# Sampling in an Aseptic Process

# Risk Mitigation & Regulatory Compliance

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PDA
Parenteral Drug Association

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# Agenda

1. Introduction to Sampling – Where, What & Challenges
2. Regulatory recommendations and corresponding needs – Key Drivers
3. Complexity and Risks of traditional sampling methods
4. Key considerations for Closed & Disposable sampling options

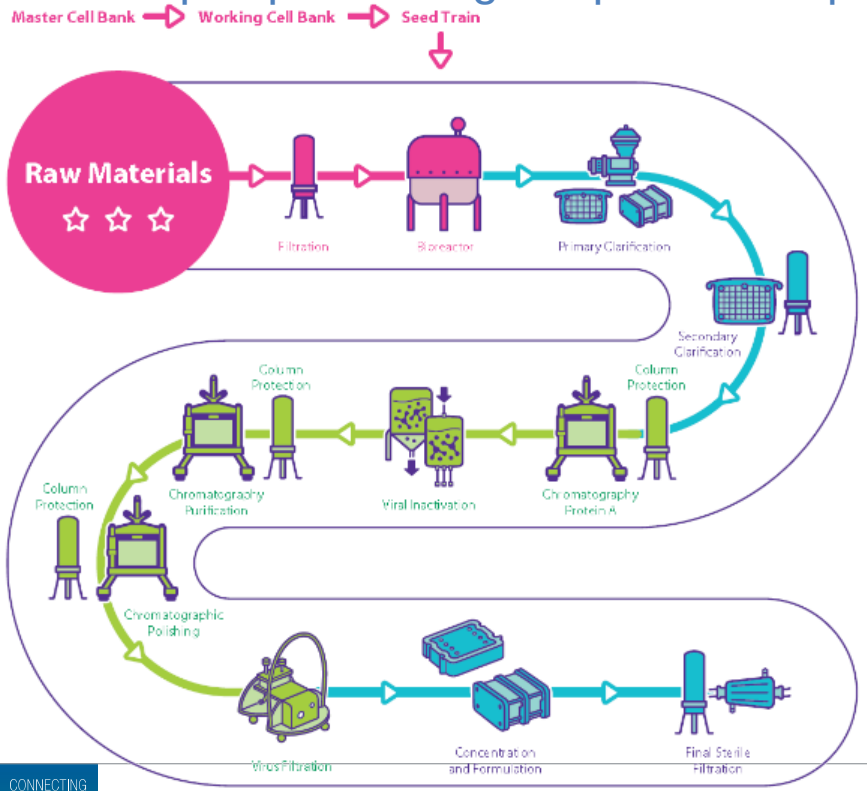
# Introduction to Sampling

# Where, What & Challenges

# Biopharmaceutical Drug Manufacturing



## Aseptic processing – A path full of pitfalls…



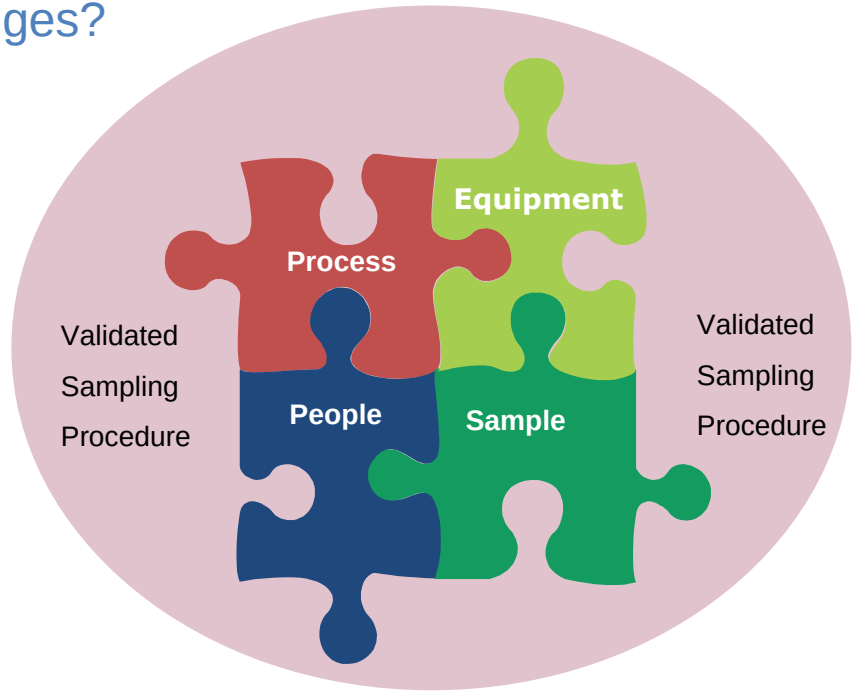

Biopharma manufacturing operations require substantial precautions to prevent microbial ingress:

