

## CASE STUDY: IMPLEMENTATION OF A CONTINUOUS TECHNOLOGY STRATEGY TO SUPPORT THERAPEUTIC PROTEIN PRODUCTION

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### SITUATION

The meaning and the objective of continuous manufacturing, for us, is to intensify the processes. For the upstream side, it's perfusion cell culture and for downstream it's about using parallel operations like multi-column capture and flow-through technologies. It's anything that can accelerate processing without compromising quality.

Our starting point was a plant with 15,000L bioreactors used for the fed-batch process, which are very efficient for the product we have, but the strategy was to develop novel and more flexible ways of producing to address the pipeline situation.

### CHALLENGES

There are many different components of innovation, but the last and essential step is implementation. What we can do is come up with ideas, test them and generate the data to convince others, but continuous manufacturing is such a huge change that we really need leadership on board. It was clear that change was really happening when leadership decided it was essential to invest time and resources on these questions to try and develop the technology.

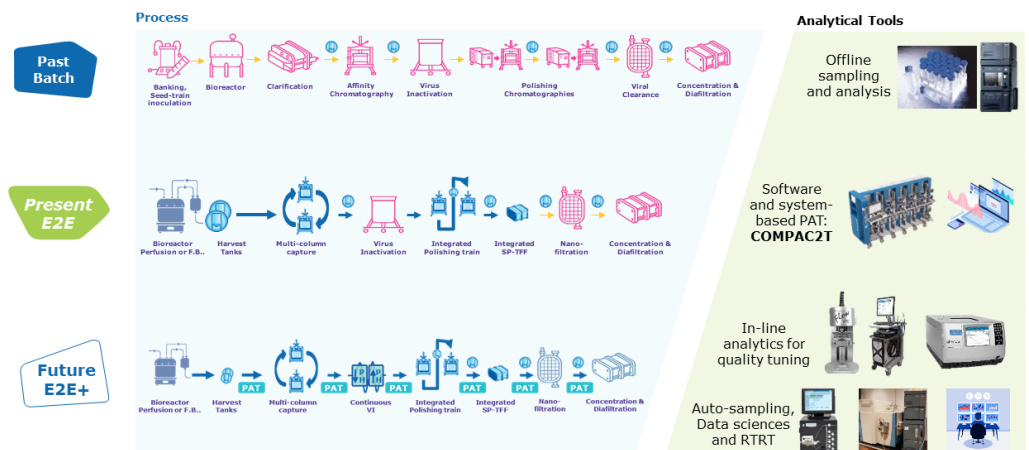
So, we had a facility where the different steps were batch operations and the aim was to implement continuous technologies, but just for a select few of these steps first. We developed a concept that we called 'compac2t' for continuous processing and cell culture technology, which is currently being implemented.

### ABOUT

Jean-Marc has been with Merck Serono SA for eight years and is currently head of the process technologies innovation team in Switzerland. The team's role is to propose innovative solutions to enable continuous manufacturing. He obtained his masters in Chemical Engineering and Biotechnology at EPFL and received the degree of Doctor of Science from ETH Zürich for his work on perfusion cell culture development.

In this case study, Jean-Marc shares his experiences in developing innovative technologies and workflows for continuous manufacturing.

### Continuous Manufacturing Concept Transition from Batch to Continuous



## SOLUTIONS

First, we had to create data to show that this technology would work. Once we had people convinced, we had to work on the development workflows, as it's critical to know where exactly we need to implement the technologies, and on which processes to apply them for the various molecules that are coming down the pipeline. We, therefore, needed to have strategies for very early process development, hence the importance of the development workflow here.

