Prove the sterilization method is effective and does not compromise the filter.

Identify, quantify, and assess impact of compounds that migrate from filter to process stream.

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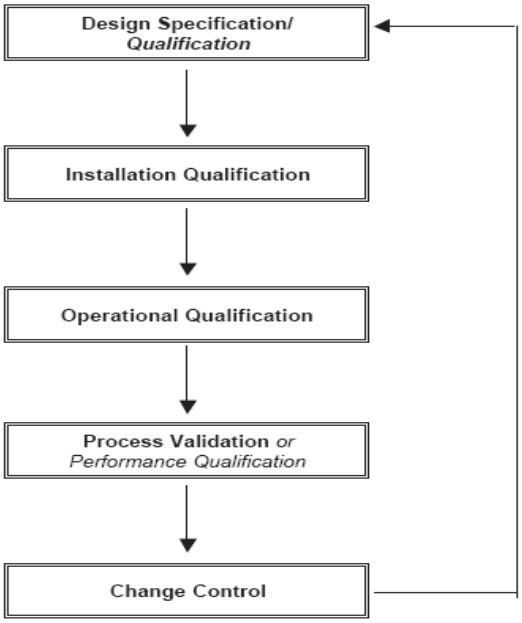
Validation Process, Key Vendor and Contract Laboratory Documentation for Sterilizing Filtration



Data Sheet

Validation Guide
Certificate of Quality
Packaging info

Adsorption study
Product Specific Integrity Testing
Sterilization qualification
Bacterial Retention Testing
Extractables / Leachables Testing
Toxicity assessment

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Moist Heat Sterilization Validation

Phases of Sterilization Validation Plan

Installation Qualification (IQ)

Operational Qualification (OQ)

Cycle Development (CD)

Performance Qualification (PQ)

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Installation Qualification

–Performed after the system is installed and connected to the appropriate utilities

–Pre IQ test cycles should be performed to ensure valves, controls and other components are functional and were not damaged prior to installation

–IQ: ensures that the system has been installed according to the manufacturer and the end user specifications

IQ Activities

Verification that all design specifications have been met

Verification of utilities

- Water supply (feed, RO/DI, distilled)
- Water quality
- Water line pressure
- Steam generator (plant/point of use)
- Water discharge (handling of hot condensate to waste stream)
- Electrical service
- Compressed air pressure

IQ Activities

–Description of the equipment and controls

–Verification of correct documentation

- Standard operating procedures
- Operating manuals
- Schematics
- Spare parts list

–Preliminary calibration and Preventative maintenance plans

–System monitoring requirements

–Personnel Training

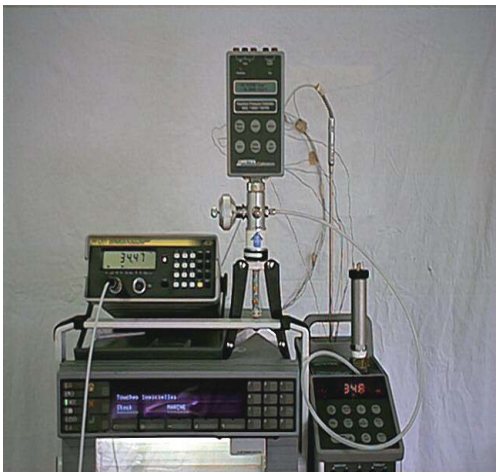
Installation Qualification

–Calibration of instruments

- Thermocouples
  - » Before Qualification
  - » Verify after Qualification or at defined intervals
  - » Pressure transducer
- Data logger & timer
- Automatic filter integrity tester

–System Calibration Status

- Pressure transducer
- Temperature
- Timer



Operational Qualification (OQ)

–Empty Chamber or Empty system trials

- Three consecutive successful runs for each cycle type

–Thermal profiling

- Find cold spots
- Establish temperature stability
- Establish air evacuation
- Determine temperature variation

–Autoclave Cycles with pre-vacuum

- » Steam quality testing (Europe)
- » Bowie Dick Test for air leaks and steam penetration

OQ Activities

–Error and alarm tests

- Recovery from power loss
- Overheat or over pressure

–Verify functionality of unit or system controls

–RF interference or EM interference

–Software testing

–Cycle sequence verification

–SOPs

–Operator training documentation

Operational Qualification
Cycle Development for Filters

–To experimentally determine the appropriate time and temperature to appropriately sterilize the filter and system without damage or degradation to the filter or system

