WATSON MARLOW Fluid Technology Solutions

Cell and gene therapies:
On the brink of commercialisation

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With their one-and-done potential and pinpoint targeting capability, cell and gene therapies (CGTs) present huge promise in the fight against a range of previously untreatable diseases. Orphan diseases, ß-thalassemia, B-cell lymphoma and spinal muscular atrophy are just some of the debilitating and life-limiting conditions that have been combated through these therapies.

The burgeoning CGT market shows no sign of slowing, valued at $4.4 billion in 2020, the market looks set to reach $34.3 billion by 2030.[1] This investment has been further bolstered by the rapid commercialisation of the BioNTech and Moderna Covid-19 mRNA vaccines, yet investment in this sector is not taken lightly. Typically, developers must invest billions of dollars in therapies that might take 10 years to reach the market as they battle the odds against high failure rates. Despite thousands of therapies in trial stages, only 22 are FDA-approved[2] and 14 are EMA-approved[3] as of July 2022.

However, many more advanced therapy medicinal products (ATMPs), such as CGTs, are now entering the commercialisation stage. Finally, they are set to bring a return on investment and deliver their promises to the patients who need them. As developers embark on this next phase, new pressures emerge. Organisations must meet ever more stringent compliance standards and ensure the very highest quality and safety levels while consistently driving down costs through efficiency.

As the industry collaborates to make CGT more accessible and affordable, this article explores the ATMP platform technology that is delivering efficient manufacturing solutions. Through flexibility, modularisation, intensification, automation and digitalisation, the industry is finding solutions for some of the most challenging manufacturing challenges it has ever had to face.

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No advancement without challenge

"We choose to go to the Moon in this decade and do the other things, not because they are easy, but because they are hard." - J F Kennedy.

Innovators in this young sector are exploring the very edge of scientific possibility, and -- like travelling to the moon -- this is no easy task.

We have seen a surge of start-ups bringing new therapies to development and an explosion of manufacturing facilities across North America, Europe and Asia, as large developers and contract development and manufacturing companies (CDMOs) expand into the CGT market. Accompanying this growth, an expanding network of catapult facilities and development projects are injecting funds, research and innovation, helping to de-risk the sector and promote further research and discovery.

CGT commercialisation is on a firm and fast trajectory, yet with any endeavour comes considerable challenges; in the case of CGTs, many of these challenges are in the manufacturing stages.

Recouping development costs

The average cost to develop a new therapy stands at $1.3 billion,[4] across 10-12 years of development. When a CGT gets to the commercialisation stage, there is enormous pressure to recoup this cost.

Already, we are seeing gene therapies pass the $1 million per dose mark,[5] a situation that is unreachable for most patients and untenable for the market. Manufacturing efficiencies are critical here to provide the cost savings that deliver payback without transferring unnecessary cost burdens to payers or patients.

For highly targeted CGTs, reducing manufacturing costs is challenging. Very small batches require single-use fermenters; in the case of autologous treatments like CAR-T celll therapy, this might be one fermenter per patient and a complete upstream single-use fluid pathway. This costly, but robust, approach is necessary because, after all, every wasted millilitre could lose thousands of dollars.

Ensuring safety for patients and operators

Contamination is a huge risk in the production of CGTs, and the very highest standard of aseptic processing is needed to mitigate this. For autologous therapies, the chain of custody needs to be failsafe; each drug manufactured could be a patient's only hope at a cure. In all cases, CGT therapies are often injected or delivered intravenously straight into extremely vulnerable patients, and sterility must be ensured.

But contamination is not just a risk to patients. Operators too must be protected against drugs, particularly with the use of bio-hazardous materials, such as genetically modified viral vectors.

The 2021 revision of the GMP Annex 1, which is the European Union's requirements for the manufacture of sterile medicinal products, will address these issues in a standardised, mandated way. It will require manufacturers to increase contamination control measures, barrier technology and automation to reduce risk to patients and operators. Requirements, such as pre-use post sterilisation integrity testing (PUPSIT) that requires sterile filter testing within single-use fluid paths, will increase the focus on ensuring each element of the manufacturing process accommodates the nuances of CGT manufacturing.

