Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Workup, and Isolation of Drug Substance May 20–21, 2014 Continuous Manufacturing Symposium

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ABSTRACT: This whitepaper highlights current challenges and opportunities associated with continuous synthesis, workup, and crystallization of active pharmaceutical ingredients (drug substances). We describe the technologies and requirements at each stage and emphasize the different considerations for developing continuous processes compared with batch. In addition to the specific sequence of operations required to deliver the necessary chemical and physical transformations for continuous drug substance manufacture, consideration is also given to how adoption of continuous technologies may impact different manufacturing stages in development from discovery, process development, through scale-up and into full scale production. The impact of continuous manufacture on drug substance quality and the associated challenges for control and for process safety are also emphasized. In addition to the technology and operational considerations necessary for the adoption of continuous manufacturing (CM), this whitepaper also addresses the cultural, as well as skills and training, challenges that will need to be met by support from organizations in order to accommodate the new work flows. Specific action items for industry leaders are:

- Develop flow chemistry toolboxes, exploiting the advantages of flow processing and including highly selective chemistries that allow use of simple and effective continuous workup technologies. Availability of modular or plug and play type equipment especially for workup to assist in straightforward deployment in the laboratory. As with learning from other industries, standardization is highly desirable and will require cooperation across industry and academia to develop and implement.
- Implement and exploit process analytical technologies (PAT) for real-time dynamic control of continuous processes. Develop modeling and simulation techniques to support continuous process development and control. Progress is required in multiphase systems such as crystallization.
- Involve all parts of the organization from discovery, research and development, and manufacturing in the implementation of CM.
- Engage with academia to develop the training provision to support the skills base for CM, particularly in flow chemistry, physical chemistry, and chemical engineering skills at the chemistry–process interface.
- Promote and encourage publication and dissemination of examples of CM across the sector to demonstrate capability, engage with regulatory comment, and establish benchmarks for performance and highlight challenges.
- Develop the economic case for CM of drug substance. This will involve various stakeholders at project and business level, however establishing the critical economic drivers is critical to driving the transformation in manufacturing.

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INTRODUCTION—THE FUTURE FOR CONTINUOUS DRUG SUBSTANCE MANUFACTURE

Successful innovation in manufacturing and the adoption of continuous manufacturing (CM) has an important role to play in the industry's future. The vision for CM in the pharmaceutical industry is to exploit continuous processes to convert raw materials into safe, effective, and high-quality medicinal products. This vision is driven by the potential to improve control over quality, reduce costs, enhance process safety, and significantly reduce the timelines currently involved across the medicines' supply chain. In the shorter term, continuous processes in Good Manufacturing Practice (GMP) manufacturing will likely be single steps or reactions in series with batch workup and isolation, rather than the longer term vision of fully continuous end-to-end processing. As new continuous

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systems and technologies become fully established so the industry's ability to continue to meet the demands for existing as well as new, safer, and increasingly personalized dosage forms will be enhanced.

This whitepaper is focused on the opportunities and challenges associated with the first stages of this emergent pharmaceutical manufacturing paradigm, specifically continuous synthesis, workup, and isolation of new chemical entities, active pharmaceutical ingredients (APIs), or drug substances. In particular, the challenges and opportunities associated with each of these operations are highlighted alongside other important considerations when deploying continuous processes. Ensuring quality and consistency through control are key drivers for CM, and considerations for delivering the required levels of quality at each stage are discussed, highlighting some of the important differences from traditional batch manufacturing approaches. Flow chemistry is often cited as having advantages for safety in enabling access to hazardous chemistries in a safe and controlled manner.[1–5] However, a broader range of issues needs to be addressed to ensure safe operation at all stages. CM also changes the development paradigm (e.g., how and when process development is carried out) and the facilities strategy (e.g., current footprint versus future) and places markedly different demands on organizations and their staff compared with batch. Successful deployment of CM is therefore dependent on changes in organizational culture and workforce skills as well as in the science and technology. This whitepaper draws on the experience and informed views of many individuals from the industrial and academic community and recognizes that delivering this advanced manufacturing vision will require significant change across the industry and the wider pharmaceutical value chain.

REACTIONS: THE WIDER ADOPTION OF CONTINUOUS FLOW STRATEGIES IN PHARMA

Continuous flow synthesis has matured as a scientific area translating from a principle domain of chemical engineering to a technological tool now routinely used by many chemical synthesis laboratories and increasingly in process development and scale-up.[1–5] Conducting synthetic reactions in flow can be used to access a variety of benefits that may include: (1) reduced hazard/increased safety from smaller reactor volume, relative ease of containment, reduction/removal of headspace, reproducible delivery of conditions to ensure consistent quality with no accumulation of reactive/toxic intermediates; (2) reduced cost from lower capital and operating costs as well as improved consistency; (3) enhanced mass and heat transfer rates; (4) improved yield through enhanced selectivity; (5) expansion of the feasible reaction space offering a toolbox that can support many "forbidden reactions" through access to highly selective chemistries that would be difficult or impossible using batch, particularly at manufacturing scale; (6) ability to operate cryogenic processes at higher temperature; (7) safe, controlled access to higher pressure and temperature operation to enable operation at conditions that maximize yield and minimize impurity formation; (8) increased robustness, control, and stability inherent in steady-state operation of continuous processes; (9) easier, well-defined scale-up routes for laboratory to production scales; (10) increased throughput with a dramatically reduced equipment footprint; and (11) greener operation from reduced solvent consumption. Clearly, the actual benefits will be process specific; however, methods for assessing these and informing the early decision processes are required.

