Biosimilar monoclonal antibodies development simplified

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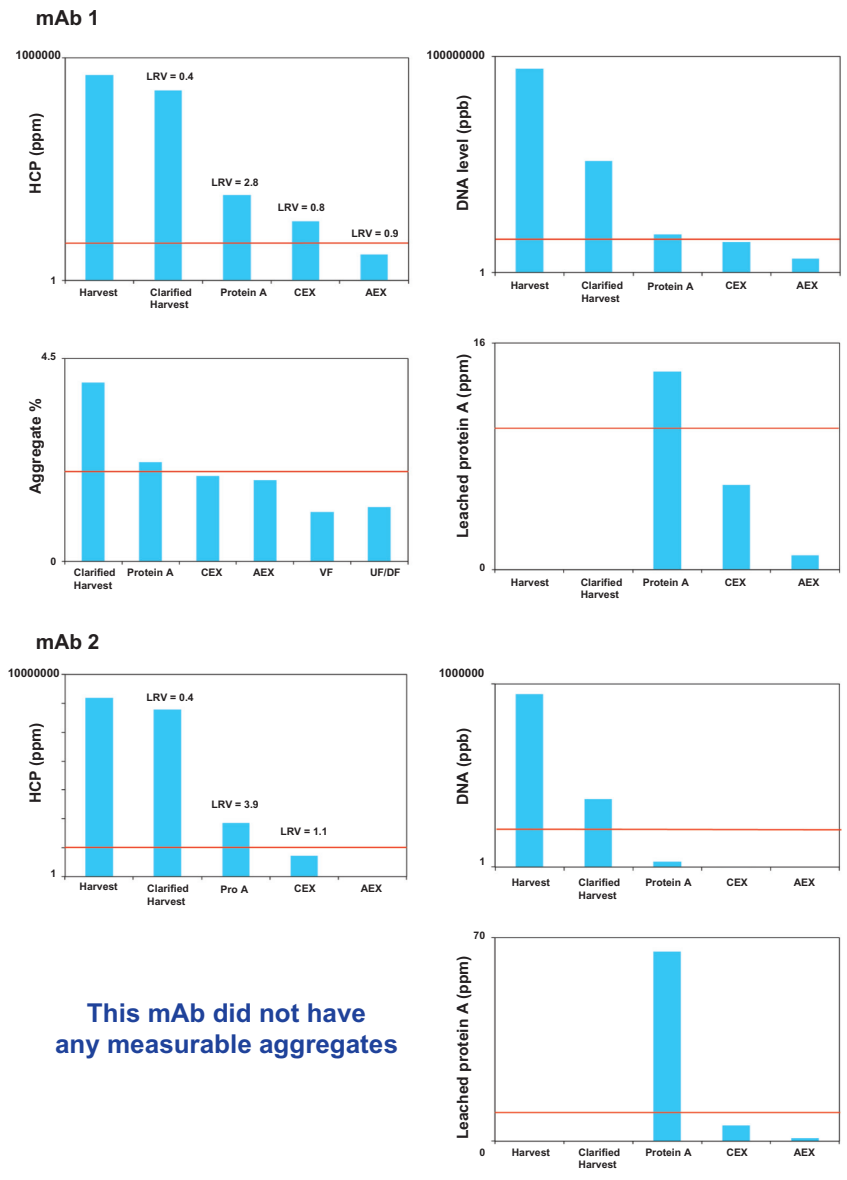
Biosimilars have many challenges. Speed to market is essential, coupled with the need for consistent batch-to-batch production. The biosimilar drug product must demonstrate 'similarity' to the innovator molecule, which requires definition of a corridor of critical quality attributes and demonstration of the ability to reproducibly manufacture drug product within these specifications. Add to this the race to clinic to gain market share, and biosimilars represent one of the biotechnology industry's greatest challenges.

