**Manufacturing Recombinant Protein Therapeutics
under Cost Constraints**

**Presentation at the "PepTalk: The Protein Science
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Therapeutic proteins play an increasing role in the treatment of serious diseases such as cancer or autoimmune disorders. Besides monoclonal antibodies (mAbs) also other protein classes such as fusion proteins or recombinant enzymes are important additions to the arsenal of drugs.

As Contract Development & Manufacturing Organization (CDMO) Rentschler is focused on the establishment of effective and economical process solutions for the manufacturing of proteins. Due to its experience with a broad variety of proteins, the company can rely on a rich portfolio of different process solutions. At this year's "PepTalk" conference in January 2016 in San Diego, CA, Dr. Stefan R. Schmidt, Vice President Process Science and Production, presented a selection of these solutions with emphasis of the protein purification in downstream processing (DSP).

A first aspect impacting the manufacturing costs is the protein structure. Dr. Schmidt presented an overview of the DSP step sequences for a number of different complex proteins such as mAbs, Fc-fusion proteins (FcF), protein vaccines (Vac), enzymes (Enz) and fusion proteins without Fc part (FP). There are some similarities, but also significant differences. This even applies to a molecule class such as the Fc-fusions. Common to all Fc-fusions is a capture step with affinity chromatography (Protein A). For other non-mAb molecules frequently ion exchange chromatography is used for capturing, which is significantly less effective.

The capture steps for the Fc-fusions results in yields above 75% and contact times less than 6 minutes (Figure 1). In this respect, Fc-fusions and antibodies show a similar behavior. However, the affinity chromatography has a lower capacity for Fc-fusions than for mAbs, which is partly caused by steric hindrance.
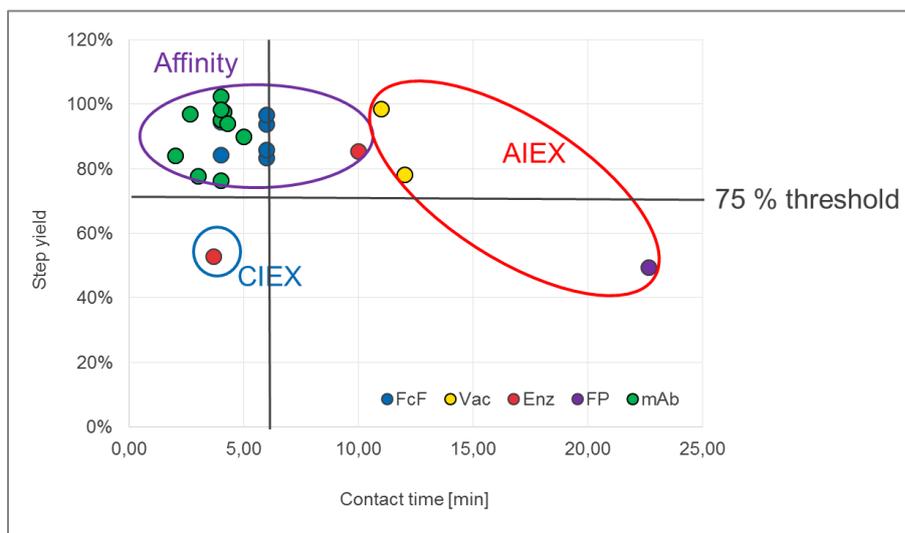

Figure 1: Capture step yield and contact time (AIEX = anion exchange, CIEX = cation exchange)

With regard to the full purification process Fc-fusions do not need more purification steps than monoclonal antibodies. But they achieve in general lower overall yields due to the lower efficiency in the polishing phase (Figure 2).