Quality without compromise

As new processes evolve and adapt to manufacture pioneering treatments, manual tasks are often added to fill gaps in automated workflows; however, with every manual step comes an added quality risk. Add to this the challenge of transferring highly sensitive cells between manufacturing stages, and it is easy to see how quality issues emerge and whole batches can be ruined.

CGTs require an evolution of current practices, yet seemingly small issues, such as part per million residues of vaporised hydrogen peroxide (VHP) in sterile containers, can destroy a sensitive therapy. These issues, in addition to chain-of-custody challenges, require a new approach to manufacturing process design.

Although individually, developers are designing quality packages to tackle these challenges, the sharing of good practice is still limited. This lack of cross-industry standardisation makes regulatory approval for CGTs a long, drawn-out process, further adding to the costs and delays in bringing products to market.

Safeguarding a stable supply chain

CGTs for rare diseases and autologous treatment are usually manufactured in smaller quantities, but if CGT development carries on its current trajectory, we could soon have therapies available for indications with larger populations, such as Alzheimer's Disease.

As the number of therapies increases, the pressure on all parts of the manufacturing supply chain likewise increases, with more demand for vectors and plasmids to equipment and single-use assemblies.

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Driving safe, compliant and cost-effective manufacturing through efficient ATMP platforms

After over 10 years of development, the 10% of therapies that make it through regulatory approval should be passed, without further delay, into a manufacturing process that is compliant, safe and cost-effective. Only then can developers achieve the ultimate goals of treating patients and recouping the investment.

ATMP manufacturing platforms, drawing on the latest technology and industry experience, are ideally placed to fulfil these goals, but they must contain certain key attributes.

Flexibility

CGTs are a broad and diverse range of therapeutics, so manufacturing platforms need to reflect this. There is strength in standardisation from modular equipment and single-use pathways, but this should not come at the expense of flexibility, which is the only way to ensure the most efficient and effective production.

Platforms need to accommodate different batch sizes, from clinical production to small batch processes. They also need to be suitable for scale-up to meet increasing batch sizes as the market demands. Ideally, this scale-out potential needs to be incorporated in the research and development (R&D) stages. By using systems in R&D that have manufacturing-scale counterparts, small batch production can be easily and predictably upsized for larger allogeneic production.

Flexibility needs to extend to different container sizes and fill volumes too, as varying therapies and their product manufactures demand.

Modularity

Modular systems that are pre-validated, enclosed and automated address many of the pain points of regulatory compliance, safety, waste reduction and changeover between products. Far from restricting flexibility, these systems are often fully configurable. ATMP filling platforms, for example, can now be configured to process a range of different products, with or without containment. Modular equipment often brings intensification benefits too. Connecting disparate functions and process steps into one intensified platform can better protect cells that need highly controlled conditions. Different manufacturing functions, even from different regions or facilities, can be brought together in one integrated system, in the same cleanroom, from bioprocessing through to formulation, aseptic processing and fill/finish. This can be a game-changer for products with a short shelf life.

When data management is also integrated, greater efficiencies, flexibilities and more robust quality control are realised, ultimately driving down the cost and time needed to produce the therapy.

Automation and digitalisation

Managing the 'human factor' is central to meeting the 'contamination control strategy' element of the new GMP Annex 1 requirements, since quality assurance is constantly challenged if automation is not employed. Human errors are mitigated by automation and human commensal contamination is further reduced by the use of barrier technologies powered by automation.

That said, robotics and barrier technology should always be fully accessible to humans. This means flexibility must be added to the design process so that interventions can be made without compromising the aseptic, grade A environment or ruining batches.

With automation also comes digitalisation, for both control and monitoring. Standard operating procedure (SOP) driven human machine interfaces are critical to maintaining a good connection between humans and machines, enabling double confirmed actions where manual and automated processes join. Intensified systems should communicate seamlessly to ensure quality oversight monitoring and establish complete control over the chain of custody. Robust environmental and process monitoring should also be employed to measure the parameters of viable and non-viable contamination and include trend data for longer-term quality assurance and efficiency improvements.

