The Future of Monoclonal Antibody Manufacturing

Incremental Improvement or Industrial Revolution?

by Dan Stanton

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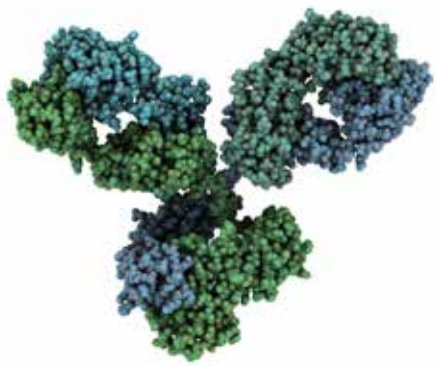
Monoclonal antibody manufacturing is at a crossroads. Biomanufacturers could continue exploring new technologies and fine-tuning proven systems such as mammalian cell expression systems in stirred-tank bioreactor fed-batch cultures. But some experts say an opportunity is arising to turn the industry on its head by taking lessons from other branches of bioprocessing, such as the industrial enzyme sector.

Drug makers are criticized often these days for the high prices of their products. The lay media, governments, payers, and patients themselves all have voiced their share of grievances against "Big Biopharma's" pricing strategies. For example, Alexion's monoclonal antibody (MAb) eculizumab (Soliris) was questioned in a 2014 guidance from the UK National Institute for Health and Care Excellence (NICE), the independent drug assessment body for the National Health Service (NHS) in England and Wales. The agency demanded to know why, from a manufacturing viewpoint, the atypical hemolytic-uremic syndrome (aHUS) treatment was priced at £3,150 (US$4,280) per 30-mL vial. That equates to £340,200 ($460,000) to treat one patient over 12 months, which is over 30× price of other antibodies on the market. This is an extreme example, but other MAbs are far from inexpensive.

"The annual acquisition cost of adalimumab (Humira) to the NHS is £9,295 per patient (based on 26 injections per year)," NICE wrote in a 2010 guidance document recommending AbbVie's bestselling MAb (**1**). The agency eventually recommended that the NHS in England and Wales fund Soliris, recognizing its value to patients despite not being presented "with a justification of why the overall cost of eculizumab was materially higher than the overall cost of other highly specialized technologies" (**1**).



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Driving Value

Criticisms aside, it is important to realize how far MAb manufacturing has come over the past 30 years, especially when we attempt to assess how the biopharmaceutical industry will evolve over the next three decades. In a refreshingly positive keynote session at this year's BioProcess International European Summit, Jorg Thommes (senior vice president of pharmaceutical sciences and technology at Visterra, Inc.) took a moment to praise the people involved in bioproduction. Those involved in process development, biomanufacturing, quality assurance and control, and working across the whole biopharmaceutical supply chain are producing lifesaving therapies in ways unimagined in even the recent past — and with efficiencies that were inconceivable just a few years ago.

"People said that antibodies would never be a product, not because the science is bad, but actually because they were so incredibly difficult to make that nobody would be able to make enough of them for viable products," he told delegates in Amsterdam this past April. But that clearly is not the case, especially when looking at the current list of bestselling drugs, which is dominated by biologics — and MAbs in particular. "It's about time that all of us walk around with our chests puffed out and say, 'We have created enormous value. We have changed from being an enabler to actually being the root that drives value.'"

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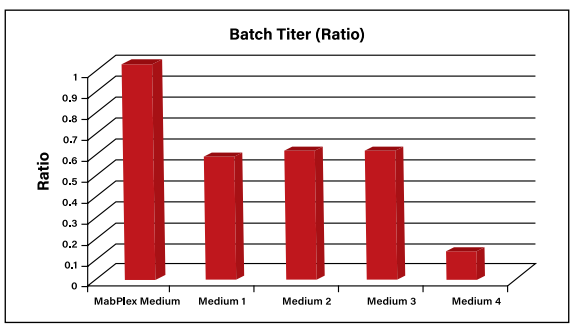

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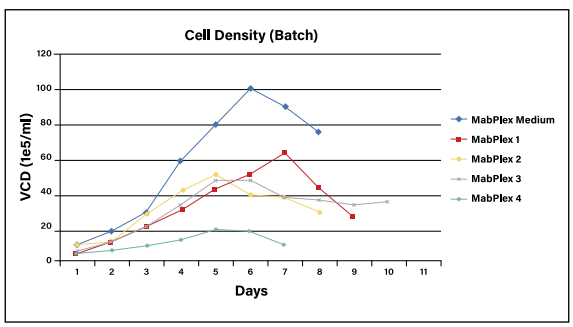

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How Did We Get Here?

