CASE STUDY: INCREASED BIOBURDEN EXCURSIONS IN AN AGING FACILITY

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SITUATION

We were faced with an ageing, fixed stainless steel facility that was relatively inflexible in the sense that 'you've got what you've got' in terms of equipment and configuration. Over time, slight modifications were required but over time those modifications turn into something that is not optimal and this has resulted in some bioburden excursions.

Today, there's a huge amount of scrutiny when it comes to bioburden and endotoxin hits, not just in drug product or sterile manufacturing but in drug substance manufacturing too. What's required now is to have your whole facility is under the same umbrella and make sure you have complete control over the environmental systems surrounding and in your process.

ABOUT

Ron has more than 20 years of experience in the biopharmaceutical industry holding roles of increasing responsibility in process development and MSAT with Pfizer, Allergan, and Bristol-Myers Squibb. He is active in the scientific community with over 50 publications and presentations, and he is a member of the Editorial Board of the Biotechnology Journal. Ron earned a B.S. in Chemical Engineering from Rensselaer Polytechnic Institute and a Ph.D. in Biochemical Engineering from the University of Maryland, Baltimore County.

In this case study, Ron walks us through his experience of updating ageing steel facilities to eliminate bioburden excursions and endotoxin hits.

CHALLENGES

There were several challenges, but the biggest one was eliminating the microbial hits, be it bioburden or endotoxin. Of course, the regulatory scrutiny and implications are significant, but the other issue is that it's a huge time sink, as investigations are needed to establish the cause. It's also a cost sink if you need to throw away media and buffer, repack chromatography columns or, worst-case scenario, you have to throw away batches of drug product.

So, it's important to have a facility that doesn't incur a lot of environmental hits. Unfortunately, in ageing facilities, modifications are constantly happening, which involves a lot of new equipment or flow path alterations and floor changes. Often, this means just adding an extra layer on top of your existing floor, rather than going down to the foundation. The result is the formation of areas where water can get trapped and moulds can form.

The constant modifications of flow paths can lead to unwanted configurations known as 'dead legs' where liquid can pool, so if you're flowing cleaning solutions, no matter how much or how fast the flow you're going to get an area where the liquid may or may not come into contact with steam or with the caustic solution. These situations are unintended consequences of design.

This is why environmental hits occur in these types of facilities and the aim is to eliminate rather than minimise.

SOLUTIONS

Whenever you do any major modifications to the piping, cleaning or flow systems, in a validated system you run into the problem of maybe having to revalidate, so there are several things that can be done; the first is to just increase your cleaning. You could also look at changing your current practices, i.e., using a different caustic, increasing the steam temperature, changing the flow rates.

Another option is to change your facility and replumb the areas where there are dead legs. In terms of facility modifications, you could also replace your steel lines altogether and assess whether disposable tubes are more suitable, theoretically eliminating the potential for microbial growth. The overarching goal is to minimise the opportunity for liquid to build up and for bacteria or moulds to grow.

In our case, we looked at the situation and started with the simplest option first, which was often re-cleaning. Sometimes it worked and sometimes it didn't. Another quick option was to change out our diaphragms, valves and O-rings in some tanks, tubes and valves, as some were badly deteriorating. Changing exposure time, steaming for longer or increasing flush volumes and using higher pressure when steaming are also effective solutions. In short, we first sought to do what we could, as quickly as possible to get ready for the next batch.

The consequence of these approaches can be that you're outside your validated range and if that occurs, cleaning validation will need to be re-done.

If more repetitive events occur after trying those solutions, then facility modification is the next step, which is what we did. Some fixes may seem simple but often, in ageing facilities, a dead leg may be part of one line in a matter of a hundred, so you need to figure out what makes the most sense for your facility. The other question is can you reach them? Some old facilities have just grown and grown and some sections can be almost impossible to reach. The facility will also need to be shut down if it requires cutters and welders etc. and then it needs to be recleaned, so sometimes facility modifications aren't a suitable solution, but those are the ways to eliminate not to minimise.

If it is possible to replumb and remove problematic areas, does it then make sense to replace with stainless steel but then encounter the same problem in 5-10 years? Disposable tubes and bags could be integrated into places where it makes sense.

Outcomes

The reality is that improving cleaning protocols are usually a short-term fix, then comes the question of what to do once the decision has been made to modify the facility.

For us, the answer was really clear, there were some parts of the facility where this was not possible but where it was applicable, we replaced stainless steel with disposables – disposable tanks, tubes to connect bags of buffers to skids or media to the bioreactors. Those made a lot of sense. It also became clear that where we had a lot of hits in the inoculum room which involved a lot of small transfers, disposable technology would be advantageous here. 50L biobags and connectors as opposed to a 50L portable tank. In those areas, it was an easy decision to switch to disposables.

LESSONS

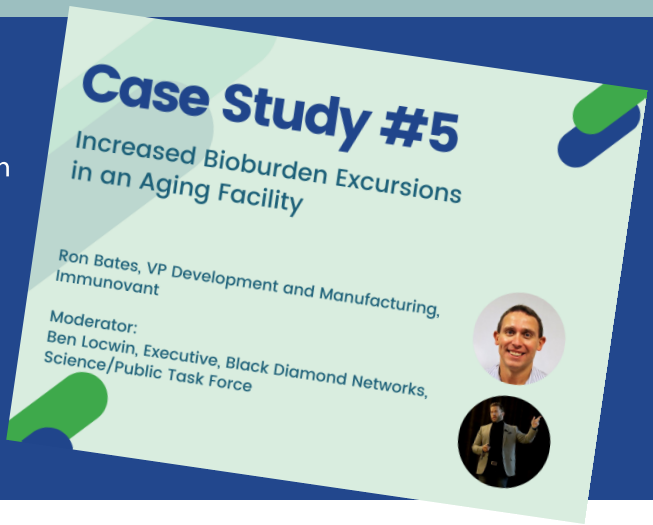
There is a cost to disposables beyond the financials, you need sufficient warehouse space to stock up, as supply chains are an added element of risk, especially right now.

If you have a little bit of money in your budget and some forward-thinking from management, it will allow you to more easily make these hard decisions. Organisation, strategic planning and leadership are key components to making these improvements.

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 Ron's case study in full and on-demand here



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