Accurate Biopharmaceutical Dispensing: Peristaltic or Piston Pumps?

Peristaltic pumps offer a serious alternative to piston pumps for the production of biopharmaceuticals – particularly with the trend towards more widespread use of single-use technology.

By Flemming Jørgensen and Peter Lambert at Watson-Marlow Flexicon

Flemming Jørgensen is the founder of Flexicon A/S which in 2008 joined the Watson-Marlow group. During the past 22 years he has been a project manager and a driving force behind the development of peristaltic filling equipment and disposable fluid paths to be applied within the biopharma industry.

Peter Lambert is Filling Division Manager of Watson-Marlow Flexicon, a world leader in aseptic peristaltic dispensing technology. He has over 15 years’ experience in supplying the biopharma industry with leading-edge utility and process equipment. Since 2003, his focus has been to promote a unique and proven technology that he believes is a key element of the single-use approach to drug development and drug manufacturing.

The pharmaceutical industry has had to adapt to major changes and challenges over the last decade. This has been mainly driven by the fact that many blockbuster drugs are running out of patent, forcing the industry to focus more on R&D with a greater interest in developing biopharmaceutical products. This trend has highlighted the need for efficient, small batch, aseptic liquid processing and fill/finish operations. In addition, ever-increasing FDA demands, especially regarding cleaning validation, have forced the industry to look for more efficient and safer production technologies.

The traditional filling technologies have been piston pumps and time-pressure filling systems, but new challenges and more stringent validation requirements have put the focus on peristaltic filling technology. Peristaltic pumps are extremely convenient to use. They are often the preferred choice for fluid transfers in all types of environments, such as in the laboratory or in the heavy chemical industry.

On the other hand, piston pumps are also very popular and have proven themselves over the years, but they can have drawbacks in some applications. A piston pump is designed with many mechanical parts such as valves and seals that are in direct contact with the product. These components – which will eventually wear out – need to be taken apart, cleaned and re-assembled between each use. Even the high-end, valve-less ceramic piston pump comes into direct contact with the product. Additionally, diligent care is required to prevent damage to the piston in these extremely fragile pumps.

When using peristaltic pumps, the product only comes into direct contact with a single piece of tubing, which can easily be cleaned or replaced after use. This single-use feature makes the peristaltic pump an attractive alternative to piston pumps for dispensing biopharmaceutical injectable drugs.

For the last few years, the pharmaceutical industry has been searching for ways to reduce the cost of developing and producing new drugs, and the concept of the disposable or single-use production factory is becoming a reality.

This article will explain recent peristaltic pump design innovations specifically developed to dispense injectable drugs. We will show how these innovations already contribute to reducing the cost of bringing new drugs to market, and how changes may be made in the way products are mass-produced.

As a point of reference, it is important to note that while most of the existing drugs used today are chemically based, most of the promising new drugs are biopharmaceuticals, which are developed, in liquid form.

PULSATION-FREE PERISTALTIC TECHNOLOGY

An innovative breakthrough for making peristaltic pumps accurate occurred 21 years ago when Flexicon A/S of Denmark created the ‘pulsation-free’ peristaltic pump. Once pulses were removed, the potential for high accuracy dispensing was made possible. Today, and five generations of improvements later, peristaltic dispensing pump accuracy rivals piston pumps down to micro fill volumes. Two key design features allow the peristaltic pump to be accurate for dispensing: the use of multiple rollers; and removal of the typical peristaltic flow pulses by using offset rollers.

It has been determined that the optimal configuration for a pump head design is to have two sets of six rollers, with each set of rollers offset with respect to one another. As two tubes through the pump head draw the product, they merge into a single tube via a y-connector, and thereafter the pulses
add up to cancel each other. The resulting pulsation-free flow is then controlled using precise positioning motor and special software allowing for accurate dispensing.

THE PUMP IS THE TUBING
There is a huge selection of tubing available made of many materials and of various sizes, many of them made specifically for peristaltic pump use. Nonetheless, to allow for consistently accurate dispensing down to the micro litre level, it is imperative that both the tubing and the pump head are designed to work together from the beginning, and that they must both have close dimensional tolerances.

Key mechanical characteristics in the selection of peristaltic pump tubing include:

- Uniform wall thickness
- Consistent material hardness
- High mechanical ‘memory’ after compression

Finally, and in consideration of dispensing injectables, the silicone tubing must be of the highest quality to meet the FDA’s cGMP requirements.

PERISTALTIC PUMP FEATURES AND BENEFITS
When compared with piston pumps and other dispensing technologies, peristaltic pumps offer the following benefits:

A Wide Range of Fill Volumes
A single peristaltic pump can fill volumes of between 0.1 ml and 250 ml, simply by changing the tubing size. More than one piston pump would be required to meet a similar fill range.

Fast Set-Up and Calibration
It can take less than five minutes to load the tubing, purge the system, make one calibration and begin filling.

No Cleaning Required and No Risk of Cross-Contamination
Peristaltic pumps do not require cleaning when utilised for single-use dispensing, since each batch is produced with new tubing that creates a new fluid path or set of contact parts. In comparison, when filling injectable drugs on a traditional piston filling line, it is not uncommon to buy dedicated piston pumps for each product in order to prevent cross-contamination between batches. These pumps then require cleaning, sterilising and maintenance.

