LABOUR'S LIFE SCIENCES PLAN ASSESSED

FROM SINGLE-USE TO REUSABLE CONTAINERS IN PHARMA PACKAGING

NAVIGATING THE EU'S NEW HTA REGULATION

european PHARMACEUTICAL manufacturer

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ELEMENT TECHNOLOGIES

Assessing Single-Use Systems for Biopharmaceutical Production

OIL AND GAS TECHNOLOGY FOR CONTINUOUS BIO PROCESSING IN PHARMA

The move in manufacturing from batch processing to continuous has been reported frequently for decades, and the challenges are well documented, whether that is regulatory, data capture or more technical in terms of, for example, accuracy of dosing reactants, metering or maintaining their environment.

However some of these challenges have still to be fully resolved and this is particularly relevant as bioprocessing, with its unique use of live reactants, is increasingly being used to manufacture medicines in the volumes needed.

A technology which is widely used by the oil and gas and petrochem industries is now providing a solution to these challenges in pharmaceutical manufacture.

THE CHALLENGES PRESENTED BY THIS SHIFT TO CONTINUOUS PROCESS

One of the technical problems moving to continuous processing is product composition control.

Paul Davis, Managing Director of Wanner International

This is significantly affected by the pumps which drive the reacting fluid through the system. Pumps that are not able to regulate flow rate accurately make control of product composition and the whole process difficult, in a number of ways.

Flow rate can affect pressure, temperature, and the composition of the fluid. Ideally it needs to be consistent, predictable and independent of discharge pressure. It is largely dependent on the pulsation of the flow which can be minimised by reducing the pulsation of the pump.

Minimising the pulse means also ensures that the dosing of the reactants into the continuous reactors can be achieved with a high level of accuracy.

This is key, especially for those processes relying on a catalyst, where speed of reaction can markedly change depending on amount of catalyst. This can have consequences for quality of end product and can increase impurities , say if temperature exceeded limits.

Also within bio processing, fragile material is often a key part of the process. This can include cells or viruses which can be damaged if exposed to rapid changes in pressure or temperature. In some bio reactions these can also be affected by shear, where adjacent layers of fluid move parallel to each other with different speeds.

HOW OTHER INDUSTRIES HAVE SOLVED THESE PROBLEMS

The oil and gas and petrochemical industries had similar problems, albeit for different reasons. They found a solution with seal-less, packing-free, positive diaphragm pump technologies that provide a low shear pumping action, and deliver an extremely low pulse flow.

Wanner has patented this technology with their Hydra-Cell series of pumping solutions, with dosing accuracy exceeding API 675. The company has invested in in-depth research, critical for flow chemistry and HPLC applications, to design pumps that produce extremely low pulse flow and also exceed API 674 performance standards.

The Hydra-Cell technology removes the need for pulsation dampeners, delivering an accurate and smooth flow over a large adjustable range of flow rates.

The Wanner team ran a series of tests comparing two different pump technologies. The graph overleaf shows the pulsations delivered by a typical metering pump and a Hydra-Cell pump – both without pulsation dampeners.

In another test the Hydra-Cell was set at 467 Lph and varied by less than 1 Lph (< 0.2%), well within the API 675 standard, while a single diaphragm plunger operated within a range 416-530 Lph (+/- 13%), clearly a huge increase in pulsation. The smooth, constant flow of the Hydra-Cell enabled controllable, consistent delivery of reactants to the process, and also makes using a calibration column much easier.

It achieves this by operating up to five diaphragms in sequence in a single pump head. This significantly reduces pressure pulsations to such a level that in 99.9% of applications no discharge pulsation dampener is required, reducing the cost of installation and ensuring a more consistent performance. This also eliminates pipe strain, delivering an accurate and smooth flow for flow chemistry dosing applications over a large adjustable range of flow rates .

Low acceleration head losses on the suction side are greatly reduced due to the multiple diaphragm pumping elements, which operate in sequence with short stroke lengths, compared to hydraulically balanced plunger diaphragm pumps with one, two and even three seperate pump heads.

CROSS FERTILISING THIS TECHNOLOGY INTO THE PHARMACEUTICAL INDUSTRY

This is how to reduce pulsation and is critical for flow chemistry and HPLC applications. Also key in these applications is shear.

Findings of research at the University of Wyoming

> **The Hydra Cell technology removes the need for pulsation dampeners, delivering an accurate and smooth flow over a large adjustable range of flow rates.**

published earlier this year showed that these pumps produced over 90% less shear than another typically used plunger pump technology in one common application in another industry.

Low shear ensures the liquids in pharmaceutical processes, which can be sensitive to small changes in environment, reach their target areas with their properties intact.

This pump has other characteristics which make it relevant to pharmaceuticals:

- The first is leak free. Many pharmaceutical manufacturing processes require movement of corrosive fluids. With a hermetically sealed pump chamber, these pumps do not leak by design, they eliminate leaking discharge pipes as pipe strain is significantly reduced with the practical elimination of pulsation.
- Secondly they are very energy efficient. A Hydra-Cell can reduce the total energy usage by up to a half for some industries that rely heavily on pumps for their processes.

The pump's true positive displacement action and minimal internal losses achieve high efficiencies from pump shaft to hydraulic power; this combined with the wide range of flow rate controllability ensures optimum energy usage.

