CASE STUDY: A RAW MATERIAL ISSUE DERAILS PPQ AND CAUSES A TWO-YEAR PROCESS DELAY

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SITUATION

The team at Immunovant were working on a low demand fc fusion protein that was produced in a small number of lots with a very small clinical history. The last campaign was about a year ago and preparations were in progress for a PPQ, everything was ready to file.

The PPQ consisted of five runs but things didn't go as planned; the first run went smoothly but the second run started deteriorating and that continued. Quality attributes dropped to unacceptable levels and the cell health declined after day 10 of a 14-day process.

It was very clear that this PPQ was going to be a failure, but we did what we could to try and figure it out in real-time at the manufacturing scale. Nonetheless, we can't save it in time and the PPQ fails.

We then had to quickly assess what could have gone wrong.

ABOUT

In this case study, Ron shares his experience of a process performance qualification failure, his journey to identifying the cause.

Did Ron's team manage to pass their PPQ...?

CHALLENGES

To find the cause of this unexpected disaster, we looked at three things; did the cell bank fail? Were there facility or equipment changes? Were there any raw materials changes or inconsistencies? As there were a small number of clinical batches, we had a small number of lots of raw materials.

We also had to focus on what we could rule out quickly and consistently, as senior management quickly became aware of the PPQ failure, and it suddenly became their top priority. So, we needed to try and fix this as soon as possible.

The first step was to conduct a suite of lab experiments with some straightforward, one-off tests to see if there are problems with the cell line. We had a good scale down model, so it was possible to run these tests in the lab and mimic roughly what was going on at scale.

Second, we examined the facility, looking for any changes between this and the last campaign. There were a couple of changes that mostly involved moving from stainless steel to single-use for bioreactors, transfer cans to bag and tubing, but there was no obvious link between this and the cause of the problems during the PPQ runs. So, systematically, we tested what we could and very quickly we realised it wasn't the facility change.

So, the cell bank and the facility changes were easily ruled out and were not the cause of the problems.

We concluded that it was probably a raw material issue. Luckily, a small number of production lots equates to a small number of vendor lots so then the question was which raw material is the source of our problems or are there multiple? We set up a range of small-scale experiments to test raw materials one at a time. This wasn't easy, as we didn't know what we were looking for and testing a few raw materials from a few different lots didn't amount to what was needed. We had to really go back and look at what was going on and when, and to do that we sent out different lots of raw materials out for material testing, including tests for metals, amino acids and vitamins.

A lot was being conducted and coordinated in parallel; lab tests, samples sent out to vendors, water sources, glucose and supplement testing. We slowly started to rule out things and get results data in over 3 to 6 then 9 months. Water was the easiest to rule out. The media was more complicated, as we couldn't' simply get a new lot from the vendor and test it, we had to contact all the media vendors to find out whether they had changed their suppliers or manufacturing processes.

As the data was trickling in and we received information from the vendors, it became very clear that there were a few differences. Some were in the media itself, and we were able to obtain the pre-change and the post-change samples from the supplier's manufacturing process and tested those in a lab, the results showed no problems there. We tested the basal and the feed and looked at the glucose contest and there was no change here either.

Eventually, we turned our attention to the base and realised that the base supplier (a carbonate source) is actually mined, and they had changed the physical location of where they were mining. This made obtaining pre and post-change materials to run tests a challenge.

We did get some information around the same time from the metal testing lab that showed the concentration of a few of the metals were different, specifically, copper, manganese and zinc. We have some clues but now need to pinpoint the exact source of the problem. At the same time, we discovered the supplement had been manufactured using a different process and the metal analysis shows significant results. Coupled with the fact that CHO cells are prone to metal issues, we start thinking that we're on that deficiency threshold and start doing some further experiments.

Finally, we confirm there is a manganese deficiency so now we're getting to the root cause of the problem, which is:

Impurities in the base solution had a major effect on the cell culture.

SOLUTIONS

Now that we know the problem and that it can be fixed, we contact our vendors to ask them to use the previous process. These are small batches of bicarbonate and sodium carbonate, so the answer is no. Although now we know we don't have access to the same raw materials with the same impurity levels that we had before.

As we changed the media supplier, our base supplement also went down in the exact same metal, not at huge levels but enough to compound the situation further. So, we're now at the PPQ stage, we have a process that has already been through clinical development and any major process change means more clinical studies so we need to minimise what can and can't be changed i.e., what's a major amendment to our IND and what do we think we could handle?

The first discussion is whether there's a way to cherry pick lots. Yes, but it's not a long-term supply chain strategy and was quickly dismissed. The next option is to make up a solution of the metal and feed it into the bioreactor as a supplement, but the question here is one of timing and frequency. It needs to be established whether the supplement should be added before inoculation, daily or somewhere in between.

This led to a new system of experiments and a new level of complexity to our control strategy. We set about an extensive process development type activity where we looked at these different scenarios and conditions. Luckily, the results determined that we could add it as a single bolus one time.

OUTCOMES

We added a metal supplement with one of the feeds or media additions and it worked.

It took about a year to do complete this and then a series of individual runs were conducted at the lab scale, it was then scaled up to a pilot scale and, finally, we did an engineering run at manufacturing scale. Everything worked as expected and we talked to our vendors again to ensure there were no further planned or unexpected process changes that would result in too much manganese.

Within two years we had done two PPQs – one failed and one passed – and we're on our way to writing our BLA.

EVALUATING BIOPHARMA

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This case study was presented at a recent virtual event 'Pharma Shifts to Biologics', which included six in depth case studies and networking sessions.

Details of future events can be found here.

You can watch Ron's case study in full and on demand here

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