Workshop on

Industrial scale cultivation of cells in pharmaceutical or antibody production systems

23 April 2009

Royal Institute of Technology
Stockhom
Sweden

CEFFORT®

Workshop on
Industrial scale cultivation of cells in phamaceutical or antibody production systems

Venue: Royal Institute of Technology,
Albanova, Roslagstullsbacken 21
Stockholm, Sweden (room: FA31)

Overview Programme
09.30 **Registration with coffee/tea**

10.00 **Welcome** - **The intention with this meeting** (Gunnar Hörnsten, CEFFORT AB)

Plenary program:
10.15 - 10.45 **Fed-batch or perfusion for the production of biopharmaceuticals by animal cell cultivation?** (Veronique Chotteau, Royal Institute of Technology)

10.50 - 11.20 **Responding to Increased Demands on Media and Supplements in Platform Production Systems** (Nicoline Ruijs, Thermo Fisher Scientific)

11.25 - 11.40 Short break

11.45 - 12.15 **Image analysis and Transmission Electron Microscopy – your new tools in quality assessment** (Josefina Nilsson and Ida-Maria Sintorn, Vironova AB)

12.20 - 14.00 Lunch and networking

14.00 - 14.30 **Viral safety evaluation of biotechnology products, emphasizing on how "virus validation" studies are carried out successfully** (Bertil Eriksson, BEON Biosafety)

14.35 - 15.05 **Metabolic fingerprinting, spent media analysis and biological activity prediction of cell cultures by LC-MS and NMR** (Sven P. Jacobsson, BioPharmaLinx AB and Stockholm University)

15.10 - 15.40 **SimCell - Robotic system for process optimisation** (Giles Wilson, Novo Nordisk A/S)

15.45 - 16.00 Coffee

16.00 - 16.10 **Non invasive on-line monitoring of pH & oxygen** (Johanna Kullenberg, LAB)

16.15 - 16.50 **Suggestion and discussion of possible collaboration**
- Advanced course on industrial cell culture
- Evaluation of select technologies in cell culture

16.50 - 17.00 **Summary and Closing remarks**

17.00 **Drinks**

Abstracts

The intention with this meeting
(Dr. Gunnar Hörnsten, CEO, CEFFORT AB)

Following on the traditions of NbiNet and DiagISN, this meeting contributes to information exchange and development of business and R&D in the Nordic region.

A key ambition is to support our members in the strengthening of their international competitiveness. This is done through promoting networking among companies in the Nordic region that use Cell culture commercially. We do also aim for collaboration on evaluation of technologies and competence development.

Fed-batch or perfusion for the production of biopharmaceuticals by animal cell cultivation?
(Prof. Veronique Chotteau, Cell Technology group, Royal Institute of Technology, School of Biotechnology)

Fed-batch or perfusion modes are today's options for the cultivation process development of new candidate drugs. In the cases of unstable proteins, perfusion is the obligatory choice. Otherwise, this choice is dictated by the need of simplicity, the existing technical know-how in the company and the available equipment (e.g. bioreactor size, perfusion device, etc.). The higher risk of contamination and higher technical challenge of perfusion processes often lead to the selection of fed-batch for commercial processes. This is reinforced today in the case of antibody production in established biotech companies by the use of generic fed-batch processes with high yield production and low accumulation of toxic by-products (e.g. lactate, ammonia). However perfusion can be a valuable option due to the usage of smaller bioreactors, today's availability of scalable low shear force perfusion system (e.g. ATF) and potentially the lower requirement of process development for perfusion. Perfusion can therefore be an attractive choice for instance for the production of glycoproteins, which are not antibody, and/or for small companies, which do not have a generic process.

Responding to Increased Demands on Media and Supplements in Platform Production Systems
(Nicoline Ruijs, Thermo Fisher Scientific)

Manufacturers are applying an increasing number of qualification criteria to their production culture media and process supplements. They now specify SFM and strongly recommend animal component-free materials. Recombinant and plant-derived proteins and hydrolysates are currently acceptable, whereas the demand for completely chemically-defined formulations is growing. Defined media support the many initiatives, including reduction in material lot-to-lot and common cause variability, and facilitating process verification and understanding.

Goals in media and supplement qualification during process development have evolved, and now include such

criteria as:

- Operational culture mode (e.g., batch, fed-batch, and perfusion)
- Product quality and yield
- Use of concentrated feeds
- Regulatory and risk considerations
- Clone stability in continued passage
- High growth rates and culture density
- Improved process control parameters
- Increases in process robustness
- Platform production approaches
- Single-use production systems

Optimization of nutrients, cofactors, and ion-concentration/ratios is now simply a starting point in the development of high-efficiency platform production media and supplements. This workshop will provide contemporary data on SFM and culture feed materials designed to support such increased demands.

Image analysis and Transmission Electron Microscopy – your new tools in quality assessment
(Dr. Josefina Nilsson and Dr. Ida-Maria Sintorn, Vironova AB)

Transmission Electron Microscopy (TEM) is the best technology for visualizing nano, virus and virus-like particles, but the full benefits of it are rarely understood nor utilized. Combined with new image analysis technology TEM is a powerful tool for optimizing development and production of vaccines. Vironova will introduce to you the general possibilities of TEM and what particular benefits the company's image analysis service portfolio can provide you – from R&D phase to quality assessment of end-products.