The world's first MAb was generated in 1975, and just 11 years later Janssen-Cilag's muromonab-CD3 (Orthoclone) became the first fully licensed such product when it was approved for prevention of kidney transplant rejection. In the 1990s, the biopharmaceutical industry picked up the pace of its progress thanks to approvals for chimeric MAbs. Genentech/Roche's rituximab (Rituxan) and Johnson & Johnson's infliximab (Remicade) were approved in 1997 and 1998, respectively, by the US Food and Drug Administration (FDA) and continue to dominate the bestseller lists. They helped pave the way for an influx of humanized MAbs in the following decades when adalimumab (Humira) became the first fully human product to gain approval in 2003. AbbVie's rheumatoid arthritis MAb remains the world's top-selling drug, with sales in 2017 of $18.4 billion.

Today about 75 MAbs are approved in the United States and/or Europe (2), with many more in clinical-stage development. Over the past 30 years, scientists have developed a much better understanding of biology, leading to steady improvements in biomanufacturing processes. Along the way, we have seen improved cell lines, increasing expression titers, optimized culture media, modernized purification platforms, and new designs for flexible facilities and bioreactor configurations.

"Manufacturing has evolved from a few small plants to a number of fairly similar large-scale stainless steel biologics plants across the globe," Dana Andersen (vice president and global head of technical development project and portfolio management at Genentech, a member of the Roche group) told me. "Correspondingly, as productivity has increased along with capacity, it has been quite remarkable to see the development of the ability to supply metric tons of antibody products to patients, when producing even a few kilograms for clinical studies was once a significant accomplishment."

Genentech is a tier 1 industrial member of the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL), a cooperative agreement with the National Institute for Standards and Technology (NIST), which is part of the US Department of Commerce. NIIMBL launched in March 2017. The Institute's mission is to accelerate biomanufacturing innovation, increase production efficiencies, and provide education and workforce training for the US industry, academia, state governments, and nonprofit organizations.

Andersen currently serves as cochair of NIIMBL's governing committee. He said that cell culture productivity sticks out as one of the biggest factors improving biomanufacturing efficiency over the past decade. "[This] resulted from a combination of improvements including better cell lines, improved media, and intensified feeding and processes. Combined with improvements in the ability to recover higher titers, such as by using higher capacity chromatography resins, the result has been significant increases in batch sizes and improved efficiency."

Biomanufacturing at a Crossroads

Despite an interest in new biotherapeutic modalities such as cell and gene therapies, antibody fragments, oligonucleotides, and so on, MAbs

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NIIMBL

http://www.niimbl.us/

A national network of >140 partners, NIIMBL is part of the Manufacturing USA initiative for increasing US competitiveness, facilitating technology transition, and training the manufacturing workforce. The network of "Manufacturing USA" institutes reaches across manufacturing, government, and academia. NIIMBL funds projects for manufacturing innovation. The second call for applications is going on now: http://www.niimbl.us/PC2_1.php. NIIMBL's 2018 National Meeting was held on 16–17 May in the Washington, DC area.

For more information: Lee K, Springs S, Carbonell R. Introducing NIIMBL: Accelerating Innovation in Biopharmaceutical Manufacturing. *BioProcess Int.* October 2017 http://www.bioprocessintl.com/business/careers/introducing-niimbl-accelerating-innovation-biopharmaceutical-manufacturing.

