WATSON MARLOW
Fluid Technology Group

Watson-Marlow on Continuous Processing

The Quest for Efficiency – Moving Towards Continuous Processing

Contributor:

O'HARA TECHNOLOGIES

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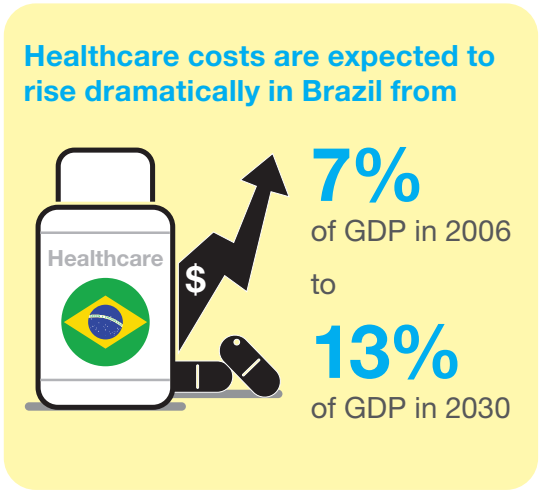
PREFACE

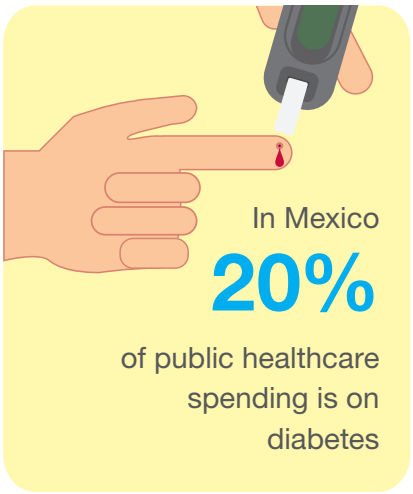
By John Milne, Training Director at the National Institute for Bioprocessing Research and Training; Jim Marjeram, Technology Director at O'Hara Technologies; and Chris Palmer, Tubing Product Manager at Watson-Marlow Fluid Technology Group.

Today the pharmaceutical industry faces the challenge of an aging population. Life expectancies across the developed world are increasing, thanks to growing wealth and better medicines. Germany's average life expectancy has increased by over 10 years since 1970[1] and in Latin America the increase is dramatic, with average life expectancy increasing by almost 20 years since 1960[2]. One consequence of people living longer, combined with rising GDP, is that an increasing number of patients are now living with chronic, complex conditions, such as heart disease, Alzheimer's and Type II diabetes.

In the US, these are some of the most common causes of death, with millions more patients living with these diseases[3]. Rates of diabetes in Mexico are increasing at three times the rate of population growth and almost 20% of public healthcare spending is on diabetes[4].

In Japan, on average men suffer from at least one serious disease during their last nine years of life, while women suffer from at least one serious disease during their last twelve years of life[5].