The key to biosimilar development is speed. Faster to market means the lion share and better return on investment. Innovator drugs can take more than 10 years to bring to market. Biosimilar drugs are on the fast track, with development times as short as a few years. Since biosimilar drugs are reverse-engineered using the structure and critical quality attributes (CQAs) of the innovator molecule, there is limited research required for drug development. The technical hurdle in biosimilar development is adequate reference drug product analysis and achieving similarity to the innovator molecule. After the ideal clone has been selected and optimized in the cell culture media, the downstream purification process needs to retain the CQAs of the molecule produced by the clone. The manufacturing process must be robust and validated to produce a consistent product batch after batch, which falls within the acceptable corridor of CQAs, and gains regulatory approval. The majority of biosimilar drug products are monoclonal antibodies (mAbs), and these are highly complex molecules to reverse-engineer. For new entrants to the mAb space, this could present a technical challenge. Pre-optimized templates will alleviate some of the necessary development effort.

The biosimilar market is highly fragmented, with many partnerships, licensing relationships, and acquisitions of molecules. It is probable that biosimilar molecule processes will be scaled up and transferred between development and manufacturing locations frequently, as many transfers are global. During the manufacturing transfer process, the consistency between batches must be retained as well as the CQAs of the biosimilar. In a fragmented industry such as biosimilars, highly templated,

Figure 1: Impurity clearance for two different monoclonal antibodies at bench scale*



*specification limits are indicated by horizontal red lines.
mAb: monoclonal antibody; CEX: cation exchange; AEX: anion exchange; UF: ultrafiltration; DF: diafiltration.

scalable, and disposable processes will ensure greater consistency in production, as well as reduced risk in transfer.

Monoclonal antibodies are the dominant class of molecule within the biosimilar industry [1]. The average mAb process today is approximately 200 kg per year of production, with blockbuster mAbs processes as large as one ton per year [2]. It is estimated that innovator molecules will retain a large share of the total market, and the market will expand by predictions of 50% or more as lower prices for biosimilar drugs enable more patients to access life changing medicines [3, 4]. If we use these market estimates for production quantities, coupled with predictions that each blockbuster mAb will have five or more biosimilars taking market share, we arrive at estimations that 300 kg of demand per year will be split multiple ways, with the innovator retaining a large portion of its original supply of 200 kg, and the five new entrants sharing the additional demand. Using this model, it appears that many biosimilar mAbs will have production demands in the vicinity of 25–50 kg per year, making them ideally suited to single-use manufacturing approaches.

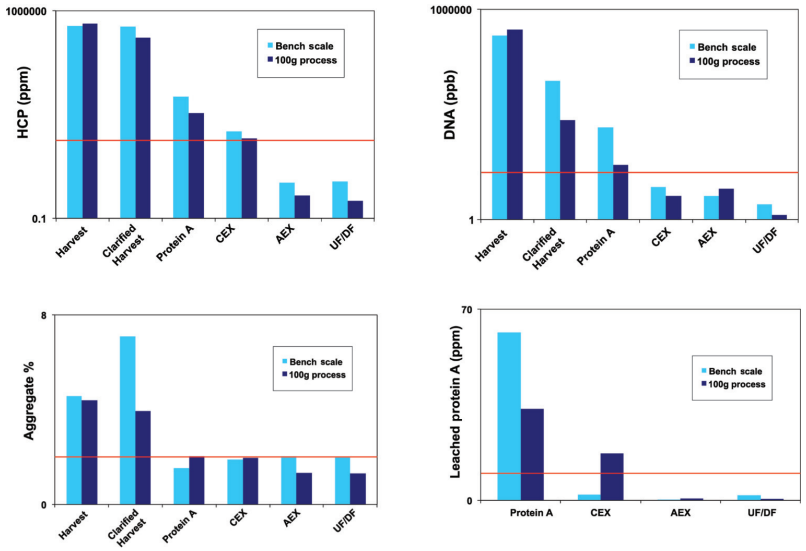
At Merck Millipore, we are in the business of helping our clients develop and manufacture drug products. We combined our best-in-class products with our decades of process development and applications expertise, to design a streamlined downstream process development and implementation approach. Using a platform approach, we can save months of screening and optimization time, as well as provide a robust process which scales and transfers with minimal risk. Whereas process development normally commences with months of device screening, followed by months of parameter optimization, our platform provides pre-determined operating parameters and can save up to six months of screening and optimization time. This timesaving is critical when speed to market means market share. Six months of timesaving represent a large cost advantage to the developer.

