How Development and Manufacturing will need to be structured – Heads of Development/Manufacturing

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Executive Summary

Continuous Manufacturing (CM) is a process technology that has been used in the chemical industry for large-scale mass production of chemicals in single-purpose plants with benefit for many years. Recent interest has been raised to expand CM into the low volume-high value pharmaceutical business with its unique requirements regarding readiness for human use and the required quality, supply chain and liability constraints in this business context.

Using a fairly abstract set of definitions, this paper derives technical consequences of CM in different scenarios along the development-launch-supply axis in different business models and how they compare to batch processes.

- Impact of CM on functions in Development is discussed and several operational models suitable for originators and other business models are discussed and specific aspects of CM are deduced from CM's technical characteristics.
- Organizational structures of current operations typically can support CM implementations with just minor refinements if the CM technology is limited to single steps or small sequences (bin-to-bin approach) and if the appropriate technical skill set is available. In such cases, a small, dedicated group focused on CM is recommended.
- The manufacturing strategy, as centralized versus decentralized in light of CM processes, is discussed and the potential impact of significantly shortened supply lead times on the organization that runs these processes.
- The ultimate CM implementation may be seen by some as a totally integrated monolithic plant, one that unifies Chemistry and Pharmaceutical operations into one plant. The organization supporting this approach will have to reflect this change in scope and responsibility.
- The other extreme, admittedly futuristic at this point, would be a highly decentralized approach with multiple smaller hubs; this would require a new and different organizational structure. This processing approach would open up new opportunities for products that, due to stability constraints or individualization to patients, do not allow centralized manufacturing approaches at all. Again, the entire enterprise needs to be restructured accordingly.
- The situation of CM in an outsourced operation business model is discussed
- Next steps for the industry are recommended.

In summary, opportunistic implementation of isolated steps in existing portfolios can be implemented with minimal organizational changes, the availability of the appropriate skills are the determining factor. Implementation of more substantial sequences require business processes that consider the portfolio, not just single products. Exploration and implementation of complete process chains with consequences for quality decisions do require appropriate organizational support.

1. Definition of Scope for Continuous Manufacturing (CM) Implementation Scenarios

For further discussion of organizational impacts, it is important to define key scenarios along the spectrum from batch to horizontally integrated, fully continuous operations. Along with these scenarios, three definitions are also needed:

Definition 1: a material transformation shall be defined in broad terms as a conversion of a specific material under the influence of physical or chemical conditions into another material of fundamentally different properties. This transformation can incarnate itself as a chemical reaction where the raw material of choice is changing its chemical structure under the influence of another material (or multiple materials) reacting with it or it can incarnate itself under the influence of physical conditions as a change of material properties. Examples would be: melting, dissolving, wetting (during wet granulation), where the material properties would change purely in a physical sense (e.g. changing its rheology, its phase or any other property).

Going with such a broad definition of transformation, chemical, biological and pharmaceutical operations are equally well covered and the distinction between the big disciplines in the context of CM is just the set of properties and conditions of materials that are transformed.

Definition 2: Continuous operations can be defined in broad and abstract terms as material transformations that are characterized by simultaneous inlet of raw materials and outlet of transformed material at any time point.

In the following we shall use these definitions to understand and develop the structural requirements for development and operations in implementing CM in a variety of ways, all of which encompass continuous elements in a more or less radical way.

CM had its modern roots in the idea of process intensification, which means more material transformation in less reaction space, which in turn leads to the big technical benefits: better process control thru stringent enforcement of process conditions on a microscopic scale and ultimately the option for smaller equipment. In order to get the most intense processes, we need to minimize the reaction space thus maximize the concentration of the transformations over space. In order to eliminate loading and unloading times of the reactor that do not add to the transformation as such and hence do not contribute value, a simultaneous inlet and outlet of materials is needed. As a consequence of this approach, all elements as there are inlet of material, transformation and outlet of material are then theoretically without discrete elements, except for start and finish, hence the process is truly continuous and can be operated at any desired length of time. This basically is CM in a nutshell. It is a process that is essentially run without interrupt or reset, characterized by a controlled production **rate** instead of a production **volume**.

CM processes can be found in Chemical reactions, purifications, crystallizations, mixing, blending and filling operations, granulations, particle generation technologies and many more.

Going strictly by that definition, a variety of practical installations can be conceived, which have a different set of characteristics and a variety of consequences. In practical installations, CM can follow two philosophies: continuous operation of networked unit operations, which *per se* may or may not be truly continuous, but meet as the network the definition of CM. Second, as an optional precursor, the unit operations *per se* can be also CM. So, the declaration of a process as CM may depend on the scale or the granularity of the process definition. In the bigger context of a pharmaceutical operation which has the goal of engineering a sequence or networked system of transformations that generates a material with a guaranteed set of quality attributes, this declaration depends primarily on the process control strategy: at what points in the process chain do we monitor and control the transformation? It is these anchor points that need to be the basis for the application of the CM definitions above and to determine whether or not a certain unit has to be seen as a CM operation. In the most simple and straightforward implementation, many classical unit operations meet the definition of CM and CM elements of process control are the *de facto* industry standard. Examples would be a roller compaction process, a tablet compression process, a capsule filling process or reactions in a tubular reactor. As an example, let's look at a roller compaction process: we have a continuous flow of incoming materials, a

truly continuous compaction and a simultaneous outlet of compacted matter. Looking at it at anchor points of material flow inlet and outlet and compaction, without doubt this process would meet the definition of CM. Slightly different is a tablet compression process: the material flow into the hopper can be designed as a continuous stream of granular material, the machine dispenses discreet elements of material, compresses them into discreet chunks of material and releases these chunks of material as outlet. Only the effect of resolution (or scrutiny of scale) allows us to see a stream of tablets as a continuous entity. It does not make practical sense to look at the material transformation (compression) step at a larger magnification than the unit dose dictates, even though nobody will disagree that the tablet (as well as most dosage forms) is the opposite of a continuous process, as the compression without doubt has a major impact on the quality attributes of each individual tablet and it does as such not meet the definition of CM if it is applied at too small of a scale. This shall illustrate that the scale defines the declaration of a process element as CM or batch. A dividable tablet is in that sense already a sort of a campaign, the compression of the tablet produces two or four unit doses for the patient and the control strategy needs to take that into account. It becomes obvious that in the industrial practice it makes sense to classify the anchor points for process control even in this case as the powder flow (whether steady, pulsating as in most pneumatic PTS systems or batch based) and the stream of unit doses called tablets and classify the sequence of compression events as a CM operation. By the same principle, one can classify any unit operation as a CM operation, if the choice of the anchor points makes the process meet the Definition 2. If this is not desirable, the anchor points of the control strategy need to be developed differently and the process may be better dealt with as a batch process.

Definition 3: A CM Unit operation shall be defined as a transformation whose process control anchor points shall not be divided any further for a given process chain.

This principle now makes it clear that the technical reality AND the process control strategy thru the definition of the anchor points are the deciding factor to classify an operation as a CM operation or a batch-based operation.

The CM unit operation is the smallest cell of operation, which shall be described in the process control strategy. It can be truly continuous even in all its technical elements or can appear as CM thru the appropriate choice of control points and described adequately.

Any technical operation that BY PROPER CHOICE of control anchor points can be made compliant to the CM Definition 2 and can be dealt with as a CM operation and will deliver the quality attributes that are typical for CM within the constraints of its technical implementation shall be considered CM. Implementation of any CM unit operation can also be achieved without declaring it as such, if the inlet is implemented and described as a batch of material, e.g. a container of a finite amount of material and the outlet is described as a batch of material as well. At a higher level of granularity the operation may be classifiable as a CM unit operation, but if the anchor points just describe the containers of material, it certainly does not meet Definition 2 and needs to be classified as a batch process as a chunk of material is transformed into another chunk of material in whatever operation, that has a discrete beginning and end. This would be seen as a bin-to-bin implementation of a CM operation.