Tried, tested and pre-validated technology

CGT manufacturing requires an evolution of existing methods, rather than a revolution. It is already known how to safely transfer cells in the biologics sector, using peristaltic pumps with fast, non-shearing processes, and we already use reliable bioreactors and suspension-based culture systems in biologics manufacturing. Where tried and tested equipment is fit for purpose, it can easily be incorporated into new CGT workflows.

Single-use technology is an obvious choice, giving the option to remove every fluid pathway associated with a batch and replace it with a new pre-validated system. Without clean-in-place (CIP) or sterilise-in-place (SIP) requirements, single-use systems can guarantee sterility and meet small-batch and bespoke needs.

Single-use pathways often come pre-validated for regulatory compliance and this is extended into some automated, modular equipment too. Pre-validated, standardised systems bypass bespoke validation and design processes, provide a key part of a robust CCS and can lead to faster regulatory signoff. These are all important aspects of an efficient manufacturing process that is designed to get CGTs to commercialisation faster.

Investing in people, processing and equipment for a more efficient future

Whether manufacturing occurs in-house or through a CDMO, robust ATMP platforms are critical to meeting GMP compliance and optimising manufacturing to quickly recoup development costs.

As the CGT market evolves, modular, scalable, flexible, automated and intensified platforms, along with their single-use pathways and connected data management, will meet the novel challenges of this growing sector. Much of this enabling technology already exists. With collaboration between academia, developers, CDMOs, NGOs and regulatory bodies, this enabling technology can be used most efficiently and effectively to deliver the best quality products to patients at the lowest possible price.

ATMP platforms require initial capital investment, but the payback is fast and delivers many long-term benefits. Although fit for purpose now, many of these platforms are also ready to meet the rapidly changing regulatory and market demands.

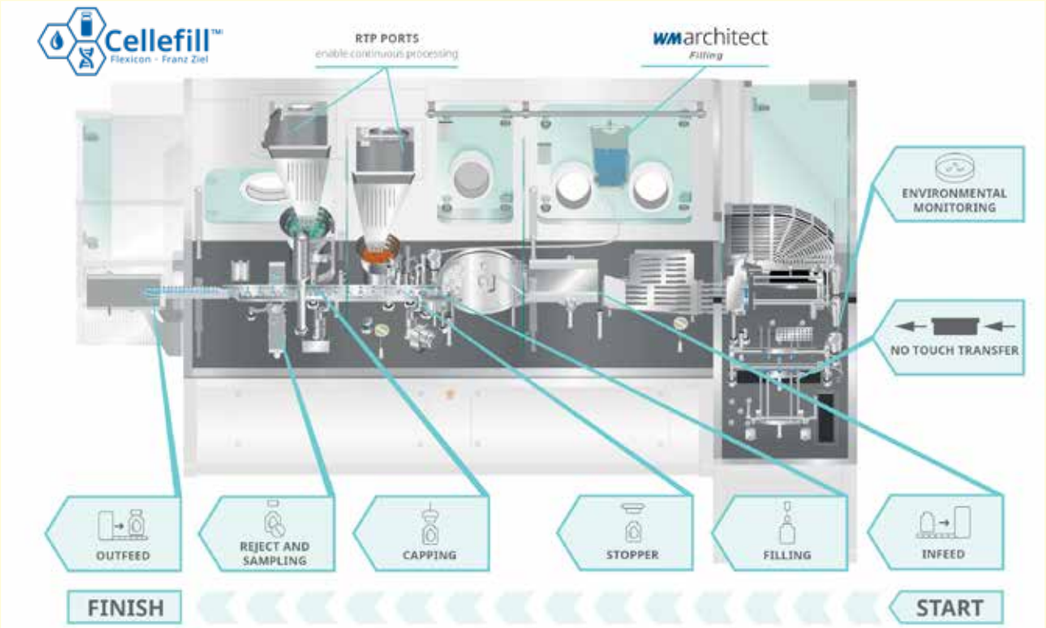
Safety, quality and efficacy will continue to be at the heart of all decisions as more and more CGTs come out of the laboratory, through commercialisation and into the caregivers' toolbox. Only through close collaboration and sharing of best-practice and skills will the industry be able to achieve its primary goal: to drive down the cost of treatment so that more and more patients have access to these lifesaving therapies.