Costs are influenced by various chromatographic parameters such as the column capacity, the contact time, the geometry and the resolution. For example, larger columns reduce the

process time but increase the costs. Cost savings are possible e.g. by replacement of expensive affinity resins, use of disposables columns and reduction of the number of steps in platform processes. An additional option to process simplification is the use of generic buffers which are adoptable to all chromatographic steps. Cost savings result in this case from less buffer definitions and simplified logistics.
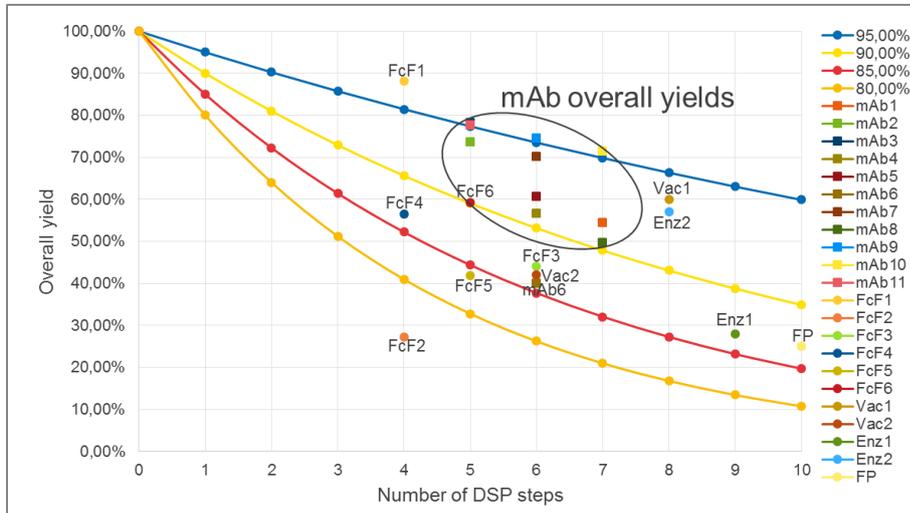

Figure 2: Step yields in downstream processes

In the context of the renaissance of continuous processes Dr. Schmidt finally presented a case study for a perfusion process with cell separation via alternating tangential flow (ATF) and subsequent continuous purification. Two downstream scenarios were highlighted: scenario 1 in a campaign mode with a complete downstream process for each harvest and scenario 2 in a split mode with uncoupling capture form polishing and storage of the intermediates.

A modelling of these scenarios according to the prerequisites, either manpower and suites or column material costs resulting in almost identical costs. However, the important difference is that in the first scenario the suite and manpower costs are significant higher, while in the second scenario the column material costs dominate (Figure 3). Therefore, scenario 1 is appropriate when sufficient suite capacity and manpower is available. If these are limited, it is recommendable to use scenario 2. In this case, sufficient cold storages and verified hold times for intermediates are required.
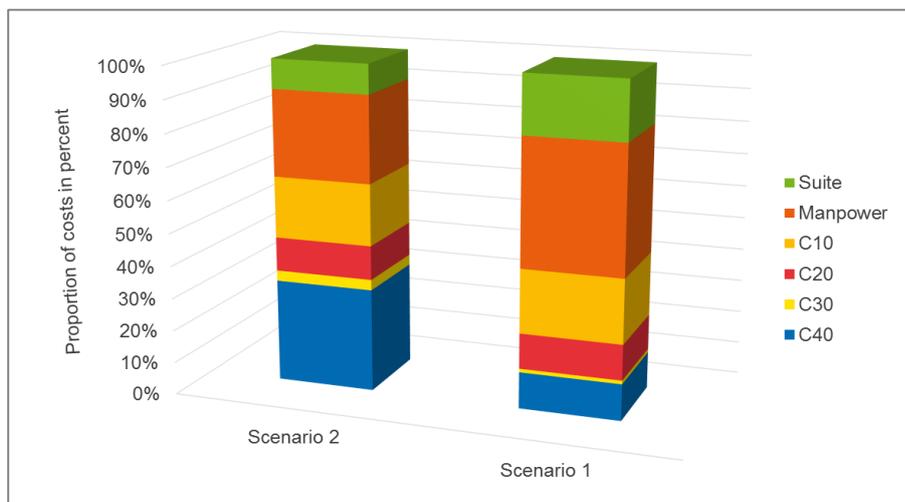

Figure 3: Case analysis for a continuous purification in a campaign mode (scenario 1) and in a split mode (scenario 2). (C10, C20, C30, C40 = chromatographic columns)