Let us apply this thought process practically:

1.1. Bin to bin approach: single, disconnected, continuous unit operation

A bin of raw material is characterized by a set of samples to prove homogeneity in space, for example top-middle-bottom samples of whatever attribute and a bin or product is also characterized by a set of samples that characterize top-middle-bottom to prove homogeneity of the second bin. Whether or not the transformation at a smaller level of granularity of description can be classified as CM does not matter at the end of day, if the train of quality attributes is controlled from bin to bin and the quality of the transformation is described as converting one bin of homogeneous material into another bin of homogeneous material.

1.2. Partial integration of unit operations in a bin-to-bin approach

Thinking the same thought presented in section 1.1 one step further, any series or sequence of CM unit operations will in itself meet the CM Definition 2, by applying the first and the last anchor point of the series of CM unit operations as the anchor points for the classification decision. As such all consequences that have been discussed under a. apply to the bin-to-bin case of sequences of CM unit operations as well. In a streamlined setup, sequences of CM unit operations can be dealt with from a control or anchor point perspective as a single, 'mightier' CM unit operation, if the granularity of control is adequate for the technical process and its quality attributes. Usually a higher degree of granularity gives more degrees of freedom to react to disturbances and as such may result in better quality. A poor control strategy or poor sensor quality, even at a higher level of granularity may be inferior to a simpler one at a lower level of granularity. With this in mind, the optimal definition of the anchor points and the control strategy should consider a change of granularity of control and the concept of CM unit operations and its definition allows adequate quality assurance of the processes. The selection of the level of granularity of control should consider the inherent process variability, disturbances and available sensors as well as the general data quality. The theoretically best control strategy does not buy much practical benefit, if the available sensor quality or data quality is not supportive; surprisingly, often doing nothing and leaving a process running without interfering is better than over controlling and destabilizing a process by too frequent or too detailed controls based on shaky data quality. In that sense, the proper choice of the anchor points has an impact of the performance of the controls meeting the CQAs but also on the classification of the operation as CM.

1.3. Integration of entire chemical unit operation chains

The concepts discussed in Section 1.2 allow a generalized approach to any kind of sequences of unit operations and allow for the adequate control strategy from a technical as well as a Quality/Regulatory perspective. An in-house full manufacturing chain implementation allows full control over every aspect of the control chain and gives the ultimate in terms of freedom to design the best possible process to achieve the best possible quality. However, sometimes constraints or other means of maximizing business value blur the perfect vision and special aspects shall be discussed here for the chemical synthesis case. In the case of chemical synthesis, special constraints need to be considered carefully, as certain chemical intermediates have strategic importance for synthetic routes and may have other limitations as well, e.g. environmental constraints that limit production only to certain countries, widely divergent process cycle times between early intermediates, more advanced intermediates and endgame steps. Often synthetic routes are designed as convergent synthesis routes, which have the consequence that the early intermediates are generally smaller molecules, with larger molecular weights dominating the latter steps of the synthesis. Practical consequence is that early reactions are more often highly energetic and the larger the molecule gets during its assembly, the gentler the reactions need to be, the poorer the solubility gets and the slower the processes will be. (This may be a bit too general, as it is true for coupling steps and not for deprotection and salt formations, but indicates the general concept. It also focusses purely on technical aspects and does not consider market considerations such as outsourcing and tax situations.) Which in turn makes it easier to find suitable reaction candidates in early steps as compared to endgame, whereas the desire from a quality perspective contradicts just that: the closer we get to the endgame, the more important the achievable quality aspects become and hence the greater the desire for CM delivering against its promise.
The result in this case is that we need to consider the development phase of the entire route and all its components, however may only see certain elements in CM technology at all or only selected steps in big Pharma's manufacturing operations.

1.4. Integration of Solid Oral Dose Chains

The most widely used pharmaceutical dosage form is, without doubt, still the tablet. Hence, no discussion of any pharmaceutical manufacturing strategy can be done without reflecting on solid oral dosage forms, with all its complexities and benefits.

The solid oral route is well understood in the industrial practice from a process and managerial perspective, less so from a technical or scientific perspective, even though tremendous advances have been achieved. Granular materials are often complex in their characteristics, stickiness, flow behavior, compressibility

characteristics are overlaid by dissolution, hardness, friability and other material properties that are somehow manageable; experience and the material science of DS and excipients plays a big role in managing the complexities of what is often nonlinear or uncharacterized behavior. The target of a robust and reproducible process can be a function of trial and error or the use of generalized linear model approaches like DoEs. Either course suggests that, while the underlying physical principles are not understood, they are manageable by approaches that experience has proven practical.
The big benefit of going with classical oral dosage form technologies for CM is that despite the inherent technical challenges, the vast majority of development scientists and manufacturing specialists have been exposed to these technologies and patients are used to the tablets as the end product and expect and accept this dosage form.

The integrated solid oral dosage form CM chain will start with a DS at a well-defined interface. This interface has been the backbone of the pharmaceutical industry since its inception and defines the creation of the structural features of DS as the endpoint of the chemical process trains and as the beginning of the pharmaceutical process trains. The crystallization of DS has to fulfill the purpose of purification often as well as the shaping of the primary particles, which includes salt formation, polymorph control, sizing and habit engineering of the particles. Functionalization can be supported in certain cases by forming pharmaceutical intermediates at this stage through blending in formulation aspects such as co-spray drying with an excipient amongst others. It can be debated, whether this 'crystallization' step needs to be considered the last DS operation or the first DP operation. For purposes of this discussion we will define the completion of the chemical structure and its purification as the DS operation, and everything after that the DP process. From a process control perspective this is a fundamental anchor point, as in most operations this point determines the handover between what are typically two major organizational silos and the handover of responsibilities. So the definition of the DS specification is the most important anchor point in the current organizational setup in all Pharma companies.

1.5. Integration of entire pharmaceutical unit operation chains

Taking the thoughts as presented in Section 1.4 one step further, it can be conceived that the entire pharmaceutical chain can be integrated, starting from a purified DS in solution and can be crystallized, formulated into an intermediate and then further processed into a tablet or any other dosage form. This would open the door towards the integration of chemical and pharmaceutical unit operations.

1.6. Total integration of chemical and pharmaceutical unit operations

The holy grail of CM is the total integration of all manufacturing steps into a single monolithic chain. This requires the satisfactory solution of both DS and DP process chains independently and ties them together into one long chain. From a technical perspective this assumes that every step can be implemented in a CM mode. Going with the Definition 2, this would be the invite to think how to close some of the gaps that current the technology portfolio still has. It is often possible to create 'quasi CM' steps, meaning converting a batch operation into a CM operation by joining several units together and switching them around in a circular buffer manner. An example for that would be SMBC chromatography.

It remains to be demonstrated under which conditions this setup would be feasible both from a technical perspective as well as from an economic perspective. The economic aspects that need to be considered in this context are the specialization of CMOs that might not cover the entire chain but just specific elements, the distribution of value generation according to economic and political considerations like market access. Interesting aspects there would be the opportunity for a drastic reduction in lead times, with the associated inventory costs, but much more importantly, with the better manageability of the demand-supply balance. This scenario would, without doubt, have the biggest impact on organizations that would need to operate it. It would suggest that the separation of Chemical and Pharmaceutical operations and Development is no longer needed; it would open the opportunity for cross-functional teams across the entire technical chain with one common set of objectives (broken down into sub-objectives within the same team). This shall be discussed further in this paper and all the variants that are hybrids between fully integrated CM process and a fully non-integrated batch mode. In a very futuristic setting a completely different highly decentralized Drug

Product supply chain could be conceived, changing the role of the local pharmacy. This shall not be discussed here as it is considered so far out of the current business environment that it requires almost a different company and is discussed in another paper.

