Equipment and Analytical Companies Meeting Continuous Challenges

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Executive Summary

This white paper focuses on equipment, and analytical manufacturers' perspectives, regarding the challenges of continuous pharmaceutical manufacturing across 5 prompt questions. In addition to valued input from several vendors, commentary was provided from experienced Pharma reps, who have installed various continuous platforms. Additionally, a Small Medium Enterprise (SME) perspective was obtained through interviews.

A range of technical challenges is outlined including; presence of particles, equipment scalability, fouling (and cleaning), technology derisking, specific analytical challenges and the general requirement of improved technical training. Equipment and analytical companies can make a significant contribution to help the introduction of continuous technology. A key point is that many of these challenges exist in batch processing and are not specific to continuous processing. Backward compatibility of software is not a continuous issue per se. In many cases, there is available learning from other industries

Business models and opportunities through outsourced development partners are also highlighted. Agile smaller companies and academic groups have a key role to play in developing skills, working collaboratively in partnerships, and focusing on solving relevant industry challenges. The pre competitive space differs for vendor companies compared with large Pharma. Currently there is no strong consensus around a dominant continuous design, partly due to business dynamics and commercial interests. A more structured common approach to process design and hardware and software standardization would be beneficial, with initial practical steps in modeling. Conclusions include a digestible systems approach, accessible and published business cases and increased user, academic and supplier collaboration. This mirrors FDA direction.

The concept of silos in Pharma companies is a common theme throughout the white papers. In the equipment domain, this is equally prevalent among a broad range of companies, mainly focusing on discrete areas. As an example, the flow chemistry and secondary drug product communities are almost entirely disconnected. Control and PAT companies are active in both domains. The equipment actors are a very diverse group with a few major OEM players and a variety of SME, project providers, integrators, upstream downstream providers, and specialist PAT. In some cases, partnerships or alliances are formed to increase critical mass.

This white paper has focused on small molecules; equipment associated with biopharmaceuticals is covered in a separate white paper. More specifics on equipment detail are provided in final dosage form and drug substance white papers. The equipment and analytical development from lab to pilot to production is important, with variety of sensors and complexity reducing with scale. The importance of robust processing rather than over complex control strategy mitigation is important.

A search of non-academic literature highlights, with a few notable exceptions, a relative paucity of material. Much focuses on the economics and benefits of continuous, rather than specifics of equipment issues.
The disruptive nature of continuous manufacturing represents either an opportunity or a threat for many companies, so the incentive to change equipment varies. Also, for many companies, the Pharma sector is not actually the dominant sector in terms of sales.

Key words: equipment, analytical, collaboration, technology companies, systems, academic consortia

1. Predictions for Take up of Continuous Equipment in Pharma Across Supply Chain

1.1. Overview

Many large Pharma companies have an internal advocacy group pushing the development of continuous processes and installation of equipment for continuous operation. Most have worked on showcase examples of continuous processing. There are a small, but growing, number of FDA filings describing continuous manufacturing steps.

A current view is that the originator industry may continue to apply continuous processing only in cases of an immediate benefit concerning development cost or speed, process safety capability to reach reaction conditions or product quality. The generics industry could apply continuous processing in cases where the changeover from conventional batch processing can be described as "small change" and has substantial benefits concerning production cost, including investment cost for hardware. This has most relevance to supplying affordable generics to people in developing countries.

Early developments in this field struggled as too many novel elements were introduced, which the industry and regulators found difficult to "digest." The transition to continuous manufacturing is being led by large Pharma in oral solid dose processes. This is because it takes a considerable investment in expertise and capital to make this change. After large Pharma proves the process, and the process matures, the contract manufacturers will quickly follow. With the compelling cost savings, ultimately the generics will follow. Continuous manufacturing in solid dose also offers significant value related to the speed of process development and material requirements. These new technologies also have minimal start up and shutdown losses because a steady processing state is reached quickly and the amount of product in the process is minimized.

Adoption is restrained due to, existing investments in batch capacity, the trend toward small volume/high potency drugs, regulatory uncertainty, desire for simplicity and robustness, and training, experience, and confidence in batch synthetic approaches by process chemists.

Feedback from equipment companies working with customers engaged in continuous reaction and crystallization processes is usually mixed. Some say that the whole move to continuous is a waste of time, while others are enthusiastic advocates. Advocates tend to be people who have been tasked with participating on a specific continuous project. The number of advocates is growing. Some companies have top level CEO support for continuous and manufacturing in general but strategies vary considerably. A key point is that many of the technical issues exist in batch and have been overcome in move to continuous in other industries. It is also easy to overcomplicate through bundling of challenges many of the barriers to adoption. Many examples of successful adoption were shared during the conference. There was unanimous agreement that more needed to be published.

1.2. Cost

To date, the equipment companies' view is that there have been two different main drivers for investment:

i. Creating suitable platforms for future drug development with an expectation of future benefits

ii. Investment based on a current business case with "near term" payback

For a number of years investment was limited by the lack of suitable small-scale equipment and by the availability, and cost, of raw material required to develop processes at larger scale in new equipment.

