Transcript for “Continuous manufacturing in pharma: advantages and challenges”

Nigel Langley: In the next minute, 250 babies will be born to add to the world's population. In the next 30 years, the world population is expected to reach 10 billion people. These are the 10 billion reasons we do what we do every day. Please join us as we explore innovative pharmaceutical solutions and sustainability and digitalization initiatives that will help us rise to the challenge.

So, hi everyone. My name is Nigel Langley. I'm the host for a special podcast series that we're having of which the latest podcast is today, where we'll be talking about continuous manufacturing in the pharmaceutical industry. With me today, I have two very special guests, Krizia, and Joao, and I'll ask them both to introduce themselves. And then we can actually start to talk about this important topic. So, Krizia, would you mind introducing yourself to everyone?

Krizia: Not at all. And thank you for having me, Nigel. I'm responsible for Global Technical Marketing in BASF Pharma Solutions. And, with regards to experience in the industry, I have 10 years of experience working in process development, technology transfer, as well as process validation for continuous manufacturing, including PAT support.

Nigel Langley: That's fantastic. And, and Joao, would you mind also introducing yourself?

Joao: Great. Thank you, first of all Nigel for having me here. So, I'm Joao Assis, Global Technical Marketing Manager, responsible for BASF Orals Platform. I am pharmacist with over 10 years of experience in R&D in pharmaceutical companies, especially in generics and also raw material suppliers, working as a pharmaceutical formulator and technical services manager.

Nigel Langley: Thank you very much. So continuous manufacturing, maybe Krizia you can, give us some background why this particular manufacturing process is important now in the pharmaceutical industry. Just tell us a little bit more about it.

Krizia: Indeed. And maybe what I can start Nigel is defining what's the difference between traditional batch manufacturing and continuous. And in traditional batch manufacturing, we essentially have discreet unit operations in which you have material moving in, it stops, then you have material moving out. So, in between every unit operation, you have a room. You have either some holding time of a couple of days, but very discreet unit operations.

When you compare that to, for example, continuous manufacturing, you have a system of integrated unit operations and why I mean a system is because these unit operations talk to each other and that talking to each other, it's based on a control strategy, on a control system. So, essentially in continuous

manufacturing, as you may imagine, batch sizes are not necessarily, I would say defined by the equipment size. Instead, you can actually base them on produced material, on consumed material, on time. So, batch sizes are flexible, which allows for supply chain agility among other things.

Nigel Langley: That's, that's interesting. So, what would you say is, are the advantages of continuous manufacturing actually in the pharma area?

Krizia: Supply chain agility for sure is one, especially during these COVID times. In addition to that, I would say shorter development times. So, you use less material in order to, I would say develop the process and you can not only that, but accelerate development, because you can run DOE's (Design of Experiments), much faster by just changing the process parameter. As you are, let's say, during the process trials. You also have no scale up because as I mentioned, you just, you can increase a batch size by just increasing the amount of time that you process.

You have smaller footprint, you have a system that typically starts from some feeders to a blender and then to a tablet press, if you think about continuous direct granulation, continuous direct compression, sorry. And essentially, I would say numerous advantages, not only for the pharma manufacturer, but also to the end consumer, to the patient. So higher quality tends to be one of those.

Nigel Langley: Okay. So, would you say this is a, a new area for the pharma industry or, I mean, continuous manufacturing in different industries it's been round for many years and what makes it new then in the pharma area?

Krizia: I think it's the way that we are looking at it. But indeed, it's not, it's not something new, like you very well said, Nigel. I would say that the new part into it is how it's being adopted. So, how you're actually implementing a higher level of control for your drug product and how you're taking this, to the patient essentially.

Nigel Langley: And would you say there's quite a few drugs that are manufactured already by continuous globally manufacturing globally?

Krizia: Indeed

Nigel Langley: Can you elaborate?

