Regulatory Challenges Associated with the Development of Cell and Gene Therapies

The development of safe and effective cell and gene therapies (CGTs) relies on regulatory compliance and critical selection and qualification of raw materials. Regulatory classifications for advanced therapy medicinal products (ATMPs) vary globally and it is imperative for both manufacturers and suppliers to understand the requirements and obligations from each party, to achieve international compliance.

For example, raw materials of biological origin must undergo in-depth control procedures throughout every step of the manufacturing process. The risks associated with the use of biological raw materials must be understood, considered and mitigated with appropriate risk methods and quality control strategies. In this article we discuss the regulatory environment surrounding bio manufacturing of CGTs and the significance of compliance with appropriate regulations to ensure safety, quality, and efficacy of the final product.

Brief overview of ATMPs

Advanced therapy medicinal products (ATMPs) are a rapidly growing field of novel CGTs and tissue-engineered products for complex diseases such as cancer and consist of products that contain modified genetic material or engineered cells and/or tissues.[1] Their development is costly, highly complex, and lengthy due to stringent quality processes and ever-evolving regulatory requirements. The regulatory scope, definitions, and approval processes for development of ATMPs differ globally, particularly between the US and EU, increasing the time required to develop and bring these therapies to market. However, recent global events have demonstrated the urgency at which these medical solutions must progress, for example the effective yet prompt development of the COVID-19 vaccine for the SARS-CoV-2 virus.

Global international collaboration between manufacturers, researchers and regulators has been key in the rapid distribution of the COVID-19 vaccine, exhibiting that through the establishment of networks and exchange of information, the development and validation processes can be accelerated, for a faster route to market. A similar collaborative approach between manufacturers, raw material suppliers, and regulatory bodies should be followed in the development of CGTs to allow patients to more rapidly access and benefit from these innovative treatments. Manufacturers are required to have a thorough understanding of the entire supply chain and the processes expected by regulatory bodies. They should also work closely with certified suppliers to obtain high quality raw materials which will comply with the required quality standards, in order to maximise safety and chances of obtaining approvals.

Overview of the regulatory landscape

To ensure the highest quality and safety standards of ATMPs, both manufacturers and suppliers must comply with strict regulatory requirements. There is a concern surrounding the traceability of the biologic raw materials used to produce ATMPs, and the risks with the lack of traceability raw materials could pose to the safety and efficacy of the final product. The regulatory requirements set expectations and provide guidance for manufacturers so that ATMPs can be authorised and brought to market as swiftly as possible. As the field of ATMPs is still in its early days and the regulatory landscape surrounding their development is constantly evolving, collaboration between different suppliers, manufacturers, and regulators is especially important.

The regulations governing the development of ATMPs vary from country to country. Here we focus on the regulatory landscape of Europe and the US, where the majority of ATMPs are developed. In both regions, ATMPs are classed as biologics, however the sub classification groups vary across the two geographies. The European Medicines Agency (EMA) is the regulatory body responsible for reviewing and approving ATMPs across Europe. The EMA defines ATMPs as "medicines for human use that are based on genes, tissues or cells".[2] In the EU, ATMPs fall under four subgroups: gene therapy medicinal products (GTMPs), tissue engineered products (TEPs), somatic cell therapy medicinal products (sCTMPs), and combined advanced therapy medicinal products (cATMPs).

There are only two subgroups in the US: gene therapy and cellular therapy.[1] In the USA, the Center for Biologics Evaluation and Research (CBER), a part for the FDA, regulates CGT products. According to the CBER, cellular therapy products include "cellular immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells for certain therapeutic indications, including hematopoietic stem cells and adult and embryonic stem cells".[3]

Currently there are 11 approved CGTs in Europe,[4] with over 1000 ATMPs in ongoing clinical trials.[5] In 2017 the FDA approved the first CGTs, with 20 approved on the US market today,[6] and nearly 400 in development, as of 2020.[7]

It's important to understand the differences in classification and requirements to generate the most appropriate data for regulatory submission. The differences in subgrouping must be well understood and considered to classify the product appropriately. An important difference between the US and EU in terms of regulatory scope, is that the FDA controls the clinical trials, whereas the EMA does not. Clinical trials in Europe fall under the jurisdiction of the country in which the trial is taking place and are overseen by national authorities. For example, in the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) is the competent authority for clinical trial authorisation. The review and approval process also differs significantly between the EU and US.[1] Manufacturers should anticipate these variations in times and processes and adapt their development efforts accordingly.