Hence, the recent traction in secondary processing has been driven by the creation of smaller scale equipment, which has been specifically designed in order to minimize the amount of material required during

development. Many major Pharma companies are 'investing' in continuous flow (e.g. GSK, Novartis, Pfizer, Lilly, and Abbott)., Continuous flow, however, is not universally viewed as 'the way' to do small molecule development, scale up, or manufacturing. Currently it appears that while many Pharma companies have efforts to adopt continuous chemistry over conventional batch, they will only move forward if the financials are highly favorable.

Small, fully enclosed processes, with a high level of automation, and reduced manual intervention, will enable companies to reduce variability, deliver higher yields, increase profitability and lower operating, inventory, and capital costs. Facilities are less costly to build and 100% of capacity is utilized when they are in operation. A major part of the savings comes from not having to take batches to the laboratory for analysis, which can shrink the time taken getting the product to the patient from a few months to something in the order of less than 10 days.

There is also a counter opinion that changing from batch production equipment to continuous production equipment will not result in a good return on investment. This view is principally influenced by the Pharma industry's high inventory of batch production equipment, which is under-utilized in many cases. Pharmaceutical companies fear that the business case for investing in new continuous equipment is not strong enough compared with optimized utilization of the currently installed base.

Demonstration of benefits is on a case-by-case basis and has to be considered not only in the step itself, but also with its impact on upstream and downstream operation (less effluent could be, in some cases, a must if the effluent treatment plant is overloaded or if the current plant is already close to the authorized limit.) In some case, a reduction of an impurity may allow skipping a downstream distillation.

The cost of lab-scale equipment may be considered high. It includes, however, all of the experience, training, and continuous support provided by the supplier, which is much higher in the case of emerging technology than for a conventional piece of equipment.

In some cases the financial considerations for flow were considered to be unimportant in the business case for the site. As an example, it is often difficult to build an Return on Investment for continuous processing. Pfizer is looking for other and business drivers including safety that are appealing to API manufacturing. Cost and speed are usually not as important as safety, robustness, and reproducibility for new products.

A compelling business case has been developed at Pfizer and other for the development and deployment of modularized continuous drug product manufacturing, which is attracting the interest of other leading Pharma companies.
Miniaturized and modularized API manufacturing is a vision for future demand where it makes sense, but probably driven less by the demands of personalized medicine than drug product would be. Tax considerations will continue to complicate the picture for portable API manufacturing with access to markets and incentives additional factors.

A more pragmatic approach to flow at Pfizer applies for new products that were initially driven to implement continuous for a large volume product and but eventually decided not to make the investment. We are continually looking for the right business drivers to implement flow over batch rather than focusing in showcase examples for the purposes of learning.

Continuous processing and personalized medicine (or small volume products or decentralized manufacturing) are not inherently linked and the link is not automatic. Personalized medicines are one step further and they will require quick, high-quality production in disposable small-scale devices (advanced small-scale chemistry in the hands of a layman is feasible: Polaroid did this 40 years ago.) Personalized medicine is less of an opportunity for continuous manufacturing because in many aspects it depends upon patient specific materials and the need to avoid cross contamination of patient specific DNA reduces the opportunity for continuous manufacturing.

Personalized medicines offer a huge opportunity for made to order decentralized therapies, once the regulatory framework can accommodate such innovation. Caution is required as it could be distracting to broader continuous objectives. Small, highly configurable automated platforms, allowing chemistry, synthetic biology, and formulation to co-exist, will be key. There are challenges to handling a supply chain where the producing unit may be very small, but the solvent and raw material stream required may be very large. Further study is required in assessing the benefits of batch versus continuous in this type of multi-purpose facility.

Vendors see more and more groups piloting continuous skids and the feedback is that personalized medicines are playing a role here, with small quantities required periodically. They see it as very novel to have production capability at the lab scale, but sometimes have the impression that they have really figured out what to do with it. GSK and Lilly are cited by one vendor as notable exceptions where continuous processes clearly play a role in their current plans and future strategy.

2. Technical challenges for processing equipment and analytical development

More recent developments have been focused on making continuous processing principles accessible to the industry by using familiar unit operations operated in a continuous fashion. However, in the longer term the sequence of technology development for oral solid dose manufacture might be characterized as :

- Continuous operation of known transformation steps with known feed materials (i.e. continuous wet granulation of existing and variable API)
- Improved control of upstream processes to give better behaved feed materials allowing simplification of existing drug product manufacture (e.g. direct compression API)
- Redesign of upstream processes to create single homogeneous powder ready for production of powder based tablets (i.e. liquid formulation and direct compression)
- Replacement of tablets with new oral dose forms, which do not require the upstream process to deliver compressible powders

Predictable features of processing equipment over all scales are important. These include: cheap/quick supply of spares, handling of multi-phase reaction systems, accepted routines of cleaning/start-up/shutdown/maintenance. On the analytical side: method validation of continuous analytics; effective data crunching and integration into learning process models supporting continuous improvement. There is a lack of focus on understanding and controlling physical material properties and behavior. Measurement tools, which enable prediction of impact of material properties on product performance, are required.

In the short term, consolidation of the vendor base for laboratory flow chemistry systems, which could result in the emergence of a series of platforms to support continuous chemistry development, is a key step. These systems will be more robust, with improved (easier to use and more powerful) software, and will support the development chemist and engineer. Analytical systems to support continuous processes will continue to develop. Real time monitoring of these processes typically utilizes HPLC- UPLC, FTIR, NMR and MS. Each of these techniques face specific challenges that range from sampling issues, time resolution and the quality of the sample (is it representative?), probe and sensor fouling, ionization suppression issues (MS), system robustness and cost per sampling point.

