Enhancing Process Flexibility with Automated Filling

SONOTEC

During the production and filling of highly complex biopharmaceuticals in cell and gene therapy, precise flow measurement and accurate air bubble detection play a crucial role. Flow meters and air bubble detectors ensure consistently high product quality to provide patients with effective and safe drugs. Using the example of the RoSS.FILL platform, developed by the Austrian company Single Use Support, ultrasound specialist SONOTEC explains how non-contact clamp-on flow meters and air bubble detectors can significantly increase the accuracy of automatic filling.

Challenges in Aseptic Filling

Accurate and efficient filling of biopharmaceuticals in single-use bags, bottles, or vials is crucial. Even the smallest deviations in the filling volume can have a huge impact on the production process, or finally on the patient's therapy.

For example, if a liquid needs to be frozen for transport, overfilling or an inconsistent volume of single-use bags seriously increases the risk of bag leakage and product loss. In most cases, it is absolutely important that a patient receives exactly the same volume of medication per injection.

Operational errors in aliquotation processes often occur due to manual intervention or limitations. The major challenges in aseptic filling are:

- Accuracy
- Consistency
- Flexibility
- Scalability

By implementing automated filling solutions with leading flow measurement technology, product and material loss, human errors, as well as the risk of contamination can be significantly reduced, while process flexibility can be substantially increased.

Solution Provider: Single Use Support

Innovative automated fluid management solutions provided by the company Single Use Support set a new standard in biopharmaceutical manufacturing.

The company offers specific expertise and fast solutions in processes regarding cell and gene therapies (CGT) but also commercial bulk drug substance handling and vaccine manufacturing transfers, and drug productions. With its expertise and advanced bioprocessing solutions, Single Use Support has become the market leader in the accurate filling of very small volumes in single-use bags.

Highest Accuracy for Better Operator's Control

With its fill & filtration platform RoSS.FILL, Single Use Support offers unlimited scalability for aseptic filling from laboratory to commercial production. The modular platform is designed for filling multiple smaller and larger volumes between 1 mL and 1000 L into single-use bags or bioprocessing containers.

For low-volume dispensing at a commercial scale, accuracy and repeatability are essential. To achieve a filling accuracy range of even less than ± 1 mL with the RoSS.FILL platform, Single Use Support decided to implement SONOTEC's SONOFLOW CO.55 V3.0 ultrasonic flow meters. The sensors are easily clamped on the tubing and measured without any

SONOFLOW CO.55 V3.0 flow meters installed in the RoSS.FILL CGT system, Sources: SONOTEC, Single Use Support

contact and therefore without any risk of contamination or leakage.

Designed with a special focus on low-flow applications, SONOFLOW CO.55 V3.0 clamp-on flow meters combine excellent measurement accuracy over a wide flow range and highest clamp-to-clamp repeatability. Hence, the noncontact sensor is perfectly suited for single-use environments with regular tubing replacements.

With the smallest footprint in the market, the compact and reliable flow meter with built-in electronics has been easily integrated into the RoSS.FILL platform. All non-gravimetric small-volume filling lines are equipped with an ultrasonic SONOFLOW CO.55 V3.0 sensor to precisely measure and subsequently control the dispensed fluid. Thus, Single Use Support guarantees exact filling in bags from laboratory to commercial production.

Unlimited Scalability and Flexibility

In biopharmaceutical manufacturing, it is crucial to maintain accuracy while also acknowledging the importance of flexibility. If bag sizes or batch volumes vary due to scale-up or scale-down requirements, the filling system must do so accordingly. The modular RoSS.FILL platform can be adapted to the customer's needs: increase or lower the batch volume or bag size per rack. The highly accurate SONOFLOW CO.55 V3.0 flow sensor ensures the configured filling volume in the single-use bags or bioprocessing containers.

Advanced Process Safety with Bubble Detection

To ensure stable and safe filling processes, proactive and well-considered fluid management is necessary. With the integrated bubble detectors of the SONOCHECK ABD06 series, Single Use Support guarantees airless filling of biopharmaceuticals in single-use bags or containers. The non-contact clamp-on SONOCHECK ABD06 sensor detects air bubbles via ultrasound in the tubing.

Hence, RoSS.FILL users benefit from advanced process safety, flexibility, and scalability with accurate and airless volume dosing.

