QP Decision Making

Tara Hogan
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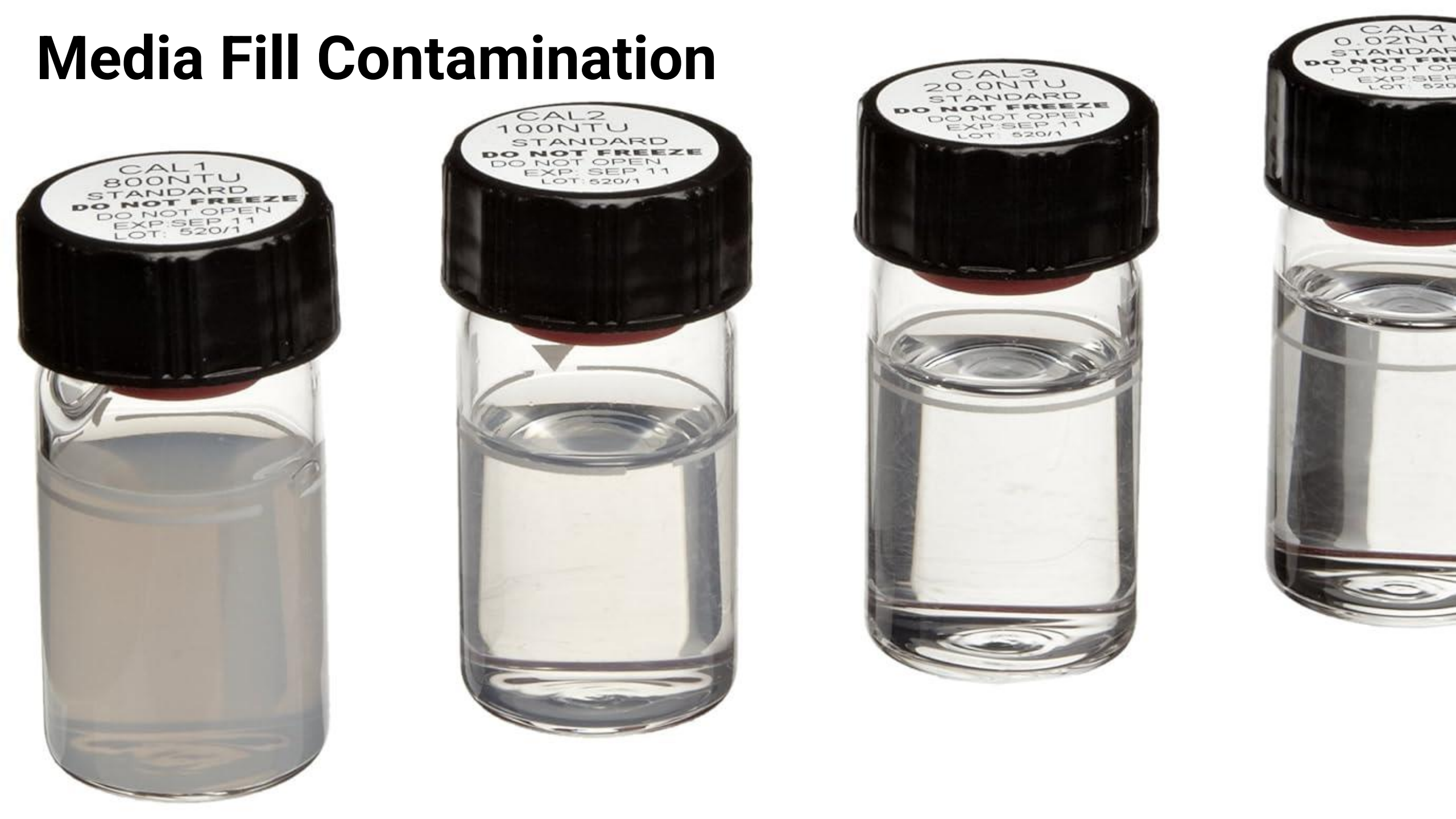
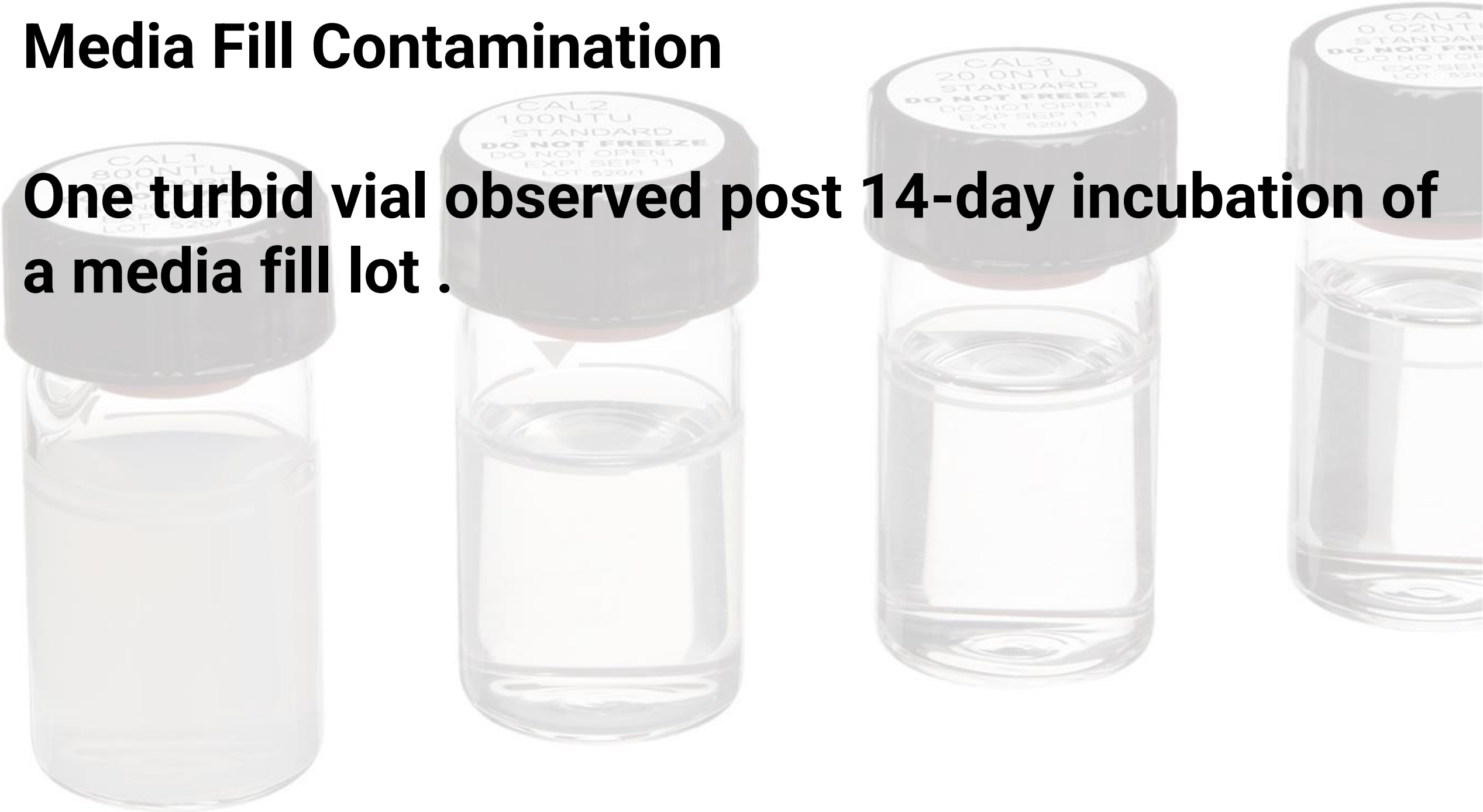
Amgen Technology Ireland