Batch processing has the same fundamental issues as software, including calibration, robustness, and qualification and this should not be ignored. Similarly the importance of a well-understood and characterized process based on first principle understanding is critical in batch and continuous. The data rich environment of continuous processing makes this even more of a prerequisite. This also provided the opportunity to predict mechanical failure. An alternative view of the overall technical challenges is: miniaturization, automation, and re-configurability.

2.1. Particles

Solids are a significant problem for flow chemistry. Existing process are designed specifically for batch rather than continuous flow. A typical example is that of the type of solvent: in batch the choice of solvent may be dictated by a low boiling point to compensate the poor heat management of the batch reactor by using the vaporization enthalpy of the solvent. As this point is no more requested in flow, another solvent may be used to increase the solubility of solids. Clogging by solid has to be checked in any case, good and bad surprises may occur!

There should be differentiation between synthesis, crystallization etc., and Oral Solid Dosage formulation. Uptake of continuous is seen as faster, as in synthesis where small scale is less of an issue. This may be hindered more by lack of investment in work up, crystallization and OSD formulation, which can start later in the development cycle and are more difficult to introduce due to solids handling aspects. Technical feasibility for crystallization has been shown many times for many products – and is standard in other industries, albeit at larger scales. Effective and representative slurry transfer for cascade MSMPR crystallization processes is important. There is also the key question of how to link upstream and downstream processes to a continuous crystallization process. In downstream there is filtration, drying, and milling, which also have significant particle related issues.

2.2. Scalability

A seamless scale-up can be achieved when moving form a small continuous reactor, to a larger one, by applying the same parameter as in the lab (temperature, residence time, concentration, stoichiometric ratio), the same result will occur in production (conversion, yield, impurity profile, etc.)
A seamless scale-up does not require any pilot study, or any process optimization. It can be a straightforward process that does not require much time. As nearly every chemical reaction is specific (mixing or temperature sensitive, fast, exothermic or not, with concurrent reactions, parallel, etc.), making a
specific reaction 'seamless' does not mean that all of the scale-up will be always seamless.
Various vendors provide a range of equipment with scale up through numbering up or out (additional size/diameter)

2.3. Fouling/Cleaning

The implementation of new technologies may also change the view of the regulatory authorities, according to the constraints and/or better control of the process, and they ultimately may ask for higher quality standard as far as the best available technology will increase the control possibility.

There is a need to educate regulators on continuous equipment, processes, and control strategies, particularly field inspectors. It would be helpful for Pharma to share experiences on regulatory filings containing continuous and to collaborate on outreach to regulators. A challenge is that not all regulatory bodies around the world will have a similar level of knowledge and acceptance of continuous flow technology and control strategies

There is reluctance from the end-user side regarding the capability to properly clean a continuous flow reactor. Consider first how easy, or difficult, it is to clean a batch reactor. Then objectively consider positive advantages regarding the cleaning of small equipment as compared to larger (batch). Ultimately, there is a need to consider cleaning operation as a full part of the manufacturing process, not just a side operation. Cleaning validation is considered from a regulatory perspective in other white papers.

When using a batch reactor, cleaning procedures exist and are implemented. There is no universal method of validating the cleaning efficiency. The most common ways are solvent reflux cleaning with residues HPLC analysis in the solvent, or the so-called 'white tissue test.' It consists of wiping the surface of the reactor with

a white tissue and visually checking for the presence of residue or dirty particles. This last method, although validated in cGMP process does not give any information of the status of all parts connected to the reactor (piping, pump, exchanger, etc.) In terms of cleaning, the main advantage of a flow reactor, as compared to batch reactor, is the reduced volume and surface.

Operators can always go inside a 6 m3 reactor, open a tubular heat exchanger for examination or mechanical cleaning (high pressure water), dismount piping to clean each single element or replace it. This is not the case for a continuous flow reactor, and a plant manager would be pleased to have one issue in case of plugging or presence of undesired product, that could not be, for any reason, removed by fluid circulation. If the customer is unable to manage this operation by himself, it can be subcontracted to external contracting companies or laboratories (e.g. Corning can manage this operation for its customers).

The challenge of executing a reliable, quick and efficient cleaning is of upmost importance both for quality issue and for equipment usage efficiency. Cleaning procedure at lab-scale is very important to save time during the implementation of the industrial process. Furthermore, as the preliminary tests are usually performed in a glass reactor, it is very easy to first guess, by visual inspection, the efficiency of a cleaning method.

In drug product manufacture, the latest equipment solutions are built to withstand frequent changeovers and can be adapted to different types of containers through adjustable robotic handling equipment and operating systems that can be controlled by the touch of a button. The latest filling and closing machines are able to handle different sizes of stoppers, caps, and vials, allowing for simple changeovers between low-volume production runs. Flexibility is further enhanced by the ability to switch between different filling systems, including disposable rolling diaphragm pumps, or peristaltic pumps with single-use hoses.

The specification, design, and verification of manufacturing systems and equipment that can affect product quality and public health has to follow a risk-based and science-based approach. It is a part of process qualification and as such an important element of process validation as stipulated by FDA in their 'Guidance for Industry: Process Validation: General Principles and Practices' (January 2011).