Greatly Reduced Cleaning Validation
Cleaning validation is a cGMP requirement to demonstrate and document that the equipment used for processing an injectable drug is clean and free from contaminants.

For a multiple-use piston pump filling system, cleaning validation typically requires two qualified resources up to four months to write up the protocols and then execute them. For each subsequent production batch, cleaning in accordance with the validated procedures has to be maintained and properly documented each time throughout the drug’s commercial life.

In addition to these labour costs are other expenses associated with the use of water for injection (WFI), such as for washing, rinsing and sterilisation using pure steam, and finally the cost of detergents and water disposal.

Flow Control
It is very easy to adjust flow speed via the peristaltic pump interface in order to prevent foaming or splashing of the product. It is also possible to adjust how fast the fill speed is reached using the ramp-up and ramp-down feature. This is helpful in optimising overall fill time to permit greater throughput from the filling machine.

Gentle Handling for Shear-Sensitive Products
The valve system in the piston pump generates high-speed flow through small orifices, which can potentially damage biological products. Even valve-less piston pumps generate higher pressures and shear factors and – by design – inherently produce a ‘dead volume’ with each stroke. Peristaltic pumps, on the other hand, are valve-less and only apply low pressure to move the product.

FILL VOLUME ACCURACY
Peristaltic pump accuracy rivals piston pump standards. The typical industry standard for fill volume accuracy is ±0.5%. Peristaltic dispensing pumps meet this requirement for fill volumes as small as 0.5 ml. Below that fill volume, accuracy can be as good as ±1%. When peristaltic pumps are integrated into high-speed filling machines, an automated closed-loop weight-check weight control system assures that the fill volumes remain within tight tolerances.
While piston pumps need to cycle through a recovery or suction phase between each dispensing stroke, there is no such downtime required with peristaltic pumps. Consequently, peristaltic pumps will dispense product immediately upon demand.

High-end peristaltic dispensing pumps are designed to run at high RPM to minimize fill time, and are equipped with a control system that provides an immediate response from a filling machine input signal. Therefore, using a peristaltic dispensing pump instead of a piston pump will not slow down the filling process.

Peristaltic pumps do have limiting capabilities for dispensing viscous products. In general, a product with the viscosity of olive oil can be dispensed using peristaltic pumps. Slightly higher viscous products will also work, but may exhibit potential loss in accuracy and flow rate.

While piston pumps have the capacity to generate significantly greater pressure for dispensing more viscous products, high-end peristaltic dispensing pumps do not. In fact, one of the underlying principles in achieving accurate peristaltic dispensing down to the micro fill volumes is to apply very little pressure on the tubing. When used for micro filling, peristaltic pumps are calibrated to provide no more than approximately 1.3 bar of pressure.

In recent years, biotech companies have embraced single-use technology as an efficient method for developing and bringing new drugs to market. Single-use process components – such as small reactors, filters, mixers and fluid handling bags – have been available for the last few years. The use of peristaltic pumps and single-use tubing is also becoming more commonplace, as it allows for simple fluid transfers with no need for cleaning and no risk of cross contamination.

New drugs – and in particular biopharmaceutical drugs – are often designed for a specific population, and therefore are more likely to be made in relatively small batches than general-application ‘chemical’ drugs. As new drugs evolve to offer a more specific spectrum of applications, batch sizes will become smaller and the need for efficient product changeovers on filling lines will become greater.

Many articles about single-use technology have been written regarding the efficient use of utility and process equipment for upstream processing. Benefits of single-use technology include reduced costs of labor, equipment and energy, increased plant flexibility and faster turnover with significantly less risk of contamination.

In addition to R&D, there is now a requirement for greater reliability and efficiency for the fill/finish side of mass manufacturing of biological drugs. Therefore, it is expected that single-use technology will make its way into production facilities, where accurate peristaltic dispensing pumps will eventually replace pistons and other mechanical dispensing systems, potentially enabling 100 per cent single-use biopharmaceutical manufacturing.

Until now, the pharmaceutical industry has used single-use silicone tubing and fittings for peristaltic dispensing, but has not been able to provide a single-use filling nozzle. In an effort to offer a complete solution to single-use aseptic filling, Flexicon has developed a plastic nozzle for single-use applications. It is now possible to purchase single-use, ready-to-use tubing set assemblies. These sets include the required pharmaceutical grade silicone tubing, connectors and single-use filling nozzles. The assembly is double-bagged and Gamma-irradiated, and includes a complete validation package.

Various single-use tubing set configurations are available. These may include a sterile filter, aseptic quick-connect fittings and a pre-filled product bag. In most cases, tubing and connectors bring the product directly from the product holding tank to the filling nozzle for dispensing on the filling machine – making the entire process single-use.

The pharmaceutical industry is implementing single-use technology in both the R&D laboratory and the large-scale production of injectable drugs. Peristaltic pumps have benefited from major technological improvements that have made them very accurate, fast and reliable.

Today, single-use peristaltic pumps offer a serious alternative to piston pumps for the production of biopharmaceutical drugs.

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<th>Fill volume (ml)</th>
<th>Tube size (mm)</th>
<th>Filling time (sec)</th>
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Table 1: Fill volume and times for the PD12 peristaltic dispenser