Media Fill Contamination



Media Fill Contamination

One turbid vial observed post 14-day incubation of a media fill lot .



Media Fill Contamination

One turbid vial observed post 14-day incubation of a media fill lot .

- What does this mean for the media fill?
- What do you do next?

Media Fill Contamination

Media Fill Contamination

Two turbid vials observed post 14-day incubation of a media fill lot .

What immediate actions should be taken

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Two turbid vials observed post 14-day incubation of a media fill lot .

What immediate actions should be taken

Manufacturing

Disposition

Notification

Cross-functional team

Lot Tying Strategy

128 lots manufactured since the last media fill

102 have been released and on the market
26 are within the company's control
12 lots on the market are needed to maintain critical patient supply

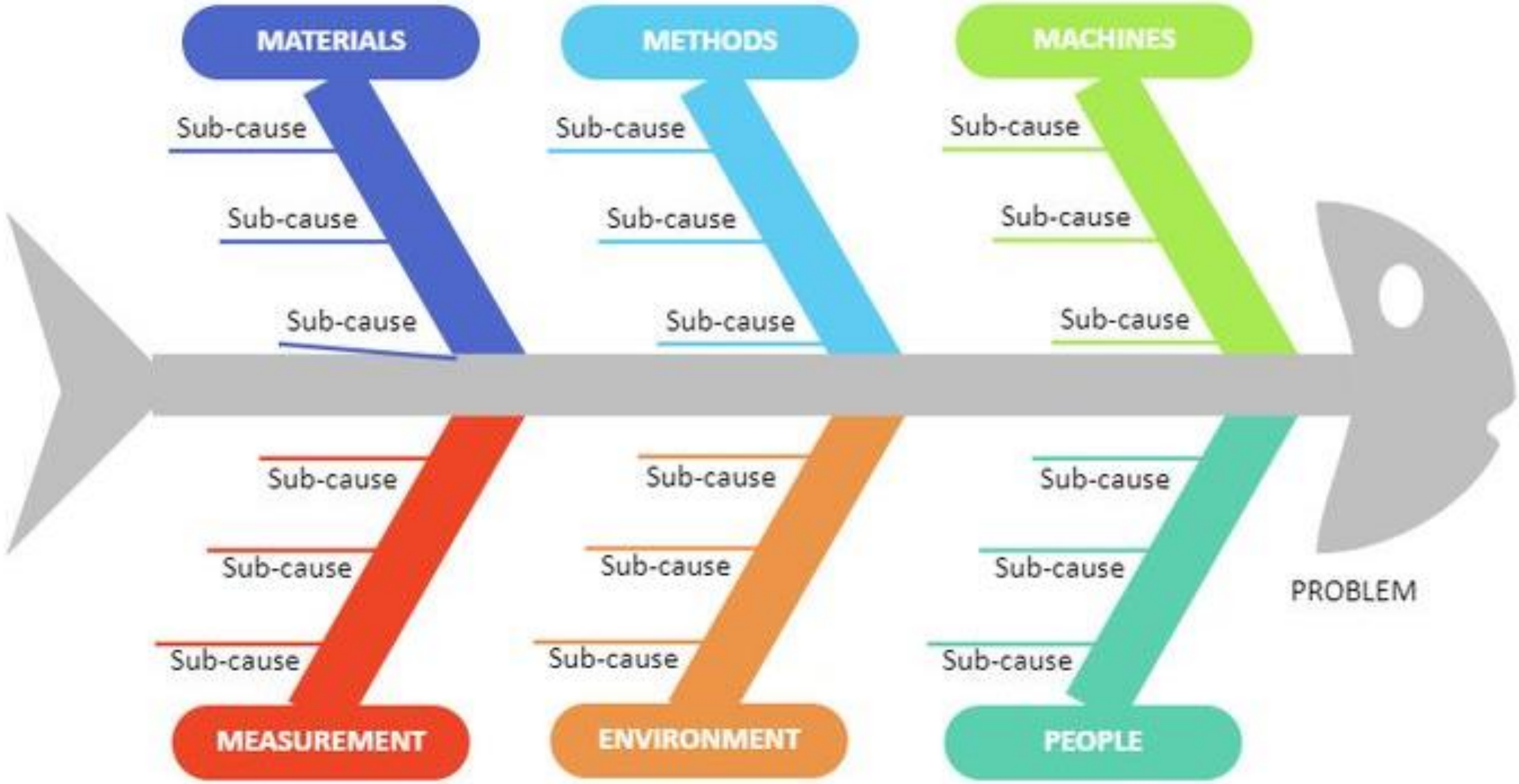
Lot Control Strategy

128 lots manufactured since the last media fill

102 have been released and on the market
26 are within the company's control
12 lots on the market are needed to maintain critical patient supply

