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Continuous Processing in the Manufacture of Active Pharmaceutical Ingredients and Finished Dosage Forms: An Industry Perspective

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ABSTRACT: Continuous manufacturing as a way of producing fine chemicals, active pharmaceutical ingredients, and finished dosage forms is gaining widespread attention. Although potential benefits over traditional batch-wise production have been discussed at many occasions and appear evident, continuous processes are only slowly being implemented. The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable has defined "continuous processing" as one of its research priorities[1] and performed a survey of its members' opinions, the status of implementation, and perceived hurdles blocking implementation of continuous manufacturing processes. Here we discuss the most important results of this survey and their relation to present trends in this industry to "go green".

INTRODUCTION

In 2005, the American Chemical Society (ACS) Green Chemistry Institute (GCI), and several global pharmaceutical corporations founded the ACS GCI Pharmaceutical Roundtable (hereafter referred to as the Roundtable). Currently, the Roundtable consists of 15 corporations including Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Codexis, DSM, Dr. Reddy's, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Novartis, Pfizer, Roche, and Sanofi. The activities of the Roundtable reflect the joint belief that the pursuit of green chemistry and engineering is imperative for a sustainable business and environment. After defining "continuous processing" and "process intensification" as "Key Green Engineering Research Areas for Sustainable Manufacturing", the Roundtable members decided to perform a survey on the status of implementation of "continuous processing" within the Roundtable member organisations.

Observations and statements have been collected to reflect the status of implementation of continuous manufacturing principles and to elucidate their opinion on stakeholders, fields of application, and potential hurdles. The eight largest pharma companies (covering approximately 40% of the global pharmaceuticals market volume) and one supplier of intermediates and active pharmaceutical ingredients (API) contributed to the survey. The survey results, together with an overview of the state of the art and an analysis of the stakeholders to install continuous processing were presented to the roundtable members. This paper contains the stakeholder analysis and the survey results.

CONTINUOUS MANUFACTURING: STAKEHOLDERS/PLAYERS

Implementation of continuous processes in pharmaceutical manufacturing appears not (yet) standard practice. We compiled observations and opinions of representatives of the member companies on who in their opinion would actually drive or enable the implementation of continuous processing and how pronounced the effect of the respective party on the pharmaceutical industry is. Three groups of companies are seen to act as drivers:

(1) Equipment manufacturers and manufacturers of analytical equipment.
(2) API and intermediate or secondary (toll) manufacturers with a focus on cost-effective processing and engineering expertise.
(3) Large pharma companies[2] with in-house production of strategically important steps (API, formulation).

Equipment Manufacturers. There are quite a few equipment suppliers on the market. Two main categories are distinguishable: the traditional manufacturers of often larger-scale, continuous process equipment such as Heatric, Rousselet Robatel, or Alfa Laval and the newer ones focusing on "flow chemistry" using mainly micro- or milli-scale technology such as Corning, IMM, Ehrfeld Mikrotechnik, or Chemtrix.

Several of the "flow chemistry" companies initially started developing laboratory equipment, and it was not clear how successful results in the lab could be realized on the pilot or manufacturing scale. There now seems to be a trend among the "flow chemistry" companies to address the scale-up by producing pilot-, and small commercial-scale, equipment. However, there is still a question concerning how reliable the scale-up will be from small-scale lab equipment to manufacturing. Some companies, e.g. Corning, are advocating combinations of scale-out (numbering up) and scale-up as the solution. This has led to modular reactors that can be parallelized. Technical challenges associated with this approach such as the high numbers of connectors between the flow elements and the problem of exact flow distribution have been overcome.

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Another weak link is the workup or downstream processing. Most "flow chemistry" companies market reactors, and there is clearly a lack of small-scale extractors, distillation units, crystallizers, etc. as models for pilot-plant or production-size equipment. Consequently a significant number of scale-up errors have occurred in the workup sections of the respective production steps, especially in solids handling.

