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Process Intensification: Leveraging Established Processes—Intensifying with Minimal Risk

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ABOUT

Stefan Schmidt is the head of operations and chief operating officer of BioAtrium AG. In this session, Stefan and John Bonham-Carter, Vice President of Erbi Biosystems discuss how companies can minimize risk in process intensification by working within established processes.

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John Bonham-Carter: Welcome Stefan, let's start with some practical bits about process intensification. How do you first approach that question with customers and what are the factors you take into account?

Stefan Schmidt: I think the point is you have to be aware that everything changed in the process comes with a cost. No one in the world does process intensification just for the fun of it. It really has to deliver something—some benefits in sustainability, some cost-driven metrics, circumventing some shortages you have in the plant. One example would be volume restrictions and vessel size. But the original question is really focusing on how to make an intelligent decision—and based on what. There are two questions you have to answer. Where in the lifecycle is a product? Is it something in the clinical phase to where it's a lot easier to process changes; or is it in a late stage or even commercial phase where it is harder to implement process changes. The other point is where do you want to implement process intensification? In principle, you could optimize every single step if you wish, but some have more impact, more benefits than others.

Let's pick the example of a small startup biotech, with just enough money to run a Phase I study. For them, time is the essence. The real impact is how fast can they get their stuff produced, and how fast can it get to the clinic and to the next step. A lot of the large corporations—Novartis, Amgen, Roche—will have a totally different approach. They know what they want, they have the facilities, they very often have platform technologies where they have optimized every single bit of the process. It makes a lot more sense, because everything they invest in can affect multiple products.

JBC: To rephrase, for a small biotech with one product, they just want to get first in human, get the data, get next payment and see what the clinical relevance is. But as a company gets bigger, is there a reason you would not intensify given what would seem to be the gains, whether that drives cost, or throughput, or sustainability?

SS: I would probably not do process intensification if the process I'm running delivers good output and I can more or less anticipate what the market size is. If I have a product where I know where the market is going, I probably have no need to intensify. But if I have something like a blockbuster, where I have a dramatically increasing demand, then I probably need to think a lot more about what can I do to get more material out? How can we squeeze out the last drop of product from my facility?

JBC: That leads into the timing for making the shift. Let's take the example of that small- to medium-sized biotech that rushed to Phase I. When is the right time to start thinking about process intensification?

SS: If this is an example of a small biotech with one product, it could potentially make sense. Let's say it's an antibody. It could make sense to restart from scratch with simulated moving bed chromatography. One of the limitations is you have to buy really expensive resins and probably don't use up the full column in the lifetime of your resin because at this point, you never know when the next batch is going to be produced. But if you go with simulated moving bed, you utilize, in principle, the full capacity of the resin in a much shorter time. You utilize a smaller column much faster. Then you have a direct financial benefit. I would probably recommend to small startups with just one antibody product, to look into options how to intensify this process. If you look later in your process, it's a bit related to the strategy you have in the clinical trials. In the majority of cases, you focus on a single indication with a clear, easy endpoint to get the product to demonstrate safety, efficacy, and then try to expand indications. This could also be the next starting point for process revision. Now you have a much broader range of indications. Demand might go up. Also, the demand on the clinical side might go up and at Phase III, so it might be relevant to look into more intensification steps, because then it would have a benefit.

JBC: Are we at a stage where it's realistic to start implementing a standardized intensified platform? So, in the large companies that in-licensed something, you just go through that platform and it's two, five, 10 times as intensified as previously. Are we able to do that now, or are we not yet at that technological level?

SS: You should be able to do it. But let's change focus now, moving away from the small one-trick-pony startups to CDMOs. CDMOs have an interest to utilize the established capacity of investment in tanks, reactors, columns in the best possible way. This means you would like to minimize the runtime in your facility for the customer process. One of the most expensive parts of the process is how long the product is in the main reactor. You can simply reduce the time to manufacture if you start with an N-1 perfusion process. It is relatively simple to establish, you just need to have sufficient media supply. Typically, you can reduce the time directly by 30%. This means your facility can have a 30% higher output of products and higher revenues. From a CDMO perspective, it would be beneficial fo N-1 perfusion; and from a customer perspective, N-1 plus simulated moving bed. These are the two first steps I would potentially recommend.