Widespread adoption of flow processes in pharmaceutical manufacturing facilities has not yet taken place. Until recently, this processing approach was almost exclusively confined to petrochemical and bulk chemical manufacturing settings. Perceived barriers in Pharma application include high skills and technology requirements combined with a limited ability to support multiple products because of product specific requirements of CM plant. Plant economics ultimately determined that such units were mostly commercially viable for very large-scale production generating large volumes of relatively simple compounds. The challenge for adoption of continuous flow manufacturing by the fine chemical sector has always been the diversity and complexity of the molecules of interest and the associated need for complex and diverse processing conditions. Typically, pharmaceutical and agrochemical molecules require 6–10 synthetic steps (sequential or convergent), involving chemo- and regio-selective transformations, that also necessitate multiple rounds of quenching, workup, separation, and purification. This is an important reason why batch processing dominates in pharmaceutical and agrochemical production as a small number of temperature- and/or pressure-controlled, agitated vessels can be used for virtually all of the reactions, liquid–liquid extractions, distillation, stripping, adsorption, and crystallization unit operations associated with a long and complicated synthetic route. The creation of integrated, self-supplying continuous processing streams is challenging. Although reaction kinetics can be manipulated using temperature, pressure, or solvent choice, for example, robust integration requires the controlled and steady balancing of reaction rates and process flows of sequential steps in addition to consideration of subsequent downstream operations. Adding buffering capacity between groups of synthetic steps is one option to help mitigate integration issues.[6]

One of the main impedances to the wider adoption of flow processing has been the delivery of readily tailored and amenable chemistry. Most routes conceived during small-scale laboratory development have historically been batch based and have therefore subsequently progressed through the various rounds of scale-up using related processing strategies. Only recently has an appreciable acknowledgement been made that potentially different development routes are required for continuous flow-based manufacturing sequences. This has resulted in a steady increase in the adoption of flow-based reactors at earlier stages of the development pipeline ensuring continuous processing is more readily built into the design and synthesis of new chemical entities. Automated flow-based techniques enable optimization and determination of chemical mechanisms and kinetics determined at the milligram scale.[7,8] Classical chemical reaction engineering concepts can then allow scaling of several orders of magnitude to production systems. Automated flow reactors are of particular interest as they offer rapid ways to quench reactions chemically or thermally and improve chemistry selectivity. Achieving improved selectivity is of considerable importance in integrated processes as it can lead to simplified workup stages downstream. Even so, continuous extraction, distillation, crystallization, filtration, and drying unit operations will be needed in some circumstances to achieve 99.9% purity APIs or in end-to-end continuous processes.

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Although flow reactors offer many advantages for controlling chemical processes, there are still a number of areas where complex chemistries and operation at small scale present additional challenges. These include low tolerance of solids in small channels, challenges in maintaining constant phase ratios and interfacial areas for multiphase processes, dealing with the distribution of residence times inherent with laminar flow at low flow rates, potential for gradual accumulation of foulants or encrustation, low turnover numbers of solid catalysts requiring frequent changes, significant control challenges, reliable pulse free pumping wherever pulsation impacts on process performance plus a restricted palette of well-demonstrated workup possibilities.

Flow Chemistry Equipment

There is a need for equipment that can support a wide range of chemical transformations in continuous operation. The main classes of reactor are described below. However, continued chemical reaction engineering is required to ensure that equipment designs continue to develop to deliver the optimal level of control over individual process conditions for successful operation with the required level of safety, automation, and control at the scales required.

A major enabler of continuous processing has been the commercialization of standalone laboratory bench top flow systems capable of performing chemistries under a broad range of temperatures and pressures. This availability has been matched by the provision of larger scaled processing units and the provision of off-the-shelf easily assembled components (including passive and active mixers, tubing unions, chemical resistant tubing), which can be assembled to create bespoke flow units. Extensive coverage of continuous reactor platforms has been published providing varying degrees of detail on their operating principles and characteristics. Detailed understanding of the system dependency to flow geometries and characterization of the equipment should enable seamless scale-up (or numbering up) with only minimal additional development. The essential requirement for realizing the benefits of flow is to ensure that robust control of each particular chemical and physical transformation involved is delivered by appropriate equipment whether that is bespoke or multipurpose.

Often several unit operations need to be integrated to perform laboratory synthesis in flow reactors. Pumping and metering of reactants, mixing, control of the reaction temperature, chemical and/or thermal quench, pressure control, and collection of product. Early efforts in the field used discrete components comprising stand-alone pumps, mixers, and reactor units. However, commercial units at the laboratory scale now integrate all operations into compact units that require the user only to provide the reagents. The reactor unit is typically either a tube or microstructured reactor device (microreactor), although continuously stirred tank reactors (CSTRs) are also used.

Tube-based laboratory systems (typically coiled) are commonly made of copper, stainless steel, hastelloy, tantalum, zirconium, polyether ether ketone (PEEK), or perfluorinated polymers. Their volumes range from 1 μL to liters with channel diameters from 100 μm to 16 mm depending on the specific requirements of the system in terms of mixing and heat transfer. They are simple to operate and easy to create, but rely on diffusional mixing. All real plug flow reactors (PFRs) are prone to dispersion effects, whether the mixing is by diffusion, turbulence, or mechanical. However, in each of these three mixing cases, dispersion effects can be minimized by design of reactor dimensions. In this context, perfluorinated tubes have the advantage of broad chemical compatibility, but suffer from poor heat transfer characteristics, which becomes an issue in running fast, highly exothermic reactions. They also suffer from low pressure rating at elevated temperatures. Consequently, although clear perfluorinated tubing is used in many commercial systems, this is a non-optimum material for scaled operation. However, polymers do offer some unique advantages. For example, the tube-in-tube reactor is convenient for gas–liquid reactions, for example, hydrogenation.[9] This is also a specific example of a membrane reactor that functions to allow selective partitioning of species between two or more flow streams.

Microreactors are machined in glass, silicon-glass, ceramic, polymers, or stainless steel with volumes typically ranging from 50 μL to 100 mL and channel diameters from 50 to 1000 μm. They can include mixing units, flow distributors, multiple channels, and means for immobilizing catalyst. In both tubes and microreactors, the effects of mixing and dispersion can be explored experimentally and predicted to establish guidelines for running reactions under favorable mass and heat transfer conditions. However, CSTRs may be a necessary alternative if the process requires solids in flow, immiscible liquid phases with long reaction times, induction times, or autocatalytic reaction.

