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Fluid Technology Group

# PERSONALISED MEDICINE

## Biomanufacturing Challenges – Succeeding Beyond the Blockbuster

By James Drinkwater, Head of GMP Compliance and Aseptic process integration at Franz Ziel GmbH (Germany); Melanie Bull, Director, Oxbox and Fill Finish Operations at Oxford Biomedica; Elizabeth Wahl, PhD, Strategic Product Manager at Gemini Bio and Jim Sanford, Sector Manager, Biopharm Fluid Paths, Watson-Marlow Fluid Technology Group (WMFTG).

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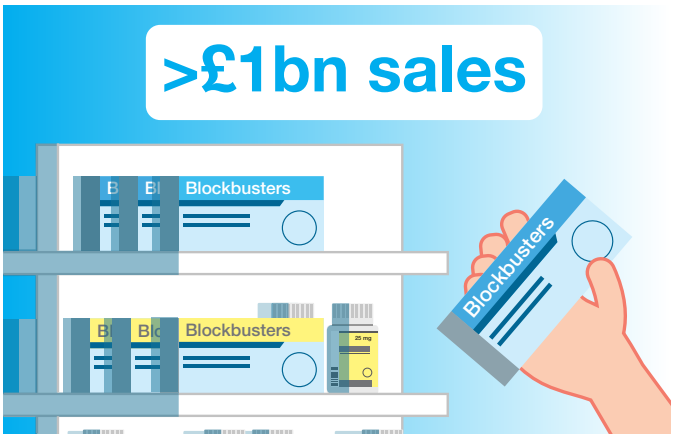
# PREFACE

Over the last two decades, the pharmaceutical industry has faced major challenges to its traditional business model. The cost of drug development is rising while the number of FDA approvals is, at best, slow[1]. High levels of competition in existing markets and more stringent criteria for US drug approval and healthcare insurance pay-outs, mean that pharmaceutical profits are in decline[2].

With fewer blockbuster drugs (those with peak sales exceeding £1bn[3]) reaching the market, pharmaceutical companies are turning to the lucrative promise of personalised medicines. This new medical paradigm uses advances in genetics and bioinformatics to target drugs to the patients who will most benefit. The hope is to help those who don't respond to existing broad spectrum medicines – a major problem in medicine. For example, a 2001 study found as many as 40% of patients did not benefit from common asthma and diabetes drugs[4].




Like many novel treatment approaches, adoption of personalised medicines varies considerably around the world due to different healthcare systems, relative cost and local GDP. South East Asia is a prime example of this, with significant adoption in Singapore and Thailand, compared to much lower elsewhere[5]. Both China[6] and South Korea[7] are investing heavily in this area, offering significant space for development. Other regions are also embracing the shift towards personalised medicine; The African Genomics Centre opened in Cape Town in 2018 with the aim of harnessing the science of genomics to improve understanding of South Africa's diverse gene pool and improve treatments for common diseases[8].

As personalised medicines are tailored to specific genetic profiles, understanding genetically diverse populations is a key area of interest. Whilst significant progress has been made creating extensive genome databases, starting with the likes of the Human Genome Project, existing genetic databases are significantly populated with Caucasians' data. The genetic diversity of other populations, such as Latin America[9] and Asia Pacific[10], should be fully investigated in order for everyone to fully reap the benefits of precision medicine.

Another emerging trend is a shift towards cell and gene therapies. These therapies, which use genes or cells to cure disease, form a key part of advanced therapeutic medicinal therapies (ATMPs). For example, current CAR-T therapies, such as Yescarta® from Kite Pharma, involve modifying a patient's cells to treat blood cancer[11]. Cell and gene therapies, along with other biologics, have increased their share of the global pharmaceutical market by 9% in a decade and this shows no sign of slowing down[12]. The majority of biologics sales are currently in the US and unsurprisingly emerging markets fall a long way behind with less money to spend on expensive novel therapies.