2. Key characteristics of the different scope scenarios

2.1. Technical Development

Obviously it is necessary to understand the situation an organization is in and how much impact a new paradigm adoption will have for the right structures. Structures in this case will be driven by development roadmaps driving the resources and gating processes, which in turn should be reflected by an appropriate organization. It needs to be mentioned that the education scientists receive in their universities has a major influence on the toolbox they will use throughout their career, so a successful change management includes the educational component in the long run.

Developing CM processes requires different skills and development procedures as compared to batch processes. The skills required include a CM-focused mindset, as CM presents problems that are different from batch and offers a substantially different toolset to solve those problems.

It is generally advisable to develop single CM unit operations in an uncoupled manner first, if possible, and characterize the properties as well as the operating windows. This may be based on empirical data or statistical models or mechanistic-model-based to allow further investigations thru simulations to drive both process understanding as well as simplifying scale changes and the development of the coupling of process steps. Model-based development is complex and time-consuming initially, but it often enables an in-silico planning of the commercial process train, including in depth understanding of the control strategy. Model-based scaling of 1:100 has been readily achieved in cases of chemical reactor technology. Thermal management is also significantly safer and, in some cases, a prerequisite to having a good quantitative model. Model based development becomes significantly more difficult as the material laws become less precise or nonlinear. Specifically, management of granular media, as in solid oral pharmaceutical processing, may become prohibitively complex in model-based development. In these cases, linear approximations may be the route of choice, and even then only with small windows of validity.

The use of CM will require changes to the structures and development paradigms currently used in small molecule process development:

- Development of CM procedures *per se* is initially more complex and requires more material in early phases. This needs to be carefully balanced with the attrition seen in early phase programs.
- Reason for this is that CM requires knowledge of kinetic information for all unit operations and the experimental verification consumes constantly material as soon as the experiment is started. So, CM tends to cross into larger scale sooner as compared to batch procedures. Development of miniaturized pieces of equipment holds promise to mitigate this and the situation may change in the future. Challenge in this context is, that miniaturization towards very small dimensions may cross into areas, where other driving forces become increasingly important and change the scenarios of importance. E.g. the clogging behavior of sub-mm tubes will be different as compared to cm range tubes. The same applies to flow patterns and capillary forces. Downscaling equipment to support smaller scale experiments will help to overcome challenges, but this is current R&D topic.
- CM processes almost inherently require more process understanding as soon as they are employed compared to batch processes but allow to generate this in an empirical way efficiently. Lab and process automation holds significant promise to streamline these procedures and create protocols that allow the extraction of more information at earlier stages, but this is not industry standard yet and further opportunities need to be realized.
- Implementation of technology platforms and broad application will generate more experience, which in turn will help to overcome this current limitation.
- CM processes typically save a lot of material during late stage development and tech transfer. This can sometimes be accomplished through in-silico process development. Alternatively, the ability

to screen very quickly through various parameter setting can also save material as long as the process is robust to this type of variation.

- In summary, CM currently requires more frontloading of development efforts, both in terms of material consumption as well as technical complexity. This frontloading makes of critical importance the selection of the right project and the right time-point to start CM implementation. With more development work on the side of process automation, downscaling process equipment and implementation of platform technologies this may change in the future.

Once all desired unit operations are developed in a CM mode, connecting them into a contiguous train is the last step, which can be facile if the operating ranges are 'in sync' and well centered around robust process operating points.

A few aspects of CM process development merit special consideration:

- The material never sits still at an intermediate stage and hence does not need to withstand a holding time or a larger buffer time, when the CM Unit operations are coupled. This opens opportunities that would not the feasible in classical modes, but do require that processes are developed in a connected mode from the onset. With experience this approach might and in certain cases does fly. In these cases a batch mode even for early phases would not be helpful at all and the only option is to conceive the process train in CM from the beginning. Coupling in this context pertains to any couplings, be it sequences or the entire manufacturing chain.
- One of the fundamental organizational questions is being driven by the Business purpose. Originators create the value from qualifying patent protected structures for therapeutic use and hence the time needed to get an approval is critically important, mostly dominating the technical development timing. The consequence is that the faster development process is usually creating the larger value as opposed to the cheaper or technically better process. For a generic company that goes with known molecules mastering the supply chain effectively is key as this is driving the value generation. The development time is not critical, it is more the development cost than the overall value generated is significantly less compared to an originator model. So, here the fast generation of a viable process is less of an issue than the total cost situation. The third main class of companies would be specialty companies that focus on mastering special technologies, regardless of the molecule or the therapeutic category. Here the uniqueness of the process and the IP generated around that drives the value, ideally combined with some technical advantages of the product that can drive exclusivity of some sort, be it thru patent protection as such or thru business arrangements. In these cases technological investments can be supported by a multitude of products, making huge specific investments more manageable. Obviously the focus of such business is very different from that of an originator and hence the structure needs to be different. As the business purpose (originators vs. generics etc.) heavily dictates different *modus operandi*, as the clinical trial situation is substantially different, these cases need to be distinguished.

2.2. Clinical supplies

No development program exists that does not require the generation of clinical supplies. We need to distinguish the three cases again:

- Originators: Practically speaking, the development programs are designed to support the clinical development path at its various stages. As the clinical programs are the main risk, cost and opportunity drivers for originator companies are designed around this imperative. Technical Research and Development (Chemical and Pharmaceutical Dev) are seen as the service provider to drive the clinical performance evaluation predominantly and act as the process donor for Manufacturing Operations to multiply the product at manageable manufacturing costs, not necessary at the lowest possible. The Supply question during the clinical programs should not be on the critical path, so a minimum of time needed to translate a prototype product into one that is fit for human use is of the essence. Every aspect supporting this goal is helpful, one being that the least number of development steps is the winner. Examples would be: no scale up, no

redevelopment of similar functionalities, no change of synthesis routes, no technical transfers, as much as this is achievable.

- Generics: the clinical supply situation is not critical, as typically BE studies are the only required clinical studies. Hence, the focus here is much more on the technical side to optimize manufacturing cost and develop convincing technical solutions, which finally need to be verified a single time against the originator's product PK performance. As there is no loss of exclusivity driving the development timeline, but the lowest manufacturing cost and the ability to create niche IP to secure advantages instead of complete blockages, the focus is different.
- Specialty companies have their focus on specific technology basis with the intent to broaden the applicability of a certain investment into as many products as possible. The nature of the product normally is not of the essence here. It is, rather, the exception than the rule that these companies have to deal with NCEs and their inherent desire for short development timelines, but focus more providing steps they are really good at and create IP around it to protect the market share or even better, create unique positions. The values generated for these businesses per step are often much lower, as the cost structure is different, but can be still very substantial and the businesses are often sustainable and long term oriented. As CM is an example for such a technology basis, it is no different than any other specific technology from a business process perspective. The technical expertise of these companies is often huge, as they focus on making a particular technology a success and apply it as broad as they can. So the chance to generate a broad and robust experience base is excellent.

2.3. Launch support

Launching a product is no different between the business models described in previous paragraphs. Questions that need to be solved are the establishment of robust supply chains for raw materials, equipment, processes and the demonstration of robustness and repeatability of the supply under predicted commercial conditions. The key focus is to manage risks, identify threats, provide solutions for upcoming issues on the fly and develop a convincing data package both to the regulators, as well as the customer to demonstrate that the production can support a massive investment into a launch without the risk of interrupted supplies, as well as unpredicted quality risks. One element of significance is the uncertainty of market demand, translating to uncertainty of required launch volumes and the sustainable market supplies. Predictive marketing data seems to have often more uncertainty than Operations can manage easily as reported in literature. Various strategies do exist to overcome this, being it oversizing the supply chain, extremely flexible manufacturing organization with identical parallelizable manufacturing trains, or utilizing launch facilities which only deal with the first 1-3 years of market life of a product (thus deferring larger investments until the market trajectory is known). Any strategy that adds flexibility to the net product flow over time of a particular plant helps. For the case of CM this could be the time-based scaling principle.
The other point to consider is the likelihood of getting approvals from major authorities. As the emancipation of non-US and non-EU markets is growing, the education and willingness to cooperate with a variety of health authorities needs to be planned for.