–To identify lag time to temperature at coldest (slowest spot)

–To identify complete cycle time including

- Time to exposure temperature (come up)
- Time at exposure
- Cool down to safe handling of system

Operational Qualification
Cycle Development for Filters

–For SIP

- Post-integrity test, pre-SIP filter drying
- Filter and Filter housing orientation
- Condensate drainage and Air evacuation
- In process filter differential pressure control
- Post SIP cooling

–For an autoclave

- Determine the appropriate loading pattern
- Orientation of components for sterilization
- Sterilization wraps
- Cycle type (slow exhaust, vacuum pulse)

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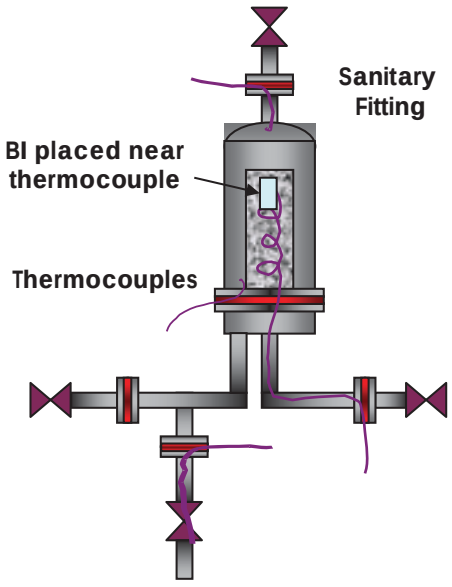
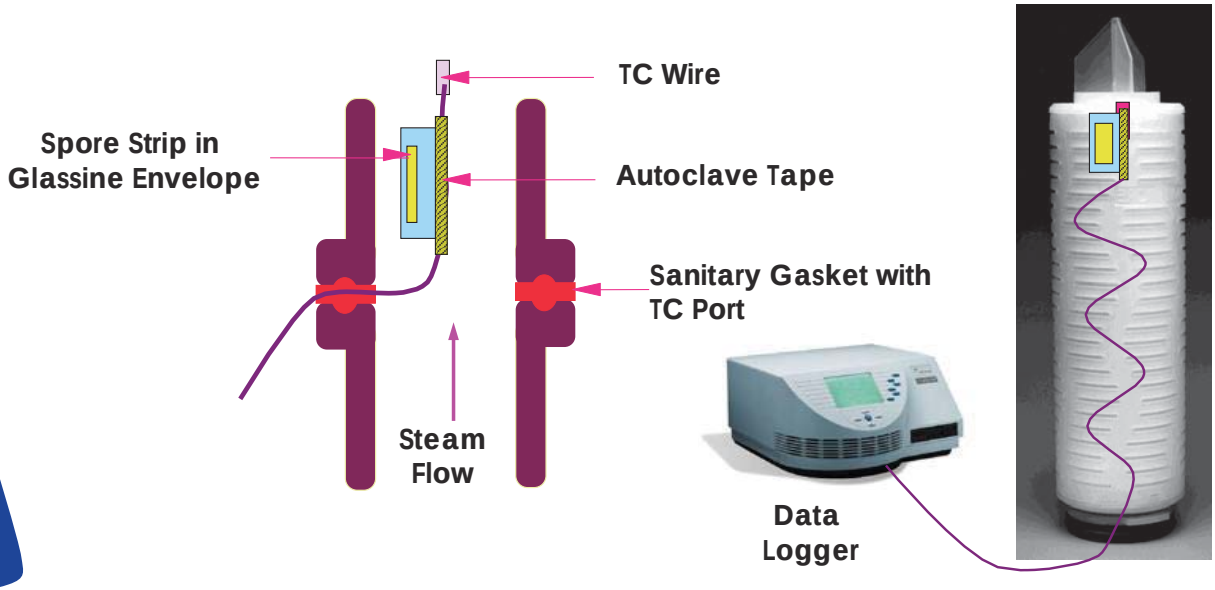
Cycle Development
Expected cold spots for Filtration Systems

– Tools
  - Thermocouples/Datalogger
  - Biological Indicators

– Targets
  - Dead legs, instrument ports
  - Vent bleeds
  - Low Point drains/traps
  - Dome and base of filter housing (upstream)
  - **Inner top core of filter** (downstream)