# A NEW CHALLENGE FOR PHARMACEUTICAL COMPANIES

The growth of personalised medicine is creating new challenges for pharmaceutical companies – both at the R&D and manufacturing stages. Companies are under pressure to get to market quickly both due to lower return-on-investment (ROI) and quicker regulatory approval of personalised therapies. Personalised medicines mean lower ROI because the market is smaller, with fewer patients benefitting from each therapy. This is balanced by higher costs of ATMPs but there are limitations on what patients and health care providers can afford which in turn makes the market even smaller.

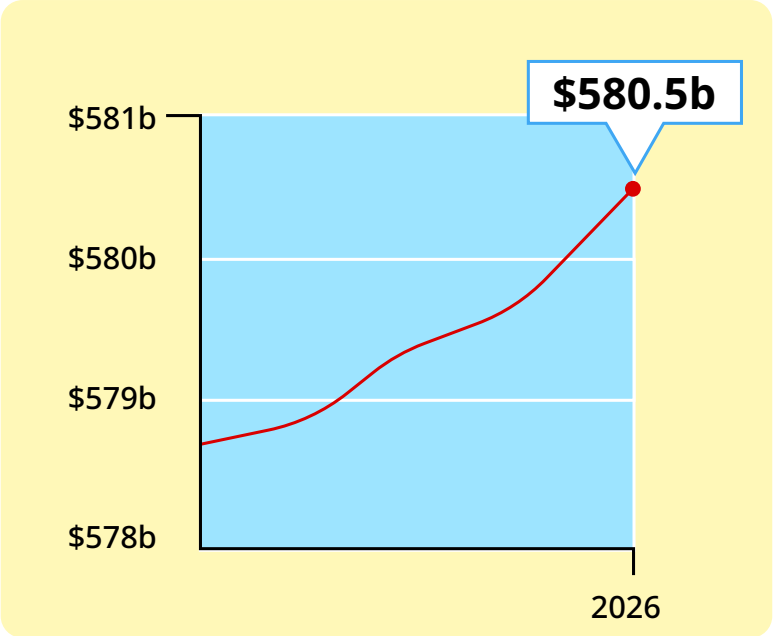
With smaller patient populations and lower ROI, companies face a more competitive marketplace. Fast-track regulatory approvals are increasingly being sought, and granted, to drug developers keen to gain an early market lead[13]. In addition, as patents expire, companies face competition from cheaper generic therapies. For example, multiple biosimilars have now become available, or are in development, for anti-TNF therapy adalimumab – a treatment for psoriasis and other autoimmune diseases[14].

Uptake of biosimilars varies significantly depending on both drug and location. For example, Scandinavian countries have the highest use of biosimilars for Infliximab, another TNF-α inhibitor, compared to very low uptake in both Canada and Japan[9]. Emerging markets have the greatest potential benefit from biosimilars due to their increased accessibility and affordability.

In the R&D phase, personalised medicine presents a challenge in Phase III trials. Companies need to identify a subset of patients who will benefit from the therapy – sometimes with a very rare disease *(see boxout page 7)* or who show specific genetic or other biomarkers. The genetic mixture in Latin American populations is a prime example of this and could result in different outcomes from one population to another (pharmacoethnicity)[15]. Identifying the correct biomarkers and finding these patients adds time and cost to drug development. In addition, the smaller number of patients adds time and complexity. According to Forte Research, 85% of Phase III clinical trials fail to retain enough patients to successfully complete a study[16] – and precision medicine compounds this problem.

# BIOMANUFACTURING: A PARADIGM SHIFT?

With the growth of personalised medicines, biomanufacturers are facing a disruption to existing business models. Whereas small molecule blockbuster drugs used to treat common diseases were often cheap, and produced in high volumes, personalised medicines use smaller batches with high costs per batch. Cell therapies Yescarta® by Kite Pharma and Novartis' Kymriah, for example, have costs of $373,000 and a one-time cost of $475,000, respectively[17]. Each batch of these therapies treats a single patient – a far cry from Pfizer's blockbuster Viagra[18].




With personalised medicines so expensive per treatment, biomanufacturers increasingly need to minimise product loss during production. In addition, with many companies now producing several drug types in a single facility (e.g. CAR-T, viral vectors and monoclonal antibodies) – it's essential to minimise cross-contamination and ensure that production technology is as flexible and configurable as possible. Another challenge is ensuring sterility of the product as biologics, including cell and gene therapies, can't be heat-sterilised at the end of the manufacturing process.

