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Isolator and RAB systems in aseptic processing: Applications in advanced therapies, vaccine development and environmental microbiology

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Abstract

In aseptic processing, restricted access barrier systems (RABs) feature translucent rigid barriers that confine and separate the aseptic operating area from the surrounding cleanroom environment in a Grade A environment. Similarly, isolators are essential in gene therapy production, creating hermetically sealed and sterile environments with HEPA filters to protect products from microbiological contamination. In this sense, isolators are crucial for the manipulation of cells and viral vectors, enabling the aseptic production of advanced therapies such as those based on chimeric antigen receptor-associated T cells (CAR) *ex vivo* gene therapy and viral vectors *in vivo* gene therapy. For both isolators and RABs, the materials used in glove systems must be defined through strategic contamination control. Thus, isolators and RABs act as a bridge between research and clinical application, being fundamental for the manipulation of vectors with genetically modified viruses that deliver therapeutic genes to target cells, ensuring quality through good manufacturing practices and proving the efficacy of the most advanced treatments. These gene therapy processes require the use of isolators to guarantee an aseptic process with microbiological decontamination, being considered ideal for small-scale production with smaller and customized batches of advanced therapies. In short, isolators and RABs are the backbone of the safe and efficient production of gene therapies, ensuring that transformative innovations reach patients without risks and free of contaminants.

Keywords: Chimeric Antigen Receptor T Cells; Isolators; Aseptic Process; Gene Therapy; Viral Vectors

1. Introduction

In aseptic processing, it is essential to ensure the sterility of finished products by reducing human intervention in critical production areas to minimize the risks of microbiological contamination and cross-infection, whether for the development of a biopharmaceutical or for the manipulation of cell cultures, for example. In this context, this article reports on the use of isolators and RABS (Restricted Access Barrier Systems) in pharmaceutical production. As these systems are equipped with a variety of sophisticated protections and physical barriers, they protect the operator from harmful chemicals and safeguard the product from pathogens and other particulate contamination.

Currently, there are eight advanced products for use in advanced therapies in Brazil that utilize mechanisms of action in viral vectors and the use of CAR-T cells. The objective of this study is to map a scenario regarding the action of viruses as delivery vectors and the importance of in vitro modified cells for establishing patients under aseptic laboratory conditions. In this context, it addresses therapeutic strategies that use recombinant rAAV vectors in various pathologies of a neurological, muscular, hematological, ophthalmological, and oncological nature [1].

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Advanced therapies involve (i) cell therapy with the administration of whole cells, stem cells, for targeted treatment; (ii) gene therapy which involves the injection of genetic material (DNA or RNA) in order to induce, block or replace a gene of interest; and (iii) tissue engineering from the development of artificial tissues for use in humans (an alternative to obtaining organs for transplants) [1].The manipulation of viral cells and vectors requires the aseptic production of advanced therapies such as ex vivo gene therapy based on CAR-T cells and in vivo gene therapy using genetically modified vectors. These gene therapy processes require the use of isolators and RABs to ensure aseptic processing free from microbiological contamination, considered ideal to produce small batches customized for use in advanced therapies.

Figure 1 Production flow stages for cell therapy with bioprocess scalability.

2. *In vivo* gene therapy with viral vectors

Experimental approaches in gene therapy commonly use viruses as vectors to insert genetic material into the cell. Knowledge of the complex interaction between a virus and a host cell is applied, which includes several steps. These include interactions with cell membrane receptors (adsorption), viral entry into the cell (penetration), partial or total denudation of the viral capsid and release of viral nucleic acid for replication within the cell, as well as early and late protein synthesis, assembly and release by exocytosis, viral budding, cell lysis or even syncytium formation. Vectors currently used in human gene therapy suffer from several limitations regarding safety and reproducibility using animal models, toxicology and distribution studies [2].

Viral vectors for gene therapy can be enveloped, such as lentiviruses, and non-enveloped, such as adenoviruses. The key point of gene therapy clinical trials in humans is the production of a therapeutic vector, which can be a virus from the *Retroviridae* family, such as the chimeric Moloney-Human lentivirus (HIV-1 prototype). In addition, adenoviruses, adeno-associated viruses (AAVs), chimeric AAVs, and vaccinia viruses are other possible types of biological vectors [2].

It is worth noting that Adenoviruses, according to the Baltimore classification, comprise double-stranded DNA (DNAα) genomes grouped in Class I. The genomic DNA of this class of viruses is internalized in the cell nucleus and is transcribed into mRNA for subsequent translation of viral proteins. Later, during viral replication, structural proteins are synthesized and assembled for the assembly and budding of viral particles. They are non-enveloped viruses with icosahedral symmetry, diameter between 70 and 100 nm. They are formed by 252 capsomeres, 240 are hexamers and 12 are pentamers at the vertices [3]. Adeno-associated viruses (AAV) are small viruses (approximately 26 nm nanometers in diameter), non-enveloped, linear single-stranded DNA (ssDNA) genomes of approximately 4.8 kilobases (kb), which belong to the *Dependoparvovirus* genus, *Parvoviridae* family classified group II viruses according to the Baltimore Classification and that infect humans and some other primate species [4].