Cycle Development
Installation of BIs



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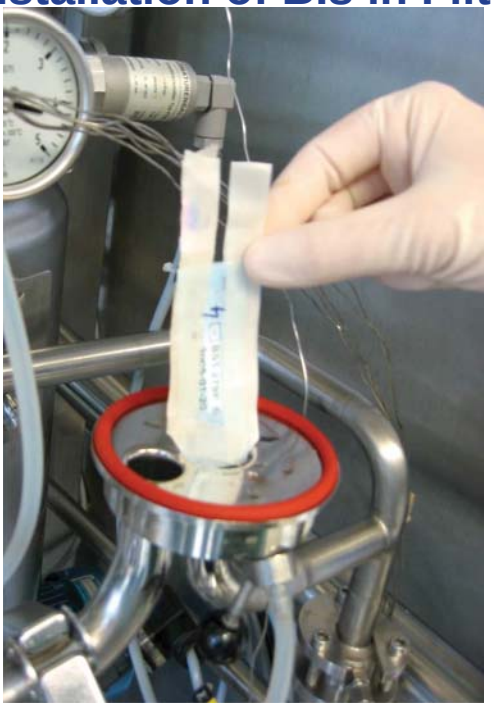
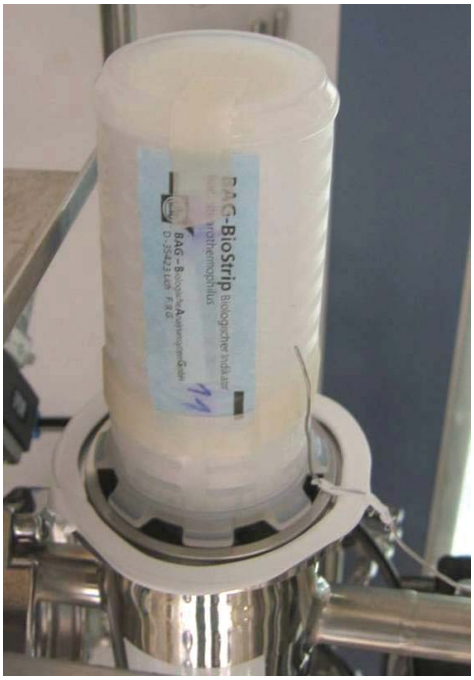
Cycle Development
Installation of BIs in Filters

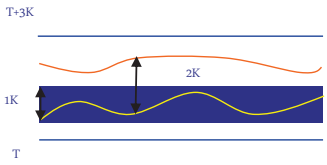




Operational Qualification Acceptance criteria

– Perform tests in triplicate (or as based on QbD)

- Control pressure, temperature & time
- Temperature distribution
  - » USP23, PDA TR#1: ±1°C of the mean value indicates proper heat distribution (empty chamber)
  - » EN554, ISO11134: All TCs within sterilization band (T, T+3K) do not differ from each other by more than 2K do not fluctuate by more than 1K
- All BIs inactivation indicates proper heat penetration



–Pre & Post sterilization filter integrity testing

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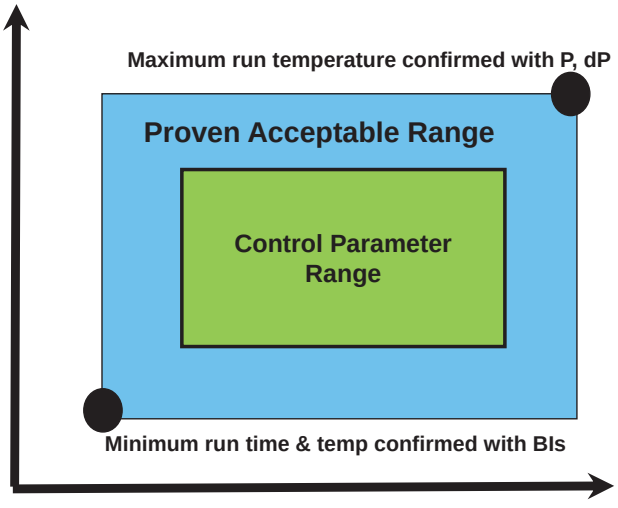
Mapping Design Space for Filter Sterilization

Temperature

Maximum established by cartridge passing integrity test after SIP cycle

Minimum established by sterilization validation to achieve required “kill”



Maximum established by cartridge passing integrity test after SIP cycle

Minimum established by sterilization validation to achieve required “kill”

During whole cycle, important to;

