Complex Parenteral Drug Manufacturing — A Foundation for Success

By Kurt R. Nielsen, Ph.D., President and CEO, Pharmaceutics International, Inc (Pii)

Developing and manufacturing complex parenteral drugs is one of the most difficult processes in the pharmaceutical industry, it requires a great deal of skill, firsthand knowledge, and attention to detail and still the risks are significant. When adding the complexities of a highly potent compound, an aseptic environment, small amounts of API, or a combination product of a drug in a medical device, risks increase and so does the need for even greater levels of skill and knowledge to assure success.

Based on my personal experience, and the decades of collective experience among the people with whom I work, successful drug manufacturing for the kinds of complex products described above is built on a solid foundation of skilled professionals, quality systems, and comprehensive risk management. A foundation like this creates an organizational culture that has the confidence to efficiently address the inevitable challenges associated with complex parenteral drug manufacturing and be successful.

People Foundation

The most critical component of all effective processes and systems is a team of experienced, skilled professionals. The difficult process of manufacturing a complex parenteral drug requires the precise integration of diverse skills across an organization.

My use of the term team is intentional; like a sports team in which no two members of a team have the same skills and talents and who work interdependently and cohesively, a complete unity of effort. A team like this is hard to build, difficult to find, vital to sustain, and an invaluable human asset once it is developed.

Experience is a vital component of the people foundation. Of course, we want engineers and scientists who have experience manufacturing complex parenteral drugs, but there is an

important distinguishing characteristic beyond that. The experience I value most is what people gain from having lived through the emotional ups and downs of the drug development process. People who have given their all to a successful product, or a product that did not make it, is priceless, especially as a product owner seeking a service provider.

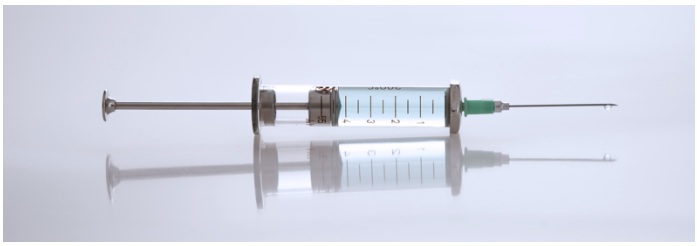
The final feature of the people foundation is the integration of specific, critical skills. More so than other drug manufacturing processes, complex parenteral drugs require a precise blending of science, regulatory acumen and engineering. Parenteral drug formulations drive the manufacturing process and the process is critically important to the outcome. Neither is more important than the other, they must be developed symbiotically, and this requires a science-engineering team that works with a spirit of teamwork, cooperation, and inter-reliance.

Quality Foundation

Quality is the cornerstone for any solid foundation in the pharmaceutical industry. Successful organizations that have been around a while have developed and continually sharpen the focus of their culture of quality. The focus in driven by a quality statement backed by me and the entire the executive team, a detailed quality plan with robust systems, and a quality council that proliferates accountability for the plan across the organization.

However, quality is not simply an organized assembly of titles, guidance, plans, checklists and batch records completed accurately and on time. While these are essential tools and critical deliverables, for me and the professionals with whom I work, an effective quality foundation is a durable outcome of a continuous and relentless pursuit of excellence. There is not a finish line we cross that is a signal to stop and relax, instead, it is a culture of continuous improvement, one in which we are always reaching for something better to assure safe and effective products for patients.

The drive for continuous improvement requires a quality mindset individually and organizationally. I think about it like this, embracing a quality mindset ensures the structural integrity of a quality foundation. Everyone must know what to do, why they are doing it, and why it matters. If they cannot answer those three questions with confidence, they must have the authority and pledge to pause to gain the understanding they need.



Risk Management Foundation

As I highlighted earlier, the risks associated with manufacturing any parenteral drugs are significant, and when adding the complexity of highly potent compounds, aseptic environments, and combination products, the risks are even greater. I think the key to success when managing risk is having a comprehensive perspective that not only includes the manufacturing process, people, equipment and facility, but also the supply chain supporting your operations, and a deep understanding of what may pose risks to the business and the patients we ultimately serve.

During the manufacturing process, risks can emerge that can negatively impact the drug product, those making the drug, the patient who needs the drug, and the reputation of the drug maker or distributor. Organizations with a record of having successfully and safely manufactured complex parenteral formulations have developed and refined a risk-based approach to process design, development, validation and scaling-up manufacturing as needed. Additionally, they can explain the whys of their systems for managing risk (e.g. Failure Mode Effects Analysis or FMEA) in a way that reflects the confidence of ownership accountability for the outcomes.

To effectively manage supply chain risk, it must be tuned for your short and mid-term requirements, and your long-term vision. If I were asked to describe an effective supply chain risk management program, I would use words like focus, discipline, , rhythm, and rigor coupled with deep economic insights both micro and macro. An effective short and mid-term supply chain secures the cost, delivery, reliability and quality of your current and projected needs looking out at a 12-month horizon. Notably, when manufacturing complex parenteral drugs, there are critical components of your supply chain that are not present in other types of dosage forms and routes of administration, e.g. vials, stoppers, one-time use/disposables, and special packaging.

It is important to look at your long-term supply chain needs to effectively support where innovations are moving the pharmaceutical industry. There are tectonic shifts driving change in our industry that will give birth to new therapies and drug developers are innovatively employing parenteral drugs in ways that will require supply chain transformations. E.g. depot and long-acting implants and injectables, newly styled autoinjectors and non-aqueous or highly viscous formulations requiring innovative sterilization processes.

There is a final component of an effective risk management foundation that is important to me, and all of us at Pii. As a CDMO, everything we work on is the result of someone's dream. Our customers and partners come to us having had some initial success with an idea, and they want help taking it to the next stage rapidly. Perhaps it involves support for preclinical toxicity testing, filing an IND on-time, or a batch manufactured to support a supply of a clinical trial, developing a

reliable dose form for a poorly soluble drug or complex drug delivery of a multi-active drug product. Our successes together may the catalyst for a next round of funding, NDA approval or technology transfer to our US based facilities that advances their dream of delivering a desperately needed therapeutic to a patient population.

Manufacturing complex parenteral drugs is high adventure and extremely rewarding work for all of us at Pii. Doing it consistently well for every customer and partner requires a foundation of skilled professionals, effective quality systems, and comprehensive risk management.

Dr. Kurt Nielsen is the President and CEO at Pharmaceutics International, Inc (Pii). Dr. Nielsen is a seasoned pharmaceutical executive with over 20 years of diverse experience, most recently as the President of Lupin Somerset, responsible for all their generic and branded products. Prior to Lupin, he held the post of Vice President, U.S. Development, Portfolio and Launch Management at Sandoz Inc., where he was accountable for the U.S. development of generic, OTC and specialty brand products. Dr. Nielsen has also held positions at Catalent, where he was Senior Vice President of R&D and Chief Technology Officer, and URL Pharma where he was the Executive Vice President, Pharmaceuticals.

Pharmaceutics International, Inc. (Pii) is a contract development and manufacturing organization (CDMO) located in Hunt Valley, Maryland. The experienced scientists, engineers, and staff at Pii pride themselves on solving difficult problems, it is part of their DNA. In addition to manufacturing complex parenteral drugs, Pii has a wealth of analytical testing, formulation development, and manufacturing capabilities across a variety of dosage forms. Its Hunt Valley campus has four aseptic suites with lyophilization capabilities. Our talented professionals stand ready to help!

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