The guidance reflects ideas of the American Society for Testing and Materials (ASTM) Standard E2500-07, 'Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment'. This consensus standard seeks to ensure that manufacturing systems and equipment:

- Are fit for purpose
- Support continuous process capability improvements
- Enable innovation
- Consistently meet defined quality requirements
- Allow an efficient and effective verification process

Guildat and Poechlauer will publish, further exploring the thoughts above and look at difference in batch and continuous systems. For continuous crystallization fundamental understanding of encrustation and mitigation strategy is a key work package for CMAC. Visual inspection, rinse wash analysis, swabbing, all of which feed into quantifiable, validatable cleaning processes. What is needed is a continuous equivalent set of measures understood and agreed by manufacturers and regulators. Cleaning calculations for batch do account for pipework, valves etc., assuming, for example, worst-case contamination of all surfaces based on hotspot measurements.

2.4. Derisking

One aspect hindering the introduction of continuous equipment processing is the perceived, and actual, risk. This is true particularly when contrasted with batch equipment. This leads to the impression that continuous equipment is custom made and not as multi-purpose as batch equipment, another limitation to adoption.

Vendors, however, like to design API processes from a fairly limited kit, which actually provides impressive flexibility and versatility, often to the detriment of control of heat and mass transfer. To speed adoption, better collaboration within the industry and with vendors to standardize design and plug-and-play functionality would be beneficial.

Continuous manufacturing technologies are well established in other industries and are known to be economically superior to batch processing. The regulatory landscape in pharmaceuticals creates technical challenges that are not present outside this industry. Pharmaceutical production requires material traceability. Rigorous material traceability within a continuous process requires a high level of expertise and extensive analysis of process equipment, residence time distribution (RTD) and models to account for lot level material flows within the system.

Also, the quality release process to assure patient safety requires extensive analysis to assure real time PAT methods are performed with a frequency that is aligned with the process dynamics. A closed loop control technology including measurement; supervisory control and final control element will provide continuous prediction of deviations and right-time corrective actions to keep the process with the design space.

2.5. Analytical Challenges

It is an important distinction to consider the information rich PAT techniques required to develop an understanding of mechanisms and kinetics and the actual systems used for on-line control. Many of these techniques are not required for day-to-day production monitoring and simple tried and tested systems, such as weight, pressure, and temperature, are adequate. Further, the availability of complex analytical equipment should not deflect from the primary aim of fully developed robust process. There is also the balance of on-line and off-line measurement requirements.

PAT instruments are well proven when used in a regulated environment; there is a high burden to provide proof of scientific understanding of the PAT method deployed. Additionally, current interpretations of the 21 CFR Part 11 regulations are requiring manufacturers to keep historic records of all spectral data. This is a technical burden not experienced by other industries.

For in-line analytics the following are described as key challenges:

- Increased quality and ease in Data Interpretation and ability to obtain high quality information by non-experts through the development of improved analysis algorithms and open software architectures.
- Sensor Fouling - has been seen with both API development, crystallization and downstream processes. Efforts are currently being directed at an in-situ cleaning method to keep the sensor free. (in situ) from particulates adhering to its surface and selection of materials of construction
- Price (Cost) - is another issue, presently. Efforts are being made to lower the end user price to a level more affordable level.
- Robustness – Increased product and senor robustness to increase reliability. Reduction of moving parts, system development that is designed for the continuous environment.
- Scalability – Technology to work at mL to uL/min flow rates as well as utilization of the process instruments and probe/flow cell to accommodate the higher flow rates and transfer line diameters.
- Standardized analytical data format allow seamless data integration from various instruments into a single control system and strategy through use of industry standard data formats such as those being proposed by Allotrope and OPC. Management of conflicting data
- Instrument serviceability through remote diagnostics allowing fast diagnostic and repair to optimize uptime.
- Analytical sensitivity for Real time release – assurance of low levels <0.2% impurities (the equivalent of GC in petrochemicals)

Currently, some lab hurdles are being addressed by sophisticated programs for machine controls and interactive features, with software designed for users of all experience levels. For analytical instruments, intelligent software that fully automates system functions and guides users through the measurement process is proving to add the greatest value. Software with embedded support that assists at every stage of measurement so that all users, whether experienced or novice, can make reliable measurements. Today, few users are experts in specific analytical technologies and are required to use many different instruments and methodologies. Lightening the analytical workload through ease of use, intuitive instruments, and intelligent software is essential.

Office of New Drug Quality Assessment (ONDQA)/FDA Sponsored Research on Microreactors Joint research with Center for Process Analytical Chemistry (CPAC) University of Washington, Seattle and Corning, reports challenges as:

- Need for integration of analytical tools to the control system to support implementation of feed-back or feed-forward control
- Sophisticated data management tools
- Defining representative sampling to consistently assure product quality over time
- Location of sampling probes
- Sample size and sampling frequency
- Need for enhanced process understanding
- Availability of mechanistic models for all processing steps
- Implementation of multivariate analysis for determination of product quality

2.6. Technical training

Much equipment is seen as far too expensive, leaving the impression of it being overly complicated or for 'experts only.' The availability of modular, cheap, reliable, and high-quality equipment will resolve this. Such equipment is best developed in partnerships of equipment providers and technology-driven chemical manufacturers.

