Exercise 4: Set Up of Sterile Filtration

PDA
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TRAINING

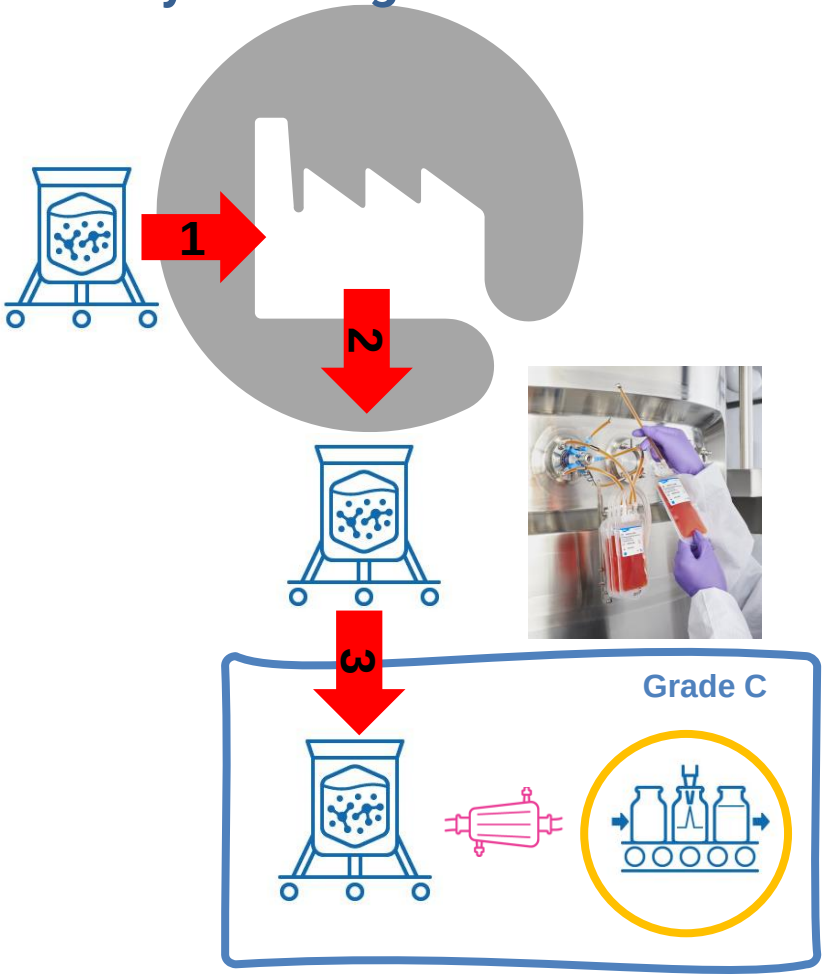
Session Content

- Best design practice: build your filtration set (Simone Biel)
    - 2 case studies will be discussed to build the appropriate filtration set-up
- Handling of sterile connection device to connect to the filling operation (Simone)
    - Every participant to practice a sterile connection
    - How does it work? (video)
- Handling of filtration process: wetting, flushing, filter integrity testing (Marco Klatte)
    - Live demo of the filtration process and best practice considerations

Build your filtration system

Case Studies

Case Study 1 – Large Batch Size



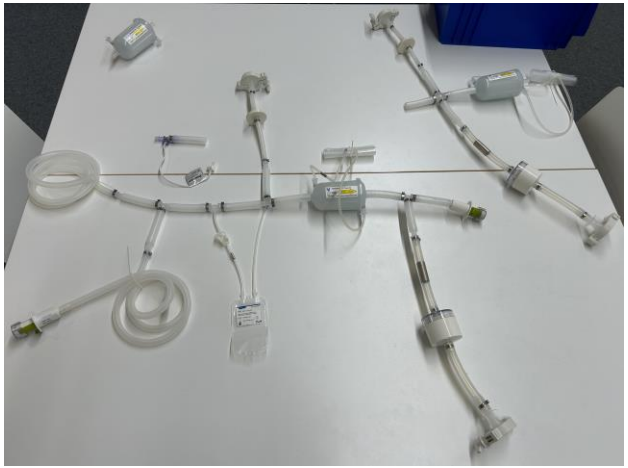
ParentiPharma is manufacturing monoclonal Antibodies. The final bulk drug product is filled into 200L closed stainless steel tanks, frozen, and shipped to the filling facility.

