Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Work-Up and Isolation of Drug Substance

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Introduction - the Future for Continuous Drug Substance Manufacture

Successful innovation in manufacturing and adoption of continuous manufacturing (CM) has an important role to play in the industry's future (ref Badman and Trout, 2014). The vision for CM in the pharmaceutical industry is to exploit integrated end-to-end processing 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. As new continuous 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 integrated manufacturing chain, specifically continuous synthesis, workup and isolation of new chemical entities, active pharmaceutical ingredients (API) or drug substances. In particular, challenges and opportunities associated with each of the operations are highlighted along with important principles that deserve consideration when deploying these continuous processes. Ensuring quality and consistency through control are key drivers for CM, and key 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 allowing access to hazardous chemistries in a safe and controlled manner[1-5], however for continuous technologies to achieve widespread application a broader range of issues need to be addressed to ensure safe operation at all stages. CM also changes the development paradigm (e.g. how and when process development is done) and the facilities strategy (e.g. current footprint versus future) and places markedly different demands on organisations and their staff compared with batch. Successful deployment will be dependent on advances in these areas 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 manufacturing vision will require significant change across the industry and the wider pharmaceutical value chain.

1. 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] Carrying out synthetic reactions in flow offers a variety of benefits including: (1) reduced hazard/increased safety from the smaller reactor volume, relative ease of containment, removal of headspace and reproducible delivery of conditions to ensure consistent quality with no accumulation of reactive/toxic intermediates; (2) the potential for 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 maximize reaction rates and achieve higher throughput; (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) the potential to increase throughput with a dramatically reduced equipment footprint and (11) greener operation from reduced solvent consumption.

The challenge remains to see widespread adoption of flow processes in pharmaceutical manufacturing facilities. Until recently this processing approach was almost exclusively encountered in 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 consequent 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, work-up, 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. Whilst 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 and can be achieved with regard to intermediate [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 work-up stages downstream.

It is also worth highlighting that whilst 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.

1.1 Flow chemistry equipment

For flow chemistry to achieve widespread adoption equipment that can support a wide range of chemical transformations in continuous operation is required. The main classes of reactor are described below however the continued pursuit of 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 commercialisation 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. Comprehensive coverage of continuous reactor platforms are available detailing the operating principles and characteristics. Detailed understanding and characterization of the equipment should enable seamless scale-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.

It is important to acknowledge that 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, but 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 either a tube or microstructured device (microreactor).

Tube-based systems (typically coiled) are commonly made of copper, stainless steel, hastelloy, tantalum, zirconium, PEEK, or perfluorinated polymers. Their volumes range from 1 μL to litres with channel diameters from 100 μm to 50 mm depending on the system. They are simple to operate and easy to create, but rely on diffusional mixing and are thus prone to dispersion effects.

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, e.g., hydrogenation. In this system a porous inner tube, typically made from Teflon AF, allows transport of a gas from one tube to a liquid flowing in the other. This is also a specific example of a membrane reactor which functions to allow selective partitioning of species between two or more flow streams. Such reactors can be broadly subdivided into two types by classification of their segmentation function being either through phase or size exclusion.

Microreactors are machined in glass, silicon-glass, ceramic, or stainless steel by microfabrication techniques. Their volumes typically range from 50 μL to 100 mL and the channel diameters from 50 to 1000 μm. They often include mixing units, flow distributors, multiple channels, and means for immobilizing catalyst particles. They typically also have the advantage of better heat transfer for heating and cooling reactions. In both tubes and microreactors, the effects of mixing and dispersion can be explored experimentally (e.g., by residence time distribution (RTD) measurements) and predicted (from fluid dynamics simulations) to establish guidelines for running reactions under favourable mass and heat transfer conditions. However, where long residence times are required the more complicated fluid distribution and increased control challenges CSTRs may become more economically viable

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 highly 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 only takes you part of the way, and then multiplying up the resulting smaller number of larger reactors. In many case 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. In addition to tube and structured reactors, trains of multiple continuously stirred tank reactors (CSTRs) are a commonly encountered solution in continuous synthesis. They are particularly well suited for reaction systems involving slurries of solid reagents or products or for systems with longer residence time requirements that make tubular reactors less economically practical.