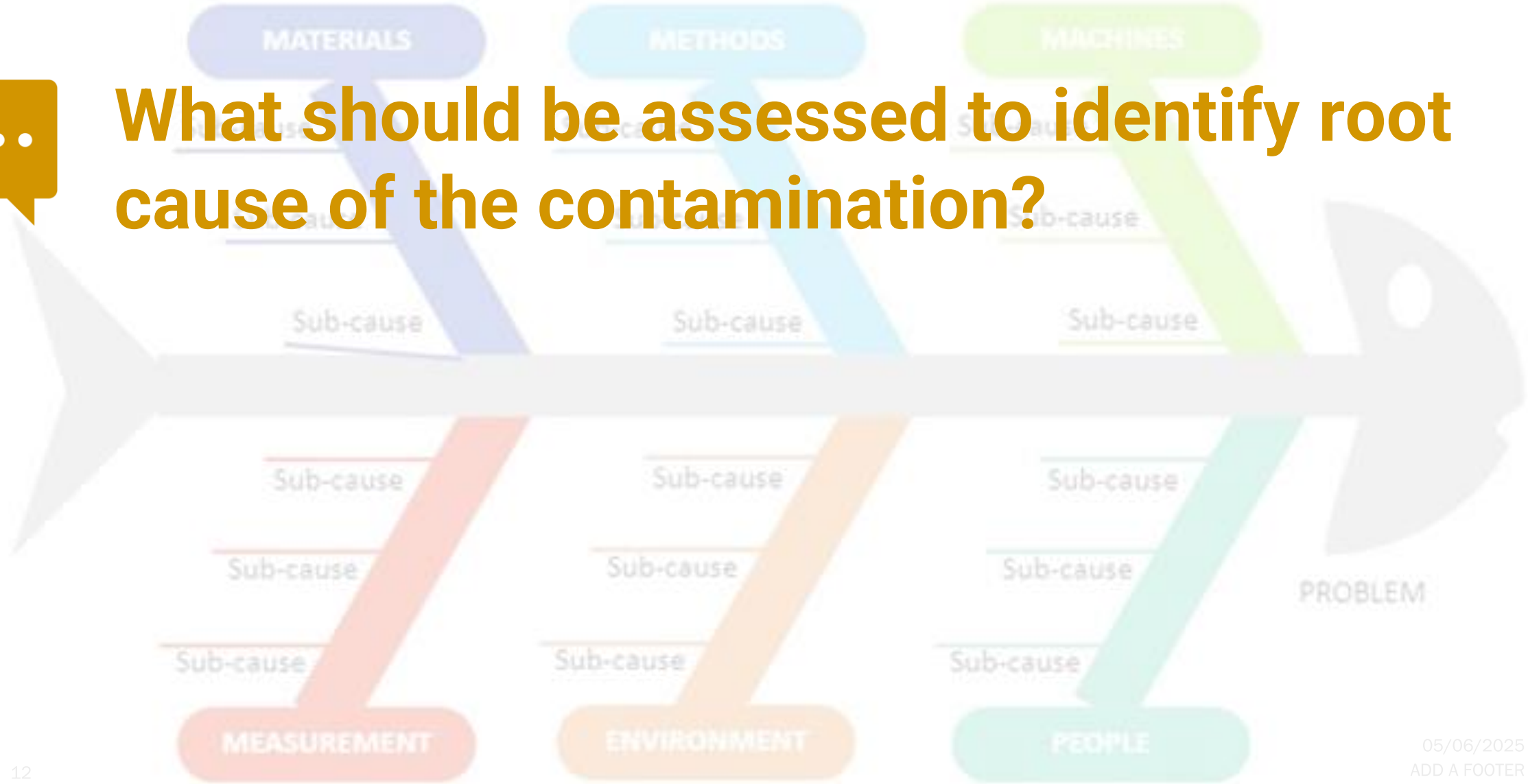
What action should be taken on which lots?

Root Cause Analysis



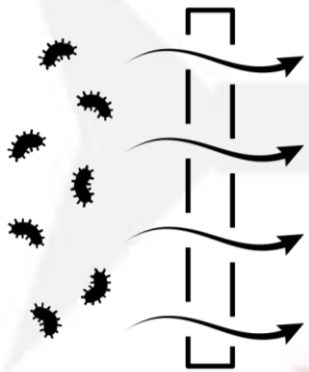
Root Cause Analysis

What should be assessed to identify root cause of the contamination?