Despite these differences, the COVID-19 pandemic demonstrates how global scientific collaboration and research partnerships can overcome regulatory hurdles, to streamline vaccine development. Achieved through facilitated information exchange, data sharing, and cross-border scientific and business support networks, these collaborative efforts aim to accelerate the development and manufacture of biologics. Agencies and governments have also contributed to this by fast-tracking the approval process and allowing large-scale manufacturing to meet increasing demand. Both the EU and US offer expedited approval processes for therapies for life-threatening diseases which offer greater therapeutic benefit than current treatment methods or meeting an unmet need. In the US, the FDA introduced the Breakthrough Therapy and Fast Track designation programs for serious disease therapeutics,[8] while in the EU, the EMA introduced the PRIority Medicines (PRIME) designation scheme to support their development.[9] In addition, working closely with trusted and experienced suppliers in the biologics field facilitates an efficient approval process by reducing risks associated with unqualified raw materials.

The varying global regulatory landscape (in EU and US)

To develop successful ATMP products, the ATMPs must comply with stringent regulatory requirements. The raw materials used for their manufacture are being increasingly assessed in terms of quality, risk, and safety, and it is recommended that they are qualified and produced consistently in accordance with a recognised quality management system. In both the EU and US, Pharmacopoeia (Ph. Eur. and USP, respectively if available), a collection of quality standards for medicinal products, stipulate the required standards that the raw materials of biological origin must comply with.

There are two European committees responsible for evaluating ATMPs prior to granting marketing authorisation: the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP). ATMPs first undergo a safety and quality assessment by the CAT, which is then passed onto the CHMP for a final authorisation decision. Manufacturers should refer to the Regulation (EC) No 1394/2007, which provides an overall regulatory framework for ATMPs in Europe. Since 2009, the CAT also provides specific scientific recommendations for ATMPs, in accordance with Article 17 of the aforementioned Regulation.[10]

Alliance for Regenerative Medicine (ARM), the international organisation promoting the development of ATMPs, supports greater harmonisation across the EU in response to the revision of the EU general pharmaceuticals legislation, and recently called for a centralised procedure around marketing authorisation and clinical trials.[11] One of the aims of the revision is to "foster innovation, including in areas of unmet medical need" and simplify the access of medicines for patients.[12]

In the US, biologics are regulated under section 351 of the Public Health Services (PHS) Act and Title 21 of the US Code of Federal regulation.[1,13] Biological products subject to the PHS Act also meet the definition of drugs under the Federal Food, Drug and Cosmetic Act (FDC Act), and therefore must be regulated accordingly.[13] In 2016, the 21st Century Cures Act (Cures Act) was passed to accelerate the development of medical products and innovations, and to incorporate patients' perspectives into the development of drugs, biological products, and devices in FDA's decision-making process. Another aim of the Cures Act is to modernise clinical trial designs and clinical outcome assessments, increasing the development and review of novel medical products. The Cures Act introduced the Regenerative Medicine Advanced Therapy (RMAT) designation to expediate the development of new therapies.[14]

Importance of regulation and Quality Attributes of raw materials of biological origin

The risk due diligence and qualification of raw materials of biological origin used to produce ATMPs is imperative, due to their heterogeneity, which makes them difficult to control, and restricts the reproducibility and scalability for other uses. The use

of animal-derived materials also increases the risk of introducing contaminants to the final product. The FDA recommends using non-animal derived materials, such as serum-free cell culture media, to minimise risk of transmission and batch-to-batch variation.[15] To avoid or minimise these risks, it is critical to understand the origin of the raw materials used to manufacture cell culture media as well as keeping tight controls on the quality and traceability of each component.