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 the slowest individual step (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 to their batch stirred tank reactor counterparts through the larger heat transfer area. Alternative techniques for energy supply being actively researched include sonication; photochemistry; electrochemical and microwave (especially for scale up applications).

1.2 Translation of flow protocols from the laboratory bench to the plant

Pharmaceutical development can be described in three general phases and considerations and tasks for translating flow processes are highlighted in the following sections. These phases are (1) Hit to Candidate – a candidate for toxicology and human studies is selected from lead molecules; (2) Clinical Development – where candidate introduced to the clinic in Phase I is developed into a commercial product and (3) Manufacturing.

Hit-identification: During preliminary research investigation only a very limited amount of time is normally invested in optimizing a particular synthetic pathway. Route selection is based mainly on the generality of the transformation as reflected in the projects requirement to produce libraries of related structures or just singleton compounds. Another important consideration is the availability of easily accessed starting materials and reagents (often commercial availability is key). However, the main overarching driver is speed, focusing on the ability to deliver rapidly small quantities of material as opposed to elegant, well-engineered and fully optimised chemical sequences. Normally the operational mode is also to conduct every transformation of a sequence as a single step transformation. Here the most appropriate reactor design offers the maximum flexibility for reconfiguration and multi-purpose usage. Ideally only small amounts of material are required because the value of starting materials is high (for novel components). Hence small scale reactor volumes are desirable, but work remains on making flow chemistry more efficient for hit-identification and to identify further integration opportunities benefiting from the deployment of flow.

Hit to lead and lead optimisation: 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 poor previous examples or are not present in the literature. Often expansion of chemical design space is also performed to validate and define greater patent coverage.

It is still not clear whether the increased scaling agility from the deployment of continuous flow in discovery can increase the probability that the medicinal chemistry route is a viable

manufacturing route (in part or whole). It is also important at this stage to determine effective continuous work-ups 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. Normally an acceptable parameter is running a reactor for extended periods of time to generate larger quantities of key building blocks or final products. With the easier scaling of continuous reactors this could also be achieved through scaling up of the reactor volumes without requiring re-optimisation 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. Key drivers at this point in development are often achieving safety with speed and the chemistry can have limited refinement as chemists need a way to make things rapidly.

Lead optimisation and Candidate selection: At this stage of development 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. Reaction kinetics, and processing criteria such as potential safety considerations are also defined i.e. 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 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 work-up and purification. With increased numbers of degrees of freedom to consider there is a challenge for DoE-centred 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 (optimising 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. IR, Raman, UV, MS, HPLC 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.

Clinical Development: 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 ensure the integration of chemistry, engineering and analytical functions. Mechanistic studies are increasingly important alongside DoEs and implementation of Quality by Design (QbD). Process analytical tools need to be considered and selected based on control needs. 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 QbD for any future CM processes. Variability is by definition controlled by the design of the process. Therefore all critical sources of variability should be identified, profiled (product quality attributes should be accurately and reliably predicted over the design space (materials used, process parameters, environmental conditions) and as far as possible their occurrence predicted and outcome explained. Whilst minimal PAT support is typically available at this stage, it is important to identify suitable techniques and develop appropriate methods as early as possible to support on going development.

Early, discovery processes may well be used for a while, but any changes or development of new routes are considered whilst 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. The challenge therefore 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 stage 1 trials, greater investment into the chemistry, reaction engineering and process design aspects to ensure robust multi-step integrated operations which can be selected quickly from the growing flow chemistry toolbox will be required.