Manufacturers of Analytical Instruments. Several suppliers of analytical instruments (Solvias, Bruker, Mettler Toledo, and others) have adapted their existing spectrometers for use as inline process analyzers. For continuous reactors the same type of inline analysis equipment can be used with batch reactors or on pipes with process fluids. Temperature and/or pH is often a good indicator at steady state, but sometimes that is not enough. Since there often is a need for fast/immediate answers, especially during start-up and cleaning, spectroscopic techniques are particularly suitable. From a GMP standpoint, continuous monitoring may provide proof-of-batch homogeneity and also allow for quality control during start-up and shutdown (e.g., signaling when a fraction of the flow meets, or does not meet, the predefined criteria).

Presently, very few examples of a closed feedback loop from an inline measurement to a quality relevant process control element in a continuous pharmaceutical manufacturing process are known.

API and Intermediate Manufacturers. Early adapters among API and intermediate custom manufacturers have implemented continuous flow processes in a c-GMP batch plant environment. Driven by the need to perform hazardous chemistry in such an environment at acceptable cost, these manufacturers have developed continuous processes to keep the holdup of hazardous materials or reaction mixtures small.[3] In these cases continuous downstream (DS) processing until a "safe" reaction mixture is reached is an integral part of the process.

Several companies offer continuous options for DS process development; however, the range of options appears to vary quite significantly from implementation of microreactor technology to the possibility of developing more advanced combinations of reactors and workup solutions.

It is sometimes difficult to get a good understanding of how experienced and well-equipped the manufacturing companies are in reality when it comes to developing continuous stages or processes for pharmaceuticals. The availability of the technology is not necessarily a good measure of the development capability, and there may also be gaps in what technology is available on a particular scale.

Another point of attention is the potential mismatch of technologies that may occur when a process development organisation transfers a processes, developed with a specific technology, to a manufacturer with different technical solutions, e.g. when a reaction has been developed on chip and must be transferred to another type of continuous reactor.

Large Pharma Companies with Inhouse Production of Strategically Important Steps (API, Formulation). There is clearly a significant interest in continuous processing among the large pharma companies both in terms of drug substance and drug product. Essentially each large pharma company has installed a dedicated group within Research and Development acting as champion to implement continuous processes. The size of investment and degree of implementation appear to vary significantly.

An interesting question is how the different pharma companies view continuous processing. Is it possible to get a significant competitive advantage in terms of manufacturing cost or a minor opportunity as a complement to traditional batch manufacture?

In the following, the single questions of the survey and their results are discussed. First a technical background of each question is given, to put its results and single comments into context.

QUESTION: DOES YOUR COMPANY INVESTIGATE, DEVELOP, OR USE CONTINUOUS PROCESSES?

Background: Manufacturing of Pharmaceuticals. The pharmaceutical industry is among the most innovative branches when it comes to inventing and developing new chemical lead structures, as well as embodying new therapeutic approaches and concepts. For the last 50 years this industry has developed cures for a wide range of ailments, albeit with a considerable number of diseases still presenting significant challenges and constituting areas of unmet medical need. Until recently the drivers for large manufacturers of pharmaceuticals to invest in improved production methods have been moderate to weak. Only lately, questions related to the sustainability of the development, production, and application of medicines have come into the focus of public discussion.

Regulatory authorities such as the United States Food and Drug Administration (FDA) have started to issue documents (guidelines) that assist the industry on their way to develop more sustainable manufacturing and that allow for a continuous improvement process.

Continuous Processing. One concept to improve manufacturing is shifting to continuous as opposed to the classical batch mode. In a continuous process to manufacture a product from starting materials, continuous flows of components enter and leave the manufacturing installation at defined entry and exit points and in between are subjected to well-defined sequences of conditions as they move continuously on a predefined path through different parts of the installation. This production concept differs significantly from the presently used batch mode of primary and secondary manufacturing. In 2005, Roberge et al. published a critical review of the advantages and disadvantages of large-scale continuous processing of fine chemicals.[4]

Survey Results. All responding companies have experience in continuous processing. Eight of nine companies have taken a continuous process to the pilot plant or even to production scale.

QUESTION: IF YOUR COMPANY HAS INVESTIGATED CONTINUOUS MANUFACTURING, AT WHICH STAGES OF THE PRODUCT LIFE HAS IT BEEN USED AND WHY?