Whereas in an industrial plant a project team including: chemist, chemical engineer, and mechanical engineer, etc. has been implemented for a while, it is clearly missing at lab-scale. Chemists are not at ease using pumps and flow meters. Others are sanguine about the technical challenges and highlight how other industries have dealt with these successfully. Barriers are seen as cultural.

Another challenge is the need to train and educate all disciplines within a company (chemists, technologists, operators, regulatory, analytical) on merits and pitfalls. The general view is that we are still training people in traditional silos. We need engineers/scientists/technologists/statisticians/software engineers to develop a common understanding.

3. Technology companies role in helping accelerating introduction of continuous technologies

3.1. Typical Company Business Models

The companies contributing to this white paper are typical of larger vendors in this space and their individual perspectives are also more widely typical. It is important to note that while continuous manufacturing is relatively new to Pharma many solutions already exist and it is important for senior stakeholders to position themselves relative to known capabilities, rather than creating unnecessary additional barriers to implementation.

A key role of technology companies is to provide solutions and expertise to reduce the technical barriers that make continuous processing difficult. One of the key aspects of continuous manufacturing is to apply PAT to

control critical quality attributes (CQA). Emerson (and other providers) is positioned to work with the industry to overcome the control challenges. Continuous processing has more challenging control problems since variability experienced in one unit will impact the operation of the downstream unit. Emerson is providing the software environment to integrate PAT instruments, and multivariate models with process controls to provide continued process verification and assurance the production delivers on the critical quality attributes. In addition, it is providing the data management environment to use PAT instruments and models in a compliant manner.

Continuous manufacturing will make continuous process verification easier, provided there is a sound continuous monitoring (product and process) technology in place to measure, control, and capture data. Emerson can work with the unit operation providers and help develop a data model that will thread data from each piece of equipment and facilitate integration.

Mettler Toledo (and others) has been involved with the continuous monitoring of reactions and crystallizations for over 13 years. Through developments of employing miniaturization of technology in the past three years it has developed lab-scale systems and sampling technology for continuous chemistry. In addition, it has worked with various vendors, universities, and customers exploring the use of continuous chemistry and continuous crystallizations in the Pharma and chemical industries. It recognizes continuous chemistry having a growing demand in the Pharma industry and therefore are continuing to develop smaller, less complicated (intuitive to use and requiring limited training) and lower priced solutions for in-situ FTIR and particle size & distribution monitoring. They have and continue to invest in strategic relationships and development efforts to support the development of the continuous chemistry business. They also have an interest in understanding the role of calorimetry as a simple analytical to support continuous chemistry.

Specifically, Mettler Toldeo is pursuing product development and business development efforts in the area of continuous chemistry through strategic collaborations in academy and industry (e.g., Pfizer, Lilly, Cambridge University, MIT, etc.) in order to insure in-situ monitoring systems and software is the right solution based on form, fit, function and value.

For equipment providers like GEA, the first step to continuous processing has been the most difficult and gaining practical experience is critical. Demonstrating feasibility, and investing in facilities that show that practical solutions are available, is essential. Continuous is the core of their future Pharma equipment strategy and they will leverage on their experience in food and chemicals. The current generation of products provides accessible benefits to the industry. Their broad technology base will enable them to bridge between primary and secondary

Corning is providing many of the tools to help customers implement flow reaction including, a large range of flow reactors, ranging from low -low to G4, with a scale-up factor of 500. A nearly seamless scale-up between G1 and G4, and the possibility to make QFT (quick feasibility test), either in Corning lab, or associated platform, or Corning certified lab, or at customer site is possible). Assistance for selection of suitable feeding systems, choice of appropriated gaskets, ultimately to a turn key installation is a key part of the offering.

Existing technology suppliers must respond with everything that is required by continuous processing, otherwise a new group of outsiders (to the Pharma industry) will be created. This, however, will take some time.

3.2. Outsourced Pharma Development Partner

Technology-driven (contract) manufacturing organizations offer services comprising:

- Feasibility studies
- Continuous process development
- Equipment selection
- Process implementation at the site of the technology provider or at the site of the pharmaceutical manufacturer, including training

One of the limitations faced is the ability to effectively devote internal resources to continuous development. Thus, Pharma has worked with continuous equipment vendors in the past. However, this is an area where more could be done to leverage and share the collective knowledge gained across innovator companies.

Pfizer is in the process of developing external CROs to allow them to rapidly enable continuous chemistry at the GMP scale. These vendors will have the right engineering and rig fabrication skills to convert a conceptual design into a practical one. Rather than building an internal staff of specialists, their engineers will operate to manage the project and facilitate tech transfer into their facilities.

Technology companies have a key role to play in the adoption of continuous technologies through the development of the enabling technology, software and support structure (communication and control strategies with Distributed Control Systems), and market education. Modeling aspects are largely missing from the answer. Technology companies must deliver the capability to develop robust predictive models, as this is an opportunity for continuous. In-line monitoring will become more important as continuous verification of the process will be critical. It is not possible in, while operating in continuous mode, to simply take a sample at the end and check for quality; likewise, it is not possible (or at least cost prohibitive) to "re-work" a failed continuous process. Inline real time monitoring will be critical for any move to continuous processing. This applies also to liquid and solid phase characterization.

Another dynamic, which SMEs can also profit from, is feasibility studies, to demonstrate their technologies. Pharma should make use of this opportunity. This could be further developed to include the provision of material for product development.