1. Highly trained personnel
2. A risk-based approach to contamination control and a dedicated strategy
3. Resulting in significant costs:
   - Infrastructure
   - Day-to-day operations

# Introduction to sampling

## What are The Requirements and Challenges?

- Representative Sample :
  - Composition
  - Non-operator dependent
  - Repeatable
- Protect the Process (Contamination-free)
- Protect the Person (Contained)
- Protect the Product (Contained)
- Easy of Use
- Save Time and Cost Efficient




In today's biopharmaceutical market, sampling is critical during every step in the manufacturing process. An imprecise or false positive result can lead to a quarantine as well as the need to repeat the analysis.

# Sampling in Bioprocesses

**Where to Sample**

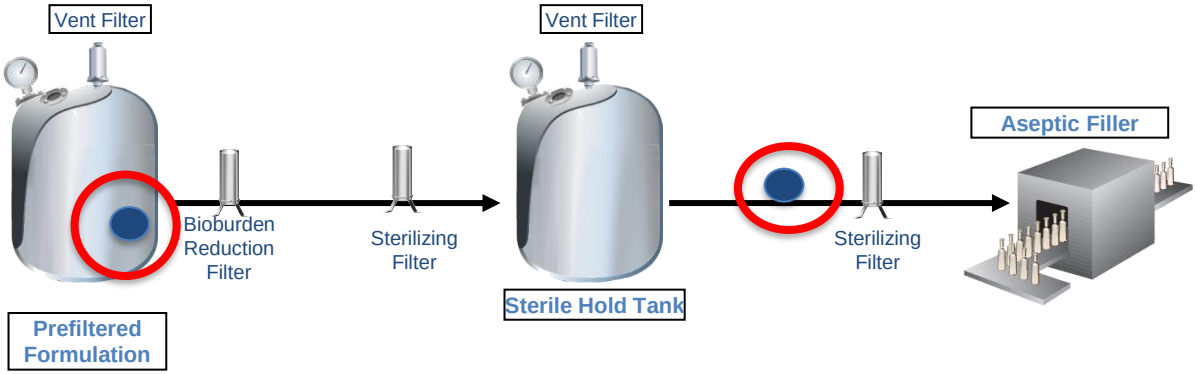
| | Bioreactor Seed train | Buffer/Media Preparation | Bioreactor Production | Purification | Sterile FIltration |
|---|---|---|---|---|---|
| pH | ✓ | ✓ | ✓ | ✓ | ✓ |
| Conductivity/ Osmol | ✓ | ✓ | ✓ | ✓ | ✓ |
| Cells | ✓ | | ✓ | | |
| Metabolites | ✓ | | ✓ | | |
| Protein analysis | | | ✓ | ✓ | ✓ |
| Bioburden & Archiving | ✓ | ✓ | ✓ | ✓ | ✓ |
| Endotoxin | ✓ | ✓ | ✓ | ✓ | ✓ |
| Other (virus, by products) | ✓ | ✓ | ✓ | ✓ | ✓ |