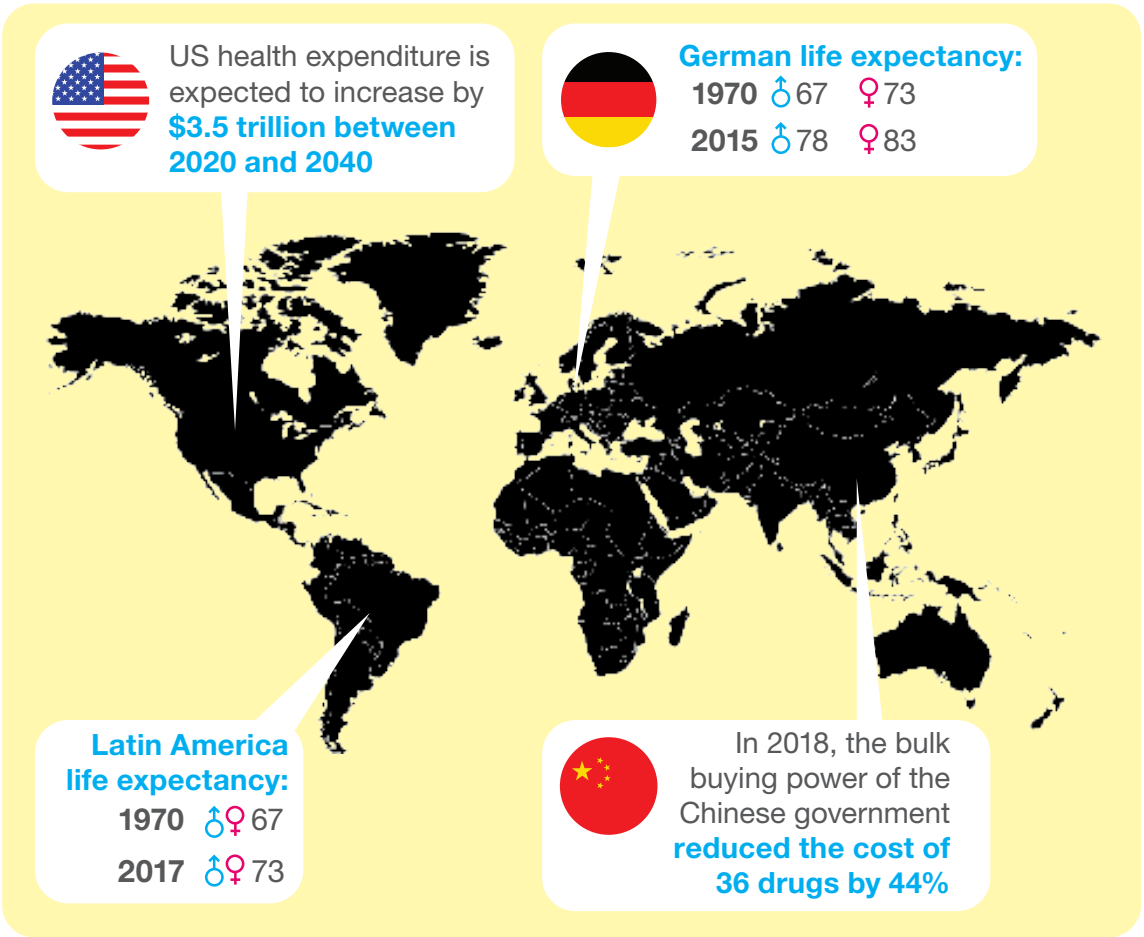
The expense of treating these patients is putting pressure on healthcare systems who, in turn, expect pharmaceutical companies to supply medications at lower costs. This is especially true in Europe and Japan where government funding restrictions mean severe constraints on drug reimbursement prices[6].

US health expenditures are projected to increase by **$3.5 trillion between 2010 and 2040[7].** In Brazil, healthcare costs are expected to rise dramatically from **7% of GDP in 2006 to 13% of GDP in 2030**[8]. Developing countries, which tend to focus more on the production of affordable generics[9], are also experiencing pressure on drug prices. In 2018,

the bulk buying power of the Chinese government enabled it to reduce the cost of 36 drugs by 44% in order for these drugs to be covered by government insurance. Similarly, India, as the world's leading provider of generics, encourages competition between pharmaceutical companies which places additional pressure on drug prices[10].

The pharmaceutical industry is responding through process intensification, a concept that dates back to the 1970s. Through novel technologies and new processing techniques, the aim is to reduce timelines, cut costs and increase efficiencies[11]. Among the methods increasingly being adopted is perfusion cell culture, also called upstream continuous culture.

Originally developed in the 1980s, perfusion involves constantly removing cell-culture fluid from a bioreactor while adding fresh media[12]. When compared to fed-batch processing, perfusion produces greater product yields with better lot-to-lot consistency in products[13,14]. In the future, both upstream and downstream processes in biomanufacturing will happen continuously and with high degrees of automation.



PureWeld XL TPE Tubing

WHERE IS CONTINUOUS PROCESSING TODAY?

Continuous processing is common in many industries, but – due to regulatory concerns – has only been taken seriously by pharmaceutical companies in the last five years. The aim is to reduce the costs of biomanufacturing by reducing down-time between production lots resulting in greater productivity. In a survey of senior executives from biopharmaceutical companies, around 20% saw improvements to some aspect of upstream and downstream manufacturing as a consistent concern to the industry[9].