Tubular and microstructured reactors can be filled with solid inert particles to increase mixing and solid heterogeneous catalysts for packed bed catalytic reactors. Several commercial systems have been developed to enable scale up of both single and multiphase flow chemistry procedures to production levels of multiple tons per year. However, simply multiplying the number of microreactors to scale-out creates complex fluid flow distribution and control challenges. Consequently, scale-up is typically achieved by increasing reactor size while preserving heat and mass transfer advantages, although this may only take you part of the way in some circumstances, and then multiplying up the resulting smaller number of larger reactors. In many cases, good heat transfer characteristics can be maintained by sandwiching a thin reaction layer between cooling plates and increasing the lateral size while keeping a nearly constant reactor channel depth. Mass transfer is kept high by multiplying out static mixer units rather than changing the size of the mixing units.

A similar, tube-based approach is to scale to larger tubes fitted with static mixing elements that increase mixing across the tube and reduce axial dispersion. The use of static mixers sets minimum flow velocities to achieve sufficient mixing across the tube to reduce axial dispersion and maintain plug flow. Baffled oscillatory flow reactors provide good mixing at longer residence times, but at the cost of greater mechanical complexity. Tube or pipe reactors are practical with mean residence times up to about 12 h. In addition to tube and structured reactors, trains of multiple CSTRs are a commonly encountered solution in continuous synthesis. They are particularly well suited for reaction systems involving slurries of solid reagents or products.

For many chemical applications, the specific reactor of choice is determined by the processing characteristics required to deliver the desired chemical transformation (or sequence of transformations) being performed. Principal considerations involve the physical state of the materials being processed

(gases, liquids, solids), the reaction thermodynamics (exothermic/endothermic), reaction kinetics, heat and mass transfer, mixing, and the required residence times which in the scenario of coupled sequences is determined by balancing rates (without inherent buffering capacity).

One of the major advantages that continuous flow-based reactors present is increased control over their internal temperature stability. Heat transfer is more efficient in the smaller volume flow systems compared with their batch stirred tank reactor counterparts through the larger heat transfer area. Alternative techniques for energy supply being actively researched at laboratory scale include sonication, photochemistry, electrochemical, and microwaves.

Translation of Flow Protocols from the Laboratory Bench to the Plant

Pharmaceutical development comprises several successive stages in which the emphasis shifts from the use of rapid and clean synthesis of molecules for testing to the implementation of a robust, cost-effective process suitable for manufacture. Broadly, the early stages use a "medicinal chemistry" approach where there are few restrictions on cost, or the use of toxic or hazardous reagents, whereas the later stages use "process chemistry" that avoids unsafe, excessively expensive reagents, and separations difficult at scale. These two extreme approaches may have similarities or be completely different depending upon the project. Pharmaceutical companies have traditionally used a med-chem route in the early stages and then devised a new manufacturing route. The availability of novel technologies such as flow chemistry together with increased cost pressures has changed the situation—and companies are now exploring how to be more effective—for example, by using med-chem routes for early clinical development material. Flow chemistry offers additional tools that provide greater opportunities to streamline the chemistry that supports discovery, clinical development, and manufacturing process development.

During preliminary research investigation, only a very limited amount of time is normally invested in optimizing a particular synthetic pathway. Projects produce libraries of related structures or just singleton compounds as quickly as possible by whatever chemistry is most likely to work. Another important consideration is the availability of easily accessed starting materials and reagents (often commercial availability is key). Elegant, well-engineered, telescoped, and fully optimized chemical sequences are not sought. Here, the most appropriate reactor design offers the maximum flexibility for reconfiguration and multipurpose usage to make small amounts of material; hence small-scale reactor volumes are desirable. Work is still required in this area to make flow chemistry more efficient for hit-identification and to identify further integration opportunities benefiting from the deployment of flow.

The broadening or redevelopment of synthetic routes is often a consideration faced early in the research pipeline where it becomes necessary to open up new areas of design space by expanding or preparing new structural motifs that can potentially be of interest to medicinal chemists but have little precedent. Often expansion of chemical design space is also performed to validate and define greater patent coverage.

As larger quantities of API are required to facilitate more in depth biological investigations, toxicology analysis and in certain cases formulation lead studies (the exact priority and level of each of these operations is highly organizationally dependent based on company strategy, precedent and to a great extent philosophy). Scales can therefore be from several hundreds of grams with kilograms potentially required to support clinical testing and trials. Consequently, at this juncture, greater consideration should be given to optimizing route selection and accessibility of starting materials for increased production. It is still not clear whether the increased scaling agility from the deployment of continuous flow in discovery and better understanding at the discovery stages of the requirements for flow can increase the probability that the original medicinal chemistry route is a viable route (in part or whole).

The clinical phase of development is where a route and (continuous) process for commercial manufacture will be developed, setting up the manufacturing phase. As such, additional inputs from control and engineering are required in order to support chemistry, engineering and analytical functions. It is also important at this stage to determine effective (continuous) workups and crystallization steps. The aim will always be to find the most efficient route to deliver the molecule as the process scale evolves and the chemistry and equipment will likely develop as a consequence as it moves from medicinal chemistry to production. The best fit reactor here is one that facilitates scaling of the chemistry. With the easier scaling of continuous reactors, this could also be achieved through scaling up of the reactor volumes without requiring reoptimization of the synthetic route as often-encountered in batch. Often the same reactor unit that was used for hit-identification can be run under extended operation to perform initial scaled synthesis for continuous equipment.

As development progresses, reaction kinetics and processing criteria such as potential safety considerations are also defined, that is, taking comprehensive exotherm measurements from reaction compositions of reagents, intermediates, and reaction mixtures. Here, a meso-scale reactor supplemented with a high level of automation, monitoring, and software offers many advantages. Automated Design of Experiments (DoE) runs can be performed screening a greater array of reaction conditions to discover the correct stoichiometries or solvent combinations not only for optimal conversion but also for workup and purification. With increased numbers of degrees of freedom to consider, there is a challenge for DoE-centered approaches particularly in relation to including a larger number of discrete variables such as solvent and catalyst where limited material may be available and attrition rates are high. The goal of rapid, automated optimization of reaction conditions however justifies further development of these approaches. Simultaneously, the identification and in concert preparation of standards for impurity profiles (for use in analysis and quality control) will be conducted, again, a smaller scale meso/micro synthesis platform is well suited to this work (optimizing for the synthesis of a by-product may require accessing different reaction space in terms of extremes of pressure or temperature). As indicated, data capture by in-line monitoring devices (e.g., infra red, Raman, ultraviolet, mass spectroscopy, high performance liquid chromatography, and flow NMR units) can be very effective and will greatly facilitate many aspects of the continuous flow synthesis allowing knowledge driven parameter design. The reaction tolerance in terms of each transformations viable temperature fluctuation, mixing efficiency variations, and resulting conversion/by-product formations can be determined. This is critical for coupling reaction steps to make integrated

chemical sequences. However, data capture is only one component of the process with data analysis and subsequent interpretation being a current limiting aspect for many current flow processing scenarios. A considerable body of work includes the development of a reaction database capturing key data to support the scale-up and filing requirements. Important in this context is consideration of quality-by-design (QbD) for any future CM processes.