Manufacturing considerations: If a continuous reactor is to be used in GMP production then several factors should be considered due to the continuous nature versus batch. This includes the scale of equipment to be used depending on whether the intent is to make a year's supply in one month or operate 24/7 and whether the plant is multipurpose or custom. In many cases a reaction can be run continuously but the feed solutions are prepared in batch and the workup and isolation is also performed by traditional batch processing. Startup and shutdown transition must be conducted in a way that minimizes or eliminates transition waste. If the product produced during the transition period still meets the required specifications then it can be forward processed even if the process was not truly at steady state during the transitions. The cleaning of a long plug flow reactor at the end of the campaign or after a process upset is substantially different than a batch reactor because it is not possible to visually inspect all the surfaces. However, the reactor runs 100% liquid filled, therefore all surfaces are wetted and will be flushed with solvent during cleaning. For GMP purposes the reactor can be declared clean by flushing with solvents of known solubility for particular substrates and the cleaning solvents subsequently tested. Diverting materials, deviation management, and deviation boundaries are handled by

understanding of residence time distribution. Operating space and design space is defined by understanding the acceptable ranges in process parameters such as temperature, pressure, mean residence time, and stoichiometry for the continuous reaction (see below for additional details on automation and quality).

1.3 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 organisation. In general this equates to approximately half of their reaction inventory that can access better selectivity, fewer workup steps and more straightforward plantwide 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 achieve faster reaction rates.

2. Workup and isolation

With the drive to develop reactions in continuous flow as part of an integrated end-to-end manufacturing 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 work-up and purification procedures including extraction, distillation, adsorption and selective separation (e.g. membrane) technologies. Ideally traditional sequences of work up 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 crystallisation; 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 (or more likely may not) 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 may be economically worth recovering. Recycles are perhaps most likely of solvent, and for flow systems of unreacted raw materials, but in general there is less economic incentive for recycling unless the "continuisation" 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 to 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. As a minimum 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), though 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. Work-up 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 – for example running under vacuum to reduce temperature may be attractive but makes the overall process engineering more complex. Process design can be done 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 a lot of 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 done counter-current multi-stage which increases separation power. Common technologies include packed column,

agitated columns, single stage centrifugal separators in series, multi-stage 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.

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.

Adsorptive techniques (run in flip/flop mode or for finite duration run) can have high specificity e.g. ion-exchange 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 are important considerations. Chromatography can be operated as a continuous separation using simulated moving bed (SMB), though 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. While 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 is growing in credibility 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 at the expense of lost product in the impurity stream. Crystallization is essentially 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, and is additionally linked to the use of the difficult operation of continuous filtration. 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 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. In terms of integration of continuous processes, continuous filtration, washing and drying steps compatible with the scale of operation at the requisite development scale are required.

The equivalent approach to the design of optimal temperature or antisolvent addition trajectories as a function of time for batch systems to follow a desired trajectory in the phase diagram, 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. Obtaining reliable experimental kinetic data on these processes is therefore vital to inform process design. Strategies for control of polymorphism and physical form (solvate, salt, co-crystal) in continuous processes need to be developed to effect control over particle and product performance.

Experimentally, a number of crystalliser 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 crystallisers, a variety of tubular crystallizers with and without baffles or mixers and segmented flow. Continuous oscillatory baffled reactors (COBRs) 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, anti-solvent 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 over particular. 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 solution supersaturations and/or solid loadings in continuous crystallizers must be controlled.

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 the capital and operating costs. Understanding the trade-off between this overhead and the wider benefits e.g. on cost of quality, is required.

3. **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. Whereas it is perfectly acceptable in processes only involving fluids to mix fluids of 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. 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, 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, work-up, and crystallization in continuous pharmaceutical manufacturing [6]. These techniques include methods for the design of integrated *plantwide* 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 critical quality attributes. 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). It is also necessary to have expertise in the design of plantwide control systems. This is compounded by a relative lack of individuals with process control specialty within the chemical engineering discipline. The benefits of employing plantwide simulation and control techniques is the reduction of operating costs, scaleup risks, and the probability that the product will be offspec. Early plantwide simulation and control, using mathematical models for each process unit operation that have been validated at laboratory scale, also enables the systematic design of mass recycles and the comparison of the total capital and operating costs of building plants around competing chemical pathways or varying amounts of work-up.