# Sampling plan & options

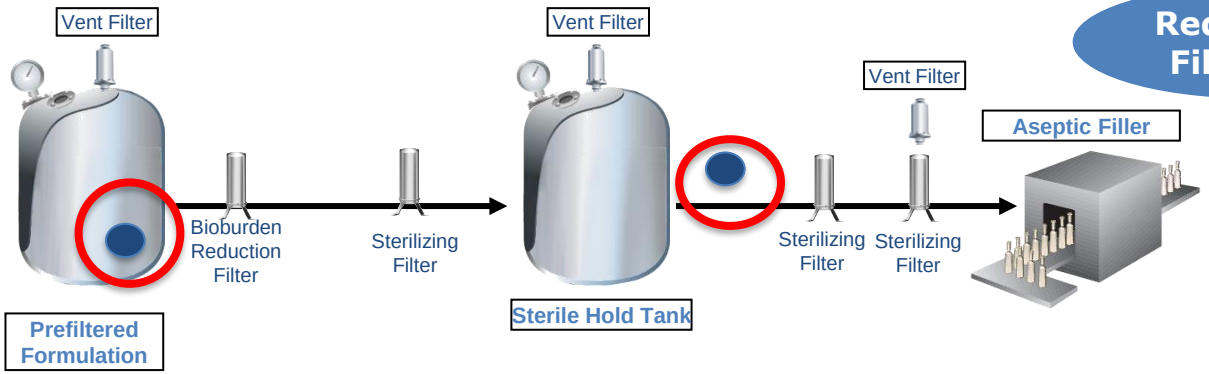
## Final Filling

Where to Sample

Sampling point



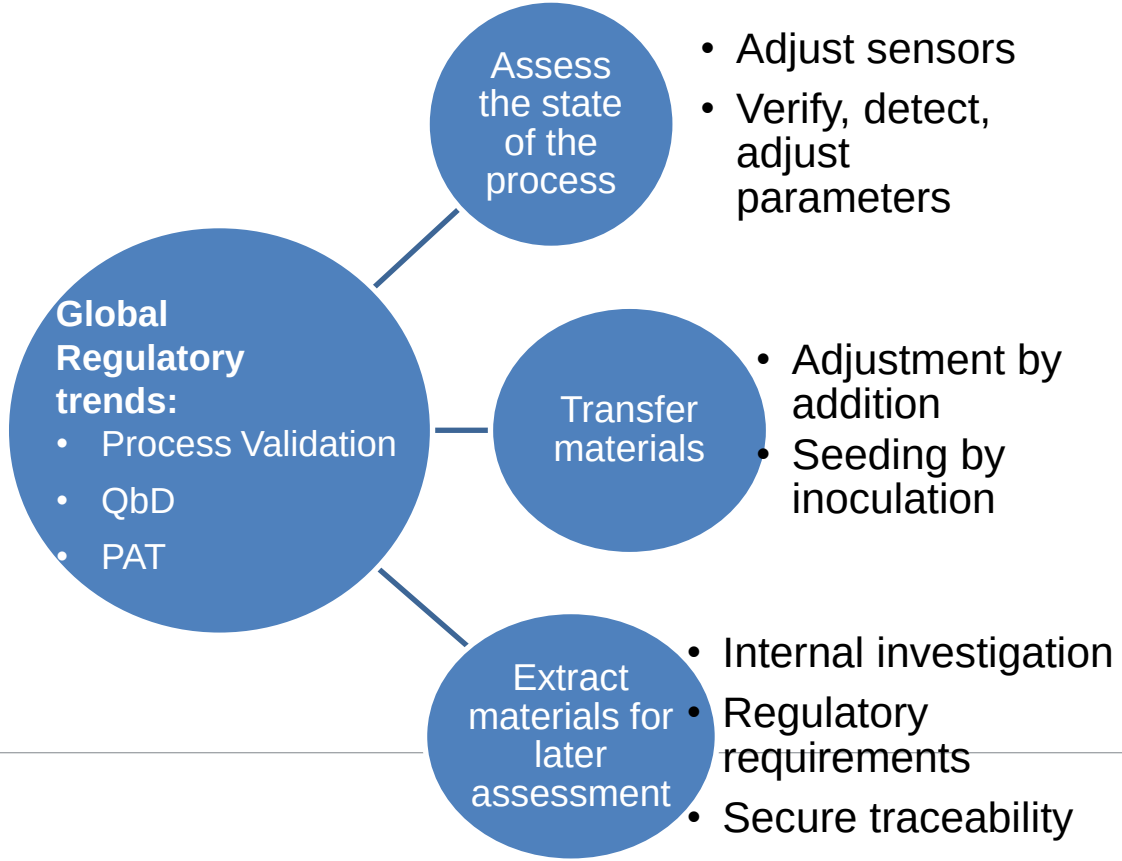

Single Sterilizing Filter




Redundant Filtration

# Regulatory recommendations and corresponding needs – Key Drivers

# Drivers for Aseptic Process Sampling



# Relevant Regulatory Agencies & Industry Associations

| Regulatory Agencies / Industry Associations | Relevant Documentation |
|---|---|
| Food and Drug Administration | cGMP guidance |
| World Health Organization | **Annex 2** – Good manufacturing guidance for API<br>**Annex 4** - Good Manufacturing Practices for pharmaceutical products: main principles |
| European Medicines Agency | GMP Annex 1 - Manufacture of Sterile Medicinal Products |
| International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use | ICH Q7 – GMP guidance for API |
| Parenteral Drug Association | Report #69 - Bioburden and Biofilm Management in Pharmaceutical Operations |
| The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme | Guide to good manufacturing practice for medicinal products – Part I |

# Extracts of Relevant Requirements

| Recommendations | Source |
|---|---|
| Contamination control<br>&<br>Monitoring before bioburden reduction | • **PICS/S – FDA cGMP** – Part 1 §5.19 –f<br>  • Use of closed system recommended from phase 1<br>• **WHO Annex 4**<br>  • "The use of disposable sampling materials has distinct advantages"<br>• **WHO Annex 2 - ICH Q7A** - GMP guidance for API<br>• **EU GMP Annex 1**<br>• **EudraLex** – Vol 4 – Part II – 2009 |
| Operator bias elimination | • **WHO Annex 4**<br>• **FDA**<br>• **European Pharmacopeia** - Guidelines for Sampling of Pharmaceutical Products and Related Materials |
| Representative sample | |
| Health & safety focus | |
| Retained samples | • **FDA cGMP** Guidance for the industry investigational drugs section F. Laboratory Controls / 1. Testing<br>• 2 years after expiration date / completion of trial and twice the quantity necessary to perform all tests |

# Sampling Process & Precautions

## WHO Annex 4: Preparation for sampling

- "All sampling tools and implements should be made of inert materials and kept scrupulously clean. […]."