Background. The design and implementation of continuous processes for the manufacture of pharmaceutical intermediates, APIs, or even drug products are a truly multidisciplinary effort. It starts with "route scouting" to define the most favorable among a number of possible routes to reach a target molecule. It requires a thorough understanding of each single-chemical transformation on molecular level, covers the knowledge of the kinetics of the desired and competing reaction pathways including factors such as activation enthalpy and -entropy, and reaction enthalpy. From these data the

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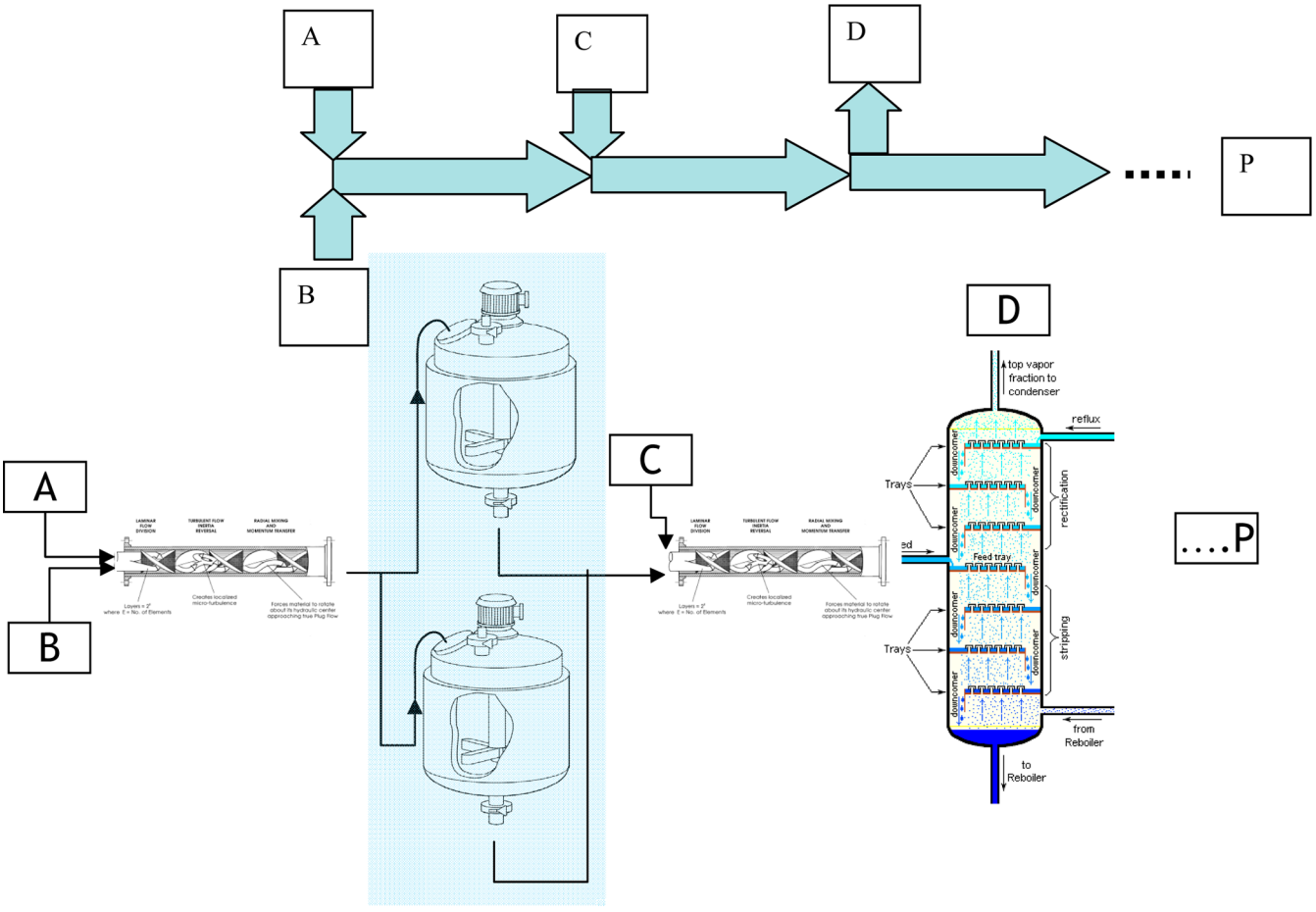
Scheme 1. Integration of devices for continuous processing into existing plant infrastructure