Krizia: So right now... Of course. So right now, you have, I think it's five approved drug products. So, as you can see, or as you may imagine, it can definitely develop into a lot more for the most part it's innovators. But one of those was actually a switch from batch manufacturing to continuous manufacturing from a wet regulation process to a direct compression process, which allowed for savings

not only in time, which then led to supply chain agility, but also reduction in QC costs for real-time release.

Nigel Langley: Also, is very interesting. Thank you. And maybe in all the advantages or some of them you've just expressed, I mean, are there any hurdles with continuous manufacturing as well, or is it all just plain sailing there?

Krizia: Well, if it were just plain, right, I really wish to see continuous manufacturing everywhere. Indeed, there are hurdles and personally I classify them in four, Nigel. I would say the first hurdle being a cost of implementation. You have already some unit operations, which lend itself to being continuous, such as the tablet press, but there is a cost of implementation. You need a continuous blender. Also, I mentioned that it is a system of integrated unit operations, so they need to talk to each other. How do they talk to each other? You need a control system. Typically, what's called a distributed control system. Also, you have, you are generating lots of data. So, you need a data management system. All of these things start to add up, so the cost of implementation tends sometimes to be a little bit too high for generics.

Now, with everything that's happening and several, I would say government led supporters and among other things, it's leading to having, I would say, more discussions around this, how the cost of implementation can be reduced. So that's the first, I would say, so cost of implementation. The second, uh, being specialized knowledge, right? So not only do you have your typical formulators, but also you now need process engineers. You also need chemometricians, because you're measuring quality during, or I would say in line.

So, you need chemometricians that can understand the PAT strategy, the PAT modeling. So, it from an FTE perspective, then of course you have to think about, you know, you need technical, highly technical resources. And, third, I would say formulation design, you need to understand material properties and how they interact with your process. And then fourth, the perceived higher regulatory barrier to entry.

Nigel Langley: Interesting.

So, Joao, we've heard some very interesting stuff from Krizia now, and then setting the scene for the importance of continuous manufacturing as a process. But can you actually elaborate a little bit on the formulation part, you know, that when you're actually formulating the drug product and what comparisons, if there is a comparison between the batch process and the continuous process with respect to the formulation? Are there any differences or are they the same?

Joao: Sure Nigel. So as Krizia also well said, so we have the impact on the formulation and the material that we are using for our continuous process. Considering a batch process, we normally add the material like by gravimetric ways. So you would just include material in a V blender or Bin blender. In the case of a continuous process, we are feeding the material, we are including, adding the material using feeders.

So, we need to pay attention on the characteristics, in the properties of the materials that we are adding So, to have a better control on the feeding rate, we have to have a better flow material. We need to also consider the properties of the material like compressibility, cohesion that also impact on the flowability.

So, we need to select better the material that are going to include. For example, like co-processed materials are very interesting. So, co-processed excipients tend to have a lower compressibility that is very important too, to reduce the variability and dose accuracy, that it's necessary for a continuous process.

Krizia: And maybe, maybe for our, our listeners, it's also important to mention, right? The compressibility refers to the changing in volume with applied pressure. So indeed, I mean, if you want to talk more about that, how would in, in continuous it's so important?

Joao: Yes, yes. To understand the powder rheology, to understand it, that we study in compressibility, that when you apply a force, what is the change in volume? So, if you have a high compressibility, it means that the material has a high difference in volume when a force is applied. And if you are just increasing the force, it can be just like the movement of the screws. So, you can have a different feeding rate. You cannot have like a very constant and more accurate feeding rate. So that's the reason we need to pay more attention on this material, this kind of properties of the material, to have a more constant, and low variable feeding rate.

Krizia: Because indeed that, that, that force can be, you know, just from the same head pressure of adding material, refilling material into the feeder.