- "The cleaning procedure used for all sampling tools and implements should be documented and recorded."
- "The use of disposable sampling material has distinct advantages"

## WHO Annex 4: Sampling Operations and Precaution

"There should be a written procedure describing the sampling operation. […]. It should ensure that representative samples are taken in sufficient quantity for testing in accordance with specifications."

## WHO Annex 4: Storage and Retention

"The container used to store a sample should not interact with the sampled material nor allow contamination. […]. As a general rule the container should be sealed and preferably tamper-evident."

World Health Organization

# Sampling of Pharmaceutical Products and Related Materials


- FDA cGMP for phase 1 drugs
  "recommends the use of closed system to minimize the risk of contamination"
- Guidance for the industry investigational drugs section
  F. Laboratory Controls / *1. Testing*
  "We recommend that the sample consist of a quantity adequate to perform additional testing or investigation if required at a later date […]. We recommend that you appropriately store and retain the samples for at least two years […]."
- Q7A GMP guidance for manufacturing API – section C. In-process Sampling and Controls (8.3)
  "In-process sampling should be conducted using procedures designed to prevent contamination […]. […] ensure the integrity of samples after collection."

# Annex 1 EU GMP (Draft)

## Regulatory requirements

**8.94 Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. Systems for taking samples should be designed so as not to introduce contamination.**

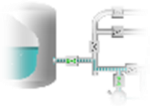
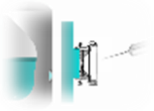
**9.7 Sampling methods should not pose a risk of contamination to the manufacturing operations.**

**7.3 Non-essential processes such as product inspection and in process testing should be conducted with the crimping option there is a validated and easy disconnection in place to further treat the sample outside the clean areas wherever possible.**

