# CELL AND GENE THERAPIES AND THEIR GMP REQUIREMENTS

By Kasia Averall

Cell and gene therapies are the latest revolution in medicine manufacturing. Unlike small molecules or traditional biotech products, these therapies introduce cells and genes into a patient to treat the underlying cause of a disease—they are living medicines.

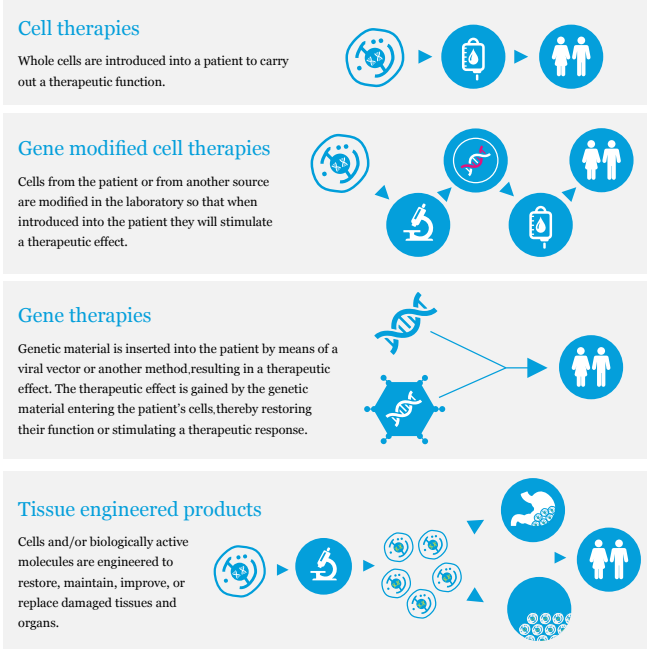
This article provides an overview of key considerations for manufacturers of cell and gene therapies. It is primarily relevant to manufacturing in the UK and Europe, but has leveraged worldwide references where possible.

## A GROWING FIELD

Broadly, this field has four types of therapies: cell therapies, gene-modified cell therapies, gene therapies, and tissue-engineered products (Figure 1) [1]. The term "cell and gene therapies" has been used throughout this article to collectively refer to these four types, also known as regenerative medicines or, in the European Union (EU), advanced therapy medicinal products (ATMPs).

Autologous therapies are manufactured using cells taken from a patient, which are then readministered to the same patient. Therefore, each batch is unique and irreplaceable. Allogenic

**Figure 1:** The four types of cell and gene therapies. Reprinted with permission from reference 1: "What Is the Potential of Cell and Gene Therapies?" ©2019 Catapult.



products are those where batches are manufactured using material from a single donor and administered to different patients (Figure 2).

The cell and gene therapy field is expanding worldwide. Data from the Alliance of Regenerative Medicine show there are now more than 906 regenerative companies worldwide, conducting more than 1,000 clinical trials [2]. Total global financing stands at $13.3 billion, a 73% increase from 2017 [2].

Some of the biggest developments for cell and gene therapies have been in oncology. One of the most advanced areas in terms of clinical development and regulatory approvals is chimeric antigen receptor T cell (CAR-T) therapy. Here, T cells (a type of immune cell) are collected from a patient and modified by adding a chimeric antigen receptor—a membrane-bound protein that recognizes cancer cells—so the CAR-T cells can more effectively distinguish cancerous cells from noncancerous cells. These modified T cells are infused back into the patient to begin attacking cancer cells [1].

Cell and gene therapies are progressing from clinical trials to approved products. In 2018, the first CAR-T therapies were approved in the EU, Australia, and Canada, following US approvals in 2017 (Table 1) [2].

Payment and reimbursement strategies are being worked out as well. The UK National Health Service offers CAR-T therapies for children and young people with B cell acute lymphoblastic leukemia, and the UK National Institute for Health and Care Excellence recommends CAR-T therapy for adults with diffuse large B cell lymphoma and primary mediastinal B cell lymphoma [3]. There is a demonstrated market demand for these products.

