WATSON MARLOW
Fluid Technology Group

Watson-Marlow on the challenges of manufacturing biologics vs traditional molecules

CONTENTS

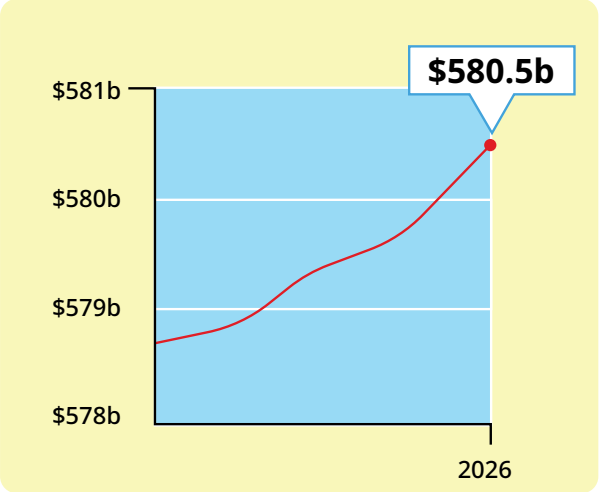
UNDERSTANDING THE BOTTLENECKS

The biologics manufacturing industry has seen rapid growth in recent years as these novel drugs provide access to targeted treatment for some of our most pressing medical conditions. As we meet the needs of an ageing global population, biologics bring the hope of a cure for some of the most prevalent diseases, such as heart disease, cancer, Alzheimer's, diabetes and rheumatoid arthritis. Biologics promise targeted treatment with lower side effects and the first tentative steps towards personalised medicine, but the field is still in its infancy. How do we nurture this fledgling industry and provide the tools and structure to allow it to thrive? How do we ensure that we aren't the bottleneck preventing its success?

Jim Sanford, Sector Manager, Biopharm at Watson-Marlow Fluid Technology Group, discusses the challenges that we must overcome to reap the rewards that biologics offer. Can we increase capacity, intensify processes and enhance product integrity to reduce bottlenecks and take the brakes off biologics production?

The growth in the biologics market is projected to be rapid, reaching US$580.5 billion (approximately €513.5 billion) by 2026[1]. The first biologic, the human insulin Humulin, reached the market in 1982 and since then we have seen a steady investment in biologics research and production, led by the US and Western Europe.

It's been a slow and steady journey to this point as facilities develop to meet the unique challenges offered by biologics production versus the small molecule: biologics are large and complex and require the use of living systems for their production. Although there have been great leaps in technological developments to support the rise in biologics, we still have a way to go to propel this industry. Single-use technology has played a significant role in bioprocess risk mitigation and production efficiency, but it will be the spirit of continued collaboration that will enable biologics to thrive.



MOBILISING MABS

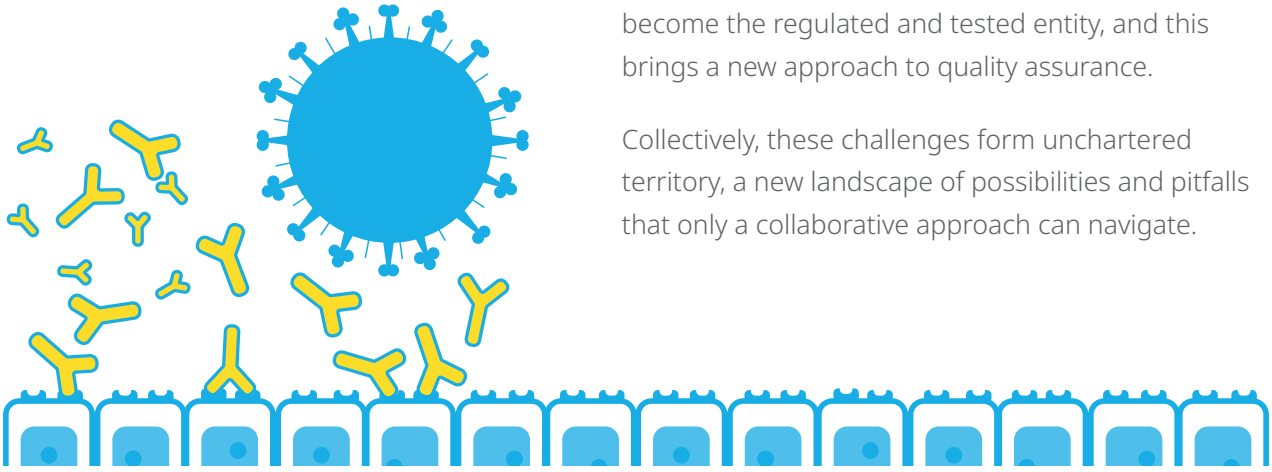
It's important to make one point clear: the rise in biologics doesn't foretell the end of the small molecule. The FDA-approval rate in the US for small molecules and biologics shows a steady increase in new molecular entities (NME) in both categories, and the FDA's Center for Drug Evaluation and Research (CDER) demonstrates a compound annual growth rate (CAGR) of +10% for both small molecules and biologics in the past decade[2,3].