In summary, discovery processes may well be used for a while, but changes or development of new routes are considered while working up clinical supplies. Armed with effective reaction engineering and process development approaches, there is the potential to consider parallel or alternative flow synthesis strategies and model or trial manufacturing routes based on assembly of telescoped processing sequences. The current position is largely that continuous process development takes companies longer than batch. However, the payback for this investment is that less scale-up is needed for continuous processes, and that it is often possible to run the commercial scale continuous unit operation in a laboratory or pilot facility for short durations. The challenge for continuous processing is to enable an accelerated route to support the economic, scalable supply of material for commercial production. Importantly, economies of scale and financial cost considerations start to play a large impact on the selected routes and processing conditions chosen. Thus, if chemistry sourcing and route decisions are to be made by the end of Phase 1 trials, greater investment into the chemistry, reaction engineering and process design aspects will be required to ensure robust multistep integrated operations which can be selected quickly from the growing flow chemistry toolbox.

Reaction Classes

Several companies have published reports stating the level or percentage of reactions that could derive a benefit from being performed using flow-based continuous manufacture within their organization. In general, this equates to approximately half of their reaction inventory that can access better selectivity, fewer workup steps, and more straightforward plant-wide controls. This classification is normally determined by consideration of two main drivers the safety profile of the reaction and analysis of the reactions kinetics (i.e., fast exothermic or mixing dependent transformations being well suited). Problematically, many reactions are subsequently excluded because of perceived issues with directly transferring the process to flow as a result of one or more components in the reaction being a solid. However, sometimes it is readily apparent that only minor modifications in the process (i.e., changes in solvents, reagents, bases, etc.) would quickly obviate this issue. Indeed, with increasing knowledge and experience, our ability to translate batch-derived chemistries to flow will certainly increase. At present, a conservative assessment of the reactions that would derive specific benefits from being run in flow would be ~40%, although many more will be capable of being delivered in flow. Although this figure may seem, on first inspection, to be low and only offer a modest prospect of success, it should be acknowledged that this only represents the translation of currently optimized batch procedures being retro-engineered into flow. Reactions already optimized for batch will rarely be attractive in flow. A much higher level of realization would be expected if the chemistries being assessed had originally been developed specifically for flow using the advantages of flow to reach new reaction conditions, for example, working a higher pressures and temperatures to allow reaction conditions that increase yield and minimize impurities.

WORKUP AND ISOLATION

Benefits of continuous reaction can often be realized even if the workup and isolation is batch. However, with the drive to develop reactions in continuous flow as part of an integrated end-to- end manufacturing strategy, it is also important to consider the optimal way to purify and isolate the products. Workup steps are often the dominant equipment and time costs of drug substance manufacturing processes and for flow processing to bring the expected benefits to the industry, the whole process from synthesizing raw materials to isolating pure, final product needs to be fully continuous. Therefore there remains a need for cost-effective continuous workup and purification procedures including extraction, distillation, adsorption, and selective separation (e.g., membrane) technologies. Ideally, traditional sequences of workup steps should be replaced by new, multifunctional, more efficient, and less-expensive steps, increased telescoping of reaction stages, appropriate solvent selection and recycle. Example areas requiring further development include: removal of trace amounts of water which will subsequently impact on downstream processing, for example in a Grignard Reaction or a crystallization; membrane(s) in series for use in solvent swap, de-water or concentrating, cost effective approaches to large-scale chromatography, catalyst separation, by-product removal and solvent swap to allow crystallization.

The starting point for workup and isolation is the definition of the purity requirements of the product (either for subsequent processing or for use as product). This requires consideration of the overall synthetic route and the nature and potential impact of impurities. The workup challenge is directly modifiable via reaction engineering and/or chemistry selection as cleaner reactions will usually give easier workups. Proper specification of the separations challenge helps to focus the search for cost-effective solutions. For drug substance production, the exploitable difference in product and impurity properties can be small and the tolerance of molecules for a wide range of processing conditions (temperature, pH, etc.) can be limited requiring particular care.

Another issue is the balance in process economics. With the low quantities typical of Pharma processes it may well be uneconomic to do more than separate the product. Valuable unreacted raw material, solvent and catalyst may be worth recovering and by-products are unlikely to be worth separating at all. This contrasts with bulks where large-scale means that even relatively low proportions of materials in products are economically worth recovering. Recycles are perhaps most likely of solvent, and for flow systems of unreacted raw materials, but in general there is limited economic incentive for recycling unless the "continuization" of the process has diluted it massively. Materials integration and recycling are likely to be secondary considerations.

The net result is that we may use a simpler separation, which only requires removal of product at the right purity, rather than fractionate the whole reaction mass into recycle and various product streams. On the other hand, we may have a much more challenging separation duty in terms of separating materials

of very similar properties including optical isomers and other materials structurally very similar to the product. Minimally, we might set out to pull the desired product into a solution or slurry that only contains materials tolerable by the next processing step, which may be isolation or we might telescope directly into the next reaction. Some separations that might normally be used in batch can be avoided by immobilization/use of fixed beds (catalysts, sorbents, etc.), although this brings with it the need to monitor the condition of the solid bed and to be able to switch to a replacement or stop the process before performance is compromised. Workup techniques that might credibly be used in flow systems include those described below. In each case, some of the potential uses and restrictions are noted.

Various types of distillation are useful for solvent removal and swaps, but may be limited in terms of product purification because of temperature limitations and a lack of volatility difference. Continuous distillation is not a new technology. For separations other than simple removal/purification/recycling of solvent, it is likely that more exotic and difficult to engineer approaches would be considered. Continuous distillations are typically under vacuum, on the order of 0.01 to 30 Torr absolute pressure. This includes wiped film evaporators, continuous stirred tank evaporators, fractionating columns, and intermittent flow rotary evaporators. Process design can be performed fairly simply given volatility data.