JBC: Does that translate over to when you're in full commercial? Does that move from continuous to efficient batch, or recycling of the batch, is that gain still present, or does it disappear to some extent?

SS: You have to think about what is the lifecycle. Many products are being submitted to authorities in 2k, still using simulated moving bench chromatography. But as soon as you move to the next level of facility a 20k, 15k bioreactor facility, then you know it's a commercial process, with many more batches. At this stage, it might make a lot of sense to switch back to the traditional, non-simulated moving bed, because you don't have the benefit anymore. Also, the the number of cycles you have to implement for one run of your 20k bioreactor is super high. I think this is really a transition point. Where you move from 2k to 20k, you would switch back to some extent.

JBC: You mentioned 30% as a gain in output and that was focused on N-1. Are those ballpark figures? And given that kind of data, which is focused on just the N-1 implementation, is there something more that can be leveraged using other technologies or other methodologies to gain intensification?

SS: From several publications, different sources, different companies, I think you're not far off if you say roughly a third of your time can be saved. The important part here is that the saving is in time of capacity of the output—you can increase the output by 30%. But what you should not ignore is: you shift the effort to another area, to your media preparation. This is something you also need to establish. In many cases, you don't have the tanks ready. So you might need to invest in that area beforehand, before you can harvest the fruits of your investment. As a long-term strategy, it certainly makes sense.

The other part of the question is: can you do something else? I've seen cases where you move from 2k to 20k and if you have a really high-output process with a high titer, which might be painful in the 2k setting but super painful in the 20k setting. For instance, you might end up with too-small vessels for ultrafiltration and this might force you instead of installing more vessels or larger vessels, to go to single pass. Because then you are vessel independent, and you can still have a good output of an existing facility without a lot of investment. This might be one of the cases where a very low level of investment could have a huge benefit or gain in output as well. There are bits and pieces you have to think about, coming back to the original question of when in the process would it make most sense to establish intensification?

JBC: We've mostly been talking about proteins and antibodies. But there is a huge investment right now in gene therapy and cell therapy, and they are behind in terms of throughput, maturity of the biologics, and process engineering. Is there something that you would take forward from this to say they're going to catch up? There's nothing particularly unique about these new processes where you couldn't use the same principles, or would you advise a slightly different strategy as those people think about intensification?

SS: I would probably start earlier. I'm a front load man, so spend more time and effort in DoE. Because what I've seen—and I've spoken to many cell and gene therapy people in the last couple of months—surprised me. I think DoE is not super established in cell and gene therapy. With DoE, you know the ranges of things, and this is still missing in cell and gene therapy. If have more intense DoE, you know your space of ranges in a much better way and have a better probability of success later to improve things. I think we will see a mix of new tools being established because the new demands of the modalities and also a new knowledge space. The knowledge base needs to be established by people who work with it in process development, process characterization, and so on to get more input. If you compare it now with antibodies, 30 or more years old, the body of knowledge accumulated from different sources around antibodies has really contributed to all these possibilities. This has still to be established in cell and gene therapy.

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This case study was presented at Evaluating Biopharma's Process Intensification: Improving the Process Status Quo virtual networking and educational event which included two additional presentations and two interactive networking sessions.

Details of future events can be found here

You can watch Andrew's presentation in full and on-demand here.

Process Intensification:
Improving the Process Status Quo

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Evaluating Biopharma is a convener of knowledge, data, and industry leaders within the biopharma and bioprocessing industries. Built upon the foundation of BioPlan Associates decades of data collection and analysis, Evaluating Biopharma brings together top industry experts, innovators, decision-makers, and leading providers so that together they can share, evaluate and discuss critical topics that will help biopharma and bioprocessing leaders advance life sciences.

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