Viral safety evaluation of biotechnology products, emphasizing on how "virus validation" studies are carried out successfully (Bertil Eriksson, BEON Biosafety)

The submission of IND or NDA applications for all biotechnological products, such as monoclonals and recombinants (including subunit vaccines), which are derived from cell lines of human or animal origin, need to be accompanied by a significant amount of documentation of tests performed to demonstrate the possible freedom from viruses and other pathogens. The currently recommended and necessary tests, as stated by regulatory authorities, for cell banks, and un-processed bulk material for further down-stream purification will be reviewed. Particular emphasis will be made on the mandatory and more specialized studies related to the validation of the ability of selected process steps to inactivate and/or separate viruses from the desired finished product, as well as the so called "risk assessment", i.e. the estimation of the possible viral burden per dose given to the patient.

Metabolic fingerprinting, spent media analysis and biological activity prediction of cell cultures by LC/MS and NMR. (Dr. Sven P. Jacobsson, BioPharmaLinx AB and Department of Analytical Chemistry, Stockholm University)

Cell cultivation is based on actions in a biochemical network, with the aim of a consistent production of a specific protein in high yields. Metabolomics concerns the identification, qualitative and quantitative analysis of the metabolites in such biochemical network. Two essential analytical tools in metabolomics studies are liquid chromatography - mass spectrometry (LC-MS) and proton NMR. Since the cell cultivation system is a highly complex biochemical mixture the data generated by e.g. LC-MS from such a system is huge and complex. To efficiently extract information from the data various tools based on multivariate statistics are commonly applied.

The present work will describe and discuss the technical approach for metabolic fingerprinting, how it can be applied not only to monitor metabolites, but also for feed analysis, and prediction of the target protein.

SimCell - Robotic system for process optimisation
(Giles Wilson, Novo Nordisk A/S)

The SimCell fermentation system from BioProcessors Corp is a mini-fermenter system where animal cells can be grown in 650 µl volumes in a format that simulates the types of control and stresses that are present in conventional fermenters. The SimCells themselves contain 6 x 650 µl mini-fermenters and allows the operator to rapidly screen many different parameters in a robotic control system.

Data will be presented showing the simulation of fed-batch, cyclic fed-batch and perfusion fermentations. In perfusion study we operated the SimCells in a perfusion mode with a CHO cell line in serum free conditions for over 30 days and examined the effects of temperatures and pH's in 50 different combinations. In the normal course of events such an experiment would utilise all of our 5 litre tank capacity for 1 year. In comparison to 5 litre perfusion fermentations (both suspension cell perfusion and microcarrier) the mini-bioreactors gave equivalent levels of growth and production, demonstrating that the micro-scale system can mimic a larger fermenter. An optimisation of pH and temperature showed that culture pH has a very strong effect on productivity and that small changes in pH can have a large effect upon culture performance.

Non invasive on-line monitoring of pH & oxygen
(Johanna Kullenberg, LAB)

PreSens technology offers chemical-optical sensor systems and they have a broad range of possible applications. The systems allow for a non invasive on-line detection of pH and oxygen and can be implemented in small scale systems as well as industrial scale systems.

Sterile on-line monitoring of culturing parameters is not only important for upscaling production in process development, but also to monitor industrial production processes and applications such as tissue engineering, stem cell research and toxicological tests.

Suggestion and discussion of possible collaboration

- Advanced course on industrial cell culture
- Evaluation of select technologies in cell culture

See www.ceffort.org for more information

Binding Registration

Workshop on Industrial scale cultivation of cells in pharmaceutical or antibody production systems

23 April 2009

Discount price for members of *CEFFORTs in Life Sciences*

□	early registration (before 090408)	600 SEK per person
□	late registration (by 090416)	900 SEK per person

Non-members of *CEFFORTs in Life Sciences*

□	early registration (before 090408)	1 700 SEK per person
□	late registration (by 090416)	2 100 SEK per person
□	Membership of ***CEFFORTs in Life Sciences***	see www.ceffort.org

VAT (25 %) will be added for Swedish participants and participants without international VAT registration number.

Name: _____

Company name: _____

VAT reg. number: _____
(non swedish participant)

Address: _____

_____

_____

Telephone: _____

Email: _____

Date: _____ Signature: _____

Workshop organiser
Gunnar Hörnsten, CEO
CEFFORT AB
www.ceffort.biz

Registration: send an email with the information above to **registration@ceffort.org**
or by mail to CEFFORT AB, Ideon Science Park, SE-223 70 LUND, Sweden
Questions on registration: Call +46 (0)46 286 3351

Confirmation of Meeting and Registration (Disclaimer)
A formal confirmation of the meeting will be sent via email to the participants on the day after the final registration date. The organisers takes no responsibility for travel or other costs in the case an unconfirmed meeting is cancelled or postponed.