susceptibility of the reaction to deviating reaction conditions such as deviating stoichiometry, temperature, or concentration of components of the reaction mixture are derived. This leads to performance requirements for the reactor in which the desired reaction is intended to run. This finally leads to required reactor features such as mixing speed, heat removal, residence time distribution, and others. It also leads to requirements regarding the control accuracy and speed of feedback loops. Consequently, stakeholders of very different disciplines are engaged in implementing a continuous process.

Survey Results. The reasons to implement a continuous process at a certain point in time during drug development vary, depending on the development status. It is generally agreed that throughout the whole development trajectory the main reasons to implement continuous processing are the following:

- to increase speed, simplify scale-up
- to increase throughput
- to increase variation, parameter space
- to improve safety
- to use hazardous reagents.

Later in development, when it comes to freezing the production process, further reasons appear:

- avoid process changes
- minimize investment
- improve process control
- reduce cost, reduce waste

Interestingly, the strongest drivers appear to be reduction of cost and waste, improvement of safety, and the ability to use hazardous reagents on all scales. This reflects the fact that continuous processing is seen as a means to "green" production processes. The "greening" of production processes by employing continuous processing has been demonstrated in several cases as exemplified by a decrease in "process mass intensity" (PMI).

QUESTION: IN WHICH PRODUCTION STEPS DO YOU USE CONTINUOUS MANUFACTURING?

- In primary (API) manufacturing?
- In secondary manufacturing (formulation)?
- In non-cGMP steps?
- In cGMP steps?

Background: Integration of Continuous Steps into a Pharmaceutical Production Process. Hardly ever will a fully continuous plant simply replace an existing batch plant; as the benefit of replacing a batch step by a continuous step heavily depends on chemical and physical parameters, there will be single steps or unit operations that will profit enormously and others that will hardly profit at all. Thus, a stepwise implementation of continuous operations tackling the most profitable, low-hanging fruits first will be most straightforward way to proceed. Conventional vessels will be used as hold-up tanks, probably in pairs to simplify analysis, batch definition, and batch release. "Active" parts of the plant such as mixing,

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heating, cooling, or extraction devices will be entered in between the vessels (see Scheme 1).

Continuous Workup. Next to having starting materials react in continuously operated equipment, an increasing number of workup operations are done continuously: extractors and phase separators, centrifugal extractors, distillation columns, belt filters, and plate driers are by their nature continuous processing equipment.

The dominant separating force in many separation principles (extraction, distillation, flotation) is gravity. Gravity (actually the weakest fundamental interaction) puts a limit on miniaturisation; as its force loses its dominant role in a small structured environment to capillary forces or effects of surface tension, devices using centrifugal forces or hydrophilic/hydrophobic interactions have been developed.

Survey Results on Application of Continuous Processing. There is agreement among the respondents that continuous processing has to be applied both in c-GMP and non-cGMP production steps and both in primary and secondary manufacturing. There are trends to design "fully continuous" production processes covering both primary and secondary manufacturing steps.

QUESTION: WHAT ARE THE BIGGEST HURDLES THAT YOU HAVE EXPERIENCED OR EXPECT IN THE IMPLEMENTATION OF A CONTINUOUS PROCESS?

Background. Already in August 2002 (10 years ago), the Food and Drug Administration launched a new initiative "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach".[5] It encouraged the industry to "use [...] scientific advances in pharmaceutical manufacturing and technology", that would, among other consequences, "ensure [...] product quality and performance through the design of effective and efficient manufacturing processes". As shown above, the industry has established internal advocate groups and worked on "proofs-of-principle" to show that continuous manufacturing in a pharmaceutical environment is feasible, but it has not been adopted as widely as anticipated by its proponents.