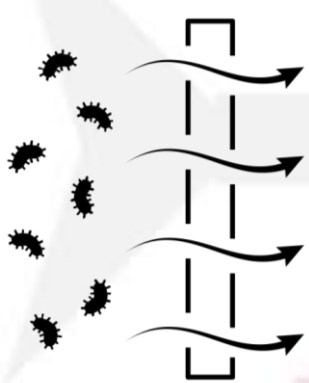
Root Cause Analysis – Part 1

What should be assessed to identify root cause of the contamination?



Root Cause Analysis – Part 1

What should be assessed to identify root cause of the contamination?



The contamination in both units was confirmed to be Staphylococcus epidermis

Root Cause Analysis – Part 2

There was one non-qualified intervention completed during the batch

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Lot Scoping – Part 2

You have another identical line where this person works.

What does this mean for the lot tying strategy?

Lot Scoping – Part 2

You have another identical line where this person works.

What does this mean for the lot tying strategy?

Now you have root cause and CAPAs, what is the strategy for return to operations?

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QP Forum

Niamh McCullagh

13th May 2025

Problem Statement

BDS Inc. is a Contract Manufacturing Organisation (CMO) involved in the manufacture of biologic drug substance.

The final purification step for the biologic drug substance is Ultrafiltration/ Diafiltration (UF/DF) which functions to concentrate the protein of interest to the desired target concentration and to exchange the buffer matrix to drug substance matrix conditions.

After UFDF step, the bulk drug substance is collected into a Single Use Mixer (SUM) where it is held under slow agitation until it is passed through a 0.2um filter and filled into containers using an automated bulk filling system.

The containers of biologic drug substance are then frozen to facilitate onward shipment to Client-nominated filling/finishing sites.

A sample of the bulk drug substance is taken directly before 0.2um filtration and filling.

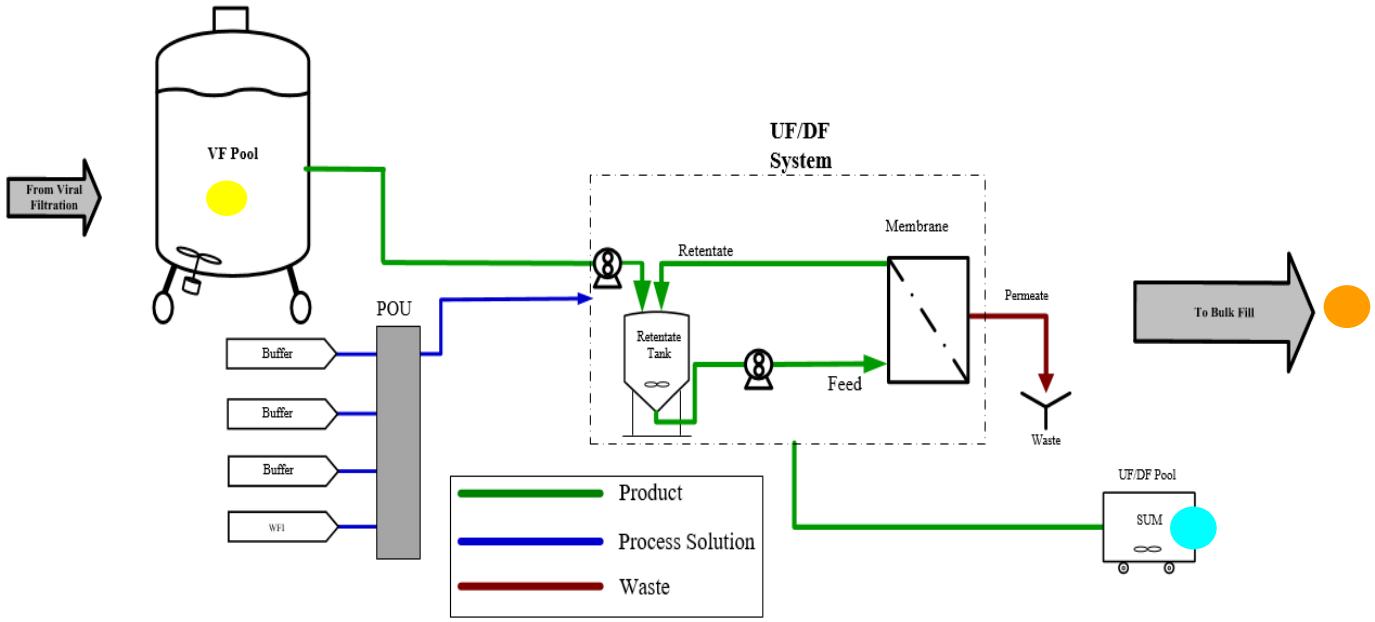
QC notifies you that an OOS result of 111 CFU/10ml (specification ≤100CFU/10ml) has been obtained for the pre-filtration bulk drug substance sample for Batch 1 in a campaign of PRODUCT XYZ. The endotoxin result for same sample is <0.5EU/ml (specification ≤3.0 EU/ml). Batch 1 is stored on-site in the freezer.