4. SMEs and Academic Groups Roles in Developing New Cost Effective Technologies for Continuous Manufacturing

4.1. Skills

Designing the most suitable equipment will need inputs on reaction kinetics, importance of mixing, limiting factor, and side reactions. The objective of the supplier is to put the most versatile equipment as possible on the market. Today, some early adopting companies are using highly skilled technologist who develop specific equipment for a specific process. In the future, chemist will make chemistry and equipment providers will manufacture equipment. Of course, both will need to work together through skill development. If continuous can be built into route selection, formulation selection started earlier, then, based on risk and financials, these points will be built into the equation that points towards developing systems, processing units, controls and analytics rather than just reactors.

If the technical challenges can be easily overcome, perhaps academic groups should focus on developing graduates proficient in the language of continuous processing. A key issue identified is to differentiate where new skills are required, such as smart sensors, miniaturization, integration, control, and where the education is sufficient to provide knowledge and capability. This may have to start at the undergraduate level, but could continue through post-graduate programs. Industry/Academic collaborations will be important to making sure that the work being done is not purely academic and has industrial benefit. The importance of teaching the 'basics' of process development with the requirements for underlying physics and chemistry are key. Process control should be in the curriculum but needs to be adapted to changing industry requirements.

Manufacturing skills are also an important factor. Managing the complex matrix of multiple skills will require consideration of alternative supply chain models. Local modular plant in multiple regions will need a range of skills in design, implementation, and production. For equipment suppliers, pre-operation training, advice on maintenance and post installation support are increasingly important.

4.2. Partnerships

Collaboration between instrument providers, academia, and Pharma companies will provide a real opportunity to identify, or define, both individual elements and a complete solution to support the requirements for continuous chemistry adoption in the pharmaceutical markets. After the collaborators have defined the elements of the "right" combination of reaction train, crystallizer, supporting unit operations along with the required analytics including the proper integration points, the correct analytical software algorithms can be developed for each technology and integrated into a single, seamlessly integrated data set. In addition, the data set needs to be accurately time stamped to ensure that the all data can be reconciled with process events in a single view. Through the consortium, solutions (both hardware and software) can be proposed, screened for feasibility, then evaluated and improved to provide the correct elements and or total workflow to support the implementation of continuous processes. This way, a "continuous chemistry skid can be developed and effectively tested" through the integration of the collaborator efforts. Such groups must have a fundamental role, not be just contributors, and trust between partners is a universally accepted key part.

Globally the pharmaceutical industry has spent (arguably wasted) over $1billion (based on informal discussions) on developing continuous manufacturing processes in silos, and in wasted drug stock. The driver is the realization that much of the processes large Pharma companies have spent millions on (more than $100 million per company) in developing continuous manufacturing could be shared without damaging drug molecule IP. There are various examples of pre-competitive collaboration including CMAC

In an effort to provide the most efficient and comprehensive processes, some equipment manufacturers, as well as technology providers, are combining expertise to create products that address these industry needs. One example is Malvern Instruments, along with collaborators ARTMiS and Powder Systems Ltd.

It is still too easy for academics/equipment suppliers/industrials to justify, design and build one offs to meet the needs of a specific synthesis. While fitting the equipment to the chemistry may be a good idea for a large volume commercial product (the time taken and quality of equipment can present too large a risk for project managers) we cannot afford the time to deal with issues such as poor construction.

A key aspect is the acceleration of the pace of introduction. There are examples of partnerships that have taken 10 years to implement. An example of K-Tron and many drug product vendor suppliers working on common layout issues in 3D to look at ergonomics, cleaning and accessibility is highlighted as an excellent example of partnership in common ground.

4.3. Problem Statements

Using industry problem statements as a focal point, various ‘centers of excellence’ have been created. In this environment, the use of cheap methods of rapid prototyping to design and build reactors “overnight,” that are tailored to a given reaction (temp, press, time, energy) at the required scale, can be undertaken.

Much more focus on integration of continuous processing rather is needed developing solution based on individual industry problem statements. In general, this collaboration optimizes the overall "solution" development and timeline. In addition, providing IP to an upcoming approach to high value chemical development processes/methods.

There is an accepted need to leverage academics, and associated SMEs, more than they have been as they are a vital resource to advance the technology particularly, as internal resources dedicated to pure technology development are directed elsewhere, if they exist at all. There is significant opportunity to improve this collaboration and to see real benefit for industry from them. The industry would like to see greater interest, in the problems that they deem important, from academia. The publication of real case studies is extremely valuable showing implemented solutions.

5. Consensus around a dominant design for continuous processes.

Presently, there is no consensus. Different groups pursue different goals, the most ambitious goal being an end-to-end continuous process from raw material to finished formulation. Probably the worst approach is, 'I just got a flow reactor. What can I do with it?' A considered view is that dominant process design criteria should result from the answer to the question: which sequence of conditions will make my reaction or unit operation perform best for my purposes (cost, quality etc.) and which piece of equipment will provide this sequence of conditions sufficiently well? There could be categories of design that match specific unit operations, matching inherent characterization. It is also noted that in the automotive and electronic industries, despite commercial interests, key standard for connectivity are available.

