CHALLENGES IN THE DEVELOPMENT OF CONTINUOUS PROCESSES FOR VACCINES

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Abstract

The development and application of continuous manufacturing processes for vaccines presents both great opportunity as well as significant challenges, both technical and cultural, for the global industry. The key drivers are manufacturing capacity and flexibility, speed to market, and improved quality through the application of Quality-by-Design and Process Analytical Technology (QbD/PAT). Given the diversity of immunogens (toxoids, conjugate and subunit vaccines, live-attenuated and inactivated viruses, VLPs, etc.), and the variety of unique processes currently utilized to produce either single- or multi-component vaccines, it is unlikely that the transition to continuous processing will happen overnight. Additionally, cultural challenges are faced whenever a new mode of operation appears to some as “too different”, especially in a traditionally conservative sector like the developed-world vaccine industry. That said, market forces, global climate change, and Nature’s propensity to fill unoccupied niches with emerging infectious diseases will undoubtedly induce a first round of pioneers to explore this exciting new design space, ultimately leading to a more nimble industry and more and better opportunities for protection for the global population.

Introduction

The rate with which new variants and previously unknown emergent infectious diseases appear is constantly challenging existing paradigms for the development, manufacture, and licensure of new vaccines. A radically new approach will be required if vaccines are to keep pace with these potential threats to human health. Legacy vaccines are also in need of modernization to keep pace with regulatory requirements, and aging facilities can put production at risk or require costly renovation to remain in compliance. Vaccine manufacturers must apply innovative strategies in these areas if they are to continue to serve the increasingly at-risk populations around the globe and to remain competitive in the expanding market. The application of continuous processing methods based on fundamental chemical engineering principles[1,2] and building on existing process understanding has the promise of overcoming these challenges while improving product quality and manufacturing consistency and output. There are however significant challenges to

the development of a continuous biopharmaceutical product such as a vaccine. Continuous processing/manufacturing has long been standard practice in the petroleum, mining, steel, and energy generation industries, and is widely employed in food and agriculture (Figure 1).

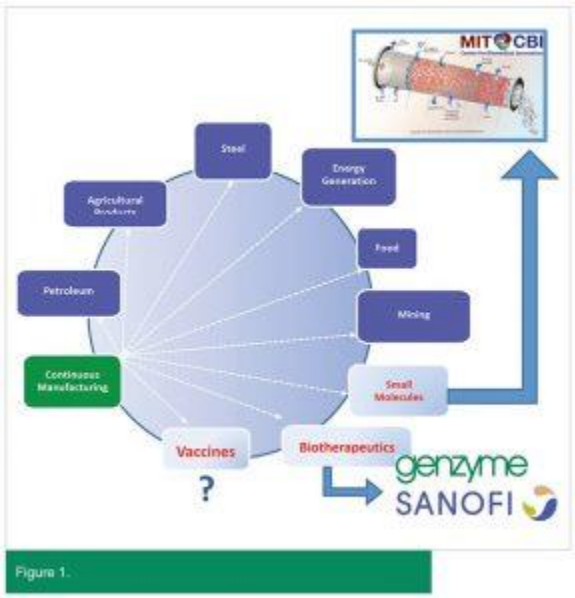

Figure 1.

Pharmaceuticals and biopharmaceuticals have relied on batch processing for most of their history until very recently, but conferences and colloquia are increasingly adding the topic to their agendas, and thoughtful publications are appearing that address the technical and cultural challenges arising when considering an initiative to implement a continuous process development program[3,4]. Researchers at MIT and Novartis have developed a fully integrated continuous process for manufacturing a pharmaceutical product that embodies many of the principles discussed below[5]. Process complexity, precise control of biological processes, and real or perceived regulatory hurdles, as well as some industry inertia that may have served as impediments in the past are all being impacted by new thinking, new technologies, and the need to adapt as the human health landscape evolves. This article with provide a brief overview of these challenges while, hopefully, providing a top-level approach to thinking about this topic.

Technical Challenges

The technical challenges for the development of a continuous process for a given vaccine will necessarily be based upon how complicated the underlying or “parent” batch process is. Batch production of the Drug Substance through Upstream (USP), harvest, and Downstream (DSP) purification is very much dependent on the immunogen. Development of a continuous process will rely heavily upon a set of well-defined process parameters established for the parent batch process. In

general, the better the process definition for the existing batch process, the greater the chance of success and the shorter the development pathway for the corresponding continuous process.