What are your initial actions?

What questions are you asking of the QC team?

What questions are you asking of the MFG team?

Root Cause Analysis (Fishbone, Time of Events, GEMBA, Batch Data and Events Review)



Sample	Bioburden	Endotoxin
Viral Filtration (VF) Pool	Pass	Pass
UFDF Pool	111CFU/10ml (OOS)	Pass
Release (From filled container)	Pass	Pass

GEMBA- Focus on the UFDF Skid:

- Walkdown of UFDF skid performed by cross-functional team with cross-check against flowpath diagrams and recipe flowpaths (cleaning, process, storage).
- Key locations identified on the UFDF skid- each location was visually inspected and then swabbed.
- Swabs incubated in TSA and R2A showed growth on R2A of a gram negative rod-shaped micro-organism. Correlation between microbial recovery and presence of liquid droplets at some locations.

Impact Assessment

Root Cause was established. CAPAs were identified and implemented.

Next step.....Impact Assessment.

- Validation and Regulatory Impact Assessment.....

  What factors should be considered?

  As a QP in a CMO, where you do find supporting information?

- Patient and Product Impact Assessment.....

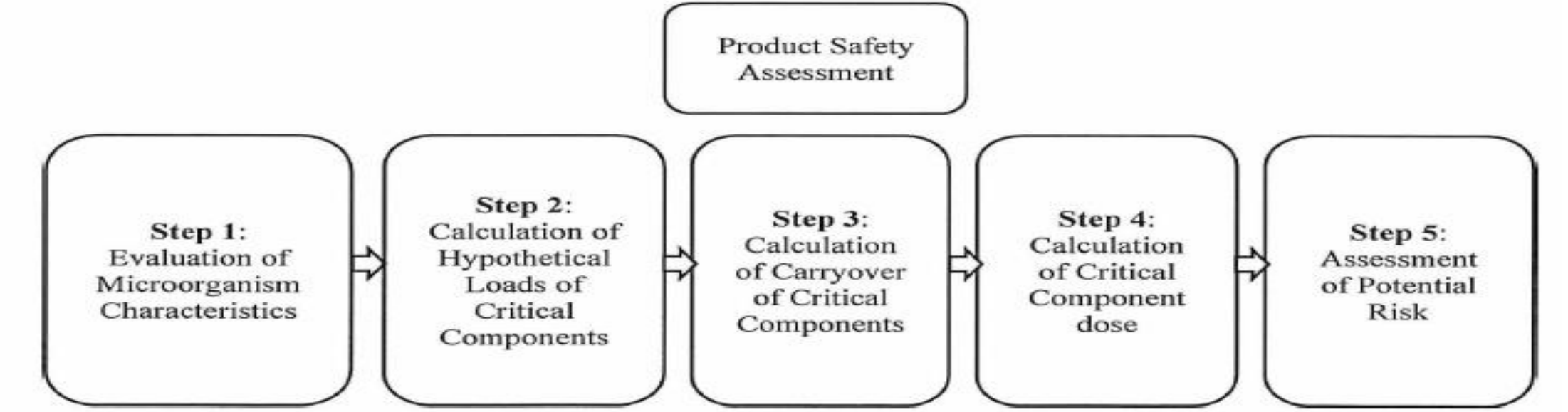
  What factors should be considered?