2.4. Continued commercial supplies

Continued commercial supply from a CM line has substantially different technical requirements that need to be reflected. The following points bear mention in this context.

Operation is continuous without interruption for a multitude of days. This implies that development, as well as operations, require an uninterrupted 4-shift operation, at least for the planned campaigns. In Development this might be addressable by pulling together temporary resources on a team basis and training master operators with a second level specialist being available 24/7 for the entire run time, but it becomes evident that it requires a consistent 24/7 operation for commercial supplies as well. It takes a crew of highly skilled first level operators, second level support specialists and engineers to support uninterrupted operations. In a coupled operation, the avoidance of unforeseen downtimes is key, as transient operating conditions such as

ramp-up and uncontrolled ramp-down are to be avoided wherever possible. In case of a severe process issue a decision considering the generation of waste along the entire chain upon a single malfunctioning unit operation and the ramp-down and re-ramp-up of the entire line needs to be taken into account.

The other point is that operation requires a special attention to a well-managed maintenance and preventative/predictive maintenance procedures as the avoidance of interruptions is critical.
Very long runtimes, as they may be realistic in commercial supply situations, might impose challenges on material buildup in a long and complex chain. This point should be considered in late phase development and continued production support.

Specifically in coupled unit operation setups, the uninterrupted operation is key, as disruptions will have negative impact on multiple unit operations simultaneously. As a flawless operation is not realistic, the availability of repair- and replacement procedures for on-the-fly changes are required and the spares need to be available with guaranteed response times of hours at most.

Lean principles suggest that buffers should be kept to a minimum and supportive of the lead-time. But as time is of the essence for the continued support of the line, both from an equipment and raw material availability perspective, the installation of buffers for both aspects is warranted, as any issue will escalate thru multiple unit operations automatically.

The quality control functions are working in a setting of different process dynamics as there is no appreciable time for offline quality determinations and decisions, the whole concept of pulling samples, analyzing them offline and making well balanced decisions is not feasible in the CM world. Materials are progressing continuously in the line adding value if they are in spec and accumulating losses, if they are outside the CQA. Real-time data acquisition wherever possible is a must and for the cases where direct assessment of the CQAs is technically not possible, the real-time acquisition of surrogates or CPPs and the availability of a model to predict the product performance is key. The importance of QC for the routine supply is likely less compared to batch world and the role of QA is likely more involved to qualify the control systems and structures.

2.4.1. Re-use of lines for multiple purposes

As with any production equipment, the question of amortization and justification of process equipment is key for the financial success of the enterprise. Any reduction in scope of supported products for equipment trains to fewer products will make the justification of the investment more difficult, so reuse of modules is a good way of spreading the installed cost across multiple products. In particular, we need to look into the originator's scenarios decoupled from the generics, OTC and specialty companies. In originators it may be difficult to commit to a specific project in an early phase to be launched out of an entirely new site with new technology at a time where the attrition may still be of relevance. It seems that the commitment to such an investment needs to be timed precisely, taking the attrition risk into account. The design and build time of a plant based on new technology must also take into account the clinical/regulatory pathway to file for approval. Reusable lines in 'launch platforms' help significantly to reduce the risk for this type of major initial investment. That said, to make the concept of flexible facilities work, manufacturing should strive for excellent knowledge of the portfolio and its very specific technical/manufacturing requirements. A balance must be sought between accommodating the portfolio and avoiding overly complex manufacturing line. This requires a significant technical knowledge internally as the expertise outside the big organizations is very limited at this time.

Certain elements for pharmaceutical unit operations are available on the external market, but others are not and system integration into a useful and practical chain is predominantly internal expertise at this point. Making these "hybrid lines" work will require a special engineering capabilities, process development skills and chemical and pharmaceutical development skills to conceive processes and subsequent multipurpose lines that are fit for the portfolio's needs. The establishment of a platform team with interfaces to Development, Operations and Quality is a very efficient way to provide the necessary skills to develop these multipurpose platforms.

2.5. Decision points and criteria

When it comes to CM implementation the fundamental question is: for which projects and which scenarios out of the scenarios discussed previously. For this decision the stepwise evaluation in the sequence given in the table is suggested.

Scenario	Decision point	Criteria
Bin to bin	Process Concept Phase: Which unit operations are most critical within the anticipated process chain and where does CM alternatives hold promise?	Quality, cost of single steps, enabling technology?
	Are the relevant unit ops available in CM?	Risk/benefit analysis for anticipated unit ops done?
	Are all control anchor points defined for the process chain?	Does it support the dossier structure of refining control?
	Development Phase: Are all required scales available?	Equipment development takes significant time and resources.Is time, risk, funding and vendor identified?
	Launch: is the reliability under control/rescue procedures defined?	Runtime demonstrated successfully?
Partial integration in bin to bin	Process Concept Phase: Where does coupling of unit operations gain value?	Does coupling enable unique routes? Does it speed up routes?
	Development Phase: Are the rates of the unit operations synchronized and process windows centered?	Coupling requires sufficient modulation of transformation rates and/or buffers.
	Are startup and shutdown procedures available?	
Integration chemical train	Candidate Selection Phase: Paper feasibility of suitable chemistry	Is the proposed reaction sequence synergistically combinable?
	Development phase: Can a shorter sequence be conceived?	Total cost contribution of sequence to TPC evaluated?
	Launch: Lines available in full scale? Lead times for conceptualization and building identified?	
Integration solid oral train	Is the formulation readily transferable?	No BE risk expectable?
	Are better formulations conceivable for the integrated line?	Immediate next step processing may enable routes that are not feasible in batch.
	Is the full scale equipment	

	adequately available? parallelization vs scale-up evaluated?	
Integration pharmaceutical train	Is the crystallization in CM opening a gate for a better performing DS which can make formulations simpler or processes more robust?	CM crystallization may offer opportunities over traditional crystallization and finishing technologies with impact on DP processes. Has this been looked at?
Total integration	Are there multiple doses that require multiple mass flow scenarios to be coupled?	Matching DS production rate and DP production rate is not trivial and have impact on equipment utilization factors and personnel costs per unit product

The first step is the identification of either the problem to be addressed or the opportunity to be realized (what is the problem/opportunity and why are we considering CM), both in a technical sense and/or in a business sense. In today's world many technical arguments get their value, once their impact has been quantified with a currency as the unit of measure. This should be looked at on a per unit operation basis with the intent of finding the best unit operation for the best project. For these needs/opportunities, the details and consequences need to be elucidated with regards to technical feasibility, equipment availability, process robustness in a long-term operation and cost implications. As the CM approach is new for most processes at the pharmaceutically relevant scales, equipment availability is a key consideration. Larger scale equipment in CM process technology in other industries has a long tradition. Addressing the specific needs of a nascent CM sector of the pharmaceutical industry will require addressing smaller throughputs and defensible GMP approaches.

If a promising solution has been identified, the next level question is to find out if there is opportunity in the coupling of selected unit operations. This topic hinges on the availability of the unit operations *per se* and in the addressing of connecting the sequenced operations (allowing this connected sequence to be characterized as a single, mightier unit operation. For this sequencing, the synchronization of the transformation rates is necessary and either the rate modulation and/or the installation of buffers should be considered to potentially decouple the unit operations temporarily and hence increase the chances for uninterrupted process operations. As long as the material flow starts in a bin and ends in a bin, the quality question can be addressed in batch tradition, if desired, but the CM mode should be considered.