2.1. Adeno-Associated Virus (AAV)

Adeno-associated virus (AAV) gene therapy is based on replacing the viral DNA genome with a therapeutic gene to generate a modified virus as a vector to deliver genes of interest to cells. The AAV vector, with the new gene inserted,

infects target cells and delivers the functional gene, which initiates the production of the missing or defective protein. This process of cellular transduction of the AAV viral vector is considered safe and effective, with the ability to reach various tissues, including the central nervous system, enabling the correction of genetic diseases by replacing or complementing a defective gene.

However, it still faces challenges such as low immunogenicity compared to other viruses and large-scale production as well as expansion to potential cellular targets such as astrocytes or microglia. For faster and more efficient gene expression, the auto complementary double-stranded AAV (sc AAV) model is being tested. Among the diseases treated are: Spinal Muscular Atrophy (SMA), Hemophilia B, hereditary retinal diseases, Duchenne Muscular Dystrophy, Parkinson's Disease, Huntington's Disease, among others. Currently, there are approved AAV-based therapies, and Brazil offers some of these innovations, although at very high costs [5].

The following are some therapeutic products and their respective characteristics approved by the regulatory agency that utilizes the mechanism of action based viral vectors (table1):

Table 1 AAV based approved *in vivo* gene therapy

Drug Name	**Active Substance**	**Viral Vector**	**Indication**	**Biopharmaceutical**
Luxturna®	Voretigeno neparvoveque	AAV2	RPE65 mutation associated retinal dystrophy	Spark Therapeutics (Novartis)
Zolgensma®	Onasemnogeno abeparvoveque	AAV9	Spinal Muscular Atrophy (SMA)	Novartis Gente Therapies
Upstaza®	Eladocageno exuparvoveque	AAV2	aromatic L-amino acid decarboxylase (AADC) deficiency	PTC Therapeutics
Roctavian ®	Valoctocogene Roxaparvovec	AAV5	Hemophilia A	BioMarin's

2.2. Luxturna® Voretigeno neparvoveque (AAV2)

Luxturna is an advanced therapy product indicated for adult and pediatric patients with vision loss due to a hereditary retinal dystrophy (HRD) caused by biallelic mutations in the RPE65 gene. Mutations in this gene impair the production of a protein essential for the visual cycle, resulting in progressive vision loss, which can begin in childhood and progress to complete blindness. Treatment with Luxturna aims to maintain or restore vision by delivering a functional copy of the RPE65 gene directly to the retinal cells.

Voretigene neparvovec is a gene transfer vector that uses an adeno-associated viral vector serotype 2 (AAV2) capsid as a delivery vehicle. Voretigene neparvovec is derived from wild-type AAV2 using recombinant DNA techniques. This vector carries the complementary DNA (cDNA) of the 65 kDa human retinal pigment epithelium protein (hRPE65) into retinal cells. The procedure involves a surgically performed subretinal injection (under the retina). Once inside the cells, the functional gene begins producing the RPE65 protein that was absent or dysfunctional, restoring photoreceptor function and improving the patient's vision. This therapeutic product was approved by the FDA (USA) in 2017 and, subsequently, by ANVISA in August 2020 [6].

2.3. Zolgensma® Onasemnogeno abeparvoveque (AAV9)

Zolgensma® (onasemnogene abeparvovec) is an innovative gene therapy used to treat Spinal Muscular Atrophy (SMA), a rare and serious neuromuscular disease. It is administered in a single dose and, in Brazil, is available through the Unified Health System (SUS). Zolgensma® is a gene therapy drug developed to combat the underlying cause of SMA, which is a mutation in the SMN1 gene, responsible for producing the survival motor neuron protein. With the absence of this protein, motor neurons progressively die, leading to loss of muscle control, movement difficulties, swallowing, and breathing. The treatment is indicated for pediatric patients with SMA with biallelic mutations in the SMN1 gene. The drug has been registered with the FDA since May 2019 and has been approved for children under two years of age. The drug works through a viral vector (AAV9), which is a non-replicating and self-complementary virus. This vector is used to transport a functional copy of the human SMN1 gene into the patient's cells, replacing the defective gene [7].