A truly continuous process will consist of a set of steady-state operations for the upstream phase where precise control of a biological process is required, a harvest phase which may be continuous or semi-continuous where the immunogen is separated from the producer cells/biomass, followed by downstream processing to purify the immunogen. This downstream phase typically involves multiple filtration and/or liquid chromatography steps, depending on the degree of purity required in the resulting Drug Substance. For subunit vaccines, toxins, virus-like particles (VLPs), and nucleic acid vaccines, for example, high purity is required so that the immunogen produces a highly specific, targeted immune response. A lower degree of purity may be acceptable for live-attenuated viral vaccines, principally because the dose-level is typically orders of magnitude lower than for protein or polysaccharide vaccines. Thus the complexity of the downstream purification process will strongly influence the development of a scalable continuous process.

The goal of the upstream phase development effort is a steady-state producer/substrate-cell culture that can be maintained at a constant viable cell density for days or weeks, while remaining within control limits for operating parameters. For microbial processes, the use of a “chemostat” bioreactor has been a part of the research and manufacturing landscape for decades. Advancing this fundamental technology to include mammalian cell culture is relatively new. Deep knowledge of the cellular metabolism and other factors influencing producer cell health, genetic stability, and control of immunogen expression is a prerequisite for the conceptual design of a continuous process. The development of a continuous upstream culture also provides an opportunity to employ process intensification strategies such as perfusion to achieve high cell density cultures that can be maintained in a metabolically balanced state for the required duration. If per-cell specific productivity is comparable to or better than that of the parent batch or fed-batch process then a significant scale-down of the bioreactor process can be achieved, essentially converting a large working volume/short time into a much smaller working volume run over a much longer time to produce same total amount of immunogen, with the added benefit of having a process that is run in a higher state of control. A direct consequence of this scale-down is the increased capability to incorporate single-use technologies (bioreactors, process containers, tubing, etc.) into the process design, thus reducing the CAPEX requirements for facilities and equipment, and enabling flexible facilities design. Sterility assurance comes through gamma-irradiated components, and the use of tubing welders and aseptic connectors to create the upstream assembly. A key new concern arising

from longer duration processes is system robustness, particularly where peristaltic pumps may be employed for fluid transfer or mixing.

Downstream purification for vaccine immunogens typically involves sequential application of filtration (dead-end or tangential-flow, TFF) and liquid chromatography steps. Capture-chromatography is increasingly important in the development of new purification processes because of the introduction of new resins with novel architecture and chemistries that facilitate separations of macromolecules. Resin or filter capacity and specific flow rates (eg $L/m^2/hr$) remain as key design characteristics, with the added challenge of robustness for long-duration, possibly multi-cycle modes of operation. Recently, new TFF cassette designs employing “single-pass” architecture have been introduced that at least conceptually can be incorporated into a continuous-process design. Chromatographic steps can be employed in continuous mode by employing column-switching equipment and simulated moving bed methodology. The longer durations that might be envisioned present the need to focus much more strongly on establishing and maintaining a closed-system, probably aseptic, process. This is made more challenging because TFF and liquid chromatography equipment typically do not have single-use flow paths, so chemical sanitization is required to establish a very-low bioburden environment. Peroxyacetic acid and/or NaOH solutions are often employed in these hybrid process assemblies, but getting the sanitant solution, as well as rinsing and conditioning solutions, in and out of the assembled equipment adds complexity to the design of the assembly and the process itself. Verifying that aseptic conditions can be established and maintained reproducibly is its own challenge, but arguably easier than the alternative low-bioburden state when considering long duration processes where the process intermediates are capable of supporting the growth of contaminating microorganisms. Toxoid or conjugate vaccines will necessarily add additional complexity because of the need to carefully control stoichiometry and chemical reaction conditions, and employ continuous mixing strategies, followed by additional purification steps in order to produce the Drug Substance.

Producing a stable Bulk Drug Product for a vaccine often incorporates straight-forward addition, dilution, or buffer exchange steps, and like the downstream processing steps described above, continuous processing designs can be envisioned. Sterility assurance through validated aseptic processing is a fundamental requirement. Likewise, adsorption to solid-phase adjuvants in continuous mode, and continuous filling of vials or syringes is, at least conceptually, achievable with current technology. Multi-component vaccines likewise have additional requirements for establishing proper dose levels for each, especially those that are adsorbed to solid-phase adjuvants or presented in an emulsion.

Lyophilization, employed to stabilize many biological products and vaccines, is a continuous-processing challenge awaiting an advanced engineering solution.