# TREATING DISEASES AFFECTING ONE IN A MILLION

Treatments for super-rare diseases, such as Huntington's and Tourette's, are part of the trend towards personalised medicine. These diseases, which affect a small number of patients, aren't cost-effective for pharmaceutical companies to develop without government help.

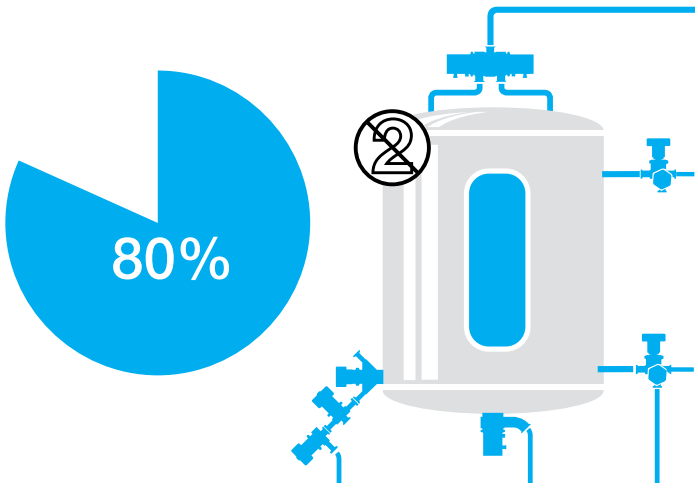
In the United States, the Orphan Drug Act of 1983 helped pharmaceutical companies tackle orphan diseases[19]. The Act gave them federal government benefits in exchange for efforts to develop new drugs, such as market exclusivity and reduced taxes.

Today pharmaceutical companies can get help with securing funding and patient recruitment, thanks to organisations like Orphanet[20]. Established in France by the French National Institute for Health and Medical Research in 1997, Orphanet involves a consortium of 40 countries and provides information through its web portal on the genetics of rare diseases as well as on clinical trials and patient organisations.

# SHIFTING FROM STEEL TO SINGLE-USE MANUFACTURING

In the days of blockbuster drugs, biomanufacturers used bioreactors and other equipment made of stainless steel. These were heat sterilised and validated between batches, which was not a problem because batches were large. Today pharmaceutical manufacturers are responding to the challenge of personalised medicine by turning to single-use systems. A study by BioPlan Associates, for example, found that 90% of biomanufacturers now use disposables for basic tubing, clamps, filter cartridges and connectors[21].

Single-use devices have also grown in popularity for bioreactors, mixing systems and in chromatography, with manufacturers now using disposable systems at every scale of manufacturing – from clinical trials to large-scale production. Again, according to the BioPlan Associates study, more than 80% of biomanufacturers now use single-use bioreactors at some stage of production[17]. Furthermore, according to a recent study, the worldwide market for bioprocessing single-use systems worldwide is due to grow by 12.8% CAGR between 2020 and 2027[22].




The advantages of single-use systems are enormous. Disposable devices arrive pre-sterilised and validated, reducing the risk of contamination of expensive personalised products. They can be disposed of between batches, saving time on sterilisation and validation and providing further cross-contamination control, which is especially useful for targeted therapies. In addition, unlike large stainless-steel devices, disposable systems require a small initial capital investment and are highly flexible, speeding up deployment and time to market. Over two thirds of US respondents to the BioPlan Survey expect to see a fully single use facility within five years. Western Europe was a little more conservative at 59.4%, but over half still expected to see this[23].

