Increasing manufacturability with a modular approach

NEXT-GENERATION PROTEIN THERAPEUTICS The manufacture of complex proteins or multi-functional antibody fragments is still a challenge. Rentschler proposes a modular approach for the purification of such complex molecules to support faster candidate selection and strategic decisionmaking.

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Bi- and trispecific antibodies, non-Fc fusions and other complex proteins offer enhanced potency and efficacy, but also entail more detailed and sophisticated manufacturing processes compared to monoclonal antibodies (mAbs), which often have highly-standardised platform processes. New manufacturing concepts therefore need to be considered to access these potent molecules in significant quantities and purity.

Modular 'quasi-platform' processes

Rentschler's vast experience with various molecule classes has led to the development of a modular approach for the manufacture of complex proteins such as non-Fc fusions, protein vaccines or enzymes (see figure). It assumes a matrix with multiple modules that can be assembled according to the specifics of each molecule to design a quasi-platform downstream process. Since modern principles of process development like design of experiments (DoE) remain the same, developers can benefit from the experience of platform processes. Rentschler has successfully implemented this concept in several projects. The modular approach is more time-saving and cost-effective than individual processes from scratch, and also allows fast candidate selection for strategic decisionmaking.

Fc fusion proteins follow mAb platform processes, producing acceptable yields. However, because of the biophysical characteristics of non-Fc fusion proteins, affinity chromatography as a capture step is not an option. This problem can be avoided by employing classic ion-exchange chromatography (IEX), which promises the required capacity but has a considerably lower purification factor than traditional protein A chromatography for antibodies. Virus inactivation must be carried out with organic solvents or detergents for molecules sensitive to low pH. Altogether, the purification of complex proteins involves more steps – in a much more variable order – while yielding much less product overall. Frequently, purification starts with a pre-concentration step of low titer harvests using ultra/diafiltration (UF/DF) to even acquire a workable concentration, followed by two or three more UF/DF steps in-between for conditioning.

In several projects, Rentschler has demonstrated that the modular approach can improve manufacturability for complex proteins dramatically. A prerequisite however, is comprehensive experience with the underlying molecule classes. Rentschler has built its expertise with the manufacture of vaccines, enzymes, fusion proteins (Fc and non-Fc) and mAbs. The company's sound track record is especially good in challenging projects, when problems like persistent aggregation or demanding glycan profiles come into play. ■

MODULAR APPROACH IN DISPOSABLE CASES

Free combinations of defined DSP unit operations after 1000l disposable USP

Affinity Chromatography (Affinity), Mixed Mode Chromatography (MiMo), Cation Exchange Chromatography (CIEX), Anion Exchange Chromatography (AIEX), Hydrophobic Interaction Chromatography (HIC), Virus Filtration (VF), Ultra/Diafiltration (UF/DF), Virus Inactivation by pH (pH), Virus Inactivation by Detergent (Triton)

	Purification	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8
mAb Platform	mAb	Affinity	pH	CIEX	AIEX	VF	UF/DF		
	mAb	Affinity	pH	AIEX	VF	CIEX	UF/DF		
	FcFusion	Affinity	pH	AIEX	CIEX	VF	UF/DF		
	FcFusion	Affinity	pH	AIEX	CIEX	VF	UF/DF		
Quasi-Platform	Vaccine	UF/DF	AIEX	CIEX	AIEX	VF	UF/DF		
	Fusion	AIEX	MiMo	pH	UF/DF	AIEX	MiMo	UF/DF	VF
	Fusion	UF/DF	Triton	AIEX	HIC	UF/DF	CIEX	VF	UF/DF
	Enzyme	UF/DF	Affinity	HIC	AIEX	pH	CIEX	VF	UF/DF

The purification of complex proteins requires more steps than with a standard monoclonal antibody purification platform.

Source: Rentschler Biotechnologie