Liquid/liquid contacting for simple or reactive extraction is perhaps the most desirable workup technique for continuous processing. There are many continuous process technologies for liquid–liquid extraction. It lends itself nicely to continuous flow, and it is a separations unit operation that can usually benefit from continuous flow because it can be performed countercurrent multistage, which increases separation power. Common technologies include packed column, agitated columns, single-stage centrifugal separators in series, multistage centrifugal separators, membrane, static mixers and coalescing screens, and mixer-settlers.

Liquid/liquid separation by settling is readily achieved if the density difference between the liquids is sufficiently large, and simple phase separators with overflow and underflow lutes can work well. With lower density differences, centrifugal separators (often combined with a liquid– liquid extractor in a single unit) may be used. Emulsifying systems can be problematic although membrane separators employing differences in surface tension can be used to break emulsions and become efficient extraction tools at small and intermediate scales. Coalescing screens can also be used to break emulsions in continuous mixer-settlers.

Solid/liquid separation including solids washing in filtration is a more challenging operation to carry out in continuous flow, and though new methods are emerging, it is an operation where there is significant risk of encountering a processing difficulty and novel technologies are required. Alternative approaches that avoid the need to isolate API and support integration of primary and secondary manufacturing need also to be considered.

Adsorptive techniques (run in flip/flop mode or for finite duration run) can have high specificity (e.g., ion-exchange) and can capture cations or anions very selectively. Operationally such systems can be complex and breakthrough detection is a critical requirement. Adsorption by flow through packed columns is a more efficient method to remove solutes compared to batch. Solid adsorbent includes polymeric resins for removal of dissolved catalyst metals and carbon based adsorbents for color and trace impurity removal. However, efficient management of automated regeneration, or manual changeover, of immobilized solids and of breakthrough detection is important considerations. Chromatography can be operated as a continuous separation using simulated moving bed (SMB), although its high-dilution requirement may make it inconsistent with other flow processing steps. However, continuous chromatography offers the potential to reduce the amount of solvent required for purification by allowing almost all solvent to recycle.

Membranes continue to be in view for continuous processing, and are readily tested for their effectiveness experimentally. Although in principle, they bring elegance and simplicity to processing for compatible systems, their current limitations on solvent, pH, and temperature range restrictions, fouling and potential need for frequent membrane replacement restricts their application. Two primary purposes where membranes have application include the separation of small amounts of water from process streams and separation of compounds based on molecular weight differences. Extending the range of solvent compatibility and molecular weight selectivity will add to the range of utility of commercial membrane offerings.

Continuous crystallization has been applied successfully as a separation technique at small scale and is discussed further below as a final isolation method. It benefits from exceptionally high selectivity for an individual molecule hence its attraction in Pharma, though this comes at the expense of lost product in the impurity stream. Crystallization is the major organic impurity removal technique used in Pharma, which translates the lack of selectivity of the chemistry into a pure material. Other workup techniques are typically applied to prepare the solution for crystallization emphasizing the value in developing enhanced selectivity in the synthetic steps. Continuous crystallization is moderately complex to design rationally, requiring significant experimentation to develop. There are many reasons why one might choose to run crystallization continuous rather than batch. Continuous crystallization may result in better impurity rejection, prevent oiling, enable wider volume ratios solvent to antisolvent, better control of crystal size distribution because of controlled steady state and narrow residence time distribution, higher yield using controlled recycle, more contained handling of cytotoxics by using smaller vessels that fit in hoods or ventilated enclosures, integration to otherwise fully continuous wet end process in addition to control of particle attributes. Each of these can be a potential advantage that results in a desired outcome by continuous that is not possible or practical in batch. Whilst a variety of continuous crystallization platforms are available at the requisite development scale there is also a pressing need for continuous filtration, washing and drying steps at compatible scales.

The equivalent approach to the design of optimal temperature or antisolvent addition trajectories as a function of time for batch systems, in the case of plug flow crystallization processes, is to design a spatial temperature profile and/or spatially distributed antisolvent trajectory that can enhance product quality. There are multiple physical transformations and hence rate parameters that dictate the actual performance of a crystallization. Although rather sophisticated mathematical models have been published for some specific continuous pharmaceutical crystallizers, the vast majority of models for primary and secondary nucleation

processes, size-dependent growth, phase transformations, attrition, agglomeration, and morphology rely on semi-empirical kinetic models. As with chemical transformations, it is important to obtain reliable experimental kinetic data on these physical processes to inform process design. This can combine well-designed experiments which could be batch (to collect kinetics for example) or in appropriate continuous flow systems where fluid mechanics affect kinetics, for example, agglomeration. Strategies for control of polymorphism and physical form (solvate, salt, cocrystal) in continuous processes also need to be developed to effect control over particle and product performance.

Experimentally, a number of crystallizer types have been applied, including continuous stirred-tank crystallizers or mixed suspension, mixed product removal (MSMPR) crystallizers, impinging jet reactors usually operated in association with MSMPR crystallizers, a variety of tubular crystallizers with and without baffles or mixers and segmented flow. Continuous oscillatory baffled reactors offer near plug flow where mixing is decoupled from net flow through the use of oscillatory flow over baffles. For the most part, each of these types of crystallizer is capable of operating with or without seeding and in cooling, antisolvent and reactive modes. Additional features such as ultrasound, static mixing or flow oscillations and agitated cell and tubular reactor configurations can, and have, been applied to effect control. Each type of continuous crystallizer does allow for the judicious use of buffers prior to (in the form of solutions) and after filtration and drying stages (in the form of stable powders). As for continuous reaction fouling or encrustation of vessels, feed lines, or PAT probes under elevated supersaturation conditions and/or solid loadings in continuous crystallizers must be controlled carefully. Fouling will occur over extended periods and strategies for monitoring build-up, mitigation, and cleaning need to be identified. It must also be recognized that the technical sophistication may be required to overcome certain limitations of current continuous crystallization technologies that may impact on capital and operating costs. Understanding the trade-off between this overhead and the wider benefits, for example on cost of quality, is required.