If current trends are realized, the number of cell and gene therapy patients in the UK is estimated to grow from approximately 200 in 2018 to around 100,000 in 2028 [4]. This dramatic growth will be underpinned by supporting systems in manufacturing, logistics, and patient treatment.

To support this expansion, robust manufacturing processes and collaboration with an end-to-end supply chain—including therapy, clinical administration, and follow-up—are required. In the EU, cell and gene therapies are medicinal products governed by medicinal product regulatory frameworks; therefore, cell and gene therapy product manufacturing must comply with GMP principles.

**Figure 2:** The manufacturing of autologous and allogenic therapies. Reprinted with permission from reference 1: "What Is the Potential of Cell and Gene Therapies?" ©2019 Catapult.

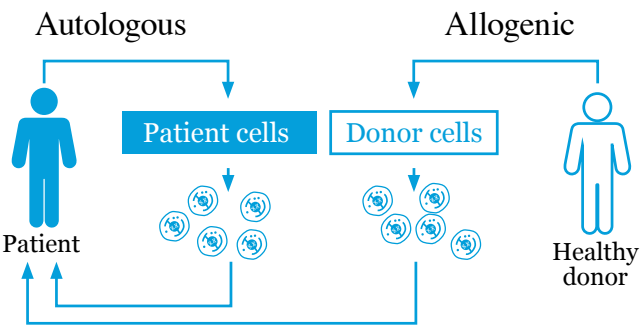
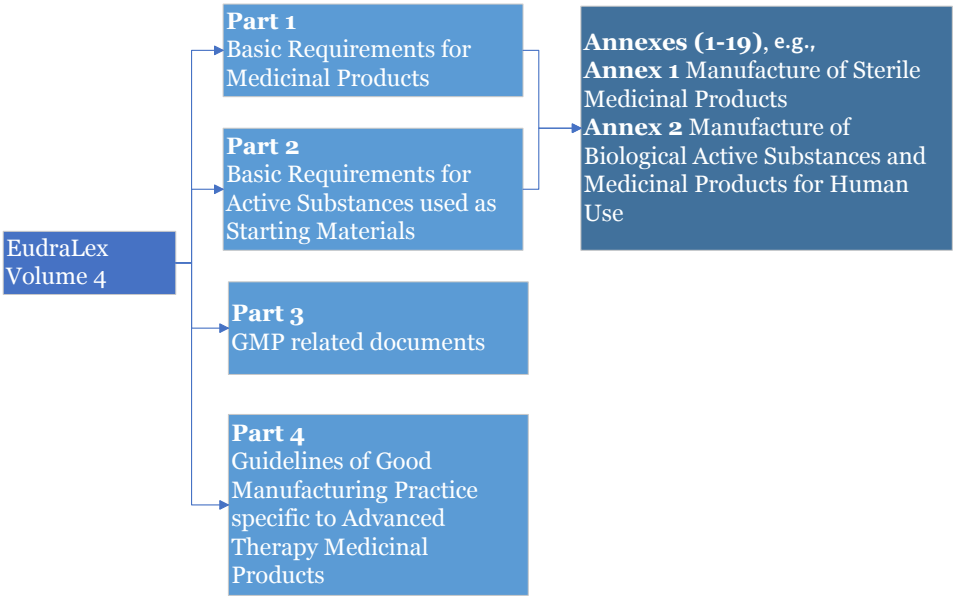



**Table 1:** Recently approved cell and gene therapy products [2].

| Name | Company | Type | Indication | Approval Status |
|---|---|---|---|---|
| Kymriah | Novartis | CAR-T therapy | Oncology (acute lymphoblastic leukemia [ALL], chronic lymphoid leukemia, and diffuse large B cell lymphoma) | US Food and Drug Administration (FDA) approval August 2017 (additional indication approved May 2018)<br>European Medicines Agency (EMA) approval August 2018<br>Health Canada approval September 2018<br>Japan approval (for ALL treatment) February 2019 |
| Yescarta | Kite Pharma/Gilead | CAR-T therapy | Oncology (B cell malignancies [e.g., non-Hodgkin lymphoma]) | US FDA approval October 2017<br>EMA approval August 2018<br>Health Canada approval February 2019 |
| Luxturna | Spark Therapeutics | Adeno-associated viral vector gene therapy | Retinal dystrophies | US FDA approval December 2017 |
| Alofisel | TiGenix/Takeda Pharma | Allogenic stem-cell therapy | Complex perianal fistulas in patients with Crohn's disease | EMA approval March 2018 |

Figure 3: EudraLex Volume 4 structure (source: Kasia Averall).