5.1. Common Process Design

One view is that end-to-end, fully integrated continuous is the only way that should be considered. Anything else can be achieved with incremental steps to existing technology. This is perhaps true, but it represents the continuum between short term and longer-term vision in this arena. As an example 'What is the common denominator of expectation between car buyers?' Is it a cheap tool to go to work everyday, driving few miles per day, long distance, driving alone, with children and pets, for object transportation, for social recognition?

Formerly (last century) organizations would have defined and executed basic research & development programs to learn about the general principles by working on model cases of substrates or transformations, hoping that the created knowledge would eventually fit their needs e.g. toolbox approaches, platform technologies. It has been observed that this has changed in some cases

People are, in principle, aware that "there should be something/someone out there" capable of solving their problem immediately once it occurs. State-of-the-art communication media enable this, so the actual competency has shifted towards quick, efficient and reliable identification who/what could help – specific networking capabilities. Process design must start with an understanding of the final product performance hence the synthesis process must take account of the final drug product format.

Overall, it is much better to avoid problems and increase availability by better process design. Standardization of Computational Fluid Dynamics (CFD) provision of continuous processing equipment is an interesting suggestion.

5.2. Hardware and Software

Regarding standardization and specification for continuous manufacturing, standards organization such as ASTM E55 and GAMP can support it. ASTM E55 already is developing guidance documents on continuous manufacturing. GAMP has a special interest group that develops standardized User Requirement Specification (URS) documents related to pharmaceutical equipment and would be open to including continuous equipment types within their mission.

Robust equipment, designed to appropriate standards, with the right interfaces for connecting to other equipment (controls, services) would help accelerate adoption of continuous as companies want their chemists and process engineers running processes, not fixing equipment, getting the vendor in to replace seals etc.

A standardized interface would create a large market that creates a compatible system across all manufacturers and hence takes advantage of the entire development bandwidth across equipment

manufacturers. The existing standards for mechanical, electrical and process control interfacing are potentially sufficient e.g. Object Linking and Embedding for Process Control (OPC).

Whether standardized or not continuous, manufacturing processes require real-time data monitoring and analysis to verify Key Performance Indicators (KPI's) and other performance expectations. Software tools are available that can receive data from various systems (e.g. supply chain, manufacturing, laboratory) to allow operations data to be seen and understood, giving a clearer picture of the process and making real time modeling possible, leading to better business decisions.

Another approach could be to write the control strategy to manage different equipment types from different vendors, for example specify a standard control platform for all process equipment/skids in the continuous manufacturing process, for example Emerson and Siemens work with various leading OEM skid vendors to allow them to offer process control infrastructure as an option on their skids.

Using this strategy, it is possible to implement real-time quality control. The move to continuous processing completely changes the process control aspects for drug manufacturing. In batch processing, the production of each unit is a batch and its output is stored as inventory. This allows each unit to runs completely isolated from the other process units but is inefficient and slow.

Variability in one unit does not impact the operation of the other units. When these unit operations are connected as part of a continuous train with the discharge of one unit feeding the next unit, the process becomes highly interactive and processing parameters become more dependent upon one another.

5.3 Business Dynamics

The most critical point here is the 'overall goal.' There is an issue regarding how to manage the differing business needs/objectives between vendor and industry partners. Each has very different goals and there are many organizations involved. This makes it very challenging to insure each party meets their desired objectives.

What is the consensus around a dominant design for a sulphuric acid plant and a petroleum refinery unit, both being continuous? The vision of a fully integrated continuous flow unit from first stage to the final product is a nice concept. In the near future, a continuous step will be most of the time between upstream and downstream process in batch. The implementation of continuous process will occur when it brings a significant advantage to the existing equipment, in terms of safety, cost, operability, waste, regulation… and that's it. There is the possibility, however, that bringing the idea that continuous flow is THE universal solution will just make people more suspicious towards this technology.

Dominance is seldom a good thing for a sector. It would be optimal to see inexpensive hardware developed that is easily connectible to enable most of the standard chemistry used in API synthesis, as now, it is heavily customized and purpose driven. An additional topic for consideration is 'preferred or proven (business) models by which companies wishing to apply this technology would recognize/create/internalize the required skills and competencies.' The respective buzzword is 'open innovation,' and it appears to work well for quick implementation of continuous processes via quickly identified strategic partners.

Pharmaceutical companies, however, tend to work with 'islands of automation,' where every unit of operation is more or less independent from an integration point of view. Integration is a challenge for the industry. Changing to an integrated approach, which is standard in many other industries, is a big step for Pharma companies. Many equipment manufacturers have only one piece of the jigsaw, but for continuous manufacturing all the pieces must not just fit together, but talk to each other. Learning from other industries can be an important catalyst, such as sensors for nuclear or aerospace.