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 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. 0.15 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 the large volumes of data produced is required.

In this context it is important to differentiate between the often quoted goal for continuous pharmaceutical manufacturing to always operate in steady state. Real industrial processes are never in steady state during startup or shutdown, and not even during regular operations due to disturbances such as fluctuations in feedstock compositions and temperatures or slow variations due to fouling or catalyst deactivation. The output of startup or shutdown phases or unit operations will often lead to acceptable quality product and as such may not need to be discarded. A more useful goal from the point of view of the customer is that the process is always "in-control" and that variability in input materials and process conditions is managed to assure consistent output is always delivered. Preferably the process and the control system should be designed so that the first and all subsequent product manufactured in the continuous process is on spec. This strategy has been demonstrated for a drying process for the continuous manufacture of polymer-drug composite films, by employed a combination of first-principles modeling, dynamic process simulation, in-process monitoring of critical quality attributes, and feedback control design. The consistency of product quality can be improved by using a combination of feedback and feed-forward control, and by monitoring slow variations such as catalyst deactivation over time at the plantwide level so that adjustments can be sent to the control systems for the individual process unit operations level so that the final product leaving the last unit operation remains on-spec. Plantwide simulation allows the occasional application of cleaning or catalyst replacement protocols to be designed in such a way that product quality is not compromised, without having to shut down the entire plant.

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. This 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 plantwide simulation allows an analysis of the effects of changes in process operations on the residence time distribution.

4. **Safety**

Continuous processing offers safety advantages, such as smaller reactors, high heat transfer surface area per unit volume, lower inventories of hazardous reagents or intermediates if generate/consume, ability to eliminate headspace and run 100% liquid filled, and higher containment for cytotoxics. It is also important to understand the new safety concerns for continuous processing compared to batch, for example preventing: overfilling, over-pressurization, flow out vents, spills, line breaks, static electricity buildup and sparks, accumulation, back flow to other parts of the process train, backflow into utilities, check valve failures, thermal expansion, plugging and fouling, stability and solubility of starting reagent solutions over time, startup and shutdown safety incidents.

If running continuous rather than batch, almost all reactions have the safety advantage of smaller reactor volume. This is because in flow the reactor runs 24 hours per day, compared to reacting only part of the day or week in batch processes. Smaller volume means there is less material in the reactor. Therefore, if there were a safety event or material release it would be smaller, and if there was a thermal runaway event it would be smaller. Manufacturing hazard reviews put a high priority on the reactor size and the total amount of material in the system, and thus the magnitude of a safety event. Reducing the size of a potential catastrophic event is a tremendous safety advantage. Furthermore, accumulation of large amounts of reaction product prior to quenching is minimized when the reaction is run continuous, flowing into a continuous quench.

Highly exothermic reactions are usually safer when run continuous rather than batch because of the higher heat transfer resulting from a larger surface area to volume ratio. This is often >50× higher for plug flow tube reactors and >5× higher for CSTRs compared to batch reactors that would achieve the same weekly throughput.

In runaway reactions, critical temperature is where the heat generation rate equals the heat removal rate. Increasing heat removal rate increases critical temperature. Runaway reaction can cause solvent boiling and/or gas generation especially in large-scale manufacturing. Higher pressure rating of continuous reactors compared to batch reactors is a backup line of defense against mechanical failure in the event of thermal decomposition and the inherently high phi-factor is a further benefit.