There is clearly a market for both products, but biologics does show a departure from mass-produced and mass-consumed drugs. Biologics offer a targeted approach to treating disease and do so with high specificity and efficacy – an approach that provides a cure rather than a treatment.

We are already seeing huge success in the use of monoclonal antibodies (mAbs) to treat cancer, Crone's disease, Alzheimer's, and a whole host of other incurable diseases, by activating the body's immune system to destroy diseased cells. There are now over 100 approved mAbs-therapies and global markets are showing steady growth. The Latin American Monoclonal Antibody market for example was worth $4.46 billion in 2020 and is expected to be worth $7.01 billion by 2025. Of course, the challenge now comes in harnessing this therapy, reducing the enormous costs and simplifying the intensive and complex production process.

From mAbs, interleukins and therapeutic vaccines to emerging cell and gene therapy treatments, highly complex and multimolecular treatments simply can't be processed in the same way as their small-molecule counterparts.

Working with live cells while ensuring drug integrity and sterility requires a fresh manufacturing approach. For example, growth vectors and end products are more susceptible to aggregation and degradation (due to temperature and light sensitivity). Equipment durability and robustness is also being tested to new levels as processes become more intensive and continuous. Finally, with new formulations and delivery methods in development, there are new challenges for critical processing and filling steps.



With a variable end product, the process has to become the regulated and tested entity, and this brings a new approach to quality assurance.

Collectively, these challenges form unchartered territory, a new landscape of possibilities and pitfalls that only a collaborative approach can navigate.

istockphoto.com

INCREASE, INTENSIFY AND MAINTAIN

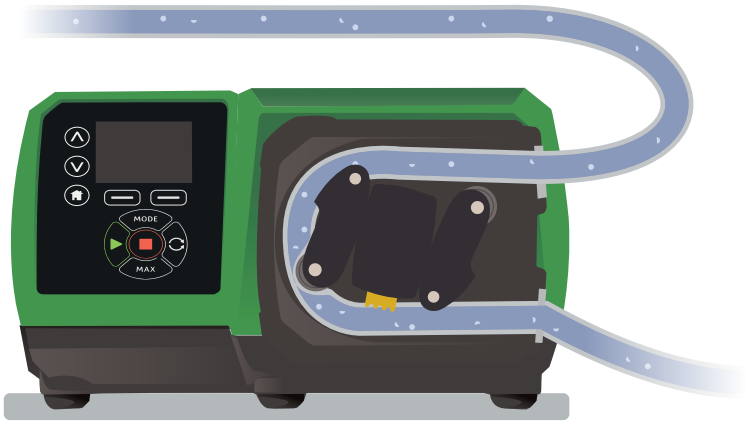
To meet the future requirements of bioproduction, a multi-pronged approach needs to be considered.

