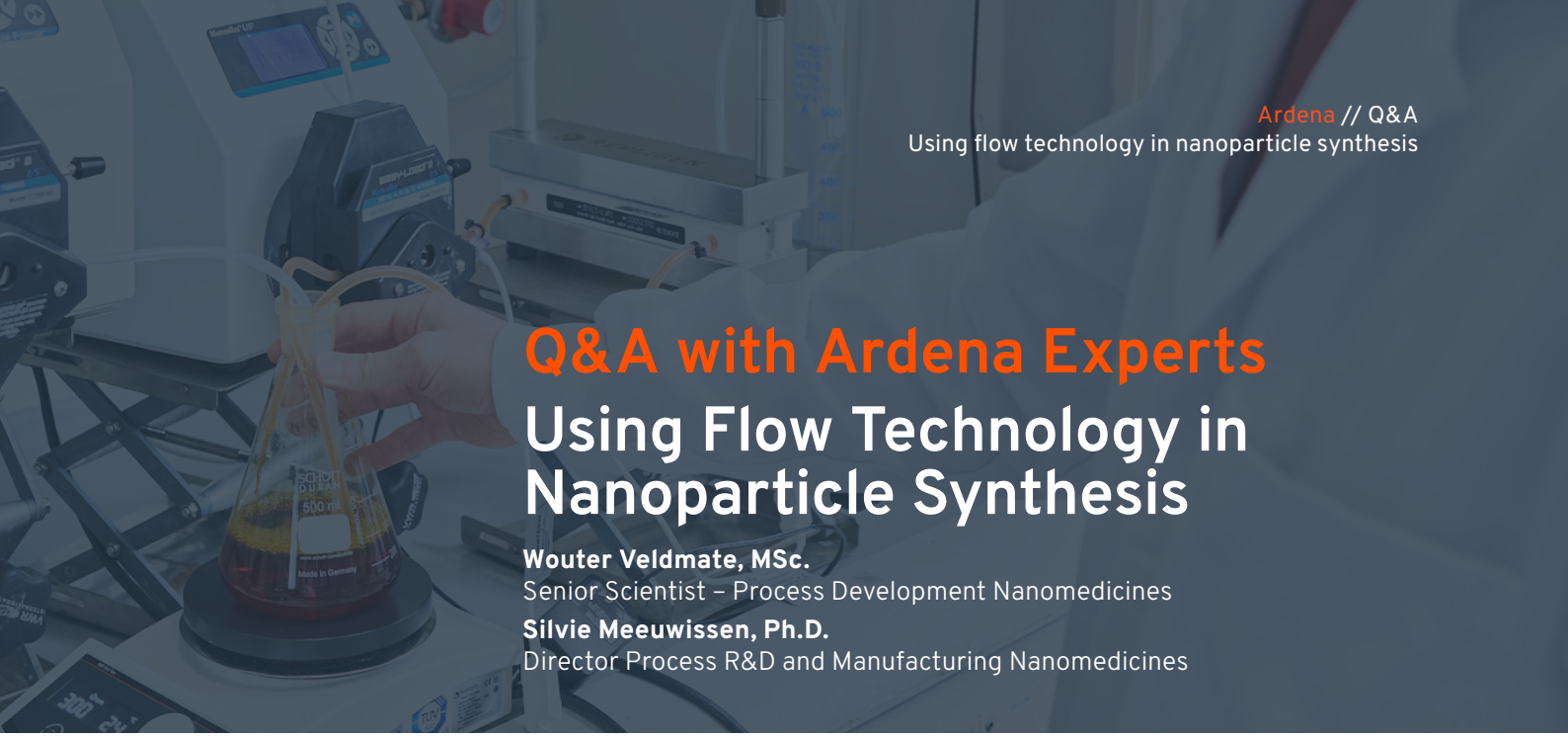

Q&A with Ardena Experts

Using Flow Technology in Nanoparticle Synthesis

Wouter Veldmate, MSc.
Senior Scientist – Process Development Nanomedicines
Silvie Meeuwissen, Ph.D.
Director Process R&D and Manufacturing Nanomedicines

Why would you consider flow technology for a nanoparticle manufacturing process instead of conventional batch technology?

Wouter Veldmate

Batch technology is the go-to technology for many nanoparticle manufacturing processes, especially for emerging early-stage clinical products that are often produced in limited quantities. These technologies draw upon decades of experience and development, and often employ reactors and equipment that are widely available and implemented. When batch sizes increase however, reactor sizes may need to be increased accordingly, often giving rise to scale-up effects such as variations in mean particle size, polydispersity or impurity profiles.

Depending on the process, manufacturing larger batch sizes may also be accompanied by increased safety risks. Often, a potential solution is sought in the production of multiple repeat batches at a smaller scale, to be combined into a single batch later down the line. This solution is time-consuming and costly. Flow technology offers many advantages to overcome scale-up issues, by (semi-)continuously operating a manufacturing process under constant process parameters, producing nanoparticle products of a consistent quality independent of the batch size produced.

How does flow technology achieve constant process parameters irrespective of batch size?

Silvie Meeuwissen

In essence, flow reactors consist of a series of tubes or channels, into which one or more substrate solutions are continuously driven by pump systems. The solutions carry the nanoparticle building blocks, such as polymers, lipids or inorganic complexes, as well as other excipients such as salts, sugars or surfactants. Inside the flow reactor, the solutions are mixed and submitted to external stimuli such as heating or UV-irradiation to trigger a reaction. The residence time of the difference streams in the system, and thus their exposure to the reaction conditions, is tightly controlled. The reaction products are then collected as they flow out of the flow reactor, or they are passed into a second flow reactor to be submitted to a second reaction step or a quenching process. As time passes, the cumulative amount of

product generated continuously grows. Larger batch sizes can be manufactured simply by operating the flow systems for a longer amount of time, without the need to consider other scale-up factors

What about process safety considerations?

Wouter Veldmate

Flow reactors are often designed with a large surface area relative to the volume of the flow reactor. Compared to batch reactors, this offers superior heat transfer and allows for rapid heating and cooling of the flow. This increased temperature control can be used to prevent over-exposure to e.g. elevated temperatures, thereby reducing impurity formation and side reactions whilst still maintaining the desired conversion.

In the case of exothermic processes, flow technology also offers an increased safety of operation. As the reaction volume is small at any given point in time, the exothermic heat can be removed more easily. The risk of a chain reaction is also mitigated as the amount of available substrate inside the system is low compared to a batch reactor.

So, is flow technology always the better choice?

Wouter Veldmate

No, not for every process.

Every nanoparticle production process is unique, and whether to rely on batch- or flow technology needs to be evaluated on a case-by-case basis. Flow technology offers unique advantages to deal with common scale-up issues, as well as technical solutions for increased parameter control and process safety.

However, the equipment required to implement flow technology is more specialized and not as multi-purpose as most batch equipment. Complex manufacturing processes, especially those containing viscous or highly heterogeneous reaction mixtures, may require custom-built flow reactors in order to effectively translate an existing batch process into a flow process. The additional early-phase investment in process development and equipment will pave the way for further scale-up, but not all processes will require sufficient scale-up to reap the rewards of this investment. For those processes, conventional batch technology provides a more effective solution.