Reactions with hazardous gas reagents under high pressure like H_2, CO, syngas, NH_3, are safer because plug flow reactors can operate more than 97% liquid filled. There is less hazardous gas reagent in the reactor at any particular time compared to batch, so the maximum release in case of equipment failure is smaller. In addition, the maximum feed rate of the hazardous gas is restricted by >100× compared to batch, therefore restricting orifices can be used on the gas feed source, and the maximum rate of release is smaller in a safety event. Aerobic oxidation can be run more safely and efficiently in continuous mode because of the high pressure capabilities of the reactors, allowing the use of low concentration O_2 in N_2 below the flammability limit, but still achieving high partial pressure of oxygen.

Operator safety can be improved for highly toxic intermediates or products by continuous processing, if the equipment train is small enough to fit inside lab hoods. This is useful for the production of cytotoxic APIs with small yearly demand for example <5000 kg/year drug substance.

All existing safety protocols for batch systems still apply to continuous systems. In addition, there are extra safety protocols due to the continuous-flow aspects. Thus, all the process safety features of a stirred tank reactor apply to CSTR, in addition to the new features due to the continuous nature of the operation. A distinguishing difference between batch and continuous-flow systems, however, lies in the pumps and mass transport methods/devices that maintain constant flow between wet-end process vessels and the additional safety concerns associated therewith. Pressure and pressure relief concerns are greater in flow systems, as is the potential for vessel over-filling, especially because continuous operation often involves multiple fill/drain cycles. Every positive displacement pump needs pressure relief and/or pressure-limiting auto shutoff. Otherwise, interlocks and/or alarms are needed measuring liquid levels in vent knockout pots. Secondary containment should be used around flow vessels or connections that could break, and the secondary containment often needs to be significantly bigger than the volume of the flow vessel itself because of the potential to flow a larger volume of process fluids out the rupture as the pumps may continue to deliver material. The volume that triggers implementation of the Process Hazard Review should be the total inter-connected system volume, including surge vessels and feed tanks, rather than just the volume of the main process vessel itself. Of course, all other safe scale-up considerations typically covered by hazard reviews, such as reactivity, thermodynamics, materials of construction, and chemical equation balancing, must still be addressed, and all reaction safety testing such as accelerated rate calorimetry, differential scanning calorimetry, and more quantitative and information rich calorimetry such as RC1 should be measured.

Pressure reliefs and/or auto shutoffs are required at the discharge of all positive displacement pumps and for all pressurized vessels used for feed, product, processing, or surge. If the continuous process has multiple reactors or unit operations in series, then consider where physical protection (shielding) of process lines or equipment might be needed to prevent accidental line breakage. Static electricity is also a concern for continuous processes because static charge can build up when fluids flow, especially non conducting fluids like heptanes and toluene through non conducting tubing at a velocity exceeding 1 ft/sec.

Selecting the proper materials of construction for a given process chemistry is critical. The potential for corrosion and the associated safety issues must be understood, preventing operation in a system with potential corrosion problems. Slow corrosion rates on the order of mm/year are more important in continuous processes than batch because continuous processes might run constantly for several months or all year and tolerances e.g. in microreactors are on the same order as the vessel dimensions. Quantitative corrosion tests over a minimum duration 200 hours during development are required using representative test coupons of contact materials.

If a continuous process is at steady state, then by definition there is no accumulation. However, it is often not easy to detect if materials are slowly accumulating over time in a continuous process after a large number of volume turnovers. This is done by controlling and verifying that

mass flows in equal mass flows out, and by measuring and controlling liquid levels and concentrations in continuous process equipment. Monitoring process conditions including pressure drops, heat transfer rates can also provide indications of accumulation or fouling in the reactor. Otherwise, accumulation could eventually cause process materials to exit through unintended pathways, possibly into the vent. Interlocks or other layers of protection should be in place to prevent accumulation and to maintain target fill levels. Measuring mass flow in and mass flow out is essential. Feed vessels and product vessels on data logging balances is recommended, but other types of level indicators on feed and product vessels may be sufficient. Interlocks should be in place so that product collection vessels do not overfill. Back flow prevention between reactors is critical.