A fully continuous system seamlessly integrates upstream and downstream processes to generate a constant flow of product. Downtime between batches is reduced and manufacturing plants can be smaller if only small amounts of product are created at a time, whilst ultimately delivering greater total product. In particular, facilities can dispense with storage tanks to hold culture and media between processing steps.

Perfusion processing is becoming increasingly popular with **33.2% of biomanufacturers keen to test continuous perfusion** within the next 12 months[9]. One advantage is that cell culture is continuously bled off a bioreactor in small quantities, allowing for downstream processing in lower volumes than in a traditional fed-batch process. In addition, perfusion culture processes can be longer in duration, reducing time for cleaning, and product quality remains more consistent as a result. Smaller production bioreactors can also typically be used in perfusion cultures when compared with traditional stainless steel bioreactors. This also has an immediate impact by reducing the required cleaning validation burden.

CONTINUOUS PROCESSING: REGULATORY AND QUALITY CHALLENGES

With traditional bioprocessing techniques, drug batches usually take 2 to 14 days to produce. Continuous processing allows for longer runs before the equipment is changed – sometimes as long as 90 days. These longer process cycles create challenges for pharmaceutical companies, such as maintaining the sterility of equipment, meeting regulatory requirements, and checking product quality.

Among the challenges in continuous processing is ensuring product quality is maintained throughout a longer process cycle. Part of this involves maintaining the sterility of the equipment, which has encouraged manufacturers to move towards closed, automated systems with minimal human intervention. Operator intervention is the largest potential source of contamination and error in biomanufacturing processes.

Manufacturers are also adopting single-use systems, which arrive pre-sterilised to reduce cleaning validation. Some plastic tubing and pumps used in single-use systems are designed for pumping cycles lasting only a few hours, but – in continuous processing – the system must withstand high flow rates and pressures for hundreds of hours at a time (see Ensuring High Performance case study, page 11).

In addition, there are a wide range of engineering challenges to implementing continuous processing. One aspect to consider is the multiple process systems, typically supplied by different vendors and operating at different flow rates and pressures, which need to be connected together in an integrated fashion. Fluid flow through the bioreactor and associated integrated downstream systems needs to be carefully controlled through the entire process, and this will require more standardised automation solutions and more complex flow control systems. When productivity is significantly increased upstream due to continuous processing, downstream activities must keep pace to avoid bottlenecks.

Companies must also mitigate for risks and potential disruption of the biomanufacturing process due to, for example, disruption to the facility's water supply. They may need extra pre-prepared buffers and processing solutions to keep the process running, but this requires additional storage within the biomanufacturing facility. Newer technologies, such as inline dilution where concentrated stock buffers that can be prepared and diluted when required, are being developed by vendors, and should make a considerable impact in the near future.

Meeting regulatory requirements is also a challenge for manufacturers. Although regulatory bodies, such as the FDA and EMA, have generally been supportive of advanced manufacturing techniques[15], there are no specific regulatory guidance for qualifying single use systems for drug manufacturing. As a result of this gap in regulations, there are a number of industry bodies who have provided best practice recommendations and standards to the market.

However, there still remain challenges around sterility, sampling, and extractables/leachables in single-use systems. In particular, there is greater concern in Western Europe where **17.1% of respondents to a recent Bioplan report cited "Leachables and extractables are a concern", compared to 7.1% in the US**[9].

This concern could be further exacerbated by materials being in contact with the drug product for a longer duration, potentially resulting in more leachables being released by the single-use systems during continuous processing. As a result, there's a greater onus on drug manufacturers to ensure that single-use components used are biocompatible and traceable throughout the production process, and that the extractable/leachable profile of the single-use component is risk assessed for the company's product fluid stream. Suppliers of single-use components can help here by testing their products and supplying documentation to the end user to support their risk assessments and regulatory submissions.