INTRODUCING CELLEFILL™

Cellefill™ is a turnkey, small batch, vial fill/finish system developed through collaboration between Flexicon Liquid Filling (part of Watson-Marlow Fluid Technology Solutions) and Franz Ziel GmbH. This automated ATMP platform combines a vial filling machine with an integrated barrier solution, and no-touch transfer (NTT) debagging system to form one fully-integrated solution.

The platform has been specifically designed to meet the challenges of ATMP production, including CGTs, and enables developers to:

- Streamline validation and qualification for increased speed to market – by applying a quality risk management approach, the platform is designed to meet the rigorous standards of GMP Annex 1, 21 CFR part 11, EudraLex Vol4 and is future-proof for traceability compliance built-in.
- Maximise production efficiency – with recipe-driven, remote set-up and no format parts for the vial range
- Embrace flexibility – with highly accurate precision filling from micro volumes to 50 ml, speeds up to 1500 vials per hour.
- Access automation and maximise safety – with gloveless operation in critical aseptic zones and with risked-based operator intervention possible.
- Embed quality assurance as standard – with fully integrated environmental monitoring in strategically risk-assessed locations.
- Reduce batch loss risk – with flexible, in-process controls, including 100% weight check and zero-waste start-up.



Three standard models are offered:

Cellefill model	Barrier Technology	Filling Line Type	Application	Cleanroom Class
oRAB	Open restricted access barrier	Aseptic process filling line with manual disinfection	Sterile product protection of sensitive biologics, antibodies, cell protein or nucleic acid-based products	Grade B/ISO 7 cleanroom
iASP	Double wall aseptic isolator	Aseptic process filling line with automated VHP bio-decontamination	Sterile product protection of sensitive biologics, antibodies, cell protein or nucleic acid-based products	Grade C/ISO 8 cleanroom
iBIO	Double wall aseptic isolator	Aseptic-containment process filling line. Automated VHP bio-decontamination providing protection of sterile products with aerosol containment features and optional post-production VHP cycle for inactivation of live product/biologic residues	Hazardous biologics, individualised or live products requiring highest levels of cross containment control or BSL2 containment	Grade C/ISO 8 cleanroom

Taking a collaborative approach

The challenges of CGT manufacturing are new to most developers and CDMOs. However, the knowledge needed to solve these challenges certainly exists. The people behind these organisations will have experience and expertise in many key areas, perhaps GMP compliance or bioprocessing, but no one group or organisation is likely to have them all.

This existing skills shortage will continue to grow as the industry expands, especially in quality assurance and GMP compliance. Wherever skills are held by a few and needed by many, knowledge transfer is key, for CGTs this will be especially important as developers make the transition to scale up and scale out for commercialisation.

Already many regions, governments and industry facilitators are recognising this need and initiating plans to foster knowledge transfer and de-risk the industry. The Cell and Gene Therapy Catapult (CGTC) scheme[6] was set up in the UK in 2012 with the key purpose of building a world-leading £10bn CGT industry in the UK. The scheme is heavily focused on helping organisations collaborate towards "translating early-stage research into commercially viable, investable therapies" and this approach is certainly bearing fruit. There are now over 90 ATMP developers in the UK, there has been a 136% increase in the number of GMP manufacturing facilities and a 45% growth in UK clinical trials since the scheme began.

Organisations, such as the National Institute for Bioprocessing Research and Training (NIBRT)[7], are now directly focused on the ATMP manufacturing industry, driving growth through collaboration between industry, government and academia. Its world-class facility in Dublin, Ireland, runs complete CGT manufacturing lines, so that developers, CDMOs and other stakeholders can gain hands-on experience in driving efficient CGT commercialisation.

It's organisations such as these that provide the industry with the connections and tools they need to train teams, establish standards and determine the most efficient and effective way to deliver the CGTs patients so desperately need.