It is important to understand thermal expansion of the solvent system and reaction product solution at reaction temperature, and to account for thermal expansion when determining mean residence time and when heating. The system should be designed so that it is not possible to liquid fill 100% a process line or vessel, close block valves on inlet and outlet side, and then heat that section. For safe operation, scalability of heat and mass transfer must be known and considered when transferring laboratory results to the pilot and manufacturing scales. Sufficient heat removal from reactor must be verified by understanding reactor surface area, heat transfer coefficient, and heat of reaction. Rate of reaction is also important, because if the exothermic reaction is relatively fast compared to mean residence time, then the heat of reaction could be released over a short fraction of the reactor length near the inlet. This is the so called “hot spot” in the tube reactor.

All sampling methods, ports, and devices must be engineered to ensure that representative samples are collected safely, especially from pressurized reactors. It is best to sample from a low-pressure product collection vessel or low pressure tubing located downstream from the reactor after the back pressure regulators steps down the pressure, rather than directly from a pressurized reactor. This guideline applies to automated sampling devices or on-line process analytical technology as well as manual sampling. Also steps to ensure that sample points do not disrupt internal flow or surfaces and as such act as a fouling point should be implemented.

It should be assumed that plugging and fouling will eventually occur in a continuous reactor. A plan should be in place to safely deal with it before it happens. 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 vs. time trends at the discharge of positive displacement pumps as well as power consumption vs. time can provide early indication of slowly building blockages.

Compound-specific and overall material balances should be calculated for continuous processing campaigns, preferably real time by the automated control system. The overall balance includes all material entering and exiting the process. It does not depend on analytical results but on balance weights and/or the combination of densities and vessel volumes. Overall material balances are necessary for such safety reasons as quantifying solvent lost to the vent and proving

that material is not accumulating in the system. Compound specific material balances rely on analytical samples and weight percent assays.

Stability of starting reagent solutions over time is tested in batch mode prior to continuous reaction experiments. Solids precipitating in feed tanks could cause plugging, ruin seals, and require pump disassembly. It is important to prove that solids do not precipitate from feed solution sitting at lowest potential hold temperature for at least one week. Given some of the distinctive features of complex pharma processes, including condensed phase processing and higher potential for reaction runaways, challenges include:

i) developing relief system philosophy and execution
ii) rapid identification of potential for domino-effect failures
iii) assessment and control of potential for blockages, favouring anticipation via condition monitoring or prophylactic maintenance
iv) generic strategies that can minimize disruption associated with start-up/shutdown of multi-step processes.

5 People, Skills & Culture

Establishing continuous processing in the Pharmaceutical industry is not simply to solve technical, engineering or scientific problems, far from it. Whilst 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 continuous manufacturing of API by the Pharma Industry. 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 realise 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 centre of developing pharmaceutical drug substance synthetic steps and route of manufacture. Their skills, typically honed through PhD and post doctoral research in academic laboratories all over the world are directed towards knowing how to best synthesise and characterise new materials first in the laboratory. The challenge of scaling to larger scales of laboratory type equipment benefits from 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 a better quality and more robust manufacturing process.

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 therefore 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 Pharmaceutical industry has a significant number of analysts to support the need for analytical method development and specification setting. The importance of measurement and characterisation 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 recognise 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.

6 Conclusions

Design and implementation of integrated end-to-end continuous processes offer significant advantages over step wise batch processing in terms of effecting significant change to medicines supply. There are strong examples where continuous processes have offered significant advantages, and there is a significant opportunity within Pharma/fine chemicals to deliver safety, quality, and cost benefits for the right products and with the right controls. In order to reap the benefits of continuous processing, the industry must:

- Develop flow chemistry toolboxes, 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 laboratory.

- 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
- Ensure exploitation of PAT-enabled real-time dynamic control. This requires 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 context of process control.
- Develop of modelling and simulation techniques to support continuous process development are also an important area to accelerate process development. This includes models of transformation kinetics, physical properties, separation processes, crystallization and particle attributes, and performance in downstream processes.
- 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.

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