In the chemical area the CM implementation offers a larger opportunity by enabling different routes thru different reactions, which would not have been otherwise executable on a commercial scale. Therefore a holistic approach holds significant promise, but nonetheless the questions discussed before will have to be addressed in sequence. The brave inception of a synthetic route under CM conditions may give access to attractive cases though.

On the pharmaceutical side the main route is the solid oral route starting from appropriate quality drug substance. The connection of well-known unit operations into a solid material flow stream sounds attractive from a risk perspective, but in reality this has considerable technical challenges because of the inherent complexities of the materials' properties. An example potential issue is wall fouling thru material buildup caused by other nonlinear material behavior. Engineering and understanding physical material properties of powders is key to develop robust and efficient CM processes.

The greatest promise and equally the greatest challenge is in the crystallization step, which defines the material properties in a physical sense and hence drives the functionalization requirements for the formulations (formulations are often required to address less than ideal DS material properties. If this step

can deliver against its promise once implemented in CM, the integration of the entire pharmaceutical chain becomes a very attractive scenario, as the functionalization requirements may become shorter or easier to achieve. This should be examined as part of the overall assessment for CM applicability.

As stated previously, the ultimate chain would be a total end-to-end coupling of pharmaceutical and chemical unit operations. The challenge here is predominantly the fact that the production rates of DS and DP are linked to each other via the dose and the formulation. This is solvable for one formulation but becomes trickier for multiple strengths. Also, the inherent complexity of such an integrated chain is significant and a decision should balance opportunities and risks. It has been shown recently in an academic environment that end-to-end coupling can be done technically, but no industrial implementation is known to the authors so far.

3. What distinguishes Continuous Processing from Batch Processing

Several aspects distinguish CM from Batch mode operation:

- CM operates in a uninterrupted way and requires constant supply of materials at given rates instead of given amounts
    - This drives the need for rate-controlled feeders and pumps that allow the necessary precision of the blends
- CM does not allow for routine and frequent resets for equipment cleaning or resetting processes as a batch operation does
    - Reliability evaluation becomes critical for technology selection
- CM needs to operate its equipment flawlessly for extended runtimes
    - Preventative/predictive maintenance and condition monitoring is needed
- CM needs to operate in 3 or 4 shift modes
- Materials in CM are always in motion and there are no holding points to make quality decisions in-between unit operations. The consequences of these aspects are twofold:
    - It allows for the monitoring of processes along the time axis and allows much tighter control of resulting processes
    - It requires excellent control of the processes along the time axis
    - These two statements give two sides of the same coin: it describes the opportunity of intensified control, which is at the same time the necessity to exercise the control. CM gives a much longer lever for the control of processes, which can be good or bad. It is, *per se*, more unstable as it removes the self-stabilizing effect of a batch operation; it exposes the transformation to a much more defined access and hence requires the accurate management of the process. This emphasizes the necessity of a much more intense process understanding to derive this control but gives at the same time a much better handle to manipulate the transformation quality and hence product quality.
- CM allows integration of multiple unit operations
- CM does not have the proven and well-tested equipment base utilized for batch processes in this industry
- CM requires the frontloading technical development of programs and saves material in late phases of development, however a full QbD adoption may balance this a bit.
- CM can offer smaller scale equipment trains relative to batch trains for manufacturing similar quantities

4. What are the key elements of business processes that need to be put in place?

If we think big, meaning a complete adoption of continuous processes from Discovery Chemistry, to Early Phase Development, Late Stage Development, Launches and Commercial supplies, what are the key elements of business processes that need to be put in place in order to streamline the deliveries of each step in order to minimize overall efforts?

CM is basically a toolset to deliver chemical structures in a well-defined quality and efficacy in large quantities to patients.

Steps required in that context are:

- Discovery of new molecules
  - This step identifies structures and verifies their activity on certain receptors, the dose-response-relationship, their absence of toxic side effects in a dose window of interest and the initial verification of efficacy for a lead indication and practically consists of:
  - Definition and supply of fragments of molecules that can be decorated with peripheral structural elements
  - Prototype synthesis based on these fragments in a highly customizable way
  - Scale-up to gram scale to support tox studies for lead structures in a first dedicated synthesis route
- Development of products based on these new structures
  - Identification of possible indications and escalation of verification of efficacy. This is a complex multidisciplinary task involving clinical development to conduct human studies, chemical and pharmaceutical development to create and supply variants of prototype products that meet certain quality requirements for testing in human trials. It is looked at in greater detail in the next section.
  - It is very attractive to implement CM technologies as early in the development process as possible or at least conceive the product in a way that allows later translation of the processes into the CM world easily. Some product designs and formulations can be produced in either way, if they are chosen as the product basis, an early phase commitment to CM can be avoided, but generally it is easier and gives more opportunity, if a product is conceived for CM. If so, at least Phase 2b would be good entry point to have the final process laid out and essentially all technology elements locked in. Entry points past that normally require bridging studies and take time, money and risk.
  - Process development of robust processes for the handover to Manufacturing Operations
- Handover to Manufacturing operations
  - There is little difference from a business process perspective between CM and conventional process equipment. One element that needs to be considered is the timing of the operationalization including ramp-up and learning of an integrated line. Due to the greater complexity and the lesser experience at this point, sufficient investment of time needs to be planned for. The amount of material that needs to be planned for production trials and process qualifications is significantly less than in conventional processes, the timing initially longer. Once more experience base is available, this will be more efficient in either dimension.
  - The other big element to consider is that the field is not well-staffed with vendors of process equipment that is compatible, tested and matured in the field. So, often single sourcing or even customization or custom development of equipment is needed and the subsequent refinement in the field is inevitable. This aspect will fade away over time, but it is a reality for now and needs to be considered in project network plans, in order to avoid predictable delays.
  - As with every new piece of equipment, sufficient improvement mechanisms should be implemented into the introduction phase, the more so as the complexity is higher.
  - As with every new manufacturing technology, great care should be taken to exercise forward planning across the entire portfolio and justify big manufacturing strategies supported by multiple products that are in development. Often decisions are based on business processes that only consider individual product launches, with individual project teams having the ultimate say on a particular product. Without a holistic portfolio oversight at a relevant managerial level any fundamental change of a platform technology is bound to fail. So, it requires senior decision makers overwriting project teams that only evaluate strategies on single projects and set objectives accordingly.
  - Once the initial ramp-up is done, faster response times can be expected, translating to later commitments of large manufacturing orders. This reduces the risk of producing materials that will not be needed in the end due to projects taking unexpected turns.

- Management involvement
    - The added value that CM brings to the business unlocks itself at a variety of levels, some being accessible to direct manufacturing cost evaluations like yield or purity improvement of single steps, some becoming visible at a holistic view of larger sequences (often fewer number of steps) or even total integration. Going one more level up, reduction of lead-times has an impact on risk spend in the development and manufacturing arena, which becomes visible only at a senior management level, not at a project leaders level. And finally, quality improvement and cost of safety and quality systems becomes visible only at the highest level, as it affects the total cost of operations and risk management across a portfolio of products.
    - CM is certainly not a panacea for all cases, but holds significant promise at all of these levels for products that are amenable to CM technologies, and to unlock its full potential for a company it requires support at all these levels. In a context where only at the project level manufacturing cost evaluations for single steps decide if a CM or a batch route will be implemented, significant opportunities on the manufacturing and quality systems level will be missed out.
    - The suggested way forward would be to identify cases that lend themselves in a technically smart way to CM technologies and implement these in a real scenario to gain experience in the higher-level operational aspects. This will help to convert the promise stepwise into realities, make necessary adjustments and develop also the arguments at the managerial level. The secret lies in the selection of the suitable cases.

