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Hot from the press!

A Novel Approach to Shear-sensitive Fluids When Research and Industry Get Creative Together

Elsbeth Heinzelmann, science + technology journalist

Abstract: ZHAW Wädenswil, a pioneer in single-use technology, and Zurich-based LEVITRONIX, the world leader in bearingless motor technology, are developing a novel centrifugal pump with support from the Commission for Technology and Innovation (CTI). By increasing process efficiency, the pump sets new standards in biopharmaceutical production.

Keywords: Centrifugal pump · Magnetic bearings · Mechanical cell stress · Shear-sensitive fluids · Single-use production

In the modern biopharmaceutical industry, liquids in upstream and downstream process steps are usually conveyed by diaphragm or peristaltic pumps. Depending on the operating point of the pump, however, factors such as pulsatile flow, pressure and the compression of the pump tubing can generate high local mechanical stress. The advent of single-use (SU) production has introduced new material and design options and thus potential for improvement.

Stressed Cells

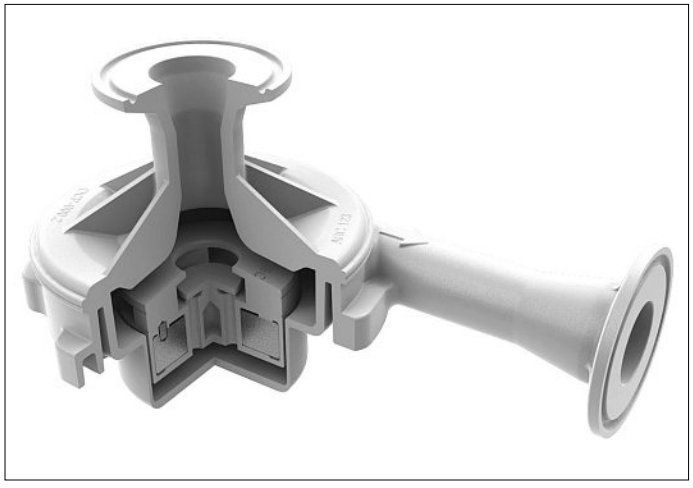
This is particularly the case in the production of therapeutic antibodies and vaccines, which often involves fragile, shear-sensitive fluids. Traditional pumps can damage cells or lead to a loss of product quality or lower yields. The level of mechanical stress is determined by the type of pump and the way it is controlled.

The problem was discussed with engineers from Levitronix GmbH in Zurich at the 2010 Single-Use Conference held at ZHAW Wädenswil and organized by ***Regine and Dieter Eibl***, both professors. Levitronix specializes in ultraclean handling systems for fluids in microelectronic, life science and industrial applications. The dynamic young company has developed a patented system that cleverly combines motor and magnetic bearing technology to create a way of pumping shear-sensitive fluids both reliably and sustainably. Thanks to the support of the Commission for Technology and Innovation, these initial discussions led to a CTI project to develop a centrifugal pump tailored to the needs of SU technology.

Combining Expertise

The engineers at Levitronix worked with ***Dieter Eibl***, an expert in the application of single-use technology in biopharmaceutical production at ZHAW Wädenswil, to develop a centrifugal pump system with magnetic bearings. The system is dedicated to the use with SU technology and ensures a pulsation-free transfer of fluids. Unlike conventional centrifugal pumps, the geometry of the pump head has been modified for use with SU systems – in a similar way to established multi-use pumps – to keep shear stress and the resulting shearing forces low. The pump head is made of plastic and can be replaced and disposed of after every use. This avoids the typical disadvantages of conventional pumps, such as leakage, and expands the operating range of SU pumps to perform at higher flow rates.

"In order to evaluate the mechanical stress generated by pumps, we performed shear-stress tests with shear-sensitive fluids such as cell suspensions and enzyme solutions," explains Dr. ***Pascal Bösch***, Manager Product Development. "We were also able to analyze mechanical stress under reproducible, cost-lowering and time-saving conditions by using non-biological model evaluation systems." The Levitronix team investigated the feasibility of the pumps in tests with protein solutions. It is important for purification processes to evaluate the mechanical stress that proteins are exposed to. The researchers used lysozyme from chicken egg white as a model protein to test the impact of



Section through a PuraLev 600SU single-use pump head with suspended impeller. Image Levitronix.

PuraLev 600SU: single-use pump system with a constant pumping capacity of 4500 l/h and a footprint of 15×17 cm. Image Levitronix.

PuraLev® 200SU: single-use pump system for gentle conveyance of sensitive media. 1200 l/h flow volume free of noise and pulsation with an 11×11 cm footprint. Image Levitronix.

Katharina Blaschczok (right) and Ina Dittler, scientific assistants in Prof. Dieter Eibl's group, are collaborating with Levitronix in the project to develop a single-use centrifugal pump with magnetic bearings. Image ZHAW Wädenswil.

various pump types on protein quality. They measured enzyme activity and particle size to document changes in the proteins.