Increase capacity

Biomanufacturing capacity is on track to increase 45% by 2023 to reach a total global manufacturing volume of 6,400,000 litres, from 4,400,000 litres in 2018[4], but with demand growing at 10% per year, the current growth plans will not satisfy the need. With over half this capacity sitting in the US and 93% of MAbs being produced in the US and Europe, there is a clear requirement for expansion.

With life expectancies rising globally and the increase in average income for many emerging markets, chronic diseases are steadily rising, especially in emerging markets like Asia-Pacific and Latin America. More urban lifestyles and less exercise are also contributing to this increase[5] with rising rates of obesity leading to higher instances of diabetes and cancer[6] among other diseases. This is driving the growth of the biologics market alongside higher acceptability for these innovative therapies. Hurdles remain, particularly regarding high-capital investment and strict regulatory requirements resulting in high cost of therapies and limited patient access.

Critical players are already investing in these emerging markets but countries and organisations with existing expertise will need to further expand into Asia-Pacific, Latin America, Africa, South America, Eastern Europe and Russia. With lower price points, we'll see biosimilars rising to meet the demand of the developing nations and this will bring its own challenges. Many biopharmaceutical suppliers, including Watson Marlow Fluid Technology Group (WMFTG), are already expanding their global operations footprints, supporting a regional approach to developing and distributing novel biologics and biosimilars.



Watson-Marlow 530 peristaltic pump

Intensify processes

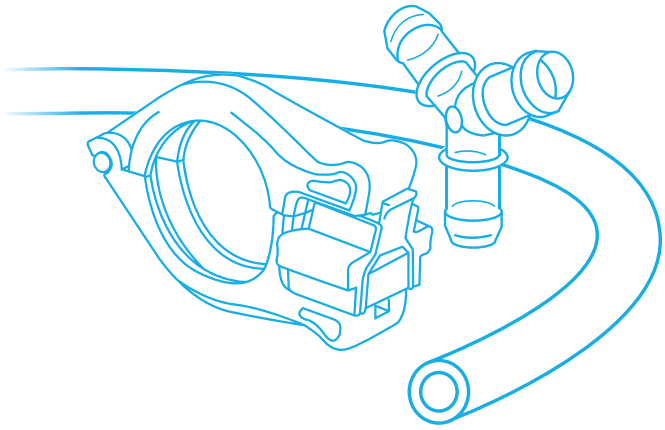
Process intensification, as a means in itself, and also as a route to continuous bioprocessing, will further springboard the viability of biologics for broader use. This will be a journey. As each process is intensified another bottleneck will be identified and will, in turn, be intensified itself, leading to a more streamlined and efficient manufacturing system. BioPlan Associate's recent 16th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production shows a commitment to this approach with 37% of respondents indicating that they would be testing novel downstream equipment, such as purification and chromatography equipment[7]. 33% also planned on testing novel upstream equipment, such as perfusion technology. 45% of US respondents are focused on developing better continuous bioprocessing downstream technologies, versus 33% in Western Europe, perhaps highlighting that the leading role that the US is taking in this field. This is mirrored in the fact that 42% of Western European respondents highlighted downstream continuous bioprocessing as a problem area, versus only 28% for the US.

Hand-in-hand with this approach comes a focus on scaling-out as a means of moving from the lab bench to production. Small systems will be run in parallel, in a continuous process to achieve the capacity needed, rather than the scaled-up batch systems so prevalent in small molecule production.

MAINTAIN PRODUCT INTEGRITY

Single-use technology is undoubtedly the perfect partner for the biologics market, offering a complete fluid pathway. With sterility safeguarded and fast changeovers guaranteed, companies are adopting disposable technology as the solution to efficient biologics manufacturing.