## REGULATORY FRAMEWORK

As with all EU-manufactured or supplied medicinal products, cell and gene therapies are governed by EU Directive 2001/83/EC, specifically as amended by Regulation 1394/2007 on ATMPs [5]. However, there are notable differences between the regulatory structure governing cell and gene therapy products—ATMPs in the EU—and that governing other medicinal products.

In the EU, GMP guidelines for medicinal product manufacture are detailed in EudraLex Volume 4 [6], which is split into parts and annexes (Figure 3). As of May 2018, cell and gene therapy manufacturers based in or supplying the EU must comply with the newly issued Part 4, Guidelines of GMP specific to ATMPs [7]. Prior to the release of the Part 4 guidelines, manufacturers were required to comply with existing GMP guidance given elsewhere in Volume 4, specifically Parts 1, 2, and 3 and the annexes. The new guidance is a stand-alone document designed to allow cell and gene therapy manufacturers to make full use of new technologies; it is prefaced with text confirming that GMP guidance given in the rest of Volume 4 does not apply. For example, when Part 4 was introduced, Annex 2, "Manufacture of Biological Active Substances and Medicinal Products for Human Use," was revised to exclude ATMPs [8]. Therefore, manufacturers of both cell and gene therapy products and other medicinal products should ensure that their pharmaceutical quality system (PQS) satisfies the requirements of all relevant EudraLex parts.

Other regulatory requirements arise from the use of human cells. Upstream of the manufacturing process, before GMP manufacturing begins, the EU's donation, procurement, and testing requirements for human cells are governed by the EU Tissues and Cells Directive (EUTCD), 2004/23/EC [9]. Once ready for manufacture, the subsequent processing, storage, and distribution of these cells comes under the remit of GMP, as detailed in Part 4 of EudraLex Volume 4.

In the UK, the competent authority for the EUTCD is the Human Tissue Authority (HTA), while the competent authority for GMP manufacturing is the manufacturer's relevant member state authority. Manufacturers must engage with both competent authorities and understand which oversees the different parts of their processes. Depending on the activities taking place on site, two authorizations may be required. To facilitate this, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) Innovation Office offers a one-stop shop—a single point of contact for all regulators involved in regenerative medicines, including the Human Fertilisation and Embryology Authority, the Health Research Authority, the MHRA, and the HTA.

The manufacture of cell and gene therapy products may include genetically modified organisms (GMOs), in which case manufacturers must also comply with relevant health and safety regulations. In the UK, this is covered by the Genetically Modified Organisms (Contained Use) Regulations 2014 [10]. Unlike GMP guidance, which seeks to ensure the therapy quality, health and safety regulations ensure that risks to the health of the manufacturing operatives and the environment have been fully assessed. These regulations mandate a containment strategy to prevent release of GMOs into the environment. Similarly, any discharge of waste streams down the drain may require local trade effluent permission.

Other regulations that apply to other medicinal products apply equally to cell and gene therapies, such as the guidelines issued by

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the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [11]. ICH Q9 provides the principles of quality risk management, which are helpful for cell and gene therapy manufacturers required to comply with the risk-based approach mandated by EudraLex Volume 4, Part 4. Another example is pharmacopoeias; Part 4 specifically references European Pharmacopoeia 5.2.12, "Raw Materials of Biological Origin," meaning manufacturers must consider these requirements for the raw materials they are using in cell and gene therapy manufacturing.