This single-use downstream process platform is proven to purify a variety of mAbs, while retaining the mAb's critical quality attributes. The platform offers pre-optimization, such as residence time for chromatography unit operations, flux for filtration unit operations, and most buffer compositions. Consultation is provided for determination of the outstanding parameters, such as dynamic binding capacity for chromatography unit operations, and capacity for filtration unit operations. This not only saves time in process development but also in the subsequent scale-up and production scale implementation where a pre-engineered approach saves time in equipment specification, implementation and validation. This can be of particular value for companies new to the market space and having limited development and process engineering expertise or resources. For companies possessing process development resources, the single-use platform offers a faster solution with a robust template to expedite development of future molecules. The platform is readily scalable, and easily transferred between facilities. The biosimilars industry is proving to be highly fragmented, and partnering, licensing and global tech transfers are the norm. Robust process transfer makes it an ideal choice for the development and production of biosimilar mAbs.

The data in Figure 1 illustrates, with two different mAbs, the ability of the single-use platform to produce two mAbs with impurity levels well below the industry specifications. This assurance that a molecule will meet regulatory requirements gives peace of mind in manufacturing. The choice of best-in-class products in an optimized and streamlined process gives excellent performance.

The single-use platform has also proven to be highly scalable, as demonstrated in Figure 2. Scalability is critical, especially when speed is a concern. The products utilized in the single-use platform have reproducible scalability from bench to pilot to manufacturing scale. This enables smooth technical transfer with no surprises during a transfer or in a new facility. Knowing in advance exactly what devices and equipment will be needed at a larger scale enables more efficient plant set-up

Figure 2: Impurity clearance for scaled-up process



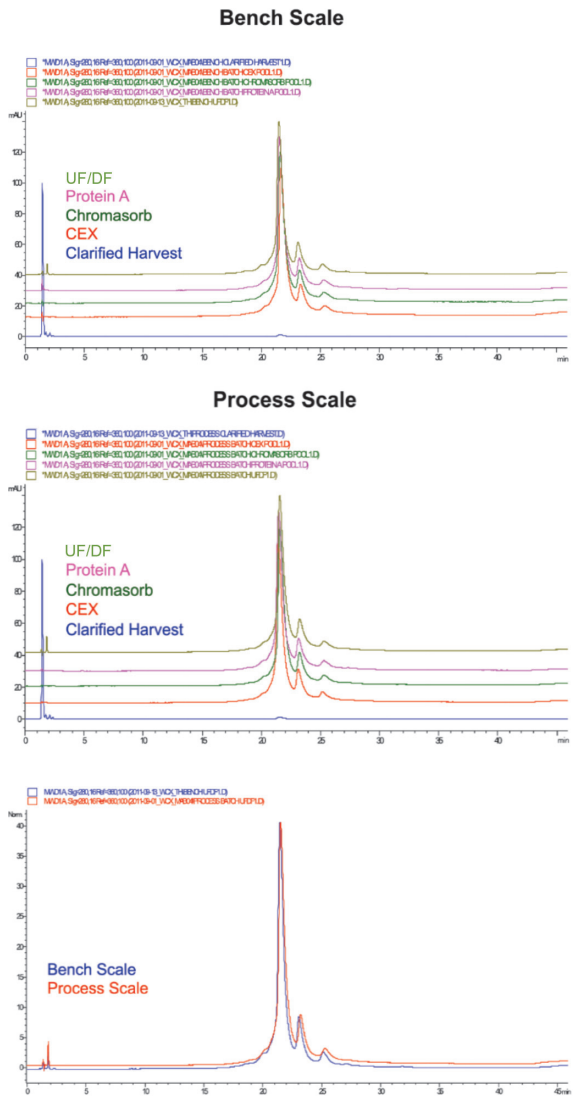
mAb: monoclonal antibody; CEX: cation exchange; AEX: anion exchange; UF: ultrafiltration; DF: diafiltration.