Central to biologics production is the need to reduce bioburden and eliminate the risk of particulate and endotoxin presence within the end product. Single-use technology is already being used in novel ways, the individual parts may be single-use but in a continuous process, this 'single-use' may run into months of service. In order to reduce risk and provide parameters in which our equipment can operate in, WMFTG has been testing its fluid paths portfolio to meet these evolving performance requirements. There are no regulatory frameworks for single-use technology in this space but by working together with other suppliers, biopharmaceuticals and the regulatory bodies we are defining best practice. WMFTG is working on committees within the Bio-Process Systems Alliance BPSA and SPP BioPhorum to address these issues and create the robust criteria that will drive success. Every one of us has a vested interest in seeing novel biologics reach the market. We know that these drugs will have lifechanging effects for patients living with chronic and life-limiting diseases and by working together we can make sure that they get to the people who need them.



BioPure fluid path components

We and many other single-use technology manufacturers work to an open architecture design. Our Watson-Marlow Tubing, BioPure fluid path connectors and select third party components enable us to design and manufacture validated puresu® and asepticssu™ single-use assemblies engineered for bioprocess.

The Q-Clamp is one such example where making the right connection not only facilitates usability with its single handed, tool free clamping system but also prevents potential contamination with its unique tamper evident identification technology and industry leading validation package.

We keep one step ahead of the current developments in biologics manufacturing by listening to and understanding our clients' challenges, ensuring that they have the equipment they need to design novel processes.

PureWeld XL TPE Tubing with the BioPure Qclamp

BEATING CANCER WITH BIOSIMILARS – A CASE STUDY

BIOCAD, a leading Russian biotech company, is developing and manufacturing a wide range of biosimilars and other drugs to treat complex health conditions such as cancer, HIV and Hepatitis C infections, multiple sclerosis and other human health disorders. BIOCAD collaborated with WMFTG to integrate Watson-Marlow Tubing and BioPure connectors into their R&D and manufacturing bioprocesses.

“We’ve seen a rise in biologics manufacturing over the last couple of decades,” says Ivan Strekalovsky, bioprocessing expert at BIOCAD. “Assuring the quality of biopharmaceuticals is more complicated than for small molecules as they are synthesised by living cells. A lot of work is needed to develop the manufacturing process - for instance, regulatory approval is required, and any minor changes must be well documented and validated.”

BIOCAD applied WMFTG products for a wide range of fluid transfer bioprocesses associated with cell culture and liquid filtration during biosimilar development and manufacturing. Having previously used different suppliers, when BIOCAD tested WMFTG’s portfolio of products they benefitted from improved logistics, quality and product availability. “Watson-Marlow’s products are very reliable – they are the golden standard of pumps,” says Ivan.

BIOCAD is using WMFTG products to develop several biosimilars, including Acellbia® (rituximab), a monoclonal antibody approved for the treatment of non-Hodgkin’s lymphoma and B-cell chronic lymphocytic leukaemia; Avegra® (bevacizumab), a recombinant humanized monoclonal antibody that has applications for the treatment of colorectal cancer, ovarian and cervical cancer, lung cancer, renal cell cancer, glioblastoma and breast cancer; and Herticad® (trastuzumab), a monoclonal antibody and anti-tumour agent that inhibits the proliferation of HER2 overexpressing cancer cells. “The launch and market success of these three biosimilars would be unimaginable without the Watson-Marlow range of pumps and tubing and BioPure single-use product portfolio,” adds Ivan.

The manufacture of biosimilars brings a specific set of challenges, such as reducing cross-contamination, reducing batch to batch variation, and meeting regulatory requirements. Monoclonal antibody R&D and manufacturing is especially complicated, creating further challenges such as ensuring prolific growth of the cell line and ensuring protein consistency and maintenance of functional features. To solve these problems, WMFTG’s BioPure range offers excellent validation documents and studies, high-quality products, and good lead times. “Watson-Marlow’s pumps and tubing are durable and resist autoclaving well, ensuring sterility and reducing the risk of contamination,” says Ivan.

How is BIOCAD preparing for future trends in biosimilar production? As the industry progresses and the range of biosimilars being developed expands, there will be increasing demands on bioprocessing equipment to reduce the risk of cross-contamination and possible damage to drug products. “The move towards more personalised medicines and the emergence of cell and gene therapies will require more specialised scientific approaches and highly trained personnel,” says Ivan. “Quality assurance and biosafety will be paramount, increasing demand for sterile equipment and single-use technologies.”