The FDA requires CGT manufacturers to provide information on chemistry, manufacturing, and control (CMC). A list of all materials used in manufacturing is required alongside the quality or grade of the materials used. The information should include the identity of the material, the supplier, the quality, the source (e.g., animal or human), country of origin and the stage at which the material is used in the manufacturing process. The manufacturer has a responsibility to establish a qualification program and provide necessary documentation to demonstrate the materials used to develop the final product meet the appropriate quality and regulatory standards. The documentation includes test results (such as adventitious agent, toxicity etc., testing) and certificates of analysis (CoAs), origin and transmissible spongiform encephalopathy/bovine spongiform encephalopathy (TSE/BSE) statements. All biological raw materials are required to undergo viral inactivation studies and confirm to be free of adventitious agents, including bacterial and fungal agents, cultivatable and non-cultivatable mycoplasmas, mycobacteria, and viruses.[16]

ATMPs that use non-graded and/or non-GMP materials without appropriate safety controls, testing and/or certifications, will require modification, such as substitution of the raw materials that are fit for clinical use, to gain regulatory approval. Many early clinical trials involved non-graded, unqualified raw materials; however, this is no longer accepted by the regulators. Increasing number of ATMPs manufacturers are struggling to obtain regulatory approval if they use non-GMP and non-graded materials in their clinical studies. Many suppliers in the entire supply chain have expert knowledge in the regulatory field and can assist with the selection of the most appropriate raw materials and tools, which is why collaboration is key in the development, manufacture and scaling of ATMPs.

In 2021, the FDA issued COVID-19-specific guidance for manufacturers of CGT products with risk-based recommendations to minimise the potential transmission of SARS-CoV-2 via the products. The guidelines highlight the need for compliance with cGMP requirements and ensuring quality-controlled evaluations of production controls. Although not specifically recommended by the FDA, manufacturers can include testing of raw materials, cell banks, intermediary and final products for SARS-CoV-2, in accordance with the manufacturer's own quality control processes.[6]

How to ensure compliance and follow best practices

Manufacturers of ATMPs should follow a risk-based approach throughout the development and manufacture of products. As part of the risk assessment, a robust quality by design (QBD) plan must be developed and should include a detailed list of identified risks with mitigation activities to minimise or remove these risks. Manufacturers should also work closely with raw material suppliers to ensure an in-depth risk assessment is performed prior to using the material in the final formulation.

The raw material grade is very critical. Raw materials must comply with compendia requirements specified in appropriate pharmacopoeia, *e.g.*, Ph. Eur., USP, BP, JP or multi-compendia. If the compendia are unavailable, additional risk assessment and justification, or additional testing should be performed to establish the suitability of the material.

The selection of appropriate high-quality cell culture media is crucial. Chemically defined media are recommended as they minimise the risks of adventitious agents and remove the effects that undefined components could have on the cell. Reliable providers of high-quality cell culture media can optimise the media to support consistent cell growth and optimal performance to meet the manufacturers' production needs while maintaining high quality standards.

It is important to understand each type of raw materials going into the product and how each material contribute to the intended use of the product. Then it is critical to qualify the raw materials to ensure safety and to demonstrate the qualification process in a well-documented traceable file. If the raw material is of animal origin, the supplier must demonstrate that all risk of viral transmissions has been removed either by viral inactivation studies or viral testing of the product. Presence of antibiotics should also be assessed to ensure that it will not present a threat to patient and/or understand the acceptable levels of such to be able to calculate the residual antibiotic quantity left in the material that is being qualified.

To obtain fully tested, highest quality raw materials, it's important for manufacturers to partner and work closely with suppliers and gain appropriate certificates such as Certificate of Analysis (CoA), Certificate of Origin (CO) for both the country and the source material, such as chemical, plant, animal or microbial-derived. The definitions describing source materials are not harmonised, so it is important to make sure supplier definitions are in line with manufacturer's definitions, e.g., animal component-free (ACF), animal-derived (AD), chemically defined (CD), xeno-free (XF), or serum-free (SF). However, all parties involved in the development and production of ATMPs such as raw material suppliers, media manufacturers, and cell processing centres must ensure safety of all materials used, this responsibility does not lie solely with the manufacturer of the final product.