- **Establish both minimum and maximum F_o ,**
- **Monitor temperature**
- **Monitor filter differential pressure**

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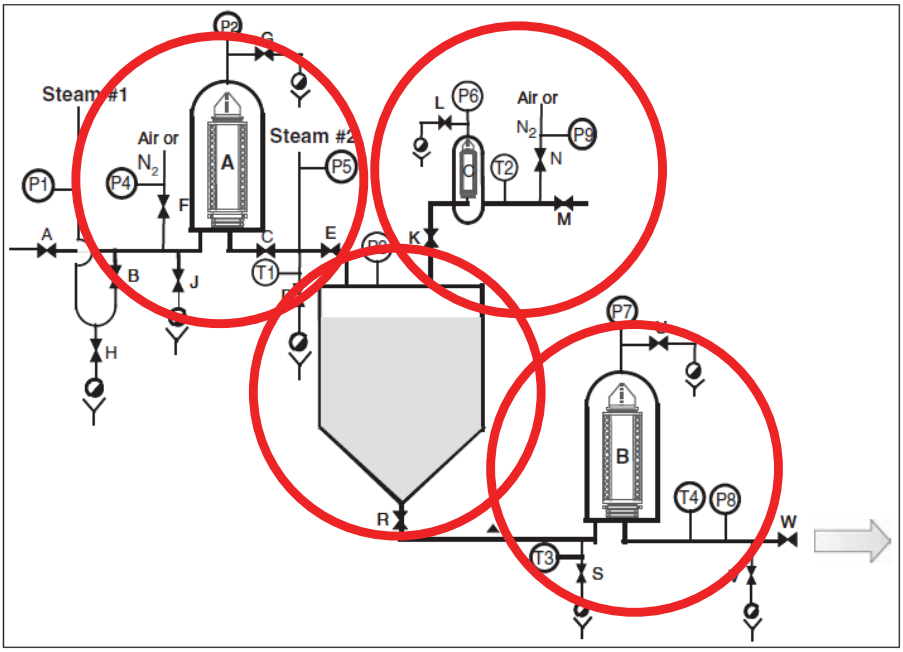
Performance Qualification

Confirm and document SOP

- Train operators

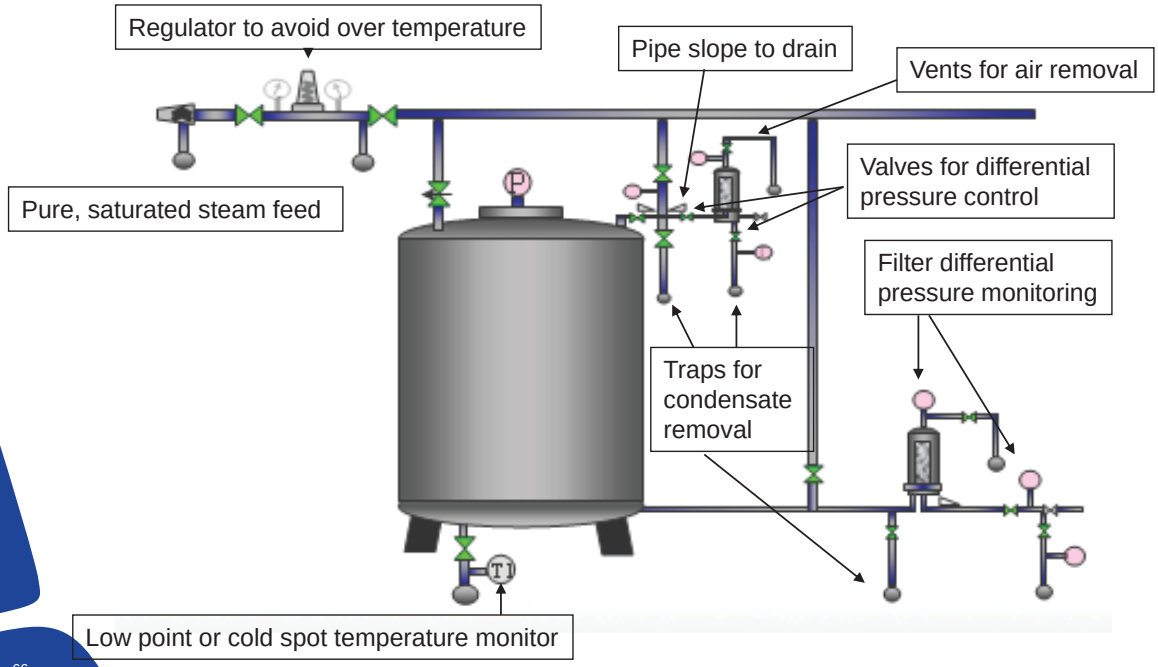
- Check that operators carry out SOP properly
  - 3 consecutive successful SIP cycles followed by
  - 3 successful media hold
  - Reproducibility & reliability of sterilization process