5. Key functions for development

What are the key functions or disciplines that we need to have in place in order to support development? Are they different from the batch approach?
Fundamentally, changes in technical skills are required to adopt CM in almost all areas and need to be embedded in the groups. In the following table the relevant tasks are introduced and discussed in greater detail.

	Chemical Development	Chemical/Process Engineering	Particle engineering	PAT	GMP supply Unit	Equipment /Plant engineering	Automation engineering	Pharma. /Process engineering	Pharmaceutical Sciences	Reg CMC/QA
Technology development	N1	N2	N3	N4		N5	N6	N7	N8	
Portfolio screening	x	x	x						x	
Lab scale feasibility	N9	N10	N11					N12	N13	
Pilot scale development ready for 1st GMP		x						x		
First GMP supplies	x				N14				x	N15
Full scale pilot scale process development		N16	x	x		x	N17	N18		
Large scale GMP supply	x				N19				x	x

Process qualification		x	x	x	x				x	N20
Process validation/Handover		x	x		x			x		x

Nxx: New and significantly different to batch processes, x: major contribution

In the following the new and significantly different skills shall be discussed:

N1: in Chemical Development, the development of new and CM compatible chemistry has to be brought forward. This comprises the development of new catalysts, reactions that are currently used in Chem. Dev. need to be accelerated to be compatible with CM reactors, new solvent systems need to be developed to avoid solids as much as possible and contribute to the Chemical Engineering team in order to develop new reactor designs. A lot of that can be done externally in academia, but needs to be mirrored internally as well and proven on the real portfolio.

N2: the chemical engineering group needs to partner with the chemists to develop reactor and process technologies and implement the reactors in test stands in routine development and lay out the pilot scale equipment. If model based development is being considered, this is the group that would do it. In N2 these concepts need to be developed and prepared for testing on real cases.

N3: the particle-engineering group needs to focus on continuous crystallization and its opportunities and risks. They also need to engineer equipment variants, periphery and processes, similar to the chemical engineering group, but solely with the focus on crystallization and finishing technologies, which is a significantly different field from batch processes. This is the same approach as N2, but different area of specialization.

N4: PAT scientists can be the same group as that are engaged in batch processes, but the focus needs to be on smaller sample windows, reliability questions like window fouling and a solid standing on non-optical techniques as well. Any new PAT tool needs to be developed, internalized or tested here.

N5: as new pieces of equipment are required for the new process technologies that are not standard, they need to be engineered and built. Even though a lot of these activities may need to be done externally at vendors, intense vendor management is unavoidable thru an internal engineering team.

N6: if more than bin-to-bin unit operations are to be considered, automation engineering becomes a critical component. System architecture as well as programming of the Process Control System becomes critical. Again, involvement of external suppliers maybe the way to go but the internal management of the tasks and system engineering is needed at this stage.

N7: new process concepts in pharmaceutics need to be conceived, equipment defined and conceptualized that can support the process ideas.

N8: the pharmaceutical scientists need to develop streamlined materials based on the process ideas. They need to work hand in hand with N8 process engineers to develop material and processes hand in hand. The more deviation from standard process technologies are conceived, the heavier the involvement of this group.

N9: here the new reactions need to be tested on real portfolio needs and the benefits of new routes need to materialize.

N10: similar to N9, but often new pieces of lab equipment need to be conceived specifically for certain reactions. Good platform technology coverage is a good start, but in practice not always sufficient.

N11: similar to N10, with special focus on crystallization, which is a group in its own due to the complexities of the matter.

N12, 13: same for the pharmaceutical area, certain generic process equipment may be available to be used for feasibility work, but may require significant modification.

N14, 15: requires the release of CM produced material for human use and as such involves the support from QA , RegCMC and the CMU for the new quality management (release) approach that CM requires, if advanced release technologies shall be employed. The operation as such is increasingly different as more steps are integrated. 24/7 operation is a must.

N16,18: both the chemical and pharmaceutical engineering teams need to develop and build new pilot-scale equipment based on the experiences gained during lab scale development, ideally concurrently.

N17: a GMP grade process control system needs to be conceived and built to support a pilot operation as the blueprint for a Manufacturing Operations facility, or one facility is being conceived to serve both purposes of development and commercial supply out of the same. Needs to be balanced with flexibility needs for Development as long runtimes are the norm the higher the degree of integration.

N19: is the proof that a reliable operation can be achieved to supply commercial needs using the CM technology. This requires a good focus on reliability management, preventative maintenance, second level support specialists availability and technical details about the processes and their glitches.

N20: requires the QA/Regulatory support of the late stage activities and management of the authority interactions. As a lot of release and quality management aspects may be different in their details, it requires an open-minded and well networked regulator to entertain the discussion with health authorities to achieve a balanced approval process unifying interests regarding commercial factors, speedy approval process and public health interests.

6. Manufacturing Operations: What is the best manufacturing model: highly decentralized or monolithic plants?

There are several options for Technical Operations models depending on the organizational strategy. As a starting point, most Technical Operations are currently organized by technology – i.e. there is a Drug Substance unit (often called API for small molecule), a Drug Product unit(s) (could be separate units for SOD and injectable), and a Packaging Unit (sometimes part of Drug Product). These units typically have different manufacturing locations, technical and quality support functions, and planning processes. In any implementation of CM, closer cooperation between these units and/or the functions within the units is required. If the objective is total integration of Drug Substance and Drug Product unit operations (discussed above), separate DS and DP organization units no longer make sense. This applies to manufacture (i.e. DS and DP must be co-located) as well as supporting technical and quality functions. This approach will also require a different approach to process design as detailed in prior sections – this might also suggest integrating GMP-based late stage Development into Technical Operations as the most efficient organizational model. At this time, we are not aware of any companies exclusively following this model – partially due to the technical challenges but also likely due to the organizational and logistics challenges. Conversion of marketed products designed for batch processing to end-to-end continuous are likely to require a total re-design similar to what

would be done for a new product. As an intermediate step the hybrid (partial CM) model of CM adoption may be an option of interest to gain experience without involving fundamental risks and could be linked to CM packaging for large markets. Depending on the size of the portfolio, this may also require a single process design/scale-up group serving both Development and Commercial Manufacturing. The role of Technical Support and Quality will also be different in a totally integrated model. Off-line testing is only possible for the raw materials and finished product. All other quality measurements must be done on-line or at-line. Similarly, Technical Support must be delivered on a real-time basis at the point-of-use – taking problems back to a development lab will likely not be an effective strategy. This may require the 'production operator' to also have roles in Quality Assurance and Technical Support (or have QA and Tech Support colleagues side by side with the 'production operators'). Some fundamental policy decisions must also be made – how to handle continuous monitoring of critical parameters when they deviate from specification (i.e. shut down? divert product? continue assuming downstream operations can handle momentary deviations). Also, which function makes these decisions (manufacturing, quality, or technical support)? Shutting down the manufacturing line to deal with a quality or technical issue will be costly and, depending on inventory policy, might lead to stock-outs. Not shutting down might be even worse if the line is producing out-of-spec product.

Companies looking to implement partial continuous processing on a bin-to-bin or individual unit operation basis (1.1 through 1.5 above) can take different organizational approaches. Separate DS and DP units are still possible and may be the most effective. DS and DP sites can also be separate which allows for more strategic locations (especially where in-market manufacture is advantageous) and can reduce risk to supply continuity. Technical Support and Quality can also be divided between DS and DP although, for those unit operations that are CM, some blurring or merging of responsibilities may be appropriate. For new products, it is possible to wait until later in the development process to begin CM implementation. Typically the decisions on which unit operations to convert to continuous are driven by ROI (i.e. bottlenecks, unit operations requiring capital investment, unit operations which cannot be done safely in batch mode, etc.) which may not be obvious in early development. A distributed model with separate Continuous Process Development groups in R&D and Manufacturing can serve this strategy. A single group in manufacturing can also be implemented provided they have access to the process designers in R&D when an opportunity to convert a step to continuous is identified. Most Pharma companies utilize a distributed model as they have sunk capital costs in large batch processing facilities, which are a barrier to wider adoption of continuous processing.