Once the raw material is qualified, the final product needs to undergo further testing to ensure it meets all the safety and quality requirements before being approved and brought to the market. Furthermore, all medicinal products, including ATMPs, must comply with Good Manufacturing Practices (GMP). In doing so, GMP minimises batch-to-batch variability and ensures safety and purity of the final product, whilst confirming the supply chain has been audited for complete certification.

Summary & looking forward

ATMPs are a novel field of therapeutics with a lot of potential, but also many challenges associated with their standardised development and manufacture. For effective and efficient scalability, the variability associated with raw materials specially those of biological origin must be minimised as much as possible by controlling the entire supply chain. Although it's not possible to eliminate the variability associated with the patient's own

cells, strict control of each and every step of the development process, including the qualification of raw materials, reduces the variability in the manufacturing process, and subsequently yields higher quality end products, with better patient outcomes. Similarly, global alignment of the regulatory frameworks is required to facilitate approvals and speed up the process to bring these therapies to market. The rapid generation of the COVID-19 vaccine demonstrates the significant impact of collaboration between researchers, suppliers, pharmaceutical companies, and regulators, to reach patients at unprecedented speeds. Both the US and EU regulatory agencies have introduced fast-tracked programms to accelerate approvals of lifesaving and innovative therapies with significant public health benefit. Manufacturers need to continue to educate on the quality of the raw materials used for these development processes and understand the complex and continuously evolving regulatory environment, bring best industry practices to the processes to ultimately ensure the production of high-quality products. Cooperating with an experienced and trusted partner who can share their knowledge and provide support at every step of the development process can catalyse and minimise the challenges seen in the field and help drive innovation, to bring life-saving therapies to patients as quickly as possible.

REFERENCES

1. Iglesias-Lopez, C., Agusti, A., Obach, M., & Vallano, A. Regulatory Framework for Advanced Therapy Medicinal Products in Europe and United States. Front. Pharmacol. 10, 921 (2019). https://doi.org/10.3389/fphar.2019.00921
2. https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview, visited on 07 May 2021.
3. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products, visited on 14 May 2021.
4. https://www.labiotech.eu/in-depth/atmp-cell-gene-therapy-ema/, visited on 07 May 2021.
5. http://alliancerm.org/wp-content/uploads/2021/04/EU-Pharma-Legislation.pdf, visited on 20 May 2021.
6. FDA, Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency. Guidance for Industry (2021). https://www.fda.gov/media/145301/download, visited on 07 May 2021.
7. America's Biopharmaceutical Companies. Medicines in Development 2020 Report (2020).
8. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review, visited on 14 May 2021.
9. https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines, visited on 14 May 2021.
10. https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapies/legal-framework-advanced-therapies, visited on 14 May 2021.
11. Alliance for Regenerative Medicine. Response to the revision of the EU general pharmaceuticals legislation (2021).
12. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en, visited on 14 May 2021.
13. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products, visited on 14 May 2021.
14. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act, visited on 20 May 2021.
15. FDA, Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs). Guidance for Industry (2020). https://www.fda.gov/media/113760/download, visited on 14 May 2021.
16. FDA, Guidance for Industry - Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (2010). https://www.fda.gov/media/78428/download, visited on 14 May 2021.

Marlin Frechette

Marlin Frechette has over 30 years of experience in the Medical Device industry, servicing Pharmaceutical and Biopharmaceutical customers. As Chief Quality & Compliance Officer at FUJIFILM Irvine Scientific, she has oversight and responsibility for the Company's quality, regulatory, and compliance departments, including Quality Systems, Global Regulatory/Product Compliance, Corporate Compliance, and EHS. She holds a Bachelor's of Science with a major in Business Administration & Personnel Management.

Email: marlin.frechette@fujifilm.com