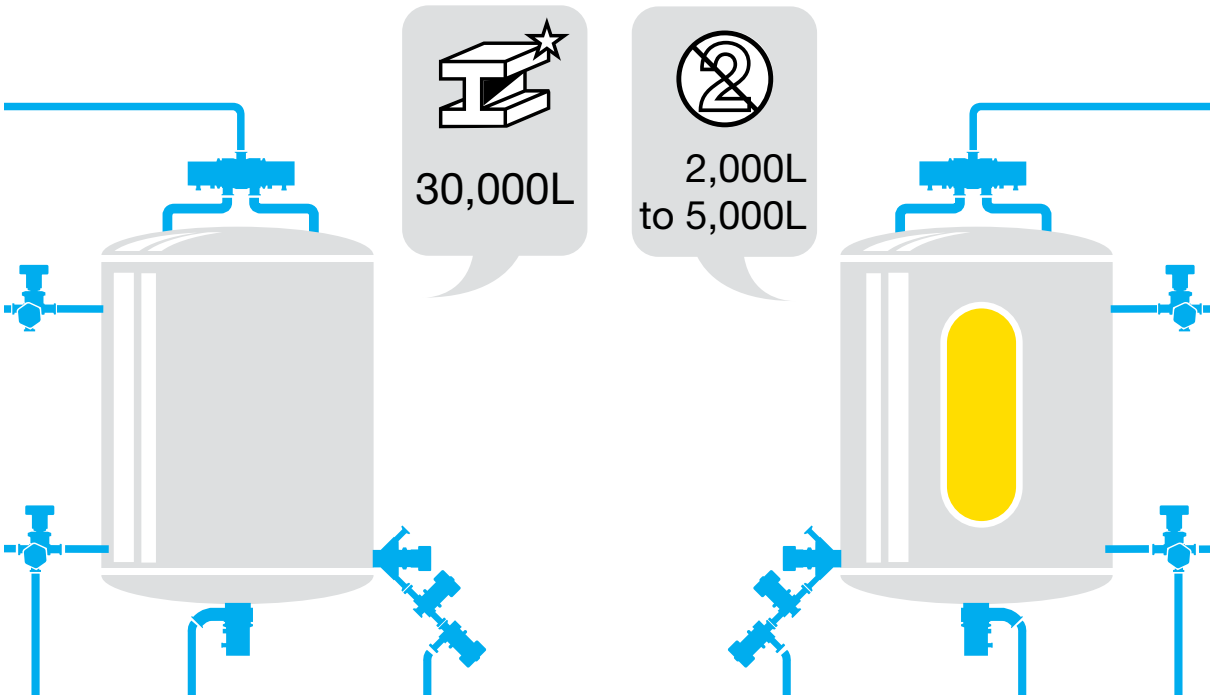
With single-use systems now widespread in biomanufacturing, suppliers are now adapting their technologies to the new challenges faced by customers involved in personalised medicine. For example, with biomanufacturers now adopting higher-titre bioreactors to produce more small batches in less time, Watson-Marlow Fluid Technology Group has developed the Quantum 600 single-use peristaltic pump to allow faster flow rates with less damage to cells[24].

# SCALING DOWN AND OUT

Blockbuster drugs are made in much larger batches than today's personalised therapies. As a result, companies need smaller systems than in the past. A typical stainless-steel bioreactor, for example, might reach 30,000L whereas a single-use bioreactor for a targeted biologic is more likely to be in the 2,000 to 5,000L range.

With companies desperate to reach market as quickly as possible, scaling up from smaller to larger-scale equipment is also declining in popularity. Moving from a 50L bioreactor to 2,000L, for example, creates problems with equipment configuration, which can slow down the drug development and biomanufacturing process. As such, companies are increasingly 'scaling out' – increasing their production capability by buying multiple identical machines.

In addition, biomanufacturers are seeking flexible machines that allow rapid change-over times and customisation between batches. The Flexicon FPC60 Fill/Finish machine[25], for example, has been specifically designed for customers seeking an affordable vial-filling solution for small batches or for scaling-out larger processes. The machine automatically measures vial dimensions, reducing the amount of configuration required between batches.



# TURNING TO AUTOMATION

With cell therapies like CAR-T costing in excess of $300,000 dollars, losing a batch to contamination or equipment failure can be disastrous. Many biomanufacturers have turned to fully or semi-automated systems to remove human error and contamination from their processes. Although it may seem as though fully robotic systems are best, many biomanufacturers prefer semi-automated hybrid systems. These limit interventions during automated filling steps, when product sterility is at most risk, but allow controlled and qualified human interventions to fix, for example, a loose vial cap in a fill/finish machine, without having to open a fully closed unit and compromise the sterility of the entire batch. In addition, suppliers are increasingly designing equipment to reduce the risk of product loss or wastage. For example, the FPC60 Fill/Finish machine has an automated inline weight check to ensure that each vial has the correct fill volume.