# Complexity & Risk of Traditional Sampling Methods

# What are the Ways to Sample?

## Traditional sampling: Pros, Cons and Limitations

| | Open Sampling Valve | Steam in place valve | Septum sampling | Aseptic Connectors | Tube Welding |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| + | **Large number of samples**<br>Low cost per sample | Large number of samples<br>**Closed sampling**<br>Low cost per sample | **Large number of samples**<br>Low cost per sample | Flexible & Reliable<br>Aseptic sampling<br>**Safe and disposable** | Large number of samples<br>**Aseptic sampling**<br>Flexible |
| − | Dead-leg<br>**Loss of product** (flush)<br>Open sampling<br>Impossible to sterilize | Complex operation (SIP)<br>Safety hazard (heat)<br>**Risk of sample dilution**<br>Container limitations | Not steam sterilizable<br>Safety hazard (needles)<br>**Sample volume limitation** | **Extra cost**<br>Potential dead-leg (tubing)<br>Limited disconnection | **Waste of product**<br>Requires utility<br>Piece of hardware |
| × | **High risk of contamination**<br>Operator & Process safety<br>Sample representativeness | Operator training & safety<br>**Sample representativeness** | **High risk of contamination**<br>Operator safety<br>**Sample representativeness** | **Operator training** | **Requires maintenance**<br>Operator training |

# Complexity and risks of traditional sampling methods

- FDA Warning letters (483) issued in 2015
- 104 – Procedures designed to prevent microbiological contamination of sterile drug products not established, written or followed
- 24 – Representative samples not obtained

Microbial contaminations during manufacturing

- Increases risk
- Results in enormous cost
- Requires complicated investigations to prevent reoccurrence

FDA U.S. FOOD & DRUG ADMINISTRATION

**Cost of sampling VERSUS cost of a shut down**

# Biologics in-process contamination

30
Percent

1-6
Months

1-14
Million Euro

*Percent of process deviations caused by contamination**

*Length of time to complete an investigation*

*Operations cost*

*Source Langer 2013, Wiebe 2014

# Biologics in-process contamination

30
Percent

1-6
Months

1-14
Million Euro

## *Impact*

- Productivity losses
- Material replacement costs
- Batch loss
- Interruption of product supply
- Delay in clinical development

*Source: Langer 2013, Wiebe 2014

# Key considerations for Closed & Disposable sampling options

# Considerations for adopting single-use

## Aseptic sampling

| Situations | Implications |
|---|---|
| Contamination of samples (out of in process specifications) | • Product batch on-hold<br>• Internal investigations<br>• Additional tests on final product<br>• Conflict between manufacturing and QAQC<br>• Risk of remarks from regulatory inspectors |
| Contamination of process | |
| Complex sampling procedure | • Risk of false results<br>• Frequent operator training<br>• Unhappy operators<br>• Internal investigations |

# Considerations for adopting single-use

## Aseptic sampling


- Labor costs
- Process/ product downtime
- Scrap of batch due to contamination
- Investigations for product/ process deviations

- Purchase price
- Taxes
- Freight
- Inventory costs

# Self-assessment: Am I suitable to adopt single-use Aseptic sampling?

| Considerations | Strong NO → Strong YES | | | Considerations | Strong NO → Strong YES | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | | 1 | 2 | 3 |
| It is difficult to implement changes to my infrastructure (e.g. piping). | | | | There is high risk of bio-contamination in my process. | | | |
| There are challenges to conduct cleaning validation. | | | | My current sampling method has risk of cross-contamination. | | | |
| My operators are very familiar with plastic components in the process. | | | | I need to collect samples anywhere. | | | |
| I have limited process time to prepare sampling assemblies (traditional). | | | | I need to collect large numbers of samples. | | | |
| I have limited cycle time. I need quick turnaround between batches. | | | | I require a varied range of sampling containers. | | | |
| I am concerned about operator safety. | | | | My process is sensitive to price. | | | |
| I have limited resources for operator training. | | | | | | | |

# Sterile sampling value assessment

## Case study example

### Background

Replace standard open sampling with NovaSeptum® sterile sampling assembly

### Outcome

10%

Overall cost reduction

### Key facts

| | |
|---|---|
| 62% | Reduced labor hours |
| 35% | Reduced product loss during sampling |
| 80% | Reduced deviation costs |
| 400 | Autoclave cycles eliminated |

NovaSeptum Total Cost of Ownership Youtube Video

# Conclusions

- There are complexity and heightened risks in using traditional sampling methods.
- Regulatory recommendations are in place and single-use aseptic sampling could help meet/exceed those corresponding needs.
- There are several key considerations to design/optimize your sampling plan.

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# Thank You

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