## MANUFACTURING CHALLENGES

With the cell and gene therapy field expanding so quickly, manufacturing processes need to deliver reproducible and safe processes at an achievable price. This section outlines some challenges facing cell and gene therapy manufacturers.

### Manufacturing Processes

Cell and gene therapy manufacturing processes range in complexity. Although some processes do not require substantial manipulation of cells, others include more detailed cell cultivation or manipulation steps, such as gene modification. None of these processes are risk-free, and all pose challenges to the manufacturer. To meet these challenges and provide guidance for a range of manufacturing processes in a rapidly developing field, EudraLex Volume 4, Part 4 describes the risk-based approach that applies equally to all ATMPs in all settings.

When making, designing, and implementing cell and gene therapy manufacturing processes, manufacturers need a process to identify the specific risks associated with the product and manufacturing process and implement appropriate controls. These risk assessments should consider the specific risks posed by autologous or allogenic therapies. For autologous products, where each batch is unique and irreplaceable, the manufacturer must implement enough controls to ensure that each batch is of an appropriate quality despite the limited batch sizes, inherent variability of starting material, and manufacturing process constraints. For allogenic therapies, batch sizes and patient populations can be much larger.

### Supply Chain Complexity

Managing supply chain complexity is not a new issue for the pharmaceutical industry. Every manufacturing process requires starting materials, raw materials, and consumables to yield product, samples, and waste. Cell and gene therapies are no different, and many existing supply chains are based on those used by traditional biotech or blood products. Additional challenges are posed by autologous product manufacturing, where vein-to-vein traceability is required. Traceability must begin before batch manufacturing, with the collection of the patient cells, and continue after manufacturing, as the therapy is administered to the patient, with the manufacturer observing all post-marketing pharmacovigilance requirements.

### Storage and Equipment

Once they are on site, human cells and the raw materials required for manufacturing must be carefully stored to maintain them. Cell and gene therapy manufacturing sites contain vapor-phase liquid nitrogen storage, –80°C storage, as well as controlled ambient, 2°C–8°C, and –20°C storage. When assessing risk in these storage areas and implementing controls to prevent failure, manufacturers must consider that patient material is irreplaceable and loss of cell culture ingredients, such as labile cytokines or growth factors, may prevent batch manufacturing from occurring within the time frame required by the patient.

Although magnified by autologous product manufacturing, these considerations are shared by allogenic product manufacturing processes. Both manufacturing processes tend to use single-use manufacturing equipment—which must also be traceable throughout batch manufacturing—such as tubing sets, bags, and filters. While some types of single-use equipment come from large biotechnology manufacturers as off-the-shelf items, many more need to be custom designed by the manufacturer, which increases the risk of loss. A humidity excursion in the warehouse may not impact these products directly, but it can damage the packaging seals, rendering them nonsterile. Although there are advantages to single-use consumables, the plastics and resins used in their construction or the methods used to sterilize them may adversely impact GMP manufacturing processes, such as cell differentiation. Cell and gene therapy manufacturers should work closely with suppliers to ensure control over plastics and resins used in the manufacture of these items—a task made more difficult by the relatively small scale of manufacturing processes. Cell and gene therapy manufacturers are small-scale customers to most suppliers, at least for the moment.

### Variability Control

As manufacturing processes work with biological material, there is a high degree of variability in both the starting and raw materials and the finished products. Starting materials received from individuals vary from person to person, and with the collection method. Raw materials, such as cytokines, can have a significant impact on cell behavior and batch quality. Cell and gene therapy manufacturers must understand the impact that each batch component can have on the quality of their finished therapy and implement controls accordingly. Depending on the phase of manufacturing, issues to be addressed will include specification setting, supplier management, or working with suppliers to supply pharmaceutical-grade materials in place of research-grade materials. Suppliers of raw materials suitable for small-scale research batches may not be suitable for or able to supply large-scale GMP manufacturing processes. In addition, there are a limited number of companies supplying the materials required for cell and gene therapy manufacturing processes. The challenges of a large-scale biotechnology supply chain are only enhanced for newer, cutting-edge, smaller-scale cell and gene therapy processes.