# DEFINING THE VECTOR JOURNEY ON THE ROAD TO PERSONALISED MEDICINE

Oxford Biomedica is a leading gene and cell therapy pioneer and owner of the cutting-edge viral delivery platform technology LentiVector®. These vectors are produced in a small, batch process for use in the very latest personalised drug developments.

Technology platforms, with their standardisation of production methods, are crucial to the future success and growth of the precision medicine market, but there are significant challenges to face when working at the cutting edge of gene and cell therapy.

“Our viral vector is the carrier of the active ingredient used to change cells,” explains Melanie Bull, Director of Fill/Finish Operations at Oxford Biomedica. “For that reason, it has to be manufactured within the most stringent aseptic processing techniques and the EU Annex 1 requirements. We have to balance as much automation as possible with the fact that we are working with very small batch sizes. We needed to install a system that could formulate and fill in one place and that required as little intervention as possible.”

WMFTG worked together with Franz Ziel to design a complete clean room and aseptic processing system for combining formulation and filling[26]. The solution included the first installation of WMFTG’s new Flexicon FPC60 fill/finish system, creating a bespoke filling environment for small-batch processing.

“The Flexicon FPC60 has been designed for organisations working at the forefront of cell and gene therapies,” explains Jørn Jeppesen, Senior specialist, Compliance & Development, WMFTG. “This machine is all about decreasing intervention and increasing automation while allowing the system to be as flexible as the client needs it to be.”

Henrik Corneliussen, Factory Sales Manager, WMFTG, added, “It’s designed for small batch sizes and fast changeover, to cope with the demands that a CMO will place on it. For Oxford Biomedica, we needed a solution that could produce sterile clinical trial batches and scale to produce the vectors needed for these treatments.”

“This machine gives us complete control from a distance,” continues Bull of Oxford Biomedica. “We can build recipes and monitor the progress of the batch from a web interface, outside of the cleanroom. The process is semi-automated so that there is no handling of the vials and stoppers and we can swap between vial sizes with no format change or mechanical rebuild. These features all combine to reduce risk and save us considerable time and money.

“We’re already expanding our manufacturing capacity to meet the demand for our vectors and the Flexicon FPC60 is a key part of our new processing designs.”

# EXPERT OPINION – TAKING BEDSIDE MANNER TO THE NEXT LEVEL

Elizabeth Wahl, PhD, is Strategic Product Manager at Gemini Bio, a leading manufacturer and supplier of cell culture media and reagents. She discusses how solving the bottlenecks of today will pave the way for the not-too-distant personalised medicines of tomorrow.

“When it comes to personalised medicine, we are scientists standing at a filled whiteboard with great ideas but no established platforms or techniques that we can draw upon. These are exciting times, but we are still taking the first few furtive steps into a hugely complex process. When it comes to breakthroughs like this, it is crucial that we share our knowledge. Only a few pioneers have gone before us, albeit with huge success, such as the CAR-T therapy, and we need to gather their knowledge, understand the pitfalls and push to find a safe and repeatable path that progresses this exciting field.

“This collaboration needs to span across all stakeholder groups, from the research scientist to the equipment and materials suppliers and the therapeutic manufacturers. We all need to be engaged in sharing best practice and understanding the challenges that we each face. When we transfer from the lab bench to the manufacturing line, we need to know that the reagents used in the discovery phase are compatible with the regulatory requirements in every market. It would be a nightmare to discover that the product can be released in the US and then later find out that clinical trials need to be repeated in order to enter the rest of the world because one of the components is a regulatory concern. Put simply, we need to think about how we manufacture these powerful medicines when we are discovering them and can’t wait until the end to start thinking about the final product requirements.