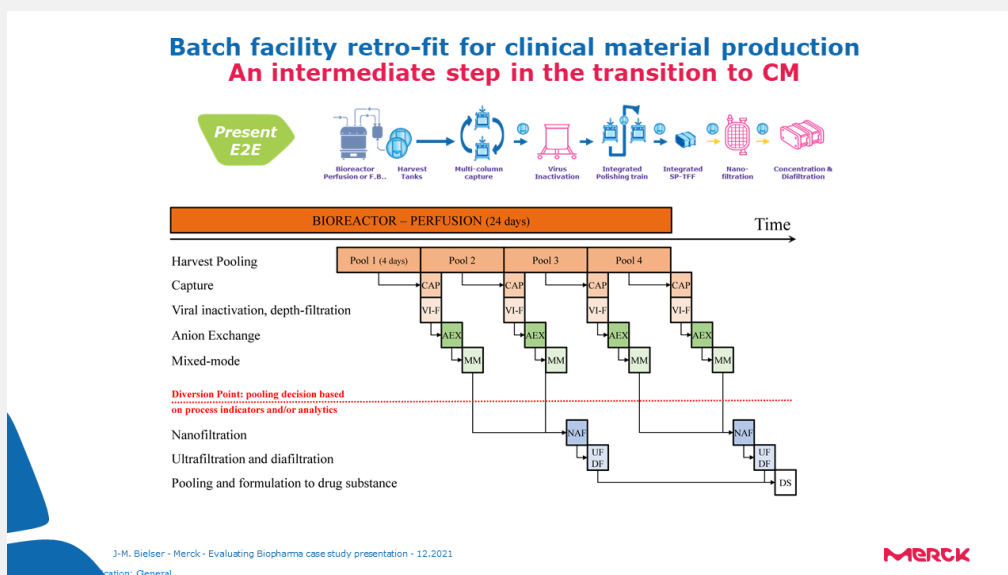
Also, to make this happen we needed to ensure cross-functional collaboration, which was an interesting exercise and contributed towards onboarding colleagues from process development, manufacturing, QA and regulatory. They really need to be on board as early as possible, firstly, to help convince leadership on the usefulness of these changes and to be aligned so that when the day comes for us to produce in the GMP facility, everything will be ready to release the materials.

What we had to do is develop schedule tools to support process development. In terms of equipment for perfusion, the bioreactors had to be adapted – we had a facility that already used bioreactors where we added the cell retention devices. We had also to work with colleagues from Merck Life Sciences to adapt the single-use bags to be able to connect all the different flows that were needed. For the downstream side, we collaborated with a vendor to develop a continuous DSP skid that was able to handle these different operations in a continuous manner.

## Outcomes

Today, we have a workflow in use including the different tools we developed, and this is constantly adapted. When we applied it to the first molecules, a lot of learning came out of that, and we were able to change these workflows to be more efficient.

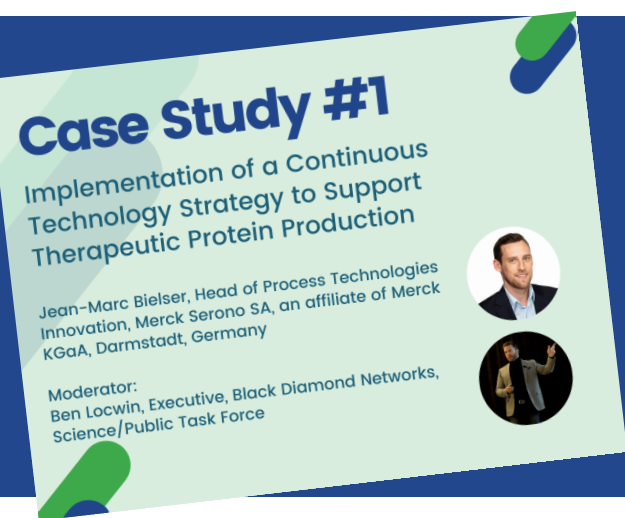
Second, we've been able to produce the first batch of clinical material. This involved upgrading the perfusion bioreactor but during this period the continuous downstream processing schedule was under qualification, so to work around this (because it could not be used for GMP) we designed a process very similar to what we would do in a continuous fashion but instead of multi-column captures in parallel, we just pooled for a longer period and then performed the DSP cascade sequentially as shown in the image below. This strategy avoids any process change when later moving to the continuous equipment that was currently under qualification.



## LESSONS

What I find fascinating about this work is that it shows the flexibility of my colleagues from manufacturing and from the process development side who had to find solutions to be on time for the project while using the technologies and the knowledge at a certain time point in the middle of our transition from batch to continuous manufacturing.



To conclude, change is challenging but if the teams are on board, they will drive the efforts to make it happen.



**Case Study #1**  
Implementation of a Continuous Technology Strategy to Support Therapeutic Protein Production

Jean-Marc Bielser, Head of Process Technologies Innovation, Merck Serono SA, an affiliate of Merck KGaA, Darmstadt, Germany

Moderator:  
Ben Locwin, Executive, Black Diamond Networks, Science/Public Task Force



This case study was presented at a recent virtual event 'Technology's Evolution and Impact on Manufacturing', which included six in depth case studies and networking sessions.

Details of future events can be found here.

You can watch Jean-Marc's case study in full and on-demand here

## ABOUT EVALUATING BIOPHARMA

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