QUALITY ASSURANCE AND CONTROL

Although systematic approaches for assuring quality are commonly applied in the chemical, petrochemical, and oil refining (CPOR) industries, pharmaceutical products require a much higher degree of quality control. Although it is perfectly acceptable in processes involving only fluids to mix off-spec and above-spec quality to achieve a mixture that satisfies product quality specifications, most pharmaceutical products are in solid form and mixing off-spec (e.g., tablets) with on-spec solid products does not produce a solid mixture that is acceptable for delivery to consumers. In fact, blending batch solutions of homogeneous liquids prior to isolation is not performed either in the pharmaceutical industry. Given the need to ensure that all of the material is on-spec, there is a need for better tools for the quantification of the effects of uncertainties on product quality than what is currently applied in the CPOR industries. Quality assurance and control systems including change management and deviation/event management, typically applied to traditional batch manufacturing, are also appropriate for the control and assurance of continuous processes.

Quality assurance and control requirements in Pharma are fundamentally more stringent, with quality defined by the critical quality attributes (CQAs) and linked directly to patient need and safety. Although there are key differences, much of the same process simulation and control techniques used in the CPOR industries can be applied to the integrated process steps spanning reaction, workup, and crystallization in continuous pharmaceutical manufacturing.[6] These techniques can include methods for the design of integrated *plant wide* control design methods, which determine how the control systems at the unit operations level need to interact to ensure that the product leaving the last step satisfies all of the specifications on the CQAs. These methods combine mathematical models at the process unit operation level to form a simulation of the overall manufacturing process, typically before the manufacturing facility is constructed, so a key barrier to the wider adoption of these methods is the lack of personnel within pharmaceutical companies who are comfortable with mathematical modeling, especially of integrated process steps. There are also gaps in our ability to accurately model the interaction between attributes and processes, particularly for particles (e.g., solubility, mechanical properties, surface properties, microstructure) and dosage forms (e.g., microstructure; release, disintegration, diffusion, and erosion processes).

Automation has the potential to improve the consistency of product quality by removing operator-induced variability, and much of the same process and product monitoring techniques used in the CPOR industries can be applied to continuous pharmaceutical manufacturing. These process and product monitoring techniques include single- and multi-variable control charts, partial least squares, and principal component analysis. Sensitivity analysis can be applied to the simulation model to determine bounds on the process variations in a single unit operation that ensure that the product quality leaving the last unit operation is within specifications. Many software packages, such as those offered by OSIsoft or AspenTech, are available for archiving the large quantities of heterogeneous data collected in continuous processes that is used in process monitoring. Some of the most useful real-time online PAT data are spectroscopic. The deployment of such sensors have been demonstrated in continuous pharmaceutical manufacturing,[6] but need to be more widely adopted in industry for the quality and feedback control and monitoring systems to be most effective. More broadly, it is desirable to have sufficient online PAT that the materials can be characterized to such a degree that offline analysis would be unnecessary. A key challenge in this regard is the ability to measure low levels (e.g., 0.10 wt % in final API) of often structurally similar impurities. Also for PAT to see wider implementation in process monitoring, analysis and real-time control automation of the analysis of large volumes of data is required. The goal for CM is to ensure CQAs are consistently achieved and minimize the amount of out of spec material produced.[10] Approaches are therefore required that can maintain the CQAs accounting for disturbances and fluctuations for example in feedstock compositions and temperature or slow variations resulting from fouling or catalyst deactivation.

Developing accurate models is often simpler for continuous processes than batch processes in pharmaceutical manufacturing, because simplifying assumptions are typically more accurate for continuous processes due to having reduced scale up in physical dimensions. For example, ideal mixing is a much

better assumption in a slug-flow or segmented-flow crystallizer in which each slug/segment of fluid is less than 1 mL in volume than in a batch crystallizer designed for similar productivity, which is typically >1000 L. The more accurate the mathematical model for the process, the better the control, the higher the product quality, and the lower the risks associated with scale up.

Plant-wide simulation also enables the optimally sizing of the individual unit operations and recycle loops to maximize overall product yield and product quality of the manufacturing facility, and to track material as it moves through the plant. Any mathematical model allows the determination of the residence time distribution, and the largest time in which the value of the residence time distribution function is nonzero indicates the largest time in which material entering the process can stay in the process before exiting. Such simulation allows the tracking of any deviation through the process, to assess which products may be affected. The overall residence time distribution can be estimated by alternative methods such as carrying out scaling analyses or tracer experiments, but plant-wide simulation allows an analysis of the effects of changes in process operations on the residence time distribution. However, challenges remain to realize the promise of plant while modeling. First, it is only possible if the properties of individual compounds and mixtures are known well enough, which is not trivial for multicomponent systems with complex multifunctional molecules. Second, the timescales available for the generation of detailed models needs to be fit in alongside the timescales of clinical trials. There might not be the time typically available for bulk chemical process.

SAFETY

Continuous processing offers safety advantages compared to batch, including smaller reactor volumes and thus smaller potential events, higher heat transfer surface area per unit volume (*A/V*) for highly exothermic reactions or reactions running at temperatures close to thermal onset of decomposition, lower inventories and on demand production of hazardous reagents, ability to eliminate headspace and run 100% liquid filled, and higher containment for highly toxic compounds. Accumulation of large amounts of reactive intermediates or by-products is minimized when the reaction and quench are run in continuous mode.

