Interview with Dr. Timo May (Richter-HELM BioLogics)

A Look into the CMO Industry from Industry Leader Richter-HELM BioLogics GmbH & Co. KG

With more than 15 years in the field of protein expression and purification, thereof more than 10 years in the biopharmaceutical industry, Dr. May has a wide knowledge of contract development and manufacturing of biopharmaceuticals. Heading the downstream processing department at Richter-Helm Biologics GMP production site Bovenau for over 7 years, he is currently Director of Production at Richter-Helm Biologics.

Richter-Helm is a contract manufacturing organization with several multipurpose GMP facilities for manufacturing of microbial derived biopharmaceuticals. Richter-Helm has substantial experience with several different biopharmaceuticals including several classes of proteins, vaccines and plasmid DNA. With more than 140 employees and more than 20 years of experience Richter-Helm is offering customized state of the art solutions for all steps in biopharmaceutical projects via contract development and manufacturing services in GMP facilities for microbial production.

Phenomenex:
The FDA has not yet approved any biosimilar product whereas there are already several such products approved in Europe. Do you think that regulatory uncertainty in the US has favoured development of such products in Europe and less regulated areas in Asia giving these companies a head-start once the US opens the market to biosimilars?

TM:
Although there was a lack of regulatory guidance in the development of Biosimilars, it could be anticipated since a couple of months that this issue will be solved. In fact, just recently FDA issued draft guidance on biosimilar product development (February 2012).

All companies that are focused on the development of Biosimilars face the fact that time to market is the major driver of any project timeline to gain significant market shares. Considering this it is obvious that these companies started their development significantly before the clearance of any regulatory uncertainty, i.e. the Richter-Helm group is currently developing Biosimilars on behalf of their shareholders.

Phenomenex:
Obviously the more popular biosimilars getting attention these days are interferons, G-CSF and EPO. What other proteins do you see coming into the biosimilar world soon?

TM:
One could imagine that the Biosimilar product roadmap correlates strongly to the timeline for patent expiry of the originator products. This is true for the mentioned Biosimilars, too. Of course, considering the patent expiry, larger and complex molecules like hormones or coagulation factors might be of interest. I would like to mention here that Richter-Helm has its own biosimilar development pipeline, with projects at advanced stages. In my opinion the middle-term biosimilar product development will be dominated by monoclonal antibodies.

Phenomenex:
What do you see as major advantages and limitations of preparative RP-HPLC chromatography of proteins?

TM:
RP-HLPC is still the most powerful chromatographic technique. When removing product related substances, there might be no alternative technology in some cases. Nevertheless preparative RP-HPLC has a dedicated position in the product purification scheme, namely as one of the final purification operation steps. Being at that position in downstream processing requires high product compatibility. This is not always fulfilled as the use of organic solvents and low pH might be incompatible regarding structural and functional aspects of the product and has therefore to be tested case by case. Additionally the solvent mixture used during RP-HPLC purification has to be removed to a very low level in the final product.

Phenomenex:
Many people do protein purification by RP in the small scale but the numbers doing it in the large process are much lower. What are some of the things you have to take into account that others at smaller scale levels do not have to consider when using reversed phase in a purification scheme?

TM:
There is a significant technical difference using RP-HPLC in small and in large scale. At small scale the HPLC system comes nearly off the shelf. Richter-Helm's experience with large scale HPLC systems is, even when systems from well established suppliers are used, that every system behaves unique. In order to control the manufacturing process at any time, the personnel must be well trained. However, large scale RP-HPLC is not rocket science, e.g. Richter-Helm-Biologics established and is using this purification technology since a number of years routinely.

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Phenomenex:
In doing prep protein purification, what are some of your biggest concerns in regards to purity? What impurities do you struggle with most in eliminating?

TM:
The products manufactured at Richter-Helm-Biologics are based on microbial expression technology using bacteria and yeast. Therefore the product purification challenge is defined by process related impurities mainly derived from the expression host, i.e. host cell protein and host cell DNA, and product related substances derived from secondary modification of the product, i.e. oxidation and deamidation. While process related impurities have substantially different physical-chemical properties, the purification might be based on standard purification / chromatographic techniques. In contrast, the difference between the product related substances is rather low, which puts highest requirements to the purification steps, i.e. resolution and selectivity. Usually, more than one purification step is required in order to achieve the desirable product quality.

Phenomenex:
It is said that the downstream processing still represents the bottleneck in the manufacturing process of biopharmaceuticals. What kind of improvements or new developments of chromatography phases would help the users of such products to overcome this problem?

TM:
The easiest way would be larger chromatographic columns, which are technically feasible, but they require larger utilities and floor space to match the larger size of the columns, which is something that is not always possible for existing facilities. De-bottlenecking the downstream processing can be achieved by reducing the number of operational steps. With a reduced number of operational steps, the production throughput will be increased. The question is how to reduce the number of operational steps without affecting the processing efficiency and therefore product quality? Richter-Helm-Biologics carefully investigates new technologies, i.e. the use of product specific ligands. With the use of specific ligands for affinity chromatography, highest selectivity leads to a significantly reduced number of operational steps while maintaining or even improving product quality. The actual disadvantage is a longer development time and /or higher resin cost. Improved ligand screening technologies as well as improved resin coupling will overcome this issue in the near future. Richter-Helm-Biologics has already successfully implemented specific affinity chromatography into a downstream process at large scale.

Phenomenex:
What would you describe as the major cost factors in the downstream processing of biopharmaceuticals?

TM:
The main downstream processing costs can be divided into equipment, consumables, labor, raw materials, waste treatment and disposal. Column chromatography is usually regarded as the major cost driver. Besides the fixed costs, the column membranes that are used for the purification of the proteins are a large proportion of the costs. During the last years the upstream titers continuously increased. While the upstream costs are inversely proportional to the titer, this is not true for the downstream costs. Driven by that trend the overall cost for downstream processing will be even higher when handling higher product amounts. On the other hand this offers the largest optimization potential, because increased yield will directly influences the manufacturing costs.

Phenomenex:
What do you see as being future needs in protein process chromatography?

TM:
As Richter-Helm-Biologics is a contract manufacturing organization we have to react in a flexible way on customer demands. This means, that the yields of different manufacturing processes differ from g to kg scale, depending on the product and/or the cutomer's demand of material. Of course, we cannot cover the whole range with one set of equipment. Additionally customers usually expect economic evaluation of the process already prior to the final scale, i.e. during production of material for clinical trials. There is always the conflict between yield and product quality. To overcome the yield / quality discussion continuous chromatography might be one favored application in order to solve this issue. This technology combines powerful purification with high throughput.