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Table 1: The evolution of monoclonal antibody manufacturing — from THOMMES J. BIOMANUFACTURING HAS MATURED FROM A KEY ENABLER TO A VALUE DRIVER, SO WHAT'S NEXT? *BIOPROCESS INTERNATIONAL EUROPEAN SUMMIT* 23–26 APRIL 2018, AMSTERDAM, THE NETHERLANDS

Year	Facility	Design	Productivity	Media	Purification
1980	Dedicated, single-product facilities	15,000-L "six-packs"	0.01–0.10 g/L	Serum based	Low-efficiency downstream processing
1985	Dedicated, single-product facilities	15,000-L "six-packs"	0.01–0.10 g/L	Serum based	Low-efficiency downstream processing
1990	Dedicated, single-product facilities	15,000-L "six-packs"	0.10–0.50 g/L	Serum based	Low-efficiency downstream processing
1995	Multiproduct facilities	15,000-L "six-packs"	0.10–0.50 g/L	Hydrolysate based	Low-efficiency downstream processing
2000	Multiproduct facilities	15,000-L "six-packs"	1.0-5.0 g/L	Hydrolysate based	Modern platform
2005	Multiproduct facilities	Single-use systems	1.0-5.0 g/L	Chemically defined	Modern platform
2010	Flexible manufacturing	Single-use systems	≥10 g/L	Chemically defined	Modern platform
2015	Flexible manufacturing	Hybrid	≥10 g/L	Chemically defined; alternate hosts	Modern platform

continue to feature predominantly in biopharmaceutical pipelines. Increased demand for accountability from payers brings additional scrutiny to biomanufacturing processes — even as the pressure to innovate and cut costs is driven further by the entrance of biosimilars to the world's healthcare stage.

Approval and launch of Pfizer's infliximab-dyyb (Inflectra) in 2016 marked the beginning of direct competition in the United States for some top-selling MAbs. With proven regulatory pathways and product patents expiring, numerous biosimilar developers are lining up to bring to market their versions of infliximab (Remicade), adalimumab (Humira), and rituximab (Rituxan) — some of the so-called second wave biosimilars. Achieving greater manufacturing efficiencies, flexibility, and/or updated technologies could give some of those developers an advantage in taking a larger slice of the innovators' market share.

So MAb manufacturing modernization has not come to a halt. It is fair to expect continued evolution in processes, science, and technologies for the near future. But although Genentech's Andersen said that he expects a continued trend toward "more intensified processes run at smaller scales in more flexible facilities, with at least elements of continuous processing to increase efficiency," predicting the level of disruption is more difficult.

According to Thommes, at the crossroads of this industry is the decision to continue with incremental evolution in its processes that has brought such success over the past few years, which would be "a very logical and justified" response, he said. "If it ain't broke, don't fix it." However, the opportunity to take a more of an "if it ain't broke, break it" approach might help cut production costs and serve much larger patient populations. That could be especially important as drug companies develop MAbs to combat diseases such as Alzheimer's and high cholesterol with patient population sizes ten times greater than in the oncology or rheumatoid arthritis markets.

"Turn biomanufacturing on its head and really change it from the ground up so we could actually deliver now on the much, much larger promise of the industry." Such a future is unlikely to be so polarized, thanks to graduations in-between those two extremes.

Industry 4.0

Talking about the future of any form of manufacturing would not be complete without mentioning "Industry 4.0." Although the term has

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been around for over a decade — and according to Thommes is "a big buzzword" — the inevitable implementation of some of its core principles has yet to influence MAbs **(3–7)**.

The concept of Industry 4.0 revolves around nine pillars of technological advancement: big data and analytics, process simulations, autonomous robots, horizontal and vertical systems integration, the industrial internet of things (IoT), cybersecurity, the cloud, augmented reality, and additive manufacturing. Each of those pillars will enable biomanufacturing to evolve incrementally, as companies invest in and integrate enabling technologies and automated services into their operations. According to Thommes, one of the most important aspects for biomanufacturing is that first pillar: big data and analytics.

"We're a data-rich environment, but we don't quite use it like a grown-up industry would," he said. "Feedback control and feed-forward control mechanisms are heavily underused in our industry, and if we were to implement them a little more smartly, then we actually could get to what's called 'right-time release.' We really need to move measurements into the process that actually allow us to control it."

