Supporting Closed Operations with Flexible Single-Use Solutions

It is important to explore the depth of application and how to utilise non-invasive flow sensors effectively, from complex use in continuous processing and single-use environments to R&D and laboratory applications

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Single-use solutions (SUS) designed for continuous processing reflect a paradigm shift in biopharmaceutical facility design. Utilised in almost all new products in early clinical trials so far, SUS are progressively applied in GMP environments as well. The combination of SUS and continuous bioprocessing is changing the industry's conception of itself – having a significant impact on facility design by offering a smaller equipment footprint and substantially lowering cleaning requirements. The implementation of a continuous process monitoring, in turn, guarantees to keep process stability and raise overall efficiency. Critical points in upstream and downstream processes are, therefore, equipped with flow sensors to fulfil regulatory goals of the process analytical technology (PAT) framework.

PAT has been defined as a mechanism to design, analyse, and control biotechnical and pharmaceutical manufacturing processes through the measurement of critical process parameters. Constant flow monitoring can fundamentally support its overall targets to:

- Reduce production cycling time
- Prevent rejection of batches
- Enable real-time release
- Increase automation and control
- Improve energy and material use
- Facilitate continuous processing

As continuous processing is closely linked to the presence of moving fluids through the system and operates different volume and flow rates fed by peristaltic pumps, non-invasive flow sensors can reliably assume the requirements of PAT. Within upstream and downstream processes, clamp-on flow sensors are successfully integrated at various critical points.

Media and/or Buffer Prep

Non-invasive flow sensors have effectively replaced lab scales in upstream and downstream bioprocessing such as in media and/or buffer prep. As media and buffer prep scales and ultrasonic flow sensors both perform highly accurate volumetric measurement, flow sensors have some considerable advantages over scales. Once calibrated to a

Upstream	Downstream
• Media prep – replacing scales for volume measurement • Inoculation – injecting cell lines into the reactor • Bioreactor (continuous/perfusion) – feeding media/nutrients, control flow into and out of the bioreactor and ATF filters • Centrifugation – determining flow/no flow	• Buffer prep – replacing scales for volume measurement • Chromatography – balancing acid/base delivery to the system • Filtration – controlling process conditions during filtration • Tangential flow filtration – measuring flow rates on feed, permeate, or retentate lines • Fill/finish – measuring volume of fluid dispensed into containers

Table 1: Non-contact flow sensors and their proven success in bioprocessing use

certain environment and flow regime, the sensor operates reliably and accurately. Its application is time, space, and money-saving since it is highly flexible in use. A modern flow sensor is ready for automation and largely insensitive to outer influences such as vibrations and air current. Hence, a clamp-on flow sensor does not come into contact with the measured fluid itself and, therefore, guarantees to keep sensitive systems closed and prevents from contamination throughout all bioproduction processes.

Chromatography

High performance liquid chromatography (HPLC) is widely used as the first separation step in downstream processing. As a constant and reproducible flow rate is critical in chromatography, flow sensors can assume a number of important tasks such as monitoring and providing feedback for pumps. Furthermore, they are used to monitor buffer solutions and can be applied on solvent lines.

HPLC is characterised by liquids under constant pressure. For that reason, reinforced tube systems are widely applied. Innovative flow sensor concepts utilise a complex algorithm to adjust power levels and compensate for the braiding in the tubing. Time-consuming and costly processes to slice in a segment of non-reinforced tubes may be prevented.

Continuous/Perfusion Reactors

Continuous/perfusion reactors are key in keeping a reliable upstream process flow. As fresh media flows into the bioreactor continuously, and media is removed from the bioreactor at the same flow rate, highly accurate flow measurement systems are essential. Non-invasive flow sensors can control inflow and removal rate and ensure that they are equal. Yet again, these sensors' flexibility and low equipment footprint is one of their most valuable advantages. Flow sensors can be easily used on flexible tubing sets, maintain reactor sterility, guarantee a stable calibration, and are easy to automate.

Non-Invasive Flow Sensors

With the influence of digitisation and increasing needs for process monitoring, lab environments are changing rapidly. Networked lab devices with smart functions, automation concepts, and efficient interface solutions have altered lab workflows and stand for the new era of R&D and lab 4.0. Therefore, a rising tide of the continuous availability of data requires easy data handling and secure data logging.

Non-invasive flow meters are the most compact, flexible, and user-friendly option to provide fast and instantaneous flow readings, volume totalising, and to start/stop volume dosing. As a modern sensor design also boasts an integrated analysis unit, there is no need for a separate and unwieldy electronics box. Thanks to their lightweight and small size, the sensors can be easily fixed almost everywhere and can also be left free. As the most innovative non-invasive flow sensors utilise ultrasound, they do not produce heating or high acoustic output that can harm cells. Additionally, there are no moving parts that are in contact with the cells causing shear stress or other damages.

In active R&D and lab practice, non-invasive flow sensors demonstrate a number of benefits. Once calibrated application-specifically, the sensors provide highly accurate and precise readings and are largely insensitive to outer influences such as vibrations and airflow caused from air conditions. Also different to scales, the sensor cannot be bumped out of calibration.

The Principle Behind Transit Time Difference Measurement

There are many different ways to fulfil flow metering needs. Ultrasonic transit time difference measurement is considered the most accurate method for non-invasive sensor solutions. As this method causes neither a pressure drop in the tube nor a risk of leaks, transit-time can work on almost all liquids viscosity, density, colour, and electromagnetic properties of fluids when appropriately calibrated. There are also no ions or particulate matter required to calculate the measurement. Modern clamp-on sensors can operate different flow rates, tubing materials, and sizes.

Transit time in and against the flow direction of a medium is measured with high precision by time-to-digital converters. In the direction of flow, the transit time of an ultrasonic wave is faster than in the opposite direction. It is like a boat that moves in and against the flow direction of a river. A simple difference of both times allows a determination of the flow.

References

1. Visit: www.nne.com/techtalk/a-perfect-pair-continuous-processing-and-single-use-systems
2. Visit: www.fda.gov/downloads/drugs/guidances/ucm070305.pdf

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