Regions reported concern on leachables and extractables

Europe
17%

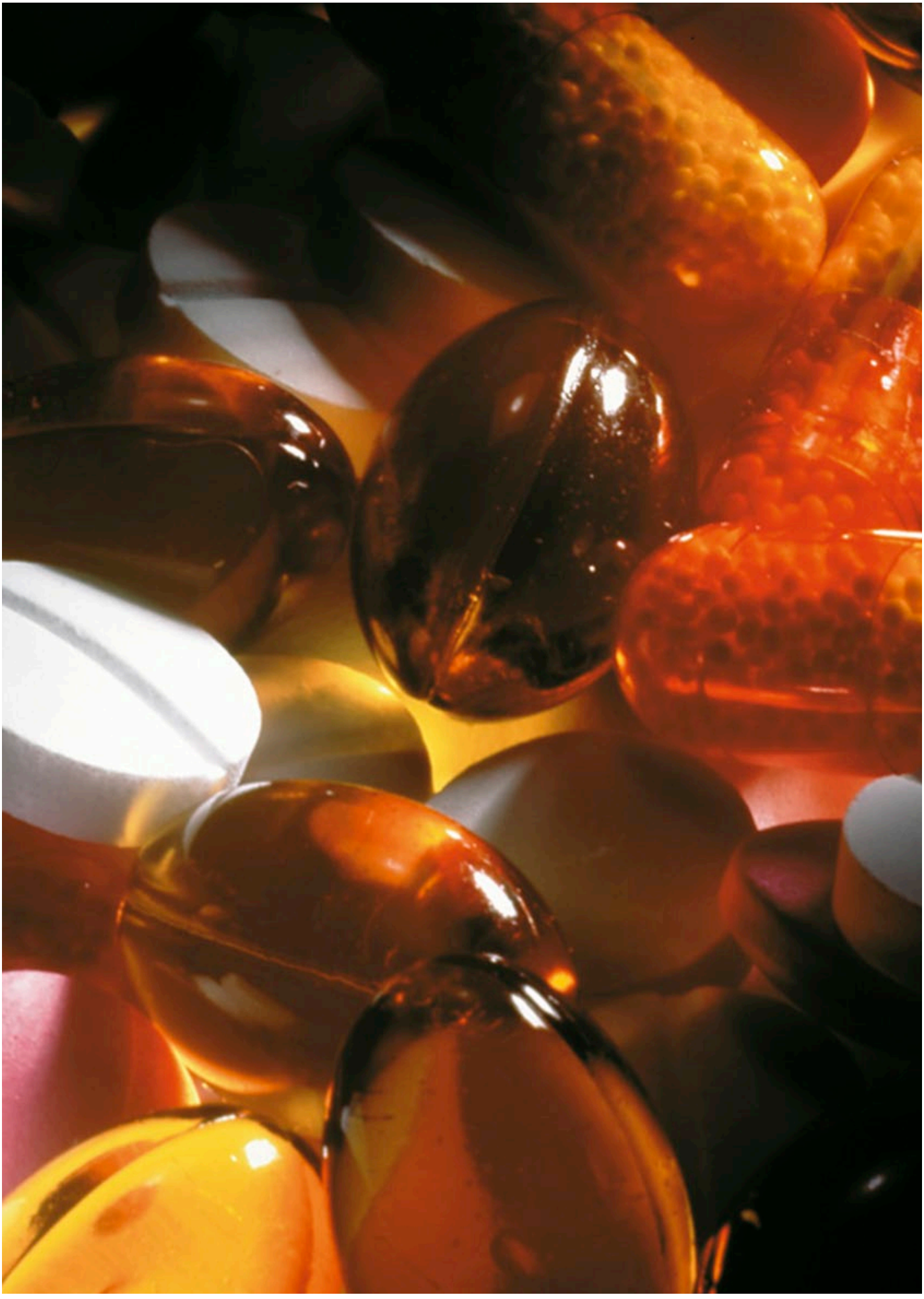
United States
7%

Verifying product quality is another aspect to consider during continuous processing.

Sampling to check for product quality and contamination should take place whilst the process is ongoing. When a sample is found to be contaminated, it's important for manufacturers to isolate the contaminated product and determine when contamination began. This is in contrast with a standard batch process where there's a finite quantity of product to the checked and it is much easier to isolate a contaminated batch.

From a regulatory point-of-view, the FDA and other regulators have defined a batch by 'the production period, quantity of material processed, quantity of material produced or production variation'[16]. They recommend that manufacturers define the batch size prior to each production run.

Existing sampling systems also need incorporating into a continuous process. For example, pH meters and Dissolved Oxygen (DO) probes may need calibration after a few hours of use. There is a question for companies about how to calibrate probes and take multiple samples in a way that's reliable with a single-use system and that reduces contamination.