A Pioneering Step Brings new Expertise

"We had experience with multi-use pumps for pharmaceutical and biopharmaceutical production and, by virtue of our company's history, with blood pumps in medical devices," explains ***Wolfgang Dornfeld***, Vice-President Field Operations at Levitronix. "But parameters such as the initial cost of disposables combined with high quality and seamless documentability were new and complex challenges in this project." Magnetic bearings and drives are established state-of-the-art technologies in their own right, but the MagLev technology developed by Levitronix – which combines magnetic bearings and magnetic drive in a single piece of equipment – is unique. This innovation gives Levitronix pumps technical advantages such as wear-free operation, no mechanical abrasion and thus no particle generation, suitability for dry runs, precise volume flow regulation and low noise emissions.

Its partnership with Dieter Eibl enabled Levitronix to get ahead of the market. PuraLev® pumps help to gently transfer sensitive media such as cells and proteins both in upstream processes – *i.e.* cell cultivation – and in downstream processes, where the resulting proteins are purified. Increased cell viability and protein activity represent a substantial financial advantage for the user. The pumps also deliver better process reliability overall as risk factors such as burst tubing in peristaltic pumps are eliminated. "The optimized pumps were originally used to pump blood during heart surgery," explains Wolfgang Dornfeld. "There the aim is to destroy as few blood cells as possible so as not to put the patient at risk. Nowadays, though, one of the main areas in which these new PuraLev® single-use pumps are employed is in biotech processing."

The engineers at Levitronix are now looking for innovative applications where the MagLev technology adds most value. Now that the technology has been launched, they are keen to find end-users and OEM companies willing to discuss ideas and write pioneering history with clever products.

Information:
http://www.lsfm.zhaw.ch/de/science/ibt-bvt.html
www.levitronix.com

Interview with Professor Dieter Eibl Head of the Biochemical Engineering and Cell Cultivation Technique section at ZHAW Wädenswil

Dieter Eibl is an expert in scaling up and scaling down processes for the production of biomass and active substances such as protein-based vaccines and recombinant proteins and antibodies for the pharmaceutical, cosmetic and food industries. His primary area of expertise is upstreaming processes as well as standard and single-use bioreactors and their qualification. One of the approaches that he and his team use is computational fluid dynamics (CFD) which enables problems in fluid mechanics to be solved approximately using numerical methods.

You and your team lead the field in single-use (SU) technology. What particular new insights have you gained from the CTI project?

SU systems have undergone extremely rapid development in the past few years and have become an established part of research and development and small- and medium-volume biopharmaceutical production. They have a presence in the up- and downstreaming market and in formulation and filling, so they make it possible to create entire SU production facilities.

The focus is currently on optimizing SU systems and on specifically augmenting the range so as to expand the applications that the technology can be used in. This is also true of the CTI project, since the Levitronix pumps expand the range of SU pumps and pave the way for new applications. Two SU solutions for conveying fluids are already available in the form of the classic peristaltic pump and SU four-piston diaphragm pumps. Both types are self-priming volume-displacement pumps. Levitronix pumps, on the other hand, are classic centrifugal pumps based on a revolutionary bearingless drive concept. When used correctly, they convey small and large volume flows in a particularly gentle manner, which is a big advantage in many applications in the biopharmaceutical industry.

What did you feel was the particular challenge in this project?

We – that's to say both Levitronix and my team – were faced with a large number of challenges! Levitronix needed to construct and manufacture a novel, GMP-compliant series of pumps as quickly as possible, using new materials and new manufacturing technologies. The engineers also had to incorporate our knowledge and experience with prototypes into

the ongoing development work, and that could only be achieved through very close cooperation.

For me and my people, the biological stress testing of the pumps was a hard nut to crack in both logistical and scientific terms. We asked ourselves when and how protein solutions or animal cell cultures are damaged when they are conveyed by pumps. We needed to find out how the appropriate tests could be designed to provide enough information yet not be too time-consuming or costly. We had to perform comparative tests at the same time and with the same culture in parallel with Levitronix pumps, peristaltic pumps and four-piston diaphragm pumps. Depending on the size of pump we were using, we had to obtain batches of 20 L, 50 L or 200 L of culture broth containing CHO cells for the trials with animal cell cultures.

What is the significance for you of working with a dynamic company like Levitronix?

I have seldom experienced such close and inspiring collaboration of such exceptional intensity throughout all phases of the project. We had working relationships with the implementation team, marketing and management throughout the entire project. Levitronix provided us with goal-oriented, project-relevant support, was always keen to hear our ideas, analyzed them critically, discussed them and then implemented them energetically.

Is there actually a need for state funding programmes like CTI?

Levitronix and my team were in fact working together prior to the CTI project, but it was the government's funding programme that enabled us to get an R&D project of this magnitude off the ground in the first place. Funding programmes of this type are exceptionally important and necessary in safeguarding Switzerland's role as a business location.

Interview by Elsbeth Heinzelmann

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