Quality and Regulatory Considerations: Process Control/QBD/PAT

Maintaining a continuous process within control limits requires continuous monitoring of both control parameters and process performance through on-line or at-line analytics, coupled to feedback control of process inputs. Thus the development of the continuous process must be coupled with the deployment of advanced process analytical technologies (PAT). The control strategy must maintain the process within the design space for the duration of the process. Accuracy, precision, as well as the robustness of these analytics must be established in conjunction with the development of the process itself. Defining the control and critical process parameters using a design-of-experiments (DOE) approach is best done at laboratory (bench) scale. Many operational parameter control limits can be established while working through the development of the underlying batch process. The resulting matrix of time-dependent control and performance parameters may then be incorporated into a conceptual design for the projected continuous process. At this time as well, the on-line and at-line process monitoring methods and instrumentation is also built into the design, along with feedback loops designed to translate the analytical signals back into the process control instrumentation. New process control and critical process parameters, necessarily, will be derived as the continuous process design evolution proceeds. The overall process control strategy itself is implemented through the development of a control algorithm – essentially a set of ordinary differential equations translated into computer code. Process simulations are run to challenge the control algorithm, and also to test scalability. The mature control algorithm should be numerically scalable in order to simplify and support the clinical development, launch, and eventual commercialization of the vaccine. The algorithm may need to be designed to suit the expression system and/or the biological or chemical entity to be produced.

The implication embodied in this strategy is that a Quality by Design (QbD) approach to process and product development will be implemented, resulting in the definition of Critical Quality Attributes (CQAs) for the Drug Substance(s) and the Drug Product. Furthermore, the regulatory submissions (eg INDs and the BLA in the US) will describe the design space, process control strategy, and CPPs/CQAs. A question commonly heard at conferences and other forums discussing the potential development and implementation of continuous processing is: “how do you define a batch?”. When asked of former regulators and industry experts the response is something like: “that is up to you, just as it has always been”. Batch or fed-batch processes provide a simple definition. With a continuous process a batch

could be all of the product produced during the full duration that the process can be maintained, or the duration could be segmented into several batches, thus reducing the risk that a OOS result would impact the ability to release a particular lot of bulk Drug Substance or Drug Product. A risk-analysis approach to setting batch size is warranted, dependent upon the robustness of the continuous process and the analytics employed to release the DS and DP.

Decision Making

Because there is so little biopharmaceutical industry experience with continuous processing, the timing of that implementation relative to the clinical phase of product development is uncharted. One approach could be to develop a continuous process in parallel with the batch or fed-batch process once the initial IND is filed and Phase 1 clinical studies are completed successfully. Another option could be to develop the two processes in parallel and wait to transfer the continuous process to manufacturing until the Phase 2 proof-of-concept trials are complete. There is no right answer at this stage, so companies will have to weigh all the risks and benefits of alternative development approaches for themselves and in consultation with regulatory experts. It is clear however, that a strong team-oriented approach, with early involvement of every function with a role to play in the development of new or improved vaccines will be required if the adoption of continuous processing is to be successful. A key consideration will be whether the cost/benefit analysis of the continuous process strategy for a particular vaccine makes sense in comparison to the traditional manufacturing methods. Again, no global predictions are possible – each analysis done for the foreseeable future will break new ground for manufacturers.

This is an exciting time for vaccine developers and manufacturers of biopharmaceuticals and vaccines. New and improved process and analytical technologies and components are being made available at an ever increasing pace. The desire to produce more and better vaccines for a changing infectious disease landscape is driving the search for new cost effective techniques to speed new vaccines to the marketplace. “Cultural inertia”, the impulse to keep doing process and product development the way it has traditionally been done, may not cut it in the coming years, given the direction of change in so many aspects of the vaccine development space. Continuous processing, despite the many challenges, may ultimately provide a competitive edge to successful adopters, and enable a more robust assault against continuing and emerging infectious disease challenges.

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Author Biography

Danny's principle role before his retirement was the pursuit of innovative manufacturing technology through academic and industrial networking and collaborations, including new technologies scouting, assessment, and implementation for all phases of live-viral vaccines process development. He was also often called upon for product & process improvement and troubleshooting for a variety of manufacturing processes across the company. He has been a Lecturer in Oxford University's Clinical Vaccinology Programme. Formerly, he was the founder and head of Process Development at Acambis from 2001-2008, responsible for ushering 7 new vaccine candidates through phase-appropriate process development, two of which are now licensed.