**Outsourcing Workshop : HYPOTHETICAL CASE STUDY COMPETITION**

**PART 2: Problems Encountered During Technology Transfer Process**

1. Process: During cell propagation in the stainless steel seed bioreactor, the CMO repeatedly experiences microbial contamination, wasting valuable materials and time. No single root cause can be found, but it is suspected there could be multiple sources in poorly designed and maintained pipework supplying CIP, steam, WFI, oxygen and buffers to the vessel.

   What options would you explore to resolve the issue? What would be the best option considering probability of success, and impact to project budget and timeline?

2. Quality: A buffer reagent sourced by the CMO is from a different manufacturer than that used at your site, but is ordered to the same specification you used in early process development work. It is suspected by the CMO that the raw material origin is the cause of atypical precipitation of the target protein in one of the unit operations.

   How would you contribute to the investigation and resolution of the problem?

*3.* Analytical: The sponsor is requiring the CMO to demonstrate that the final product have the exact same EXACT molecular weight (not average) and glycosylation pattern as the sponsor's R&D material, but your chosen CMO does not have the capability in house and has no established capable analytical vendors.

   How will you fill this gap? Who is responsible for the additional cost?

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**PART 3: Problems Encountered During Production, Testing, and Delivery of Phase I CTM**

1. Process: In the final purification run of the mAb, the collection of the mAb is based on the real time UV profile, with a cut-off range of a pre-determined UV value. Accidentally, the collection of material continued, and more material was collected than specified in the Master Production Record.

   What actions will you take, and will you regard the batch as failed and ask the CMO to produce a new batch at the CMO's expense?

2. Quality: After having carried out the quality control of the produced drug substance, it appears that the SE-HPLC target of more than 95% main peak was not reached. The content of di-and polymeric mAb was 5.5%, resulting in a purity of 94.5%.

   What actions will you take, and will you regard the batch as failed and ask the CMO to produce a new batch at the CMO's expense?

3. Analytical: A 1-minute power failure in the upstream part of the facility resulted in a down period of a major equipment of 1 minute, and data collection was fully re-established after 25 minutes. The mAb continuous cell culture (700L w/v) was on its fourth day in production mode.

   What actions will you take, and will you regard the batch as failed and ask the CMO to produce a new batch at the CMO's expense?

**ADDITIONAL QUESTIONS**

4. The litigation that was pending for your CMO is resolved with a finding against the CMO and the financial impact is staggering. The CMO is forced to lay off over one third of their work force. The CMO notifies you that they will not be able to meet the agreed upon time line. They estimate they can complete the project, but will be approximately three months late.

   What will you do? Cancel the contract, ask for financial concessions, other actions?

5. The CMO has a 2000 Liter reactor go down with an electrical problem. If the CMO you chose has redundancy, they can simply change over to the redundant system with minimal delay.

   If your CMO does not have redundancy, what steps will you take?

6. The endotoxin level measured for the first GMP batch is a little over the target specified and the CMO is in favor of releasing the batch, which is also stated in the deviation report.

7. Is that acceptable to you being the client (the endotoxin level in the intended dose is still lower than 5 IU/kg body weight)?

8. Upon intake of the drug substance, the Fill-Finish partner measures a different target protein concentration than specified in the QA-approved Certificate of Analysis.

   What action do you take?

9. During the second purification step, a human error results in a fatal deviation and the GMP batch is discarded.

   Who is liable?

10. The CMO informs you that another project is delayed and that it will occupy the facility for 2 extra weeks, thus delaying the start of your project.

    What action do you take?