THE RISE OF THE BIOSIMILAR

As the biologic patents come to an end and a wider variety of biosimilars go into production, bioprocessing will be faced with even greater challenges. We'll see new and existing producers in China and India expand biologics production as they meet the need of an emerging market in the developing world, one that can access the lower cost of biosimilar products. Herceptin is one such medicine approaching the end of its patent, resulting in Roche making deals in China and India, offering the medicine at a significantly reduced price to avoid competition[8]. Latin America is another burgeoning biosimilar market, with Brazil leading the charge due to its population and market size and Argentina and Mexico following closely[9].

Many biologic final products cannot be tested for conformity and consistency in the same way that a small molecule can. It is the manufacturing process that must demonstrate uniformity and best practice. Standardised and trusted single-use components and tried and testing fluid pathways will pave the way to success in this market. As biosimilars reach regulatory approval, the standardisation and compliance of production technology will be a major part of the success criteria.

Learnings will be taken from the US and Western European markets and suppliers will need to ensure that they can meet the demand for their products wherever they are used. WMFTG recognises the importance of regional based factories and distribution centres to meet future biologic economics and product demand.

COLLABORATING TO FIGHT A DUAL THREAT

Biologics are so important to the future of medicine because they offer a targeted approach to delivering effective treatments and cures to some of the most widespread medical conditions.

We face a dual threat in our culture today:

- Pathogens are ever evolving and we need to adapt preventative and therapeutic responses to these new threats as they emerge.
- As we live longer, we encounter more ailments and they become more difficult to cure in our ever-changing bodies.

By developing specific and targeted treatments, we can start to fight both threats while reducing side effects and treating conditions more effectively. The next few years will see huge advances. We'll see a flow of advanced therapy medicinal products (ATMP), including cell and gene therapies, reach patients and we will see the impact that they will make.

Not only do we need to develop more effective treatments, we need to do this faster, more cost-effectively, at scale and at a regional level. Without investment and focus on these goals, we will limit the number of novel therapies that can reach patients.

One thing we aren't lacking in is brainpower. As a group, we have the answers and we will solve them through collaboration. By continuing to bring stakeholders together, from the regulatory bodies to the manufacturers, license holders and suppliers, we can create a culture of open dialogue, where we all understand the challenges and we work together to solve them.

REFERENCES

Jim Sanford is the Sector Manager for Biopharm Fluid Paths at WMFTG and also serves on BioPhorum Supply Partner committees to help develop best practices in biologics production.

1. Global Biologics Market Size, Market Share, Application Analysis, Regional Outlook, Growth Trends, Key Players, Competitive Strategies, and Forecasts, 2018 to 2026, researchandmarkets.com, April 2018.
2. https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products
3. https://drug-hunter.com/2020/01/01/2019biologics/
4. https://bioprocessintl.com/bioprocess-insider/facilities-capacity/biomanufacturing-capacity-45-growth-but-new-blockbusters-could-leave-shortage/?utm_source=hs_email&utm_medium=email&utm_content=78929443&_hsenc=p2ANqtz-_X6rvi0jhFRkeH26FYoYU6MrJzFMw0AzYwxMMsBHDN6SG-Vkto8qNquk5eT7NTCW9wYqbVEkNNVn1SjjgfbuFjbZ880ww&_hsmi=78929443
5. https://www.envisioninteligence.com/industry-report/asia-pacific-biologics-market/
6. https://www.statista.com/topics/5887/cancer-in-latin-america/#:~:text=Breast%20and%20prostate%20cancer%20are,cases%20per%20100%2C000%20population%2C%20respectively
7. 16th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production: A study of biopharmaceutical developers and contract manufacturing organisations. April 2019. BioPlan Associates.
8. https://www.pharmafocusasia.com/strategy/personalised-medicines
9. https://www.pharmamanufacturing.com/articles/2019/biosimilars-are-coming/