Joao: Exactly

Krizia: Mm-hmm

Joao: And this is quite challenging also when you work with API, that is very cohesive. So, there's this interesting and to work like, combining different materials with a low cohesion and a high cohesion just to equilibrate, like in the middle term when you're blending. And you need also to evaluate… and one thing that is

interesting, Krizia. When you are making a batch process, we don't think much about the shear impact…

Krizia: That's true

Nigel: That's fantastic Joao, that really does give a nice picture of the complexity as well as the simplicity, if it makes sense. So you really, it's a driver towards, if I understand what you're saying correctly then, you know, there's a real room for a co-processed excipients because instead of feeding in four or, or four or five different raw materials or acceptance into the process, you could possibly reduce that number by, you know, even feeding one or two, because then, you know, it will become more robust.

So, I have another question going on the process itself, which possibly listeners are thinking about hopefully as well, that on a batch process, as it's more defined, and you can do analytical testing at the end of the batch, how do you actually know that the process is in control during, as in a continuous way? What are the analytics side here that, that are now necessary to implement, to actually control the process?

Krizia: So continuous manufacturing lends itself as an excellent process for implementation of process analytical technology. And by process analytical technology what I mean is how can you actually translate your critical process parameters, or even measurements of material attributes or, or blend attributes into critical quality attributes for your drug product?

So, in continuous manufacturing, even in batch processes, but mostly in continuous, you can actually have a near infrared spectrometer, for example, just right after the blender or in the tablet press to measure blend potency. And if you think about it, if you measure blend potency in the tablet press is the closest there is to a tablet, right to the end product, to the tablet. So, very good question and indeed with continuous manufacturing, you can even do, it's amenable for real-time release. So, you reduce QC costs.

Joao: And also, you can check the quality in line during the process. You don't need to wait to like, to blend and to check the drug uniformity and, and exactly in time, so on time, you're just like evaluate that characteristic and it can adjust as, as well at the same time.

Krizia: Indeed. So, you can reject at the tablet level, how can you do this in batch manufacturing?

Joao: Right

Nigel: So, what you're describing then if it's run effectively, efficiently, it's a very efficient process that you can potentially run 24/7. And as you, I think you also mentioned that the, one of the drivers probably from the manufacturing part of companies is that you can reduce the footprint.

Krizia: The footprint

Nigel: The footprint, you don't need those large manufacturing plants that possibly you had in the past when it's batch process, but this would obviously encourage much more utility there. And so, with that, and the other question I'm sort of struggling with a little bit of, is this driven by... Who's the driver on the lining man- of continuous manufacturing? Is it really the efficiencies that gain from the pharmaceutical company? Or is there another factor? Is, are the agencies actually, the FDA, are they really supporting this initiative as well? And if they are, you know, what are their reasons why they are supporting them?

Krizia: Indeed, they are supporting it. You see new guidelines like the ICH Q13, that was recently published, to set, I would say the basis for continuous manufacturing. You also have guidelines from the FDA among others. So, they are supporting the, I would say the increased process knowledge that comes with continuous manufacturing. You have to understand material attributes, you have to understand the impact of material attributes on your process and on your drug product.

So, it lends itself to excellent quality by design approaches, if you think about it, which then leads to higher quality assurance. So, from a, I would say from a regulatory perspective, and I can't speak for them, I would see how continuous manufacturing lends itself to higher quality assurance, thus higher patient safety. From a pharma manufacturer standpoint, I think the fact that you have smaller footprints, that you can reduce QC cost among other things, it lends itself to also being a platform through which now you can actually, I would say release new products, accelerate time to market and shorten development time.

Nigel: So really this just covers our podcast today. I thank you again, Krizia and Joao for your excellent contribution and imparting your knowledge in this area. And hopefully the listeners felt that was very interesting as well, I'm hoping you all do. And, and you get some better understanding of this growing field in continuous manufacturing, the pharmaceutical industry, more knowledge than hopefully you had before you joined the podcast. With that, I'd like to thank you very much for your time and attention and stay tuned because there's another podcast coming soon, just around the corner. Thank you.

Krizia: Thank you, Nigel

Joao: Thank you