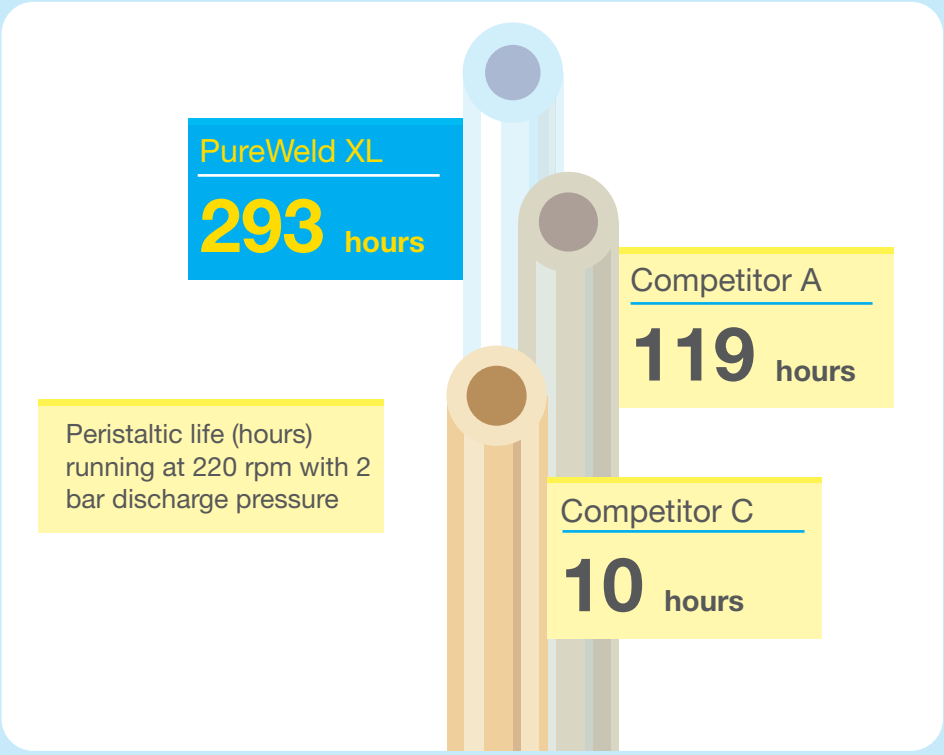


ENSURING HIGH PERFORMANCE

A consequence of continuous manufacturing is that single-use components and assemblies must perform over longer production cycles – sometimes as long as 90 days. Peristaltic pump tubing, in particular, must withstand high levels of dynamic wear.

Peristaltic pumps work by using a roller to compress the pump tube as it rotates, creating a vacuum that draws more fluid into the tube. The aim is that only the pump tube touches the fluid, reducing the risk of product contamination.

Watson-Marlow wanted to test whether peristaltic pump tubing currently on the market was suitable for continuous processing. To do this, they tested the performance of their PureWeld® XL peristaltic pump tubing when compared the flow stability, pumping performance and peristaltic life for two competitor products[17].



The test found that PureWeld XL maintained higher flow rates at stronger discharge pressures and over longer time scales than the competing products. For example, the PureWeld XL was able to pump for 293 hours at 220rpm with a 2-bar discharge before it failed to produce a flow. In contrast, Competitor C managed only 10 hours. Flow stability was also maintained over the life of the PureWeld XL product.

The study showed that not all tubing performs equally – an important factor that pharmaceutical companies should consider when choosing equipment.

THE BENEFITS OF CONTINUOUS COATING

Continuous tablet coating has been around for 20+ years but has only attracted interest in the pharmaceutical industry for the past decade – that's according to Jim Marjeram, Technology Director at O'Hara Technologies.

He argues that, until the mid-2000s, pharmaceutical companies were concerned about the reaction of regulators to continuous technologies. They were also worried about the cost of switching to a different way of working.

As such, when O'Hara Technologies first developed a continuous coating machine 2003/2004, their first customers were from the booming nutritional industry, which was less regulated at the time. Their nutritional customers were processing 500-1,500kg of tablet per hour and keen to save money by going from batch to continuous processing.