  Do you need any more information before making your final disposition?

Impact Assessment

Specific assessment for non-sterile low bioburden intermediates???

Product safety assessment for microbial contamination in non-sterile process intermediates



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Thank You

CRDMO
EVERY BIOLOGIC CAN BE MADE

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QP Forum

Alan Tinsley

13th May 2025

QP Decision Making

Scenario:

Manufacture of BDS under contract to client (MAH).

QP is informed of potential critical deviation impacting a completed batch with a potential breach of the registered details.

QP situation:

How do you navigate through to a defendable decision on the fate of the impacted batch?

What do you take into consideration?

What supports can you leverage?

QP Decision making

Considerations:

Your place in the supply chain?
Confirming partial manufacture under contract to the MAH, are you certifying to the market as MAH?

Further processing steps outside of your quality oversight?
Will the receiving site accept this batch?

Local procedures, immediate actions?
Raise a quality record, immediate containment measures, inform all stakeholders.

Quality agreement obligations?
Engage with the client.

Define scope
Has this happened before, previous batches impacted? Any batches in progress? Any batches in the market?

Define the problem statement(s)

OOS, breach of registered details

QP Decision making

Supports to leverage:

Local procedures and RCA tools
Batch data
Internal subject matter experts
External consultants
GMP Guidelines – Annex 16
Health Authority

Annex 16 – Guidance based on a real scenario

Manufacture of BDS under contract to client (MAH).

QP is informed of potential critical deviation impacting a completed batch with a potential breach of the registered details.

Definition of a batch is a single paragraph within the dossier that could be interpreted in a number of ways.

The Client (MAH) has interpreted the events described in the deviation as being a breach of the definition of a batch, hence a deviation from the details contained within the MA.

QP referred to Annex 16 Guidance, Section 3, Handling of Unexpected Deviations to support QP decision on the batch:

"Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, a QP may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical control methods from details contained within the MA and/or GMP has occurred."

Annex 16 Guide - breakdown

1. The deviation should be thoroughly investigated and the root cause corrected.

Deviation raised, investigation conducted, root causes identified, CAPAs identified and in implementation.

2. This may require the submission of a variation to the MA for the continued manufacture of the product.

There is no impact / alteration or proposed change to process parameters - no breach of CPPs /KPPs as a result of this deviation. No variation required.

3. Evaluation of the potential impact of the deviation on quality, safety or efficacy of the batch(es) concerned and conclusion that the impact is negligible.

All data gathered meets acceptance criteria and no impact to product CQA's is concluded. In the case of a recall there is full genealogy available.

4. Consideration of the need to include the affected batch(es) in the ongoing stability programme.

Client engagement required - DS or Final drug product to be placed on stability?

5. In the case of biological medicinal products, consideration that any deviations from the approved process can have an unexpected impact on safety and efficacy.

Investigation concluded that approved process was adhered to as per the dossier.

6. Taking account that responsibilities may be shared between more than one QPs involved in the manufacture and control of a batch, the QP performing certification of a batch of medicinal product should be aware of and take into consideration any deviations which have the potential to impact compliance with GMP and/or compliance with the MA.

Certifying QP engagement via client - Will Client QP agree to A16 release?

Outcome

What options exist?

1. Accept the batch under A16 deviation
2. Reject the batch

How would you defend your decision either way?

Post mortem

Once you have made your usage decision does it end there?

Factors to consider:

- Inspection
- Internal commercial pressure
- Client relationship
- GMP Implications
- Quality defect / Recall
- Where does your quality oversight end?

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QP Forum

13 May 2025

Antoinette Kelly

Head of Quality
Alexion AstraZeneca

QP Scenario Problem Statement

- Phil Pharma are a Drug Product fill finish facility, filling in a VHP sterilised isolator. On a Tuesday morning midway through the filling of batch 12345 QA were informed by Operations that the final fill drug substance (DS) bag 2 (of 4) was damaged and a leak had occurred.
- The leak was identified as operations ***transferred the DS bag onto the isolator load cell in Grade C, outside the isolator***. The leak occurred from a tear in the Drug Substance (DS) bag at the point where the tubing extends from the bag, to enable connection to the filling manifold.