Rather than the overused and misunderstood concept of "real-time release," note that Thommes said "right-time release." That at least would not require the now familiar 90 days of batch testing after each successful run to establish that material is good to go. "I believe that using data and analytics properly, we can have a stamp of approval at the end of manufacturing, not 90 days later, thereby drastically accelerating the pace with which batches move through the supply chain." Buzzword or not, elements of Industry 4.0 already have begun filtering into the biomanufacturing space and will continue to do so as the industry adopts to an ever-changing technological landscape.

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Learning from Others

If MAb manufacturers really want a revolutionary approach to their future, Thommes suggested that they take some lessons from other branches of biomanufacturing. When that term is used, BPI readers generally think of those companies involved in making recombinant proteins, vaccines, and advanced regenerative-medicine therapies. But biomanufacturing has a much longer history, its often-cited first example being fermentation used in the brewing of beer **(8)**. That process can be traced back thousands of years, and its end product is clearly a low-cost commodity and a major industry in itself.

It is, of course, unfair to compare beer with the highly regulated and scientifically complex biologics space — and not only because one product is imbibed whereas the other is injected — so there are few lessons that biomanufacturers can take directly from the ancient craft of brewing. But bioprocessing has been used in a more medical context for decades for the production of insulin and plasma fractionation. Thommes argued that biologics companies could look to related industries for future changes.

Recombinant insulins have about a decade of industrial experience over MAbs, with a focus on batch size and heavy industrial organization. That has been a very different direction from the focused move toward flexible facilities and smaller-scale disposable bioreactor systems in

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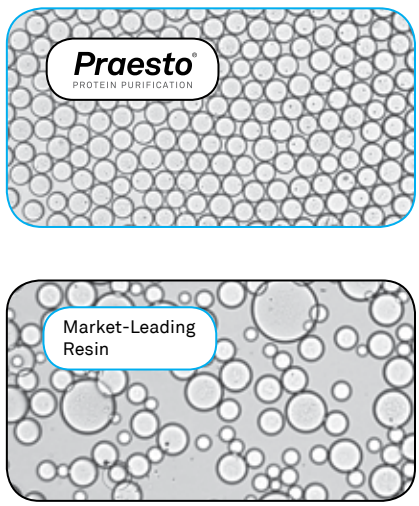

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MAb manufacturing. For blood plasma, the Cohn fractionation process developed in the 1940s involves modifying pH followed by ethanol concentration and temperature changes to separate proteins through precipitation into five fractions. It is a business driven by low margins, much lower than those for the majority of biotherapeutics. Thommes points out that plasma-sourced Immunoglobulin G sells for about $60 per gram. "Human serum albumin goes for about $4–5 a gram. Compare that with the prices we see for biopharmaceutical drugs."

Industrial Enzymes

The industrial enzyme industry operates on margins even smaller than those for plasma fractionation. But it could be the most revolutionary sector for MAb manufacturers to learn from, said Thommes. "There the scale is very large. We're talking of hundreds of thousands of liters." That contributes to very low costs. The enzyme cellulase, for example, is a significant contributor to the overall cost of cellulosic ethanol, which is a second-generation biofuel. The enzyme costs $1–5/kg.

Compare that with the approximate cost of making a MAb. For some time, producing such a product at $100/g was a major accomplishment. Incremental improvements are pushing that figure down toward $50/g, and theoretical models are suggesting that could be halved again. But even with those improvements, the cost to make cellulase is as much as 20,000× less than the cost of making a MAb.

Of course, none of these industries can be compared like-for-like. Intense regulatory demands will keep MAbs from ever being as cheap to produce as cellulase, much less beer. But Thommes asked whether it's really 20,000× more complicated. "I don't think that antibodies or any biopharmaceutical drug will be $1–5 per kilogram anywhere in the near future," he said, but then he added that it should be possible to move them a lot closer to such a model. "We need to have a look at these very large, low-margin businesses to see what we can learn."

No to CHO?

Most biopharmaceuticals are produced using mammalian-based expression systems, in particular Chinese hamster ovary (CHO) cell lines. The first human therapeutic product made by CHO cells was Genentech's plasminogen activator alteplase (Activase), which was first approved back in 1987. Since then, the cell line has become an expression system of choice for most biologics makers. Rituximab became the first commercialized therapeutic MAb from CHO cells in 1997. Adalimumab (Humira) and bevacizumab (Avastin) both are based on CHO expression platforms.