As with batch, manufacturing operations for continuous processing are best located centrally from a technical and productivity perspective as measured by Overall Asset Utilization or Overall Equipment Efficiency. This maximizes utilization and centralizes the requirements for technical support staff. If committed to end-to-end continuous processing for a specific technology with a portfolio of products, construction of a purpose-built continuous processing plant should be justifiable. However, there are many dynamics that argue for distributed manufacturing operations. Given that manufacturing locations with batch processing capacity already exist for most Pharma companies (and many have idle space), the retrofiting of continuous equipment into a batch plant may be the most cost-effective – especially if parts of the batch plant are still operating. This is generally the approach for partial or bin-to-bin continuous processing. Another case for distributed continuous processing can be made in emerging markets where advantages in approval, pricing, or reimbursement can be gained by manufacturing locally. A small-scale, continuous processing module may be cheaper and faster to install than a traditional batch plant. An interesting concept in the CM world is the highly mobile plant in a container. It offers to marry the ideas of multipurpose, highly mobile and modular setups in an interesting incarnation.

6.1. Aspects: technical expertise, know-how generation, know-how protection

One of the key differences between development of batch and continuous processes is the importance of the control strategy in process design and its implementation using real-time principles. In addition to the traditional chemist/biochemist/pharmacist/analyst/engineering skill sets that make up most process development teams in R&D and Manufacturing, Control System engineers, Analysts specializing in Process Analytical Technology (PAT), and statisticians/chemometricians are required. The control strategy is not only critical to quality control (which is true for batch processes) but also for productivity. Within a unit operation, rate and quality control of incoming materials, process conditions, and output must be integrated

into single control strategy. Off-line and even at-line monitoring is often inadequate to maintain process stability. On-line analysis (PAT) to directly measure process attributes as well as multivariate modeling are necessary to maintain stability and predict/avoid/respond to disruptions. This becomes even more critical when linking consecutive continuous unit operations. Project teams must have a broader skill set and be more closely integrated (i.e. harder to break up a process into discreet parts and assign to separate development teams) to deliver continuous processes. Finally, preparation of the CMC package for new filings and process change may require a different approach.

One advantage of developing continuous manufacturing processes is better fundamental process understanding required to control a process. This should increase 'know-how' and reduce process variability throughout the product lifecycle. The organizational challenge is to maintain and grow the process and product knowledge in a way that is readily accessible throughout the product lifecycle. Much of the operating staff are likely to be unfamiliar with high-level control strategies and will require clear documentation and easy access to the control system designers. An effective Knowledge Management strategy will be required to maintain and evolve continuous processes through the product lifecycle.

6.2. Synergies amongst common functions, critical masses for self-propelled excellence

The size and reporting relationship of continuous process development groups varies between companies, as is the case for traditional batch development. While project management can be distributed (R&D project managers responsible for clinical supply manufacture and CMC prep, Manufacturing project managers responsible for technology transfer and launch supply manufacture), Subject Matter Experts need to be closely linked if not part of the same group. If the product portfolio is small and/or the strategy is opportunistic application of continuous processing, a dedicated group of process designers, control engineers, and PAT experts serving all stages of development is likely most effective - essentially a 'center of Excellence' that maintains critical mass. Attempting to have a large group of scientists 'dabble' in continuous processing when it is appropriate for their individual project portfolio is not as effective.

In any scenario, clarity and visible commitment from leadership is critical. It must be clear when Continuous Processing will be applied and, when applied, it should be the primary processing option – not an alternative to batch processing (it will usually lose in these situations). The development roadmap needs to have a gating process to decide early enough in the process about the technology to use for the product and the manufacturing technology proposed to achieve this, be it batch or CM. A predictive data set to quantify the developmental risk involved is a good tool to ensure an aligned approach.

6.3. Lead times

It will take longer to develop a unit operation as continuous process than as a batch process and even longer for end-to-end. It will also require more material to design and tune continuous processing steps; this can be a significant drawback if starting materials are expensive (often the case in early development). However, once developed, a continuous process should have a much shorter lead-time for product delivery and can be dialed in to the required amount as opposed to fixed batch size. For products with low volume requirements to support launch (an industry trend related tin increasing drug potency), continuous processing hardware can be used to manufacture launch supplies (or duplicated if one unit is not sufficient). This can lower the risk associated with technology transfer and scale-up.

6.4. Cost

In general, development of a continuous process will require a larger investment in equipment, time, and materials than a batch process, which can be developed in discreet steps and adapted to existing equipment. However, once developed, a continuous process should be more cost effective than batch (lower variability, higher yield and productivity, smaller footprint, shorter lead-time). Batch processes can have total lead times (from order of starting materials through to release of saleable units) well in excess of 1 year. This requires inventory holding at several points throughout the process, which can quickly add up depending on unit value and financial policies around inventory holding costs. Continuous processes can significantly reduce

lead times and associated inventory costs, even when drug substance and drug product sequences are not linked.

6.5. Consequences for an effective organizational setup

The most important considerations in deciding how to organize are the business objectives. Will processes be end-to-end continuous or only partially so (where justified by ROI)? Will new products be developed with continuous process steps or will successful marketed products be converted post-launch? Will the same process be used for primary and emerging markets (regulatory acceptance and business needs may be dramatically different)? Finally, alignment and commitment of leadership, which will endure through the inevitable learning curve and funding challenges is critical to success.

7. Manufacturing Operations: how can we take advantage of much shorter response times between demand signals and delivery of product? How does that need to be reflected organizationally?

7.1. Aspects: under which conditions can we achieve them and what is the rationale to believe

The short response times enabled by continuous processing can support market segmentation if that is a corporate strategy. For cost-sensitive products (i.e. generics) where quick response to tenders and other market opportunities is key, the ability to manufacture on short notice is a competitive advantage – especially when holding large inventories is the alternative. Continuous processing can also be an advantage for low volume, high value, 'personalized medicines' where inventory holding costs and obsolescence are concerns.

7.2. How do we do technical transfers in comparison to batch?

Technology transfers should be less risky than with batch processes, even though they may be technically more complex and require higher skill levels especially on the control side. Capacity is determined by output (units/minute) multiplied by run time. Output can usually be increased by increasing the size (scale) of the processing equipment but increasing speed or run-length are often better options. Often the 'transfer' is between units of similar size and design thus minimizing adaptation of the process to the equipment. Also, as stated above, a continuous process is typically better understood by the development team, so unexpected deviations during transfer are less likely. Given the smaller footprint of continuous processing equipment, transferring the equipment between locations may be a possibility.

8. Manufacturing Operations: can we/do we want to approach outsourcing or is that business model obsolete and internal manufacture is the way to go in the Continuous world?

Outsourcing is an established element of pharmaceutical supply chains to a varying extent across the industry. To establish continuous manufacturing within the supply chain requires an understanding of current contact manufacturing capabilities, how they are used and what must change to enable continuous processes to be exploited.

It is helpful to deconstruct, in generic terms, a typical pharmaceutical supply chain to understand the extent of the partnership between Pharmaceutical companies and their contract supplier base. A supply chain typically consists of:

1. API synthesis pre-Registered Starting Materials (RSM)
2. API synthesis post RSM
3. Purified drug substance
4. Size reduced drug substance
5. Drug product manufacture.
6. Packaging
7. Distribution

There are very few (no) instances of a small molecule contract manufacturer having the capabilities to fulfill the requirements of all of these and therefore there are multiple handover points. These provide the opportunity to build stock to manage supply security, which in turn adds working capital. Clearly, in an end-to-end supply paradigm, the only outsourcing model that would work is complete outsource of the supply chain. This is unlikely to satisfy the duty of care and quality oversight required and in reality is an undesirable outcome. Therefore the only way continuous processing could be used whilst not internalizing all manufacturing activity is by employing it in each of the different elements and linking those that have most benefit.