Air Bubble Detection in Biopharmaceutical Manufacturing and Aliquotation

Air bubble detectors have become an integral part of medical technology. In biotechnology, they are increasingly being used: From process development to the production and filling of highly complex drugs. Subsequently, they play an important role in ensuring consistently high product quality and efficient production processes.

In biopharmaceutical manufacturing, accuracy is key. The presence of air bubbles can significantly affect the quality of the final product. If they remain undetected, even the smallest air bubbles can change the dosing accuracy, e.g., when filling very small volumes, and – in the worst case – can affect the effectiveness of the medication.

Aliquoting, the precise measuring and dispensing of liquid volumes, is a critical step in bioprocess technology. This is where the importance of air bubble detection becomes even clearer. Accurate aliquoting ensures the consistency and adherence to stringent quality standards of each pharmaceutical batch. Air bubble detection alerts as soon as an air bubble is detected and allows for quick adjustments in the process to save resources and production capacity.

Ultrasonic air bubble detection is based on non-invasive measurement technology: Through the walls of flexible and rigid plastic pipes using the transmission principle. The sensors' clamp-on architecture enables non-contact measurement directly on the tubing, which only needs to be inserted into the measuring channel of the sensor. Two transducers mounted on opposite sides of the liquid-filled tubing act as transmitter and receiver. The transmitter generates an ultrasonic wave that moves through the tubing perpendicular to the liquid and reaches the receiver on the opposite side of the tubing. As the acoustic impedance of air is around 3500 times lower than that of water, the reflection coefficient at the water-air interface is correspondingly high and a large proportion of the sound energy is reflected. In addition, ultrasonic waves are significantly more attenuated when propagating in air than in water. Both phenomena lead to a reduction in the amplitude of the receiver signal.

As the acoustic transmission through the tubing is highly dependent on the ambient conditions, SONOTEC has implemented a patented closed loop control algorithm in the SONOCHECK ABD06 series, for example, to counteract these effects and enable dynamic adjustment of the sensor to ensure constant bubble sensitivity. In doing so, bubbles above a certain predefined size are reliably detected without being influenced by the tube setting, ambient humidity, temperature changes or possible tubing displacement. The built-in microcontroller enables intelligent and dynamic adjustment of the ultrasonic properties to ensure reproducible results. The sensor can detect bubbles down to 0.3 µl and does not need to be calibrated.

Resume

Highly accurate and reliable flow measurement and air bubble detection have become indispensable technologies in the field of bioprocess and biopharmaceutical manufacturing. Their role in ensuring accuracy, consistency and compliance emphasizes their importance as critical process parameters (CPP) for the production of high-quality medicines that ultimately benefit patients worldwide.

SONOTEC

Founded in 1991, SONOTEC GmbH is one of the world's leading product and solution specialist for innovative measurement technologies. With about 200 employees and a modern corporate structure comprising three independent business units – Non-Invasive Fluid Monitoring, Preventive Maintenance and Ultrasonic Transducers – the technology leader operates its global sales activities from the Halle (Saale) based German headquarter. The distributed portfolio includes customized ultrasonic transducers and sensors as well as testing devices and measurement solutions for a variety of different industries.

Technical Background

ENGINEERING PRINCIPLE OF ULTRASONIC FLOW METERS

Ultrasonic transducers are the heart of any ultrasonic flow sensor. They consist of piezoelectric ceramics or composites that expand or contract when a DC voltage is applied, depending on the sign of the voltage (inverse piezoelectric effect).

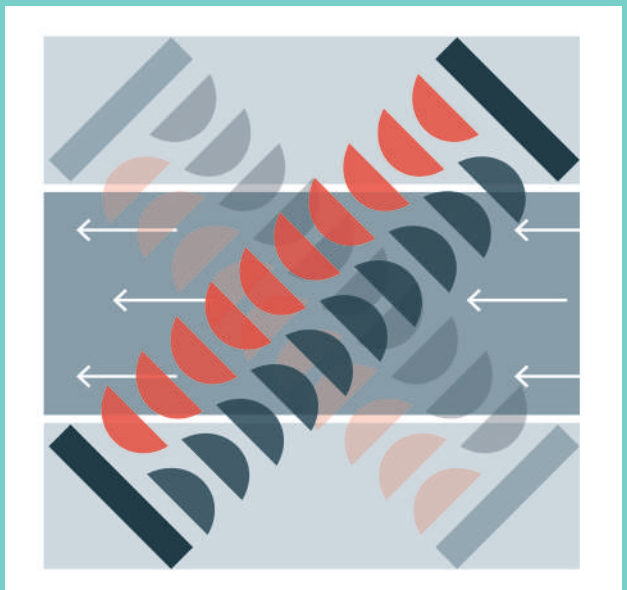
By applying an alternating voltage, the piezoelectric expands and contracts periodically and emits a sound wave corresponding to the excitation frequency. This sound wave is sent out as a pulsating ultrasonic beam from an excitation transducer and is detected by a receiving transducer. The signal is evaluated electronically and output via various signal outputs (digital + analogue).