Safety has been one of the main drivers for Eli Lilly implementing continuous reactions. They have demonstrated the safety advantages of continuous reactions for: Grignard formations; high pressure H2 and CO; thermal transformations and deprotections at elevated temperatures and pressures; hazardous reagents such as azides and containment for 5 kg/day end-to-end continuous production of cytotoxic API carried out in fume hoods. A number of similar processes have recently been scaled up to manufacturing using both contract manufacturing and in-house GMP facilities, with the main overall driver being safety. For example, a continuous Grignard reaction with a difficult initiation, a 153°C adiabatic temperature rise and potential for over-pressurization and thermal runaway, was safely scaled up to 75 kg/day in a CSTR with 40 L operating volume. The safety benefits compared with batch included: a 50× smaller reactor volume and 5× higher heat transfer area per unit volume for the same throughput, 200× reduction in the initiation event, 25× reduction in Mg to quench overall leading to 25× less H2 generated during the quench. Controlled operation at "end of reaction" conditions ensured a low chemical potential energy at all times. PFRs have also been used for scale-up to 100 kg/day of an asymmetric hydrogenation at 50 bar H2 (100 L PFR) and of a reductive amination with 50 bar H2 (380 L PFR). For both of these, safety advantages compared with batch were numerous and included: operation with >98% liquid filled reactor lowering quantities of H2 gas in the system; >100× lower instantaneous H2 flow rate; use of a portable PFR located outside removing H2 from the building and a significantly smaller reactor volume versus batch (4×–10×). As a direct consequence, the continuous high pressure H2 reaction was classified as a "low risk" process in manufacturing. Two different thermal deprotections at temperatures 70°C–80°C above the normal solvent boiling and pressures up to 30 bar were scaled up to 15 kg/day GMP in an 8 L PFR and 30 kg/day GMP in a 12 L PFR. The reactors were designed for safely reaching the extreme conditions. The PFRs were 25–35× smaller volume and 50–60× higher *A/V* than a batch reactor for the same kg/day throughput. A hydrazine addition reaction was scaled up to 5 kg/day in a 1.5 L PFR located inside a fume hood. The safety advantage was containment for the hazardous reagent, 60× smaller reactor volume and 90× higher *A/V* compared with batch for the same throughput.

All existing safety protocols for batch systems still apply to continuous systems. The distinctive features of complex pharmaceutical processes include condensed phase processing and higher potential for reaction runaways. Reactivity, kinetics, thermodynamics, materials of construction, materials compatibility, heat generation and removal rates, mass transfer rates, off-gassing, industrial hygiene, engineering controls, and chemical equation balancing, must still be addressed. Reaction safety testing such as ARC, DSC, and RC1 calorimetry should be measured.

In addition, it is important to recognize the new safety considerations that accompany continuous processing. We must prevent overfilling, over-pressurization, flow out vents, spills, line breaks, accumulation, backflow to other parts of the process train, and backflow into utilities. Check valves are only a backup line of defense against backflow into utilities or unintended process lines or vessels and cannot be relied on as a primary line of defense. Avoidance of such issues is achieved by preventing pressure-driving force for flow in the reverse direction and by pre-filling feed lines with liquid. Pressure relief is a more significant issue because of positive displacement pumping. Pressure reliefs and/or auto shutoffs are required at the discharge of all positive displacement pumps and for all vessels that materials flow into. Pressure reliefs should be installed just downstream of continuous back-pressure regulators or pressure letdown stations which protect the downstream process lines and equipment. We must be aware of check valve failures, thermal expansion, plugging and fouling, stability and solubility of starting reagent solutions over time, sampling safety, startup and shutdown safety incidents, trace amounts of small particles suspended in solutions as well as materials of construction and corrosion rates. The system should be designed so that it is not possible to cause accidental over-pressurization due to thermal expansion during process line or vessel charging.

Monitoring process conditions including pressure drops and heat transfer rates can provide indications of accumulation or fouling in the continuous section. Stability of starting reagent

solutions over time is tested in batch mode prior to continuous reaction experiments. Solids precipitating in feed tanks can cause plugging, ruin seals and require pump disassembly. It is essential to calculate mass and energy balances, verify that *mass flow in = mass flow out*, size heat exchangers appropriately, and use heat integration where appropriate as a secondary line of defense against utility failure. Sufficient heat removal from reactors must be verified by understanding reactor surface area, heat transfer coefficient, and heat of reaction. Running continuous operations also necessitates installation of secondary containment with large enough capacity to hold large amounts of materials, which could flow out of continuous lines over time. Automated interlocks are needed for high pressures, temperatures, flow rates, and liquid levels. Static electricity is also a concern for continuous processes because static charge can build up when fluids flow, especially non-conducting fluids like heptane and toluene through non-conducting tubing at a velocity exceeding 1 ft./s (0.305 m/s). Grounding and bonding is required to prevent internal sparks. There is also a general requirement for rapid identification of the potential for domino-effect failures as well as for generic strategies that can minimize disruption associated with the start-up/shutdown of multistep processes.

It should be assumed that plugging and fouling will eventually occur in a continuous reactor or unit operation. A plan should be in place to safely deal with it before it happens, including assessment and control of potential for blockages, favoring anticipation via condition monitoring or prophylactic maintenance. Safe venting valves and vent lines should be installed on both sides of reactors or other long process tubes so that pressure can be relieved from either the inlet or outlet side of the reactor, in case the plugging occurs in the middle. Double-block and bleed valves around all continuous-flow equipment allow isolation and safe depressurization. During operation, *pressure* versus *time* trends at the discharge of positive displacement pumps as well as *power consumption* versus *time* can provide an early indication of slowly building blockages. In-line filters should be used at the outlet of reagent solution feed preparation tanks to prevent plugging/fouling of pumps, tubes, valves, fittings downstream. The filters should be sized for total volume flow anticipated for the entire campaign, meaning they will be larger surface area than if they were designed only for instantaneous flow rate. In summary, continuous operations confer a wide range of fundamental safety advantages over batch operations for a range of different challenging chemistries and a number of these have been highlighted. However to ensure safety, additional safety considerations are required.

PEOPLE, SKILLS, AND CULTURE

Establishing continuous processing in the Pharma industry is not simply to solve technical, engineering or scientific problems, far from it. Although we can realistically see a way to characterize processes and equipment, to design syntheses and reactors, or to build process trains that couple multiple unit operations, there will remain significant other challenges preventing the widespread adoption and establishment of CM of API. The skills and capabilities required to design, develop, validate, and operate a continuous process are different to those recruited and developed currently. Furthermore, the established culture in many cases becomes an additional barrier that must be overcome to realize the change that is required. Taking these as two separate areas; how can people, the skills they have and the culture they create, turn continuous processing from an interesting science and technology project into and established method of generating high quality drug substances.