Thommes pointed out that no industrial enzyme producers use CHO, "and I wonder why? Maybe because CHO is a very expensive toy to play with. It's a very slow toy to play with, and maybe the properties of CHO-derived biopharmaceuticals have been hyped up." He admitted that his comments — made at an industry conference attended by many people who are intimately involved in using CHO cells to make biologics — were deliberately provocative.

But they are backed up by the actions of Dyadic International in Florida. That company's management believes that CHO cells are

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unsustainable for the biopharmaceutical industry's future, and CHO is one of the least likely cell lines the industry would have chosen if it were starting from scratch today (**9**). Dyadic developed its C1 gene expression platform based on the *Myceliophthora thermophila* fungus, then sold that platform and related enzyme and technology assets to DuPont's industrial biosciences business in 2015 for $75 million.

In addition to its use in development and production of enzymes for the stone-washing textiles industry, C1 has been used to make enzymes that turn biomass into renewable biofuels. "C1 is a proven eukaryotic cell line that is currently a 'work horse' in industrial biotech, producing proteins at very large scale — commercially in up to 500-cm^3 fermentors," said Dyadic's chief executive officer (CEO) Mark Emalfarb. BASF, DuPont, Shell Oil, and other companies are using C1 to produce a large portion of their biotechnology products.

Emalfarb and his company hope to bring C1 to the biologics industry with similar success, having retained the coexclusive rights to use the technology in human and animal pharmaceutical applications. This somewhat supports the theory that drug makers can benefit from technologies and practices taken from the broader world of biomanufacturing.

"C1 grows very robustly under wide pH and temperature ranges at very low viscosity," he continued. "The cell line has achieved very high production productivity of as much as 80 g/L of a single enzyme, with high-purity target protein — about 80% of the fermentation broth."

According to Emalfarb, the platform has achieved productivity of around 80 g/L for a single enzyme with high purity in the biofuel space. At even half that level of productivity, the platform could be a game-changer for recombinant proteins and MAbs, which at best reach titers of around 10 g/L using CHO cells.

"The industry is starting to experience painfully the limitations of CHO expression yields for the next wave of biologics: bispecific and trispecific antibodies," Emalfarb points out. "The already low yields and high cost of producing biologics with CHO cells appear to make them unsustainable and commercially unaffordable for producing these more complex molecules."

The industry is starting to experience painfully the LIMITATIONS of CHO expression yields for the next wave of biologics: bispecific and trispecific antibodies.

"Big Biopharma," Big Changes?

Dyadic has struck several deals involving expression of MAbs using its platform, although confidentiality agreements restrict the company from divulging the identities of its biopharmaceutical partners. But Biogen has been public in its pursuit of a so-called "CHO stopper." That company has collaborated with the Massachusetts Institute of Technology (MIT) to evaluate alternative hosts including fungal (yeast and chytrids), algae (diatoms), and trypanosome (leishmanial) systems. And in 2016, it funded a collaboration with Amyris to explore multiple host microorganisms as alternatives to mammalian cell lines for production of recombinant proteins.

"These efforts have cast doubt that CHO would be the optimal host in the future, whereas a nonmammalian host could be a key to realizing the most significant gains in productivity and reduction in cost of

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manufacturing," wrote a team of scientists from Biogen, Amyris, and MIT in an *ECI Journal* abstract from 2017 (**10**).

Genentech's Andersen, however, is not convinced that a major overhaul in expression systems is coming anytime soon. "I'm not sure exactly what the future will hold. I'm not sure I see a particular new expression system that will massively disrupt things, though new sorts of modalities and products could lead to some very different sorts of processes."

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About the Author

A history graduate from the UK University of Leeds, ***Dan Stanton*** *began his career as a music and travel journalist, but moved into business publications as a reporter covering the pharmaceutical industry. Specializing in manufacturing practices and technologies, contract services and drug delivery, he colaunched* Biopharma-Reporter *in 2013. In April 2018, he joined* BioProcess International *as founder and editor of online news site* BioProcess Insider. *A native Londoner, Dan now lives and works in Montpellier, France. Find him on Twitter (@Dan5tanton), or email him at dan.stanton@KNect365.com.*

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