### Sterilization

Cell and gene therapies are generally administered intravenously and, therefore, must be sterile. However, as living products, they cannot be sterilized by heat or irradiation. In addition, because human cells are larger than a 0.2-µm sterilizing filter, cell and gene therapy products cannot be sterilized by filtration. Therefore, cell and gene therapies require aseptic manufacturing processes; additionally, all batch inputs, including any viral vectors used, also must be sterile.

### Open Processing

Most cell and gene therapy manufacturing processes were developed in academia and consequently begin as open processing, taking place in a biosafety cabinet with an EU Grade B background (roughly analogous to an ISO 14644-1 Class 5 or Class 6/US FDA Class 100 or 1,000 background). Manufacturers of traditional sterile products will be familiar with the complexities and cost of running cleanrooms for this class. Open processing comes with an increased risk of product contamination from the environment or operators, and, once contaminated, irreplaceable patient material may not be recoverable. There are higher risks—and costs—associated with the increased gowning, environmental monitoring, and cleaning regimens required to support an EU Grade B environment. Therefore, where possible, manufacturers are increasingly working to close their manufacturing processes or conduct the open steps in an isolator, allowing them to take advantage of an EU Grade C or Grade D background (approximately equivalent to an ISO 14644-1 Class 7 or 8/US FDA Class 10,000 or 100,000 background). Manufacturers must consider, however, that many components in living medicines cannot be sterilized with hydrogen peroxide vapor, requiring manual transfer into the isolator.

Cell and gene therapy manufacturers cannot perform concurrent open manufacturing of different products or batches in the same area due to the risk of batch cross contamination, especially when different viral vectors are being processed. However, each patient sample represents a unique batch—especially for autologous products—meaning manufacturers produce a large number of individual, small batches. Another advantage of closing the manufacturing process is that it opens the possibility of concurrent batch manufacture, which is necessary to deliver the throughputs required to supply predicted clinical demand. Multiple closed systems processing different batches can be used in the same area when supported by control measures to prevent cross contamination.

### Waste Stream Management

Waste streams produced by cell and gene therapy manufacturing may range from small scale for autologous cell therapy processes to much larger volumes (e.g., thousands of liters) for viral vector manufacturing. Viral vector manufacturing produces large volumes of waste because of low production yields.

In addition, if GMOs have been used in the manufacturing process, they need to be inactivated before disposal. There are two main reasons for this. First, inactivation of waste may be mandated by the GMO class of the organism. In the UK, the Genetically Modified Organisms (Contained Use) Regulations 2014 [10] have different requirements for waste inactivation based on the GMP class, with increasing stringency (e.g., autoclaving in place) required for higher-classification organisms. However, for GMO Class 1 and 2 organisms, which are more frequently used in manufacturing processes, inactivation can take place outside the cleanroom using chemical methods. The second reason to inactivate waste in situ is to prevent cross contamination in multiproduct facilities or prevent contamination of clean cell processing steps.

If inactivation using an autoclave cannot be achieved inside a cleanroom, chemical waste inactivation may be required. When selecting and qualifying the inactivation agent, the manufacturer must account for the matrix within which the agent will work. This will include a background of human cells, any potential bacterial or fungal contaminants, and the environmental conditions such as pH and temperature representative of the process.

## CROSS CONTAMINATION

Manufacturing sites may be multiproduct, requiring control measures in place to prevent batch contamination. For autologous gene therapy products, where each patient sample represents a unique batch, different products can be manufactured using different viral vectors. Most of the cross-contamination measures described in this section are based on measures in place at the Cell and Gene Therapy Catapult Manufacturing Centre in the UK, where viral vector manufacturing occurs under the same roof as cell therapy manufacturing.

For these types of multiproduct manufacturing facilities, cross-containment measures start with facility design. The requirement for segregated areas can be achieved by dedicated air-handling units in each area. If the HVAC systems serving manufacturing areas provide 100% fresh air with no recirculation, different batches can be processed within isolators concurrently as long as they are supported by a robust risk assessment with appropriate control measures in place. Pressure cascades should be used to maintain cleanroom grade and containment. The latter can be achieved through either pressure sinks or bubbles.

