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## IONICON PTR-MS (Proton transfer Reaction – Mass Spectrometry) system monitors GMP biotech processes

IONICON is a partner in the Austrian Center for Industrial Biotechnology (ACIB) for the development of novel tools for real-time process monitoring of biotechnological fermentations. After the successful implementation in a laboratory environment, the IONICON PTR-technology could now make another important step and has been utilized for real-time process monitoring in an industrial, GMP (Good Manufacturing Practice) controlled fermentation process. The ability to monitor volatile microbial metabolites in the off-gas, without an adaptation to the existing process, has enabled the introduction of PTR-MS to this highly regulated area.



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Modern biopharmaceutical drugs are produced in biotechnological fermentation processes. Monitoring of these processes is becoming increasingly relevant, especially in the manufacturing sector to promote cost-effective production. To date, biotechnical processes are generally monitored using off-line analytical procedures. The disadvantages are considerable time delays between sampling and achieving analytical results – often too late for applying corrective actions. Moreover, most off-line procedures are labor- and therefore cost-intensive. Direct real-time analysis overcome these obstacles and lead to more efficient processes as well as enhanced safety of pharmaceutical products.

The Austrian Centre of Industrial Biotechnology (ACIB) has dedicated a work package with a task force of academic partners, partners from the biotech industry and analytical device manufacturers. They have implemented and assessed the suitability of several techniques for real-time fermentation-process monitoring.

IONICON, a partner in ACIB, is the world's leading producer of real-time gas analyzers based on Proton-Transfer-Reaction Mass-Spectrometry (PTR-MS). A PTR-MS can analyze volatile organic compounds (VOCs) in real-time and in very low concentrations. In a bioreactor, trace amounts of volatile metabolites are emitted as by-products of microbial growth and production. With PTR-MS real-time monitoring of these VOCs in the bioreactor's off-gas, it is possible to gauge the activity of these micro-organisms and to gain information for a better control of the fermentation process. Together with the group of Dr. Gerald Striedner at the University of Natural Resources and Life Sciences (BOKU) in Vienna, IONICON has worked on the implementation of PTR-MS for real-time process monitoring, which was reported earlier (see <http://blog.ionicon.com/2012/05/press-conference-successful-implementation-ptrms-bioprocess-monitoring/>). The first step of this implementation has been developed and successfully demonstrated on research-scale bioreactors among several other techniques that have been compared by the researchers.

Industrial fermentation processes are a highly legislated and regulated area following the quality standards laid down in so-called Good Manufacturing Practice (GMP) guidelines. The transfer of a technology that has proven successful in the lab into a GMP process is thus not at all straight forward. Any change to the process, such as the need to install additional probes into the bioreactor, can pose an almost insurmountable obstacle in practice. "The advantage of the PTR-MS approach is its non-invasive implementation, where highly relevant process information can be gathered from analyzing the fermenter off-gas.", says Dr. Hubertus Hohenblum from Boehringer Ingelheim, an industrial partner in the ACIB. The implementation is possible without any changes to the actual process. Moreover, the PTR-MS analyzer can be placed outside the GMP area. Among all evaluated real-time technologies, PTR-MS is the first, and so far the only, that has now made an important step to the "real world".

For the past few weeks an IONICON PTR-MS system had been installed to monitor fermentation processes at the production site of Boehringer Ingelheim RCV GmbH & Co KG in Vienna. The high quality of the gathered data is proven by highly reproducible results. "This is an additional confirmation that demonstrates the suitability of the PTR-MS approach for large-scale, industrial



processes”, says biotech researcher Dr. Rene Gutmann from IONICON. Furthermore, the fast analysis of IONICON PTR-MS systems allow for multiplexing to monitoring several fermentations in parallel, which easily justify the initial investment of these high-tech analyzers that are also available on a lease-to-own basis.

### **About Boehringer Ingelheim**

The Boehringer Ingelheim group is one of the world’s 20 leading pharmaceutical companies with net sales of about 14.7 billion Euros in 2012. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel medications of high therapeutic value for human and veterinary medicine.

All activities of the biopharmaceutical contract manufacturing are performed within the Boehringer Ingelheim Biopharmaceuticals GmbH, headquartered in Ingelheim, Germany and are represented by its new brand Boehringer Ingelheim BioXcellence™. As a leading biopharmaceutical contract manufacturer with more than 35 years of experience – the company has brought more than 20 biopharmaceutical products to market. Boehringer Ingelheim BioXcellence™ offers tailor-made contract development and manufacturing services to the biopharmaceutical industry, providing the entire production technology chain from DNA to fill and finish under one roof at its facilities in Biberach (Germany), Vienna (Austria) and Fremont (USA). Boehringer Ingelheim BioXcellence™ can secure product supply throughout the entire product lifecycle—transferring customer projects at any stage, delivering to almost any scale and thereby makes outsourcing easy.

### **More about ACIB**

The Austrian Centre of Industrial Biotechnology (acib) develops new products and processes with improved ecological and economical efficiency. acib is Austria’s international research centre for industrial biotechnology with 25+ years of experience in applied industrial research with locations in Vienna, Graz, Innsbruck, Tulln (A), Hamburg, Bielefeld (D) and Pavia (I). As a research center of excellence, acib is an international partnership of currently 80+ international universities and industry partners, including large companies such as BASF, DSM, Sandoz, Boehringer Ingelheim, Jungbunzlauer, F. Hoffmann-La Roche, Novartis, VTU Technology or Sigma Aldrich. Owners are the Universities of Innsbruck and Graz, Graz University of Technology, the University of Natural Resources, Vienna and Joanneum Research.

At acib, 190+ scientific employees work in more than 40 research projects. Public funding (58% of the budget) comes from the Research Promotion Agency of the Republic of Austria (FFG), the country Tyrol, the Styrian Business Promotion Agency (SFG) and the Technology Agency of the City of Vienna (ZIT). The EU funds additional projects such as CHEM21 or SUSY.

### **More about IONICON**

IONICON is the world’s leading producer of on-line VOC detectors with market-leading, real-time, single-digit pptv-level sensitivities using the unique proton transfer reaction – mass spectrometry technology. For more than a decade, IONICON is serving leading scientists with VOC monitoring and quantification instruments in many different areas including environmental research, pollution monitoring, atmospheric chemistry, food & flavour science, illicit substances detection, medical research and industrial process monitoring applications.



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#### Literature:

- IONICON blog: <http://blog.ionicon.com/2014/01/ionicon-ptr-ms-monitors-gmp-biotech-process>
- [IONICON Website - PTR-MS in Biotechnology](#)
- [Luchner et al., \*Real-time approach\*, European Biopharmaceutical Review, Jan. 2014, page 52.](#)
- [Luchner et al., \*Implementation of PTR-MS for advanced bioprocess monitoring\*, \*Biotechnology & Bioengineering\*, 2012](#)
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