“This partnership has already started, we are seeing pioneers sharing their experiences, competitors working together to discover techniques and the wider industry collaborating to create standards. Personalised medicine holds the secret to a cure for a class of diseases with little hope of treatment. Everyone wants this to succeed. This is what we get out of bed for.

“By tackling the emerging issues together and establishing clear standards, we are fast approaching the personalised medicine of the future. Logistics are a key barrier at the moment, with cells being taken from patients to labs and back. Personalised medicines will only be truly useful when they are available at the bedside. We’ll reach a point where we can identify a disease, produce a vector and it inject it immediately to change genetic code. Already, we can use T-cells to fight cancer and things look very promising for a gene therapy and cure for Sickle Cell Anaemia.

“With access to a lot of data and open dialogue between colleagues and stakeholders, we’re fast advancing towards effective treatments for some of our most serious diseases.”

# CLOSER CUSTOMER-SUPPLIER PARTNERSHIPS

In the past, biomanufacturers often adopted single-use systems for pre-clinical testing but were hesitant to use them for large-scale manufacturing. Today, large biopharmaceutical manufacturers have gone 100% for single-use technologies – thanks to harmonisation between supplier offerings and customer expectations, as well as a shift towards a scale out approach.

In traditional biomanufacturing, pharmaceutical companies had complete control over their production processes. Today, with single-use equipment, the trend is towards a partnership between suppliers and customers. Suppliers must meet customer expectations for a guaranteed supply of components. They must prove their customer can use their systems to manufacture drugs over the long term and put proceedures in place to minimise the risk of supply disruption.

To reach market and treat the patient as fast as possible, suppliers are also forming close relationships with their raw material suppliers – to ensure consistent high quality and timely production. Keeping a good stock of components ready for shipping is also essential to meet the needs of today's customer.

Customers and suppliers are also working together to ensure the best possible data on the safety of single-use plastics in aggressive environments, such as high temperatures or low pH. They are collaborating on best practices in supply chains and standardising customer requirements across the industry to ensure patient safety and guaranteed drug supplies.

# DELIVERING THE FUTURE OF PERSONALISED MEDICINE

Personalised medicine is poised to transform the pharmaceutical industry. Over the next few years, the trend towards new biomanufacturing approaches is expected to intensify.

Single-use technologies integrated into biomanufacturing and filling platforms are likely to be implemented throughout the drug development and manufacturing pipeline of a growing number of companies, changing the relationship between customer and supplier. Drug development processes will also accelerate, with companies aiming to bring cell therapies like CAR-T to the bedside. In the vaccine development world, the dream is to design a development suite in a suitcase, which can be brought to a region with an outbreak. In both cases, the timescale from patient tissue to treatment could be reduced from months to weeks for vaccine development or, for CAR-T, weeks to days.

# ABOUT THE AUTHORS

**Jim Sanford,**
Sector Manager, Biopharm Fluid Paths at Watson-Marlow Fluid Technology Group (WMFTG)
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. Jim has over 30 years' experience in bioprocessing, beginning his career in research before moving into product management with leading global manufacturing organisations serving the Life Sciences industry.

**James Drinkwater,**
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PHSS: Pharmaceutical & Healthcare Science Society Head of Aseptic processing and Containment Special interest group plus co-lead of Annex 1 & ATMP Focus group.
Together with the role at F Ziel James is the elected Head of the Not-for-Profit PHSS: Pharmaceutical & Healthcare Sciences Society Aseptic processing special interest group and Co-lead of the EU GMP Annex 1 and ATMP Focus group. Working experience includes 10 years in radio pharmaceutical manufacturing and over 30 years working in sterile medicinal product manufacturing support where increasingly aseptic processing applies to ATMPs. James is a Subject matter expert in Barrier Technology (Isolators and RABS) and Bio-decontamination with Hydrogen peroxide vapour (H202-VHP). James is also a Member of ISPE and Pharmaceutical Quality Group UK (PQG).