Table 1: Cost of Goods Sold with increasing scale of monoclonal antibody batches using single-use platform

Batch size	Process Equipment Capital (US$ million)		Consumable/ batch (US$)
	[1 × product bioreactor]	[2 × product bioreactor]	
0.5 kg/200 L	1.9	2.2	100,000
1 kg/500 L	2.4	2.8	140,000
3 kg/1,000 L*	2.7	3.0	152,000
5 kg/1,000 L*	3.0	3.4	165,000

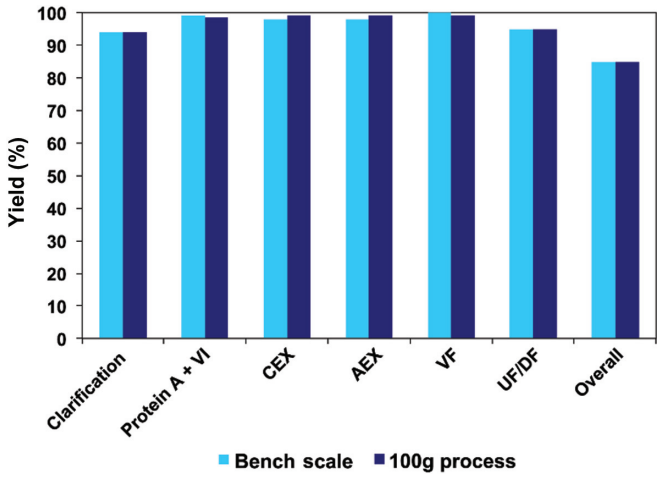
*Based on projected costs for the larger systems currently in development.

Figure 3: Distribution of change variants was unaffected by unit operations or scales



Carboxypeptidase B digestion confirmed that basic peaks are HC C terminal lysine variations.
UF: ultrafiltration; DF: diafiltration; CEX: cation exchange.

Figure 4: Comparison of yields from bench and process scales



CEX: cation exchange; AEX: anion exchange; VF: virus (nano) filtration; UF: ultrafiltration; DF: diafiltration.

and device procurement. Figure 3 shows product quality attributes for both bench and pilot scale for one of the mAbs. We see no change in the charge variant distribution pattern between scales, or indeed between unit operations. The analysis confirms the chromatography steps do not alter the molecule isoform. This is particularly important in biosimilars production, as it is crucial that the biosimilar remains within the corridor of critical quality attributes specified by the innovator molecule analysis.

Overall process yields average 85%, at both bench and process scale, as shown in Figure 4. Individual unit operation yields are up to 98%. High process yields enable a smaller scale process to fulfill annual product demand, saving facility space and cost. It also enables fully disposable manufacturing, which further enables flexibility, faster turnaround time, and reduces risk of contamination.

The advantages of disposables are many, including reduced start-up cost, flexibility, reduced risk of batch-to-batch carryover or contamination, reduced effort of cleaning, and complete removal of cleaning validation requirements. This platform is readily implemented as a fully disposable downstream process, as shown in Figure 5. It includes primary and secondary clarification, followed by protein A affinity chromatography for IgG1 capture; cation exchange (CEX) bind/elute chromatography followed by anion exchange (AEX) flow through chromatography; virus (nano) filtration (VF); tangential flow ultrafiltration (UF) for product concentration and formulation, and finally sterile filtration of the resultant bulk drug substance. The products selected work together to provide an optimal integrated mAb platform, providing high productivity and yield, as well as consistency. It can also provide flexibility, especially with respect to the chromatography steps if required. While purity alone may be sufficient for an innovator molecule, for a biosimilar matching the CQA profile of the innovator is critical, as such adjustments to the default platform may, on occasion, be necessary.

The Cost of Goods Sold (COGS) analysis for the single-use platform proves it to be a highly effective template as opposed to stainless steel, with savings up to 40% over a traditional steel facility. Facility costs show a similar order of magnitude saving (US$14 million for single-use versus US$30 million for stainless steel facility in this scenario). Process equipment capital cost is in the range of US$1.9–US$2.4 million with batch costs for disposables and expendables varying from US$100,000–US$140,000 for batches of 100 g to 1 kg. Table 1 shows that the cost of consumables in a fully disposable process does not scale linearly with increasing process scale. A 0.5 kg batch has an approximate cost of US$100,000 whereas a 5 kg batch has a cost of US$165,000. Therefore, there is a benefit of economies of scale with disposable processing, as with traditional stainless steel. An increase in process scale is economical to the extent where disposable processing is still feasible.