When making this decision, manufacturers must assess the activities occurring in each area (e.g., ensuring mitigating controls are in place to prevent particulate contamination generated from gowning activities being pushed into cleanroom manufacturing areas). Complex HVAC systems are at increased risk for failure; therefore, manufacturers must understand airflows in the event of HVAC failures and design processes accordingly. If the pressure cascade does not fail-safe and maintain containment, even a brief HVAC failure can spread contamination through an entire manufacturing facility.

Operational measures should be determined by risk assessment and be based on the types of organisms handled on site. Manufacturers must understand the risk associated with their specific materials. Factors to include in this risk assessment include the GMO class or containment level required, results of

mycoplasma or sterility testing, any microorganisms (e.g., adventitious agents) that could be transferred to the manufacturing process (for cell lines), or if any viral vectors used are capable of replicating (i.e., replication competence). Donor material should also be screened for infectious agents.

The risk of cross contamination can be further reduced by implementing segregated material, people, and waste flows; adopting a gowning regimen that prevents movement from areas where viral vectors are handled (i.e., virus-positive areas) to areas where they are not; decontaminating items leaving virus-positive areas; and closing manufacturing processes where possible. The probability of spills can be reduced by using multiple layers of packaging and using trays and totes to move materials around the facility. For selecting waste inactivation agents, cleaning agent selection should include verification with representative challenge viruses to ensure that any spills can be effectively decontaminated. Large-scale spill procedures are required for viral vector manufacturing.

## QUALITY CONTROL, PERSONNEL, AND PQS

Cell and gene therapy manufacturing processes require an underpinning PQS and quality control (QC) laboratory, and all aspects of cell and gene therapy manufacturing require trained personnel.

### Quality Control

QC tests for living therapies are complex and often lengthy, requiring specialist knowledge by analysts. With short-shelf-life batches and urgent patient need, release QC testing may require more time or material than the manufacturing process can readily support. For autologous product processes, in which each patient sample is a single batch, there is insufficient time or material to perform pharmacopoeial sterility testing; therefore, rapid sterility methods are frequently used instead. This requires enough validation and data collection to satisfy regulators, and, because these products are novel, there is a lack of data for comparability. Given the potential short shelf life of such products, manufacturers may need to adopt a two-stage release process, where sterility, mycoplasma, and environmental monitoring results are certified after the therapy has been shipped. Robust recall procedures are required to either intercept shipments or notify clinicians in the event of a specification breach.

Manufacturers need to reduce turnaround times and the amount of material that QC testing processes require. Long-term industry efforts are focusing on process analytical technology and adaptive control strategies where critical process parameters are linked to critical quality attributes. However, the therapies are still novel and supporting data sets are small.

Contract laboratories can offer solutions to start up cell and gene therapy manufacturing and remove the initial financial outlay. However, a low level of standardization in cell and gene therapy QC testing means that expertise in different tests often resides only with the manufacturer or developer of the therapy. Additionally, transporting samples to contract laboratories may adversely impact delicate samples, and turnaround times are extended.

### Personnel

To support QC needs, trained specialist personnel with an understanding of specific requirements of cell and gene therapy manufacturing is required. There is a shortage of skilled personnel, and often the scientists with the strongest understanding of the manufacturing process do not have a GMP background and have little or no experience in a GMP facility. Manufacturers need to implement robust recruitment, onboarding, and training processes to ensure their staff understands GMP requirements. In addition, as manufacturers drive toward more enclosed, automated, and predictable processes, experienced GMP staff can be recruited from outside the cell and gene therapy technology world. The requirement for trained specialist personnel is not restricted to the QC lab; manufacturing, warehousing, waste stream management, and cross-contamination prevention measures require trained personnel as well.