**Melanie Bull**
Director, Oxbox and Fill Finish Operations at Oxford Biomedica
Oxford Biomedica (LSE:OXB) is a leading, fully integrated, gene and cell therapy group focused on developing life changing treatments for serious diseases. Oxford Biomedica and its subsidiaries (the "Group") have built a sector leading lentiviral vector delivery platform (LentiVector®), which the Group leverages to develop in vivo and ex vivo products both in-house and with partners. The Group has created a valuable proprietary portfolio of gene and cell therapy product candidates in the areas of oncology, ophthalmology, CNS disorders, liver diseases and respiratory disease. The Group has also entered into a number of partnerships, including with Novartis, Bristol Myers Squibb, Sanofi, Sio Gene Therapies, Orchard Therapeutics, Santen, Beam Therapeutics, Boehringer Ingelheim, the UK Cystic Fibrosis Gene Therapy Consortium and Imperial Innovations, through which it has long-term economic interests in other potential gene and cell therapy products. Additionally the group has signed a 3 year master supply and development agreement with AstraZeneca for large-scale manufacturing of the adenoviral based COVID-19 vaccine candidate, AZD1222. Oxford Biomedica is based across several locations in Oxfordshire, UK and employs more than 580 people.
Further information is available at **www.oxb.com**

# ABOUT THE AUTHORS

**Elizabeth Wahl, PhD**
Strategic Product Manager at Gemini Bio
Elizabeth is a senior member of the Gemini marketing team responsible for developing unique solutions for customers within the academic, research, C&GT, and biotech markets. She has responsibility for portfolio expansion, product support, and product training. She is the scientific liaison between Gemini Bio's collaborators and partners and its internal stakeholders. Elizabeth has worked in research labs and held collaborations worldwide and facilitated others to find the right needs for their research and implement them.

She holds a doctorate in experimental medicine with a focus in tissue engineering and regenerative medicine and an MSc in molecular bioengineering. Her love for learning and bridging communication between fields has led her to pursue an MBA, which she will complete later this year. Additionally, she has been published in several scientific journals and been an invited reviewer for others research.

# COMPANY INFORMATION

**About Watson-Marlow Fluid Technology Group**
Watson-Marlow Fluid Technology Group is an award-winning, global leader in fluid management technology and for over 60 years has engineered components and systems for customers in the food processing and handling, pharmaceutical and industrial markets.

The company is part of Spirax-Sarco Engineering plc, a FTSE 100 company.
Learn more at **www.wmftg.com** or **@WMFTG_news**.

**About Franz Ziel GmbH**
Franz Ziel GmbH is a company based in Billerbeck, Germany and has almost 40 years of experience as a leading global provider of GMP compliant solutions for barrier technologies and environmental control of pharmaceutical processes.

**About Gemini Bio**
Founded in 1985, Gemini is a leading provider of cell culture solutions to the scientific community across cell and gene therapy, biotechnology, and academic research. Gemini also offers contract manufacturing and regulatory consulting services. Gemini's singular mission is to enhance human life by delivering comprehensive cell culture solutions that enable discovery, development, and production of transformational therapies. Our national sales force and international distribution network serves cell culture science worldwide. The Company is based in West Sacramento, California.

**About Oxford Biomedica**
Oxford Biomedica (LSE:OXB) is a leading, fully integrated, gene and cell therapy group focused on developing life changing treatments for serious diseases. Oxford Biomedica and its subsidiaries (the "Group") have built a sector leading lentiviral vector delivery platform (LentiVector®), which the Group leverages to develop in vivo and ex vivo products both in-house and with partners. The Group has created a valuable proprietary portfolio of gene and cell therapy product candidates in the areas of oncology, ophthalmology, CNS disorders, liver diseases and respiratory disease. The Group has also entered into a number of partnerships, including with Novartis, Bristol Myers Squibb, Sanofi, Sio Gene Therapies, Orchard Therapeutics, Santen, Beam Therapeutics, Boehringer Ingelheim, the UK Cystic Fibrosis Gene Therapy Consortium and Imperial Innovations, through which it has long-term economic interests in other potential gene and cell therapy products. Additionally the group has signed a 3 year master supply and development agreement with AstraZeneca for large-scale manufacturing of the adenoviral based COVID-19 vaccine candidate, AZD1222. Oxford Biomedica is based across several locations in Oxfordshire, UK and employs more than 580 people.
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