Alternative pump technologies with inherent internal losses, which get larger as internal parts wear, start to become lower in efficiency as the discharge pressure goes above 10 bar and only gets worse with increasing pressure. The Wanner positive displacement pump can handle high inlet and discharge pressures while also maintaining an accurate steady-state flow.

- Thirdly Wanner's pumps are very reliable with many pumps operating in extreme conditions for 25 years plus.

Physical footprint is important as space is often at a premium. Wanner's pumps are much smaller, saving installation space and contributing directly to other benefits. They are available with tri-clamp hygienic connections and polished internal components to 0.4 Ra.

With no dynamic seals in contact with the process liquid, non-lubricating solvents and liquids containing suspended particles can be pumped reliably at pressure in HPLC, ultrafiltration, nanofiltration, reverse osmosis and ultra-high pressure reverse osmosis systems.

The Hydra-Cell pumps also benefit from an advanced mechanical and hydraulic design, with little ancillary equipment required, and high accuracy over a wide flow range, which could also benefit a safe, fast-paced production.

A CASE IN POINT – LAXMI ORGANIC INDUSTRIES

One leading pharmaceutical manufacturer which has trialled this technology in its move to continuous processing is Laxmi Organic Industries in Mahad (India). Laxmi manufactures active pharmaceutical ingredients which are very hazardous and corrosive.

Recently the company announced that its development line was moving to commercial production after a successful trial with Hydra-Cell flow chemistry pumps. They needed flow chemistry process pumps which could dose accurately and consistently and importantly maintain the reaction at a constant temperature. One Laxmi production line needs to be at a temperature of -21°C otherwise the reactants will polymerise.

This is important in maximising the efficiency of the process, as it ensures that the concentrations of the various reactants are maintained at an optimum level for consistent manufacture. The other benefits of the pumps - leak-free (which is especially important when handling highly hazardous chemicals, ensuring operator safety and protecting the environment) – energy efficiency and reliability apply even more strongly to pharmaceuticals.

The pilot plant is being upscaled to full production. Delivering an extremely low pulse flow, the pumps will be dosing solvents at a rate of 80-100 litres per hour into the continuous flow reactors at a discharge pressure of 15 bar.

ADOPTION OF THIS MORE WIDELY WITHIN THE INDUSTRY

The pharmaceutical industry is turning to this solution in increasing numbers. Another global pharmaceutical manufacturer has adopted the same technology, with 150 systems planned to be up and running by the end of the year. It has chosen the Hydra-Cells for transferring a range of chemicals, some corrosive, within an ATEX Zone 2 environment.

Two of the major requirements for pumps within the pharmaceutical industry are dosing accuracy, and extremely low pulsation. The function of a pump in pharmaceutical production is to meet or exceed API 675 standards for dosing accuracy, delivering an extremely low pulse flow, as well as reliable handling of solvents, corrosives and slurry-laden liquids.

This includes the capability requirements for high pressure liquid chromatography applications. For example consider the complexities of running blood through a HPLC column. The different components, such as plasma, plasma, water, platelets, RBCs and white cells, will need to be handled very accurately and sensitively so that we know the exact composition, in order to separate each and every component.

With liquid chromatography, the analyte is mixed with a solvent, passed through a column (which is a membrane or filter), at certain pressure, at constant, given flow rate and separation is based on the affinity of each, with analyte and other liquids extracted at given points on the column.

For this application, a continuous flow is required, as a fluctuation will compromise the whole process. The pump needs to have a steady state with no fluctuation in flow rates. This is particularly important in the purification of proteins or drugs.

A specialist in HPLC company in the Czech Republic , standardised on Hydra-Cell pumps for continuous delivery of mobile phase, initially pumping low viscosity organic solvents, both polar and non-polar, but not excluding future use of water solutions.

With continuous processing the flow chemistry needs pumps to dose each ingredient into the reactor system accurately. This can involve aggressive, corrosive liquids such as concentrated acids in large volumes. The ratio of reactants needs to be maintained, which becomes more complicated the more pumps that are required.

This is especially important with exothermic reactions, where uncontrolled amounts of reactants could lead to unplanned increases in temperature, which can lead to the wrong reaction e.g: at a very basic level it can lead to more substitution of a functional group eg nitration of a phenyl.

This will create inefficiency in the whole production process as the reacting solution flows to the next stage. And this is why an extremely low pulse flow is so important. Pulsations will create differences along the process and pulsing pumps are also less accurate. When you are operating at micro levels of production, which some bio pharma processes are, a high degree of precision is required.

CONCLUSION

The oil and gas industry and wider petrochemical companies have been benefitting from virtually pulse-free pumps, which do not leak, are energy efficient and can run reliably for decades. This same technology is now being selected by some of the leading pharmaceutical companies in the world for these same reasons.

This will help the drive to continuous processing, particularly in biopharmaceuticals, which will increase efficiency of production.
Pump technologies that deliver an extremely low pulse flow with highly accurate dosing are playing an increasing role in making this a reality and the experience in other industries, such as oil and gas and petrochemicals, is accelerating this shift into continuous.

Pulsation graph comparison operating without pulsation dampeners