***Note all product contact components are single use**

Immediate Actions

- Inform & collaborate with QA, Sterility Assurance walk the issue & agree a path forward
- Contain – It was confirmed that the filling manifold had been clamped prior to transfer of the DS bag from the product trolley to the isolator load cell (all in Grade C).
- Clean – Perform clean of the Grade C area & ensure Operators has re-garbed.
- Ensure sterility is maintained - Change out the filling manifold in Grade A under a qualified intervention & progress to filling bags 3 & 4
- Segregate - Vials filled from product bags [1] & [2] & [3, 4] to be segregated
  - Bag 1 (BN 12345) All filled vials were segregated from DS bag 2 by re palletising the trays that had been removed from the line prior to connection of DS bag 2 to the filling manifold
  - Bag 2 (BN 12345 -1) Vials filled from DS bag 2 prior to tear. Remaining DS in 'torn' bag disposed
  - Bag 3 & 4 (BN 12345 - 2) Filled after path forward agreed
- Take additional suite of samples – Sample each segregation as if they are 3 unique batches (End/Bio/Sterility)
- Documentation – Raise Deviation to track the issue and Supplier Complaint to bag supplier

Investigation & Impact Assessment

- The investigation impact assessment encompassed all 3 segregations, specifically on impact to the vials filled from DS bag 2 prior to the leak/tear being noticed. *Note: Remainder of the DS bag was disposed
- Review of all objective evidence to support DS Bag 2 vials were not compromised/impacted:
  - Risk Assessment documented potential product quality risks – 2 risks identified and accepted based on below data
  - DS bag is connected to the filling manifold using a sterile connector
  - All tubing connected to the DS bag was manually clamped prior to movement from trolley to load Cell (Grade C)
  - No process control alarms occurred during the filling of DS bag 2
  - No out of spec fill weights occurred from review of the IPC report – indicates no change in back pressure/air introduced in the line of the DS bag thus no leak during filling
  - Manifold assembly is visually monitored for leaks – no leaks observed
  - Environmental monitoring & finished product test results all meet specification for the batch
  - Batch 12345 was put on stability program (annual commitment batch) – T_6 data available at the time of release – all results met shelf-life specifications
  - Supplier investigation supported no issue with the DS bag itself

Sequence of Events

17:53
16th July

Start of filtration of bag 2

Final fill product bag 2 held overnight

No leak observed

07:50
17th July

Filtration of product bag 2 complete.

No leak observed

Connection of product bag to the filling manifold

No leak observed

12:12
17th July

Filling line stopped to transfer product bag 2 to isolator load cell (approx. 30kg filled from product bag 2)

Clamped filling manifold and performed transfer of product bag.
Restriction noticed, tubing interlinked, manipulations required.

12:12 – 12:25
17th July

Gross leak identified
Noted garb was saturated & BDS pouring from product bag.
Filling of bag 2 did not restart.

12:30
17th July

Filling of product bag 2 did not proceed after leak identified
Remainder of Bag 2 disposed

Escalation - QA & Ops management notified.

12:30 – 14:00
17th July

Segregation & intervention 27 performed (Needles swabbed, needles & filling manifold changed).

Product bag 3 connected to new manifold, filling resumed

Sampling

12345
12345-1
12345-2

Sterility, particulate and endotoxin testing completed.
All results met acceptance criteria

Root Cause Analysis & CAPA

- Practical Problem Solving (PPS) RCA performed:
  - Machine/Material/Measurement/Manpower/Method/Environment
- **Method (Most probable RC)** - Insufficient instruction on appropriate handling of the DS bags during transfer from trolley to the load cell, ensuring tubing legs are not entangled/Inspect the product bags and surrounding area prior to the transfer to prevent damage/difficulty when transferring product bags
- **CAPA** – As an interim control an awareness session conducted on details of the deviation prior to commencement of next batch.
- SOP updated to…
  - Ensure tubing legs are free and not entangled prior to movement of DS bag when setting up on the product trolley & transfer to the isolator load cell.
  - Instruction to perform & document a visual inspection of the DS bag prior to transfer.

Thank you!