Survey Results on "Hurdles to Implementation". The number one hurdle (seen by two-thirds of respondents) appears to be concerns of major investment in new technology while sufficient capacity of conventional batch plants is available. Therefore, existing batch plants that are in operation to produce intermediates or APIs are hardly ever replaced by installations producing the same products in continuous mode, even if there are benefits related to process efficiency.

Further hurdles relate to an uncertainty whether a continuous process option will deliver sufficient benefit to justify its implementation (4 of 9 respondents). This relates to a commonly felt lack of personnel with adequate competencies to develop and implement continuous processes for fine chemicals in c-GMP environments. Indeed, the present education does not cover all required skills to do this, and therefore most industries had to form multidisciplinary internal advocate groups to pinpoint and develop continuous options of selected production processes. Financial issues and mergers and acquisitions in the pharma and fine chemicals industry have distracted the industry's focus from these initiatives.

Specific commentaries by respondents point to technical difficulties with presently available systems (leaking; insufficient technical maturity) and to a lack of equipment at different scales: laboratory equipment is available, pilot-plant-scale and larger-scale equipment is not.

Further commentaries link the reluctance to apply continuous processing to the nature of the drug development process itself.

The synthesis of a successful compound entering clinical trials has many features initially required to create diversity on very small scale. Consequently, it is hardly ever the best way to synthesize the potentially successful compound on larger scale. Nevertheless, even a suboptimal synthesis does not mean a bottleneck or a roadblock to continued, early-stage pharmaceutical development. Almost every milligram-scale synthesis will, with acceptable effort, also deliver single-kilogram amounts of a desired substance. These suboptimal processes are sometimes taken further for production of larger volumes. The reasons behind this are diverse. In the early phase, resource is often minimized as the attrition is large and the timelines are tight. Later on it may be decided that the process is "good enough" and that major changes cannot be justified.

QUESTION: HAVE REGULATORY AUTHORITIES SUCH AS THE FDA DISCUSSED WITH YOU OR AUDITED THE IMPLEMENTATION OF A CONTINUOUS PROCESS UNDER C-GMP CONDITIONS? RESULT?

Background: Authorities' Positions on New Manufacturing Concepts. Authorities such as the FDA and European Medical Association (EMA) have pointed to improvement potentials of pharmaceutical manufacturing processes.[6] Special emphasis has been put on

- the way pharmaceutical processes are developed
- the improved management of risk related to the quality of the produced pharmaceuticals
- streamlined quality control systems.

The respective guidelines Q8, Q9, Q10, issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), detail ways to set up and operate reliable high-quality pharmaceutical production systems. The basis of compliance with all of these guidelines is a sound scientific understanding of the manufacturing process of a drug product.

Continuous manufacturing is seen as one way to improve both the quality and the efficiency of pharmaceutical manufacturing processes. The most striking difference between batch-wise and continuous manufacturing from a regulatory viewpoint is the fact that a continuous process does not automatically generate "batches" or "lots" of product. So if a quality assurance concept of a manufacturer is based on the release of "in-spec batches" after passing a defined set of analyses, the manufacturer has to define a "batch" or "lot" based on current regulation.

Survey Results: Discussions with Regulatory Authorities. One third of the respondents' companies have up to now (end of 2011) discussed continuous processes with regulatory authorities such as FDA. Most of these report generally supportive behavior in discussions.

The FDA has already accepted of filings with CMC sections disclosing continuous processes, and the FDA foresees significant changes in the production and quality control of pharmaceuticals in years to come.

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CONCLUSION

The pharmaceutical industry is well aware of the impact of their production processes on the sustainability of their operations. Continuous processing is seen as one option to improve in this field, and consequently most large pharma companies have installed groups acting as internal champions to develop and implement continuous processes. Guidelines by authorities generally support the implementation of new production technologies. Continuous processing is not yet generally applied wherever advantageous. The main reasons as detailed above are in the nature of the development process and an uncertainty about required investment in the presence of idle batch capacity.

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Notes

The authors declare no competing financial interest.

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