Continuous Manufacturing Success Lies in New Technologies, Integration and Education

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On Sept. 30, ***Salvatore Mascia,*** *CEO, CONTINUUS Pharmaceuticals, will present his talk on continuous manufacturing at the* 2015 PDA Manufacturing Science Workshop *in Washington, D.C. following the* 2015 PDA/FDA Joint Regulatory Conference. *Previously, he worked for MIT on the Novartis-MIT Center for Continuous Manufacturing, a collaborative research project to develop a fully continuous integrated manufacturing system for oral solid dosages. Mascia spoke with the* PDA Letter *about his upcoming talk. The interview was recorded and will be available online as a forthcoming podcast at www.pda.org/pdaletter. Below are selected questions and answers from the interview.*

PDA Letter: You've identified "industry inertia" as one of the top organizational mindsets that present a barrier to the adoption of continuous manufacturing. Why is that? Especially considering the inefficiencies in traditional batch manufacturing?

Mascia: If we go in a manufacturing plant right now for pharmaceuticals and look at the technologies that are implemented, we realize that these haven't changed for many, many decades. So, we've been using the standard technologies, only the people using this, either in process development or manufacturing, are basically [educated] in the same way to develop processes for drugs…so with the introduction of new methods, it's very challenging. In addition to that, obviously, this infrastructure is in place, as you can imagine, because of so many years of doing batch manufacturing. And so the investment into a completely new infrastructure to make this transition is a big, big barrier in the pharmaceutical industry right now.

PDA Letter: Tell us more about the challenges you encountered in your involvement with the Novartis/MIT project. What lessons do they offer industry?

Mascia: One of the key objectives of the Center was to look at continuous manufacturing in a different way than was done previously. Instead of trying to retrofit existing process technology or batch processes running for longer, the Center is really based on developing new process technologies specifically designed for continuous manufacturing. So, we came out with a completely new technical solution for doing continuous manufacturing with the idea that all the steps in the pharmaceutical manufacturing chain, from chemistry, separation, purification and final drug product formation, can be integrated in one single production line that runs automated 24/7. So this was a big challenge, really, to try to develop the novel technology to enable this integration and to run these processes continuously and under fully automated control And we realized even when we need to develop a specific step at a very low throughput there was no equipment available. This led us to come out with new technical solutions, so that was really one of the key challenges.

And the second one was integrating all this new technology—all these new steps—into one seamless process and controlling it because now you have several unit operations connecting into one single process and you need to be able to control that and make sure the process is under control to produce a product with high quality specification.

These are also challenges that companies implementing this manufacturing technology need to take into consideration. When implementing new equipment, make sure this equipment is reliable… it's very, very important and this is why, when we refer to our vision of continuous manufacturing, we call it "integrated continuous manufacturing" to try and distinguish ourselves from many other approaches of continuous manufacturing, because it's really through the integration of this multiple set of unit operations that you can gain the full benefit of continuous manufacturing.

PDA Letter: And this certainly also fits with the move toward more modular forms of manufacturing.

Mascia: Our platform is absolutely modular. It has to be modular, otherwise it becomes like a single rigid line that can be applied for a specific compound but does not work for others. You can imagine this technology platform with multiple flow steps, different types of reactor designs, different types of purification systems, different platforms to produce dosage forms, and you can basically interchange the unit operations one with another through some sort of plug-and-play concept to make it modular, and so be able then to produce many different compounds.

PDA Letter: The system at MIT produces oral solids. Can it be configured to produce fill finish product?

Mascia: Again, the system is modular. We started with solid dosages—with tablets—because it is still the most acceptable dosage form and it's still the most challenging to produce in flow because when you think about solid, you can have issues with clogging.

When you think about liquid finish or liquid formulation, it is actually easy to handle in flow. Our concept of integrated continuous manufacturing is that the entire process is fully contained. The

process material remains in the system all time so it's less prone to contamination. And regarding the sterilization, you can use continuous microfiltration, and the use of heat as needed.

PDA Letter: You've cited statements from CDER's **Janet Woodcock** and former U.S. FDA Commissioner **Margaret Hamburg** in support of continuous manufacturing. Why do you think these regulatory leaders have expressed support for continuous manufacturing?

Mascia: The FDA is looking for more modular, agile and flexible manufacturing plants. And the reason being is because the pharmaceutical industry is changing. We're going through the advent of personalized medicines. In the future, we will need to produce many different pharmaceuticals, with different physical and chemical characteristics. And those existing large scale, batch processes do not have the flexibility to accommodate that. Same when you think about the advent of breakthrough therapy designations. So we have therapies that will have an accelerated regulatory path.

PDA Letter: Yet in other presentations you've mentioned that one barrier to adoption of continuous manufacturing in the industry is "perceived risk" among regulatory reviewers. Doesn't this contradict the views of regulators like Woodcock and Hamburg?

Mascia: I don't think it contradicts actually. That's why I mention it as a "perceived risk" among the [individual] regulatory reviewers who actually look at applications, and need to assess the new specific technology. If the knowledge of this specific technology might be lacking, then there could be some perceived risk about whether or not this would be an effective way to produce those pharmaceuticals. This goes back to the question about education, and the FDA is actually setting up numerous educational programs to actually make sure that all the people working at the Agency are actually [familiar with] implementing those technologies coming out. There is a lot of effort going into this direction, and as you can imagine in a big organization, the vision has to come from the top.

PDA Letter: For those attending your talk at the *Manufacturing Science Workshop* in September, what are some takeaways you hope attendees leave with?

Mascia: The first one is that companies should move on from being worried about the regulatory agencies being a block for this technology, because I don't think this is the case as there has been a strong statement from the regulators, especially from Janet Woodcock at the conference that we organized last year at MIT, where she said that the major regulatory hurdle comes from the company, from the actual manufacturer being worried that the regulator will balk at these processes.

And the second point is that continuous manufacturing, the way we see it with this fully integrated concept, it will enable the vision of "on-demand" manufacturing. The future will be based on this concept of "on-demand" manufacturing—producing pharmaceuticals immediately when you need it. So, we should really start looking at continuous manufacturing in an integrated fashion as we are proposing it, rather than a unit op or piecemeal approach because the huge benefit will come when you have lines that will be modular, flexible and able to produce pharmaceuticals end-to-end. This is an important concept which I believe will bring [about] change in the way we develop and manufacture drugs in the next ten years.

About the Expert

Salvatore Mascia is the Founder & CEO of CONTINUUS Pharmaceuticals. He was the former Strategic Project Manager for the Novartis-MIT Center for Continuous Manufacturing, where he led the integration of the first end-to-end continuous manufacturing process for pharmaceuticals.