Around 2010, the pharmaceutical industry started taking notice of O'Hara's machines and they developed a system for smaller volumes (300-500 kg per hour). These worked for pharmaceutical customers who compressed, granulated and coat high volumes of one or two products. These customers could increase the efficiency of their coating equipment from 30-40% to 80-90%, reducing costs by 50-70% in some cases.

Efficiency increase with continuous processing

Customers could increase the efficiency of their coating equipment from

30% to 90%

in reducing costs by

50% to 70%

In addition, the residence time of tablets is reduced from 2-4 hours to 6-12 minutes, reducing the time they're exposed to heat, moisture and tumbling forces. This increases product quality and reduces wastage.

Most of their clients are interested in high volume production of generic medicines. However, they are increasingly developing machines for customers interested in smaller volumes (50-100 kg per hour) too.

"*After all these years, people in the pharmaceutical industry now understand the business advantages of continuous coating, and we're starting to get some traction*," Marjeram explains.

O'Hara's machines use Watson-Marlow peristaltic pumps to control the exact amount of coating on each tablet. Marjeram explains the company used to use a different brand, but found the Watson-Marlow pumps to be easier to clean and reload. "*It's a very sanitary method of pumping, which lends itself to the pharmaceutical industry and the volumes we're working with,*" he says.

He adds, "*Watson-Marlow are global leaders in pumping technology, which is why we work with them. Our customers are very demanding, the pharmaceutical industry is very demanding - so that's one area where we can't compromise. We use and expect the best.*"

MOVING TOWARDS THE FUTURE

Continuous processing will be a slow evolution – not a revolution. Continuous technologies, such as perfusion cell culture, have already been adopted by some pharmaceutical companies and have been in operation for several years, with many success stories in the spotlight. The momentum of breakthrough technologies is ever accelerating.

Whilst downstream continuous processing is less well adopted, new developments in continuous centrifugation, depth-filtration, tangential flow filtration and chromatography are well underway to keep pace with perfusion productivity. In a recent survey, respondents in the US identified downstream continuous bioprocessing as a key area to address, more so than in Western Europe. **45% of US respondents cited a need to develop better downstream continuous bioprocessing technologies, compared to 33.3% of Western European respondents**[9]. This part of the biomanufacturing process requires multiple discrete operations, such as chromatography and coating. The equipment for these processes is often purchased from several different suppliers but needs to be stitched together in a continuous processing chain. Some large hardware suppliers are now offering 'factory-in-a-box' technologies and software packages to control multiple biomanufacturing systems. Other companies are offering software for real-time process analytics.

New techniques are also needed to handle the continuous output of cell culture from perfusion processes. For example, some companies are now experimenting with continuous capture whereby fluid bled off the bioreactor is fed into a series of small chromatography columns. **A survey of biomanufacturers found 37.3% interested in trialling continual chromatography in their facility within the next year**, with greater interest in new technologies for chromatography outside the USA and Western Europe[9]. Sampling technologies also need to improve to handle continuous sampling as, at the moment, samples can take 2-4 hours to be processed in the laboratory. This puts the entire production lot at risk if adverse conditions are not recognized in a timely manner.

As a result, although continuous processing has made dramatic progress in the last five years, industry practitioners estimate it will take another 5-10 years before fully integrated continuous biomanufacturing is in routine use at commercial scale.

COMPANY BIOGRAPHIES

The National Institute for Bioprocessing Research and Training (NIBRT) is a global centre of excellence for training and research in bioprocessing. NIBRT is located in a state-of-the-art facility in Dublin, Ireland. NIBRT arose from a collaboration between University College Dublin, Trinity College Dublin, Dublin City University and the Institute of Technology, Sligo.

O'Hara Technologies Inc. is recognized on the global market as a leading manufacturer of solid dosage processing equipment. O'Hara designs and fabricates a broad product line of pharmaceutical, nutraceutical and confectionary equipment for coating, mixing, blending, granulating and drying.

Watson-Marlow Fluid Technology Group is part of Spirax-Sarco Engineering plc, a FTSE 100 company. The company is an award-winning, global leader in fluid management technology and for over 60 years has engineered components and systems for customers in a wide range of pharmaceutical and industrial markets.

Learn more at www.wmftg.com or @WMFTG_news.

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