Example - Sterilization System Design for Sterile Hold Tank and POU Filter



From Simon Cole "Steam Sterilization of Filters"

Some Steam Sterilization Design Considerations



Conclusion

Process validation comes at the end of an DQ – IQ – OQ process

Validation master plans are compulsory

QbD approach begins at product development and continues through product life-cycle

Vendor documentation supports end-user QbD

User documentation identifies risk and maps the design space

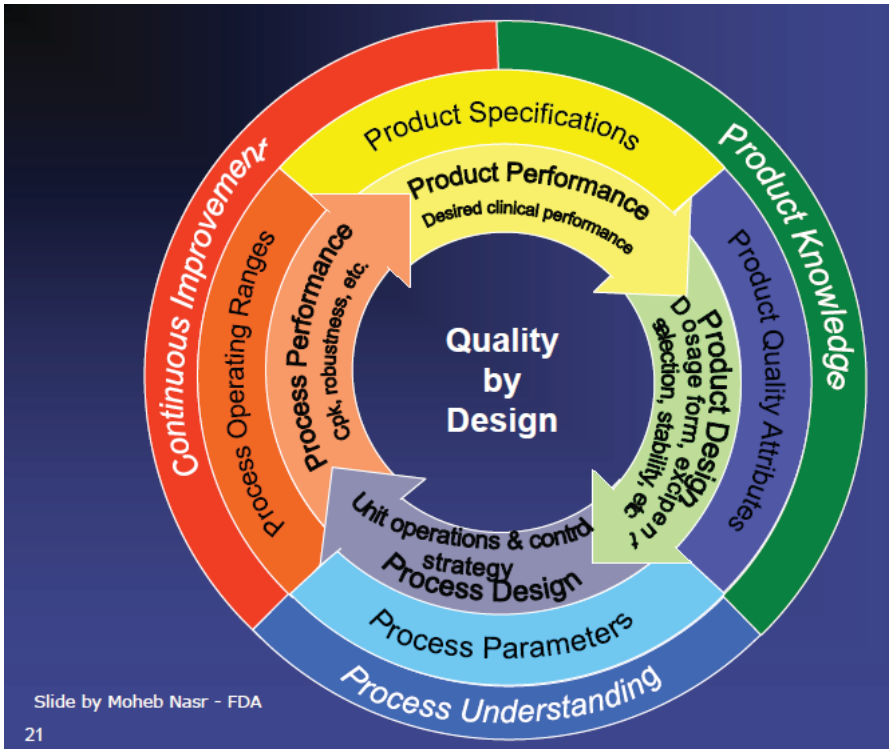
QbD is another way of looking at process information that should already be available

Quality by design and quality risk management support and strengthen cGMP approaches

Some Useful References

- US FDA Guidance for Industry. Process Validation: General Principles and Practices. Current Good Manufacturing Practices (CGMP). Revision 1. Jan 2011
- WHO A guide to good manufacturing practice (GMP) requirements. Part 2: Validation. 1997,
- WHO Expert Committee On Specifications For Pharmaceutical Preparations, TRS937, 2006.
- WHO Draft "Validation of Production Processes for Vaccines for WHO Prequalification Compliance Expectations" guidance document (July 2013)
- Health Canada Guidance Document, Validation Guidelines for Pharmaceutical Dosage Forms,GUIDE-0029, Dec 2009
- PICS Recommendations on Validation Master Plan Installation and Operational Qualification PI 006-3, Sept. 2007
- PICS Guide To Good Manufacturing Practice For Medicinal Products Annex 15 Qualification and Validation, PE 009-10 (Annexes) - January 2013
- PDA Process Validation: A Lifecycle Approach, TR 60, 2013
- PDA Process Validation of Protein Manufacturing, TR42, Oct 2006
- ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,
- ICH Q9 II.6 Quality Risk Management as Part of Production Validation

Thank You for your Attention! May we be of Further Assistance?



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