The organic synthetic chemist is at the center of developing pharmaceutical drug substance synthetic steps and route of manufacture. Their skills, typically honed through PhD and postdoctoral research in academic laboratories all over the world are directed toward knowing how to best synthesize and characterize new materials first in the laboratory. The challenge of scaling to larger scales of laboratory type equipment can be met by early engagement with process engineers. These skills have ensured the design of optimal synthetic routes and the delivery of robust batch manufacturing processes. There is however a problem if we expect those same skills to deliver continuous processes. Development of robust continuous processes requires more information and is more engineering intensive, particularly around controls, even in a multipurpose plant. On other hand, the trade-off is the potential for quality, cost, safety, and speed advantages for manufacturing.

Chemical engineers bring an understanding of time and length scales that supports a more fundamental understanding of process scale and equipment sensitivity. The chemical engineering should be driven by the manufacturing needs of the selected chemistry. The chemist defines physical conditions that will be optimal for reaction yield and purity, and the engineer then applies devices, technologies, methods, automation, and control to enable the optimal processing conditions. This cannot, however, be a hand off process. There is a need to develop engineers with lab skills and chemistry awareness to establish effective relationships with other groups. Chemists also require appropriate skills and training to support CM, particularly in terms of providing the necessary understanding and language to work effectively within multifunctional teams supporting the delivery of the chemistry using continuous processes.

The Pharma industry has a significant number of analysts to support the need for analytical method development and specification setting. The importance of measurement and characterization to provide process understanding necessary for the design and ultimately control of a continuous process requires evolution of these skills. There is both a need for alternative measurement techniques to be developed and the skills to apply chemometric tools to support their robust application. The analytical chemist must bring the measurement technique to the process tube, pipe, or flow vessel. The real innovation will come only when the chemistry, engineering and measurement science converges in the development of CM.

The established approach to developing manufacturing processes for commercial supply of drug substance is to invest time and effort improving the existing process and addressing problems identified during manufacturing campaigns for clinical supply. Introducing a new process is difficult because the starting point is that it is higher risk because of the lack of experience. It is rare that the technical benefit is so well developed and compelling that it overturns a body of evidence established through repeated experimentation at lab or pilot scale. The perceived or real regulatory uncertainty is therefore usually sufficient for inherent cultural conservatism to dominate and new approaches to stall. It is therefore important that

tools are developed to spot winners early, to de-risk the decision to develop a continuous process and to reduce regulatory barriers.

It is important to recognize the scale of the change required. Without the necessary investment, it will be challenging to progress this from an interesting science project, to an established element of the drug substance development toolbox. A greater number of chemists and engineers entering the industry with sufficient awareness and confidence in the technology accompanied by champions and senior leaders setting direction may be able to create a cultural change that ensures continuous approaches are fully considered. The change project needs to be structured and well-funded (time, people, equipment) in order to progress the technology, and keep it moving when projects and the accompanying development is stopped.

There is wide acknowledgement of the critical need to make the economic case for CM to justify the changes from current practice and procedures. This remains an important area for the community as a whole to address and will require a clear definition of the case that needs to be developed as well as accurate data to base assessments on. The economic considerations include: (i) the cost to set up and operate a single manufacturing unit for a single plant (the project level which may well be against the basis of an existing site and utility/infrastructure); (ii) the site-wide benefits of having CM fully enabled at a manufacturing site (which would play out in reduced utilities investment and costs, possibly a smaller building, etc.); (iii) the supply chain level where responsiveness to demand change and other disturbances is relevant and plays out either as overinvestment to assure the desired minimum performance of supply or reduced time and cost to adapt to external influences to prevent drug shortages for example; (iv) the drug project investment level and/or economic viability. This may be straightforward where API or API attributes simply cannot be manufactured using batch but more challenging where both options are feasible. Although it is outside the scope of this whitepaper to provide such analyses, the need for robust economic justification of CM supported by reliable data will ensure that technical advances in this area can be fully exploited where appropriate to benefit the industry and vitally, patients.

CONCLUSIONS

It is clear that the implementation of continuous processes for drug substance manufacture offers potentially significant advantages for the supply of medicines. Alongside the increasing number of examples where continuous processes have demonstrated clear benefits (e.g., hazardous chemistries), there are also areas where further developments will increase the opportunities for Pharma/fine chemicals to deliver safety, quality, and cost benefits for the right products with the right processes and with the right controls. In order to realize the potential benefits of CM, the industry must:

- Develop flow chemistry toolboxes, exploiting the advantages of flow processing and including highly selective chemistries that allow use of simple and effective continuous workup technologies. Availability of modular, or plug and play type equipment would assist in straightforward deployment in the laboratory. As with learning from other industries, standardization is highly desirable and will require cooperation across industry and academia to develop and implement.
- Develop strategies for dealing with parts of the system that change with time (catalysts, adsorbents, fouling of surfaces) while maintaining production and at a sensible cost.
- Implement and exploit PAT for monitoring and real-time control of continuous processes. This will require the development and exploitation of robust, selective analytical technologies for chemical and physical attributes (CQAs) of interest as well as the skills base to deploy the technologies within the context of process control.
- Develop suitable and accessible modeling and simulation techniques to support continuous process development and process control. This includes models of transformation kinetics, physical properties, separation processes, crystallization and particle attributes, and particle performance in downstream processes. The appropriate experimental workflows for continuous process design to standardize data acquisition including from appropriate batch experiments are also required.
- Involve all parts of the organization from discovery, research and development and manufacturing in the implementation of CM; the approach must be multidisciplinary and close working of disciplines must be fostered. This has implications for the skills and training needs of all disciplines concerned with the development and implementation of CM. This is particularly true for flow chemistry and the availability of suitable laboratory scale equipment to support training in academic institutions is required. There is also a need for enhanced physical chemistry skills to support stronger process understanding and modeling.
- The academic and industry communities should identify the workforce attributes and skills required to support CM and develop appropriate collaborative measures to support at all levels.
- Promote and encourage publication and dissemination of examples of CM to include detailed supporting data and continue to highlight challenges. This will build confidence in the community, allow engagement with regulatory comment and establish benchmarks for performance and best practice in the sector.
- Alongside developing the skills and technical capabilities, develop the economic case for CM of API. This is non-trivial, involving various stakeholders at project and business level however establishing the critical economic drivers is critical to driving the transformation in manufacturing.

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