Equipment and Analytical Companies Meeting Continuous Challenges May 20–21, 2014 Continuous Symposium

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ABSTRACT: This white paper focuses on equipment, and analytical manufacturers' perspectives, regarding the challenges of continuous pharmaceutical manufacturing across five prompt questions. In addition to valued input from several vendors, commentary was provided from experienced pharmaceutical representatives, who have installed various continuous platforms. Additionally, a small medium enterprise (SME) perspective was obtained through interviews. A range of technical challenges is outlined, including: the presence of particles, equipment scalability, fouling (and cleaning), technology derisking, specific analytical challenges, and the general requirement of improved technical training. Equipment and analytical companies can make a significant contribution to help the introduction of continuous technology. A key point is that many of these challenges exist in batch processing and are not specific to continuous processing. Backward compatibility of software is not a continuous issue *per se*. In many cases, there is available learning from other industries. Business models and opportunities through outsourced development partners are also highlighted. Agile smaller companies and academic groups have a key role to play in developing skills, working collaboratively in partnerships, and focusing on solving relevant industry challenges. The precompetitive space differs for vendor companies compared with large pharmaceuticals. Currently, there is no strong consensus around a dominant continuous design, partly because of business dynamics and commercial interests. A more structured common approach to process design and hardware and software standardization would be beneficial, with initial practical steps in modeling. Conclusions include a digestible systems approach, accessible and published business cases, and increased user, academic, and supplier collaboration. This mirrors US FDA direction. The concept of silos in pharmaceutical companies is a common theme throughout the white papers. In the equipment domain, this is equally prevalent among a broad range of companies, mainly focusing on discrete areas. As an example, the flow chemistry and secondary drug product communities are almost entirely disconnected. Control and Process Analytical Technologies (PAT) companies are active in both domains. The equipment actors are a very diverse group with a few major Original Equipment Manufacturers (OEM) players and a variety of SME, project providers, integrators, upstream downstream providers, and specialist PAT. In some cases, partnerships or alliances are formed to increase critical mass. This white paper has focused on small molecules; equipment associated with biopharmaceuticals is covered in a separate white paper. More specifics on equipment detail are provided in final dosage form and drug substance white papers. The equipment and analytical development from laboratory to pilot to production is important, with a variety of sensors and complexity reducing with scale. The importance of robust processing rather than overcomplex control strategy mitigation is important. A search of nonacademic literature highlights, with a few notable exceptions, a relative paucity of material. Much focuses on the economics and benefits of continuous, rather than specifics of equipment issues. The disruptive nature of continuous manufacturing represents either an opportunity or a threat for many companies, so the incentive to change equipment varies. Also, for many companies, the pharmaceutical sector is not actually the dominant sector in terms of sales. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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PREDICTIONS FOR TAKE-UP OF CONTINUOUS EQUIPMENT IN PHARMA ACROSS SUPPLY CHAIN

Overview

Many large pharmaceutical companies have an internal advocacy group pushing the development of continuous processes

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and installation of equipment for continuous operation. Most have worked on showcase examples of continuous processing. There are a small, but growing, number of US FDA filings describing continuous manufacturing steps.

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

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

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

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

Cost

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

1. Creating suitable platforms for future drug development with an expectation of future benefits
2. Investment based on a current business case with "near-term" payback

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

Hence, the recent traction in secondary processing has been driven by the creation of smaller-scale equipment, which has specifically been designed in order to minimize the amount of material required during development. Many major pharmaceutical companies are "investing" in continuous flow (e.g., GSK, Novartis, Pfizer, Lilly, and Abbott). Continuous flow, however, is not universally viewed as "the way" to do small-molecule development, scale-up, or manufacturing. Currently, it appears that although many pharmaceutical companies have taken efforts to adopt continuous chemistry over conventional batch, they will only move forward if the financials are highly favorable.

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

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

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

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

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

A compelling business case has been developed at Pfizer and other for the development and deployment of modularized continuous drug product manufacturing, which is attracting the interest of other leading pharmaceutical companies.

Miniaturized and modularized API manufacturing is a vision for future demand where it makes sense, but probably driven less by the demands of personalized medicine than drug product would be. Tax considerations will continue to complicate the picture for portable API manufacturing with access to markets and incentives additional factors.

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