8.1. Why do we currently outsource Pharma manufacturing?

There are three main value drivers for outsourcing commercial manufacturing activity:

1. Cost reduction; typically accessed through use of low cost suppliers in emerging markets or by obviating the need for internal capital investment
2. Mitigating business interruption risk; through dual sourcing of critical materials
3. Specialized technologies; accessing expertise and technology that will be used too infrequently to make the necessary investment in capital and expertise development.

The demands during clinical development predominantly drive outsourcing as a means to manage the volume of work and provide flexibility to deliver a more rapidly changing portfolio of products. Access to specialized technology is also a consideration as is the strategic requirement to develop a commercial supply chain and transfer processes and methods to suppliers in advance of launch.

These drivers do not wholly disappear if we consider continuous processing for commercial operations. Whilst it is envisaged the overall cost of supply may be reduced for some products through continuous manufacture, the risk of business interruption remains and some products will require specialized technologies that perhaps are not amenable to CM. Therefore it is realistic to expect that outsourcing will continue to have a place within a Pharma supply chain when continuous processing is established. To consider how it may be used, it serves to deconstruct the generic supply chain and consider the different elements in greater detail.

8.1.1. API Manufacture

The contract manufacturing supplier base for the manufacture of drug substance is relatively mature. Pharma companies have established strong partnerships and have driven closer integration and understanding of the respective needs of the companies involved. The asset base is largely traditional and technical requirements are rarely a major consideration in supplier selection. The technology base has developed in line with the requirements set by the industry. Whilst some contract manufacturing groups have innovated to differentiate their offering, it makes little commercial sense to develop a capability that customers do not seek. As a consequence, contract manufacturers have traditional manufacturing technologies with some traditional continuous capability to deliver hazardous chemistry. It is unrealistic to expect the contract manufacturing supplier base to lead the enablement of innovative continuous processing in API manufacture. The demand must come from the Pharmaceutical Industry together with the necessary incentive to build capability.

Looking again at the generic supply chain, there are a number of ways the different elements are blurred. It is worth considering the impact continuous processing may have on current approaches.

The separation of manufacture, pre and post RSMs may evolve with the maturity of the product. At launch, to mitigate regulatory risk, the same supplier may be used to manufacture stages further back in the synthetic route. As the product matures, RSMs may be manufactured by multiple suppliers to provide security of supply and cost reduction. It is unlikely that a continuous process will bridge the RSM and therefore any push

back on proposed RSM may have a significant impact on supplier selection and how this particular risk is managed.

Manufacturing API with the required physical attributes is typically managed through multiple suppliers. Size reduction contractors do not typically have the capabilities to do drug substance manufacture. The development of continuous crystallization and isolation approaches that deliver the physical properties required for downstream processing would enable single API suppliers to be used.

8.1.2. Drug Product Manufacture

Contract manufacturers specializing in drug product manufacture are less well established and most large Pharma companies typically manufacture drug product internally. This includes the construction and build of drug product manufacturing facilities in geographies to allow market access. Outsourcing of drug product manufacture is usually driven by technology selection and accessing specialist expertise. For simple oral solid dosage forms, the drivers to outsource are relatively low as the contribution to cost of goods is low and the quality risk greatly increased.

8.1.3. Conclusions

It is likely a mixed model of outsourcing and internal manufacture will persist as a consequence of the existing business risk and specialist technology drivers being unchanged by a continuous processing approach.

It is unlikely to expect innovation from the contract manufacturing supplier base in the absence of a lead from large Pharma. Investment in a new asset base without confidence of a return on the necessary investment is considered unlikely. Therefore, Pharma will have to lead innovation and create a demand that contractors can respond to.

The approach to de-risking RSM selection may have to change depending on the way the synthetic route is designed. There may be increased opportunities to simplify the supply chain by engineering the required drug substance particle properties using continuous methodologies.

9. What the Industry Should Do and Timing

9.1. First applications of continuous

The industry is driven by the maximization of benefit and the minimization of risk in every field. It can support enormous investments, if the risk-benefit ratio is healthy. The task is to identify the best contributions of benefits vs the minimal risks, both technical and business-wise. In that context, certain unit operations both in chemistry and pharmaceutics open new avenues of possibilities that are not accessible using classical technologies. Identifying and implementing solutions for these would be a useful first step, in other words, harvesting the lowest hanging fruits first. Not dogmatic, but search and implement opportunities, which require few investments and while being able to deliver quality and timing benefits. A group size of 10 people per discipline, which is highly networked and a time horizon of 5-10 years is the minimum required to make substantial progress and tangible implementation feasible.

9.2. Platforms versus dedicated

Dedicated manufacturing platforms make sense only for large volume productions. Multipurpose platform solutions are more demanding in terms of engineering as they need to be more versatile and the chemical requirements are molecule dependent, not indication or market size dependent. This means that the investment strategy needs to take the payback over a portfolio into account, whereas in blockbuster times the investment could be amortized against a single product. Profound knowledge of the portfolio is helpful in this context to support the platform approach for new molecules. A less risky way into the CM field is the stepwise conversion of existing products, if the company has enough large-scale products that justify the conversion as

a lifecycle management tool. The current pipelines in most companies are holding multiple smaller indication candidates instead of classical blockbusters with huge production volume requirements, so the recommendation is clear on the platform side with good flexibility as design goal.

9.3. Where to go next

It is helpful to have a clear strategy on which problems need long-term commitments because the technical challenge will take a while to solve and where short-term progress can be accomplished. Particularly helpful is to have the two aspects converge, meaning to lay out a long term plan, where the short term elements fit in as we implement them. More specifically, the long term plan needs to provide answers about the manufacturing model (internal vs. external, monolithic vs decentralized or even highly localized with high priority, as this drives the direction a company wants to go long term. This will then set the frame towards a smart and effective implementation plan, where each step done is a step towards that goal.

As an intermediate step it should be considered to get practical experiences in certain CM elements and explore the QA and RegCMC consequences and procedures and develop together with these disciplines routines that allow smooth implementations without risking delays in approval times due to completely new Q and Reg approaches on the occasion of a new molecule.

9.4. Aspirational Vision

The aspirational vision for CM from a technical perspective can be no less than the full integration of all relevant chemical and pharmaceutical steps into one relatively small plant or on the same token it could be driven towards highly decentralized manufacturing plants almost like a franchise model. The first may be highly attractive from a variety of perspectives (manufacturing cost, quality oversight, total quality management, lead times etc.), however is counter to a local manufacturing approach, which is pushed from certain political powers to gain manufacturing businesses for market access but may follow also a decentralized risk approach. The boundary conditions are obviously not only technical and economical, but also highly political, as due to the tremendous size reduction of the process equipment the geographic point of value generation can be decoupled easily from a firm bricks and mortar commitment, ending up in much more flexible setups of operations. And finally, one cannot short-sell the regulatory risks. While the FDA and, to a lesser extent, the EMA, may want to facilitate the use of continuous processing, most other regulators around the world are years away. CM does not offer a half way position, and most companies will not want to offer a CM approach for the US and EU and a batch process for other regulators.

Distilled down to its core essentials, CM is basically a technical progress that reduces size of process equipment and manages quality in a different way. The consequences and opportunities of that can be tremendous. The size reduction of mobile phones in the early nineties from portable shoeboxes to pocketable matchboxes transformed our life and the telecom business. Today's big names in telecom were not existent twenty years back and the whole infrastructure and business model had changed. However, the total cost per household spent on communication effectively went up and that money is harvested in different business processes. If a company wants to think in the really big picture, the sky is the limit in CM.

We acknowledge all of those who made helpful comments at the symposium.