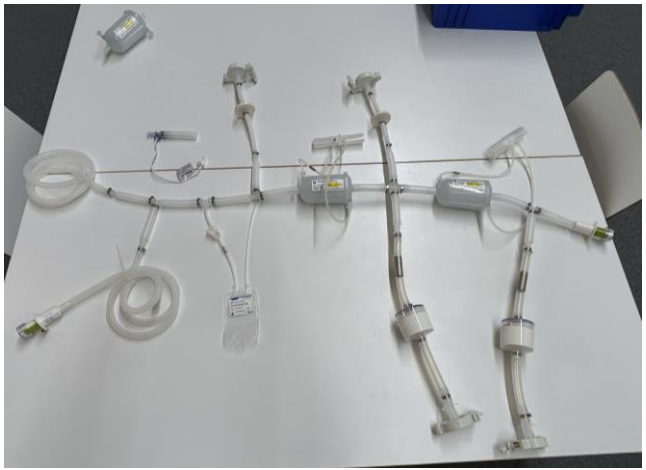
1) Reception and transfer to CNC area
2) Bioburden incoming control: sampling using a closed sampling system
   - ✓ bioburden is always below 10 cfu/100 ml
3) Transfer into Grade C cleanroom area
   - ✓ no further processing of the bulk before filtration
   - ✓ connection of the tank to the filtration set using a sterile connector to assure no change of bioburden level before filtration

- **Filtration characteristics of the product are well known**
- Historical experience: **never failed filter integrity test**
- **Annex 1 compliance required**
  - PUPSIT and post-use testing in line
  - bioburden sampling

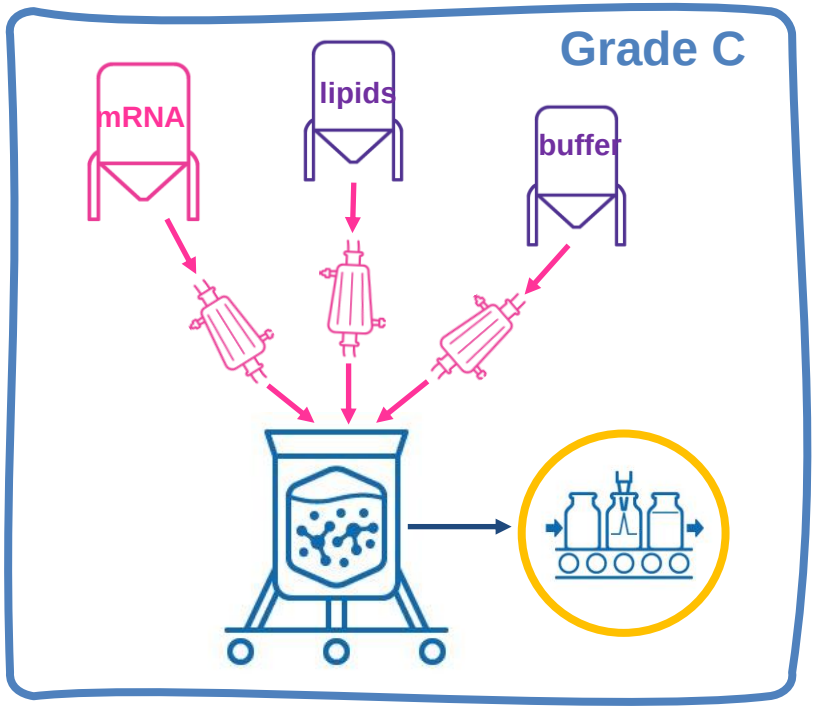
Some discussion topics:

- **Redundant vs single filtration**: not really necessary as filtration characteristics of the product are well known (easy to filtrate) and historical experiences (never failed integrity test). Therefore, one team built a single filtration while the other team considered redundant as they still wanted to keep business risk low considering mAbs quite expensive.
- **PUPSIT**: is included in the design in both cases for Annex 1 compliance although it is known that product doesn't have filter flaw masking effect and never faced filter integrity. However, PUPSIT provides additional business assurance in this case – one more reason to consider a single filtration instead of a redundant filtration (one business assurance measure would be sufficient, or a risk assessment could help to understand if redundant filtration adds additional assurance if PUPSIT is already applied).
- **Bioburden reduction filter**: was not included as a precaution as the process (low bioburden drug substance manufacturing and formulation) is very robust and bioburden requirement of 10 cfu/100 ml is always met. An additional pre-filter would increase the risk of leachables, adsorption.
- **Bioburden sample**: Annex 1 requires "*Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration*." Therefore, a sampling bag was included before the sterile filter. We could consider that this additional bioburden sample before the sterile filter being not necessary as the product bulk is not further processed and kept closed (connection to filtration via sterile connector). However, this would need discussion with the inspector. Other aspects such as time between bulk sampling and filtration/filling operation to be considered.
- **Bioburden sample of a redundant filtration set-up**: "*In case where a redundant filtration set-up is used, it should be taken prior to the first filter*." (Annex 1)
- **Pressure sensor**: Annex 1 requires to measure the pressure difference across the filter. Therefore, pressure sensors should be included before and after the filter (not shown here).





Case Study 2 – Small Batch Size



LipidoGenix is manufacturing mRNA in LNP (lipid nano particles) in batch sizes of 10L.

- mRNA/LNP is an ATMP (Advanced Therapy Medicinal Product)
- Final product (in LNP encapsulated mRNA) cannot be filtered
- mRNA (active substance), lipids and buffers (excipients) are sterile filtered before encapsulation and formulation
- The product is very expensive and batch release right the first time is key
- Filtration studies have shown that the mRNA tends to block the filter

Considerations

- ATMP in scope of Annex 1?
- Active Substance in scope of Annex 1?
- Small batch size: PUPSIT or risk assessment?
- Redundant filtration: yes or no?

Some discussion topics:

- **Annex 1 and ATMP:** There is a stand alone GMP guideline for ATMPs (EudraLex Volume 4, part IV): "*These Guidelines are specific to ATMPs. Other documents developing GMP requirements for medicinal products which are contained in Volume 4 are not applicable to ATMPs, unless specific reference thereto is made in these Guidelines*." → §9.67 of this guideline outlines "*Additional guidance on sterilisation methods can be found in Annex 1*".
- **Active Substance and Annex1:** the scope outlines "*The manufacture of sterile products covers a wide range of sterile product types (active substance, excipient, primary packaging material and finished dosage form)…*"
- **Redundant vs single filtration**: Batch release right the first time is key (drug availability for the patient and very expensive product), therefore, redundant filtration was selected to assure batch release.
- **PUPSIT**: is included in the design as the product indicates potential filter flaw masking effect.
- **Bioburden sample**: Annex 1 requires "*Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration*." See also considerations of Case 1. For very small volumes it may be worthwhile to discuss if both, sample from bulk and before filtration, are needed (my personal opinion!).
- **Bioburden sample of a redundant filtration set-up**: "*In case where a redundant filtration set-up is used, it should be taken prior to the first filter*." (Annex 1)
- **Pressure sensor**: Annex 1 requires to measure the pressure difference across the filter. Therefore, pressure sensors should be included before and after the filter (not shown here).

Another proposal discussed in group 1 for difficult to filter products: put two filters in parallel. If one filter starts clogging switch to the second filter.

General comments

- Sometimes, PUPSIT is more important for “small volumes” than for “large volumes”
- Redundant filtration is to reduce the business risk – if needed!! It should be investigated if there is an additional benefit (see Case Study 1) as other risks (e.g., leachables, complexity, adsorption) may be introduced
- Both assemblies include inlet tubes for product as well as for water (or formulation buffer). Pros and cons were discussed during the presentation.

There is no one filtration set-up fits all! And it needs of course more than 45 minutes to get to the right design ☺!

Sterile Connection Device

- Link to the video: https://www.merckmillipore.com/DE/de/Mobius-Single-Use-Manufacturing/connect-disconnect-tubing/Nqmb.qB.xg0AAAFZG5BiYtcZ,nav