### PQS

Underpinning everything in this article is the requirement for a good PQS. For cell and gene therapy manufacturers, the PQS design should be specific for onsite activities. A strong quality risk management process is required to implement the risk-based approach detailed in EudraLex Volume 4, Part 4. Especially in multiproduct facilities or those handling viruses, cross-contamination strategies based on risk must be implemented and followed. As process knowledge increases through operational experience, review of deviations, and changes to product-testing data, these strategies should be continually reviewed and updated. Therefore, interrogation and trend analysis of PQS events is critical.

The complexities of cell and gene therapies necessitate a strong supplier management and supply chain strategy based on the impact of each item on finished batch quality. When timelines are short, quality processes need to be simple and flexible with rapid escalation pathways to ensure batch certification decisions are made in a timely manner and based on correct information.

Finally, to deliver these therapies to patients, manufacturers cannot work in isolation; success depends on building direct, collaborative relationships with clinics that administer these pharmaceutical products. Cell and gene therapies can have very short shelf lives, and manufacturing must be tied to patient treatment dates, especially in the case of autologous products. Manufacturers need to carefully schedule manufacturing slots and material availability with QC testing, qualified person certification, and courier availability to ensure a patient sample is successfully delivered as a life-saving therapy.

## CONCLUSION

Cell and gene therapies are regulated as medicinal products within the EU (and elsewhere) and are required to comply with GMP requirements. However, as a new form of medical intervention, cell and gene therapies face manufacturing-related challenges unlike those associated with traditional small molecule or biopharmaceutical products. These challenges arise from the use of human cells or viral vectors, biological variability in the process,

and the relative newness of the field. Many processing component or supply chain solutions are taken from existing pharmaceutical manufacturing. Cell and gene therapy manufacturers require robust PQSs and risk management strategies to maintain product quality while working in an innovative field.

## References


1. Cell and Gene Therapy Catapult. "What Is the Potential of Cell and Gene Therapies?" Accessed 15 May 2019. https://ct.catapult.org.uk/sites/default/files/publication/The%20potential%20of%20cell%20and%20gene%20therapies.pdf
2. Alliance for Regenerative Medicine. "Annual Regenerative Medicine Data Report 2018." Accessed 15 May 2019. http://alliancerm.org/wp-content/uploads/2019/02/ARM_AR2018_Report.pdf
3. National Health Service England. "CAR-T Therapy." Accessed 21 May 2019. https://www.england.nhs.uk/cancer/cdf/car-t-therapy
4. Ward, S. "Delivering Cost Effective Advanced Therapies at Scale." Presented at Phacilitate Automation SIG meeting, Hertfordshire, UK, May 2018.
5. European Commission. "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, as Amended by Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007. Accessed 11 September 2019. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf
6. European Commission. "EudraLex Volume 4: The Rules Governing Medicinal Products in the European Union." Accessed 11 September 2019. https://ec.europa.eu/health/documents/eudralex/vol-4_en
7. European Commission. "EudraLex Volume 4, Part IV: Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products." Published November 2017; compliance deadline 22 May 2018. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf
8. European Commission. "EudraLex Volume 4, Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use." Compliance deadline 26 June 2018. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/pdfs-en/2018_annex2_en.pdf
9. European Commission. "Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells." https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF
10. United Kingdom Statutory Instruments, 2014, no. 1663: Health and Safety: The Genetically Modified Organisms (Contained Use) Regulations 2014. http://www.legislation.gov.uk/uksi/2014/1663/contents/made
11. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline: Quality Risk Management Q9." Published November 2005. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf


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## About the author


**Kasia Averall** joined Cell and Gene Therapy Catapult in November 2016, tasked with establishing the pharmaceutical quality system for the new multiproduct, multi-collaborator ATMP manufacturing center in Stevenage, UK. The facility was successfully licensed by the UK MHRA in August 2018, and Kasia now leads the quality assurance team supporting a variety of cell and gene therapy manufacturers. Before joining Cell and Gene Therapy Catapult, Kasia worked in both quality assurance and regulatory affairs over a range of dosage forms. She has a degree in natural sciences (biological) from the University of Cambridge.