About the authors:

Dr Alexander Van Hagen
Life Sciences Sector Specialist

Dr Alex Van Hagen is a molecular biologist by training. With a strong commercial background Alex has specialised in experience-based consultation taking projects from cradle to gate. Previously, Alex worked in academic research, centred on producing sustainable microbial cell factories for the production of fossil-fuel-based chemicals using renewable carbon sources, and has presented his work internationally. In addition, Alex has been a guest lecturer for bioscience continued professional development courses within the UK and sits on an industry expert liaison panel at the University of Lincoln, UK.

Dr John Milne
Training Director, National Institute for Bioprocessing Research & Training (NIBRT)

Dr John Milne joined NIBRT in 2013 in the role of Training Director and his responsibilities include working with the training team who are responsible for delivering NIBRT training and education programs to both industrial and education clients. Before he joined NIBRT, John was a consultant, working with several clients in the biologics area to develop purification processes and ancillary quality documentation. John graduated from University College Dublin with a PhD in Biochemistry, specialising in molecular enzymology. Following additional academic research, he moved to industry. He has over 25 years of experience in the purification processes for proteins and peptide products. Within the biopharmaceutical industry, he has worked with Archport Ltd. and BioUetikon Ltd., both contract manufacturing organisations. In his role as Technical Manager for BioUetikon, he was responsible for technical operations. Throughout his career in industry, he has performed in a variety of roles from process development, scale-up, tech transfer and GMP commercial production.

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James Drinkwater
Head of GMP Compliance and Aseptic Process Integration, Franz Ziel GmbH

James Drinkwater is based in the UK with a global support role at Franz Ziel GmbH, the largest isolator, restricted access barrier system (RABS) and cleanroom technology manufacturer in Germany. James is the Ex-Chairman (10 years) and current Head of the not-for-profit organisation Pharmaceutical and Healthcare Sciences Society (PHSS) Aseptic Processing Special Interest Group and Co-Lead of the EU GMP Annex 1 Implementation and Contamination Control Strategy (CCS) Focus Groups. James has over 10 years of experience in radiopharmaceutical manufacturing (Amersham-GE Healthcare) and over 30 years working in sterile medicinal product manufacturing technologies, where, increasingly, aseptic processing applies to advanced therapy medicinal products (ATMPs), particularly cell and gene therapies. James is a qualified pharmaceutical process engineer with additional education in pharmaceutical microbiology and he is a subject matter expert in barrier technology (isolators and RABS) and bio-decontamination with hydrogen peroxide vapor (H202). James is also a member of the International Society for Pharmaceutical Engineering (ISPE) and Pharmaceutical Quality Group (PQG) UK.

Steve Adams
Watson-Marlow

Steve Adams has specialist knowledge from precision benchtop fillers to fully automated systems for aseptic applications in the biopharmaceutical industry. Harnessing the global reach of the Watson-Marlow Sales team, Steve has worked with companies around the world to develop products that meet their unique needs while ensuring the new products comply with increasingly complex regulatory demands. Steve has a B.S. in Biology and several years of experience in medical device product development in sterile applications.

*Details regarding authors correct at time of publish.

Company biographies

Watson-Marlow Fluid Technology Solutions is part of Spirax Group, a FTSE 100 company. The company is an award-winning, global leader in fluid management technology and for over 60 years has engineered components and systems for customers in a wide range of pharmaceutical and industrial markets.

Learn more at www.wmfts.com

Flexicon uses highly accurate peristaltic pump technology in its configurable aseptic fill/finish systems. Flexicon offers a range of liquid filling and capping systems that grow with your business. Flexicon's portfolio ranges from stand-alone units for hand filling, through semi-automatic systems, to fully automatic filling, stoppering and capping machines.

Systems are modular and offer options which allow adaption of each stage of the fill/finish process, including vial infeed, filling and stoppering and capping.

National Institute for Bioprocessing Research and Training (NIBRT)

NIBRT's mission is to help the growth and development of the biopharma manufacturing industry by providing cutting edge training and research solutions. The Institute is based on an innovative collaboration between Industry, Government and Academia and opened its world class facility in 2011 in Dublin, Ireland.

COMPANY BIOGRAPHIES

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.

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