This template can be used to manufacture batches up to 2.5 kg. Larger scale disposable equipment is in development, with the ability to manufacture 5 kg batches with

Figure 5: Single-use monoclonal antibody platform for downstream processing

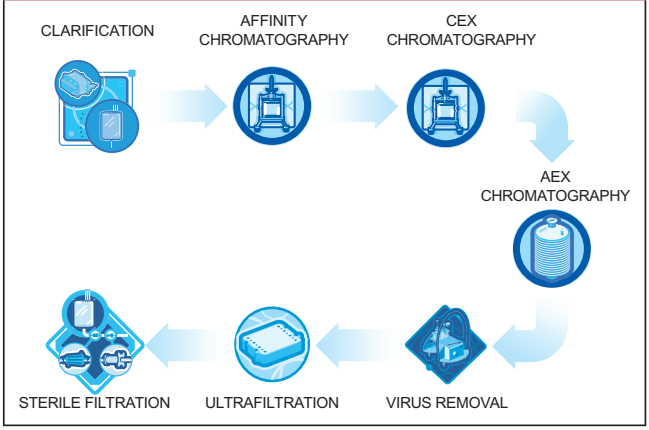
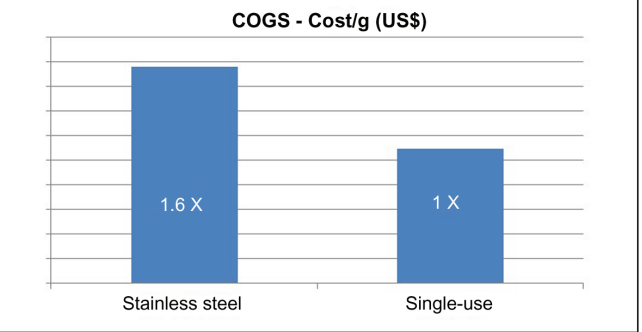


Figure 6: Cost savings of single-use disposable platform versus traditional stainless steel equipment



COGS: Cost of Goods Sold.

the next generation disposable systems. Since disposable processes also enable manufacturing in facilities with lowered environmental classifications, the adoption of a fully disposable platform with closed processing capability can enable reduced cost modular facility design, providing even more savings of start-up time, cost and utilities.

Overall COGS for a 1 kg batch using such a single-use approach is approximately a 40% cost savings as shown in Figure 6. The COGS data is based upon a 500 L bioreactor with a titer of 2 g/L, with a production of approximately 60 batches per year, with a throughput of approximately 42 kg per year. This is a fast and robust solution for biosimilar mAbs development and clinical manufacturing. As the biosimilars market will be shared by many players, it is reasonable to assume that a blockbuster mAb with a current production volume of 200 kg per year may experience demand increase to 300 kg per year with reduced pricing of biosimilars. If the originator retains half of this market demand, and the remaining half is shared by 4–5 manufacturers of biosimilar drug products, these biosimilars manufacturers will each need to produce approximately 25 kg per year. This is reasonably manufactured in 10–20 batches per year using this single-use approach. The equipment can be rapidly changed over to be used in a different process, and even in a different suite, since it is all mobile.

In summary, the optimized ClinicReady™ process template provides a robust, scalable and consistent manufacturing solution that enables speed to clinic and reduces risk of failure. It is fast, economical and easy to implement, and available with consultative support as needed. It enables flexibility in manufacturing and simplifies tech transfer at any manufacturing scale. It is an ideal solution for rapid development of biosimilars to gain speed to market while retaining high yield and excellent product quality. This fully disposable single-use platform is available for start-up costs with significant savings over traditional facilities, and reasonable COGS.

For more information, please contact Ms Jennifer Campbell, WorldWide Biosimilars Market, Merck Millipore, Process Solutions at jennifer.campbell@merckgroup.com or visit our website (www.merckmillipore.com).

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