6. Conclusions

- Process and Analytical Equipment systems must be digestible and accessible to be adopted

- End users , Academics and supplier companies must collaborate to accelerate introduction

- Focus must be on developing accessible business cases

- Need to provide confidence that:
    - Technology is robust and will operate consistent
    - Regulators will accept it
    - Adequate return to partners

Outline recommendations

	Short Term Recommendations	Long Term Vision
1.How to encourage take up in Pharma industry	• Early adopters advocacy through case study sharing of business case • Quantitative study with key industry players to try and add some analytics to the discussion. • Regulatory training	• Decentralized on-time-on-demand production of pharmaceuticals by efficient fully continuous processes (API and secondary manufacturing) operated in well-understood modular equipment. • No difference between batch & continuous equipment concerning functional qualification
2. How will technical challenges be resolved	• Sharing problem statements • Share validated models • Co-ordinated collaborative activities • Development of skills programs	• Portfolio of incremental and disruptive approaches across analytical, control and specific technical challenges • Cleaning protocols routine
3. Role in a technology companies in helping accelerating introduction of continuous technologies	• Offer integrated solutions comprising process development, equipment supply, engineering, production at an agreed site, documentation, qualification. • Shared understanding of the key application development and transfer challenges associated with continuous processes	• Deliver modular, dedicated high quality production units, based on the recipe of a required pharmaceutical, on short notice. • Universal control / data output systems
4. How can SME and academic groups be encouraged	• Development of scientific papers, whitepapers and educational/ training sessions to support the utilization continuous processing technology • Stimulate government, industry funding and in kind support from technology vendors. • Specific enabling technologies can be directly supported by direct technology funding	• Address Conflict between joint development and wide spread of the technology… • Global Skills agenda • Truly Open innovation
5. Common denominator of performance expectations and how	• Develop concept of standard process design methodology • Agreed cleaning and cleaning validation strategies for continuous equipment	• Standard process skid design • Universal connections • Open source software and developed platforms

do we specify them	• Worldwide continuous processing glossary	

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Appendix 1 An Small Medium Enterprise SME perspective:

Interviews with selected SMEs in API space (AWL, Asynt, CRD, Syrris, Scimed, Semba Bioscience, Fullbrook Systems, Zeton, AMtech) provided a rich narrative. Key points from their perspective are noted across the 5 core questions.

Predictions for Take up of Continuous Equipment in Pharma Across Supply Chain

- Continuous is 5% of business will rise to 30% - key part of turnover
- More take up in secondary, rather for personalized medicines and APIs
- Only dealt with bx (analytical company) Main sector is not Pharma
- Continuous is ubiquitous in Pharma, everyone interested and to be seen looking at continuous.
- Many new companies established.
- Human factors rather than technical factors are main barrier.
- Expect to be 30% of Pharma activity in 10 years
- Picking up dramatically companies starting to put in significant money
- Literature papers growing. Academics not teaching continuous yet.
- Petro chemicals background laughing for many years re not adopting new technology. Pharma comfortable to 'stir the batches'

Technical challenges for processing equipment and analytical development

- Analytical equipment – connecting to process with least detriment to hold up / fouling
- Time to resolve issues e.g. reliability, designed to be accepted by industry. Early adopters try to mimic the batch process (validation)
- Physical size of products / process, mechanical strength of components
- Integrating analytical + equipment all the new technology work together. Really good products from smaller companies on being accepted is one of the challenges
- Reducing costs – cost / scale per gram especially for volume
- Outsource most of manufacture – so work with generics and CMOs
- In line analysis – can do anything simila as quickly. Grab sample re hplc – all equipment different
- Typical challenges in work up solvent removal telescoping – obvious in batch – flow makes it more complicated
- Pumping solids at pressure, blockages
- Geographic variability re technical challenge and education
- Multi phase systems

Technology companies role in helping accelerating introduction of continuous technologies

- Provide necessary tools from lab to production scale to meet needs of end user. Key to adoption. 10 fold decrease in demand for new bx equipment
- Help get lab equipment into engineers hand
- Very important companies involved alongside researchers to ensure consistency QC not required by researcher. Conti core part of business.
- Continuous IS our strategy but can use in bx.
- Customer demand dictates time to develop
- 50/50 bx continuous business focus, 100% continuous focus/
- Trying to bring flow to people. Several territories don't understand – large part of role is education
- Analogy of teaching chemists to do flow chemistry is like teaching grandparents to use iPad!
- Agent role important – portfolio of product offering from different suppliers
- Generate case studies and data for business case.

SMEs and Academic Groups Roles in Developing New Cost Effective Technologies for Continuous Manufacturing

- Collaborative project and stimulating public funding
- Smaller leaner, more nimble, more focused quicker design. Driven by technology and innovations rate than shareholder rewards by providing tools
- Ride wave of success from larger activities e.g. CMAC
- Agents roles promoting equipment
- SMEs need a broader base re commercial aims not very broad base
- Alliances e.g. Syrris/Prosonic, Uniqsys/CRD
- 80 people in a flow company is very large – many are small. Ten is the norm
- Collaborative research re scalable products
- Help from government, partnerships

Consensus around a dominant design for continuous processes

- Normal bias towards companies own technology, sell its own product
- Equipment versatile
- Control systems to fit budget but ability to integrate
- Standard fitting, output 4-20mA, Modbus, OPC
- Can't see happening – standard connections but imperial and metric
- HPLC column fittings
- Each system has control system
- Easier in research environment re sharing
- SMEs can help with open innovation, but bandwidth limitting
- Technology companies coming together. Alliances.
- Core products are flagship IP, know how in software
- Maybe one day – too early
- Unable to standardize on mobile phone chargers cf niche market
- Business drivers dominate here
- More chance on control side but not easy. Several vendors with dominant position.

Background References (NB academic literature reviewed in other papers)

The ACS "Green Chemistry Institute" Pharmaceutical Roundtable has worked on questions around continuous processing and its potential benefits.
See OPRD 2013, 17 (12), pp 1472–1478 and references cited therein.

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10.1	User Requirements
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