Transit-Time Technology

There are different ways how ultrasonic signals can be utilised to calculate flow rates. SONOTEC's SONOFLOW sensors work on the basis of transit-time technology.

With this method, the transit-times with and against the flow direction of a medium are measured with high precision by time-to-digital converters. In the direction of flow, the transit-time of an ultrasonic wave is shorter than against the flow. The time difference combined with geometrical information of the tubing allows to determine the flow rate and volume.

This method causes neither a pressure drop in the tube nor a risk of leaks, as it can be applied in a completely non-invasive and non-intrusive manner. When appropriately calibrated, transit-time can work on almost all liquids, independent of viscosity, density, color or electromagnetic properties of the fluids. Ions and particulate matter are not required to calculate the measurement. Additionally, the contactless measurement method does not cause any wear or tear for the sensor. Thus, the clamp-on ultrasonic sensors are maintenance-free.



Transit-Time Principle for Non-Contact Flow Measurement, Source: SONOTEC

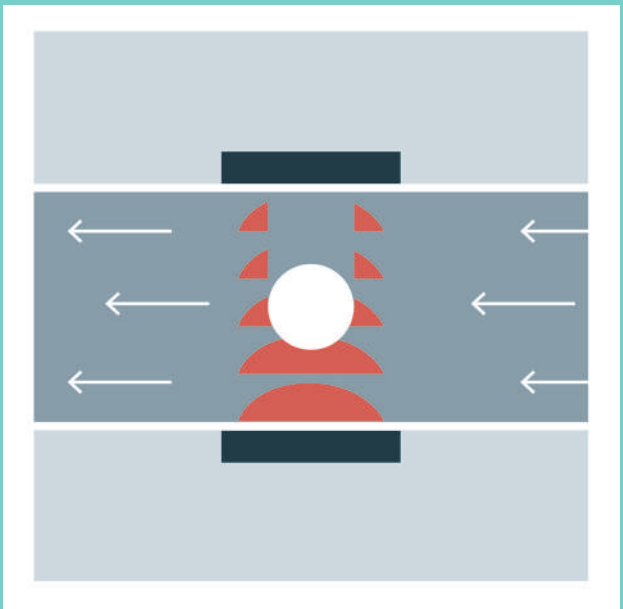
Technical Background

MEASUREMENT PRINCIPLE OF SONOCHECK ABD06 BUBBLE DETECTORS

SONOCHECK ABD06 non-contact clamp-on bubble detectors incorporate intelligent ultrasonic transmission technology. The presence of air bubbles and obstructions is detected by means of dynamic amplitude monitoring.

Ultrasound waves are mechanical waves and are thus subject to the laws of their physics. Depending on the sound impedance of the adjacent media, reflection and transmission take place at the interfaces. If the impedance differences of the adjacent media are small, a transition takes place. At larger differences, the sound wave is reflected and does not penetrate the adjacent media.

When an air bubble passes the sensor channel, the signal level drops. Hence, the higher the drop of the signal level, the larger the bubble size.



Transmission Principle for Air Bubble Detection, Source: SONOTEC

Nico Polley

Nico Polley, born in 1980, is Product Manager of the non-contact flow meter series SONOFLOW CO.55 at SONOTEC GmbH. In the Business Unit "Non-Invasive Fluid Monitoring", his main focus is the development and marketing of the ultrasonic clamp-on sensors in the global bioprocessing market. He holds a diploma in economics from the Martin-Luther-University Halle-Wittenberg. Before he joined SONOTEC, Nico Polley worked for KME, which is one the world's largest manufacturers of semi-finished copper and copper alloy products. At KME, he was Team Leader Internal Sales before he got appointed Product Manager for strip products.

Email: sonotec@sonotec.de **Web: www.sonotec.eu**