2.4. Upstaza® Eladocageno exuparvoveque (AAV2)

Eladocagene exuparvovec (AAV2), commercially known as Upstaza® in the European Union and Brazil, and Kebilidi™ in the USA, is an innovative, single-use gene therapy indicated for the treatment of severe aromatic L-amino acid decarboxylase (AADC) deficiency. AADC deficiency is a very rare, chronic, debilitating, and potentially fatal genetic disease caused by mutations in the DDC gene, which result in insufficient or absent production of the AADC enzyme. This enzyme is essential to produce vital neurotransmitters such as dopamine and serotonin, whose deficiencies cause severe symptoms, including delayed motor and cognitive development, oculogyric crises (involuntary eye movements), and low muscle tone (hypotonia). The drug uses a recombinant viral vector of serotype 2 (AAV2) that contains a functional copy of the human DDC gene. It was approved by the National Health Surveillance Agency (Anvisa) in October 2024 for pediatric patients aged 18 months to 18 years with a confirmed diagnosis of severe AADC deficiency [8].

2.5. Roctavian ® Valoctocogeno uvaparvoveque (AAV5)

Valoctocogene Roxaparvovec (AAV5) is an innovative gene therapy indicated for the treatment of severe Hemophilia A in adults, using an Adeno-Associated Virus type 5 (AAV5) vector to deliver a functional Factor VIII (FVIII) gene to the liver, allowing endogenous production of the protein and reducing or eliminating the need for regular infusions. It is approved in the European Union and the USA under the trade name Roctavian. It is administered as a single dose to adults with severe hemophilia A without pre-existing antibodies against AAV5. The drug has demonstrated proven efficacy and long-lasting safety, with common side effects being transient elevations of liver enzymes (ALT). The AAV5 vector comprises a genetically modified virus (AAV5) to carry the DNA for human Factor VIII. After intravenous infusion, the AAV5 vector delivers the gene to hepatocytes. The liver starts producing its own FVIII protein, which is released into the bloodstream, correcting the deficiency [5,6].

3. *Ex vivo* gene therapy with CAR-T cells

The isolation of the patient's T cells after their collection refers to the term leukapheresis, in which the separation from the rest of the blood cells occurs, which are then sent to the laboratory. A viral vector delivers the gene that codes for the chimeric antigen receptor (CAR) into the T cells. After expressing the new receptor on their surfaces, called CAR T cells, they will be cultured in the laboratory for proliferation and subsequently recast into the patient. Once inserted into the patient's body, they can identify cancer cells with target antigens to induce tumor cell death. This ex vivo gene therapy process requires the use of isolators to ensure an aseptic process with microbiological decontamination, being considered ideal for small-scale production with smaller and personalized batches of advanced therapies [1].

The following are some therapeutic products and their respective characteristics approved by the regulatory agency that utilizes the mechanism of action of chimeric antigen receptor-associated T cells (CAR-T) shown in table 2:

Table 2 CAR-T cells based approved *ex vivo* gene therapy

Drug Name	Active Substance	Viral Vector	Indication	Biopharmaceutical
Kymriah®	Tisagenlecleucel	Lentiviral	Acute Lymphoblastic Leukemia (ALL), Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL)	Novartis
Yescarta®	Axicabtagene ciloleucel	Retroviral	Large B-cell Lymphoma (LBCL)	Gilead Sciences
Tecartus®	Brexucabtagene autoleucel	Retroviral	Acute Lymphoblastic Leukemia (ALL)	Kite Pharma (Gilead Sciences)
Carvykti®	Ciltacabtagene autoleucel	Lentiviral	multiple myeloma (MM)	Johnson & Johnson Innovative Medicine.

3.1. Kymriah® Tisagenlecleucel

It is an innovative, personalized CAR-T cell therapy that genetically modifies the patient's own T cells so that they can use them to fight blood cancers, such as Acute Lymphoblastic Leukemia (ALL) in young people up to 25 years old and Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL) in adults, when other treatments have failed. This therapy uses a lentiviral vector that expresses a chimeric antigen receptor (CAR) anti-CD19 composed of a variable single-chain murine anti-CD19 fragment (scFv) linked to the human co-stimulatory domain 4-1BB (CD137) and the CD3-zeta signaling domain of the intracellular signaling chain via a human CD8 spacer and a transmembrane region [9].

Tisagenlecleucel is an advanced gene and cell therapy, of the chimeric antigen receptor T-cell (CAR-T) type, approved for the treatment of certain types of hematological cancers. Tisagenlecleucel, marketed under the brand name Kymriah, is a personalized treatment that uses the patient's own cells to fight cancer. The process involves collecting T cells (a type of white blood cell) from the patient, which are then genetically modified in the laboratory to recognize and attack cancer cells that express the CD19 antigen. These modified cells are then reinfused back into the patient. The modified T cells selectively identify and destroy cancer cells that have the CD19 marker on their surface [9].

Kymriah (tisagenlecleucel) is approved by regulatory agencies such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) to treat: B-cell acute lymphoblastic leukemia (ALL) in pediatric and young adult patients (up to 25 years of age) who have relapsed or have not responded to other treatments and Diffuse large B-cell lymphoma (DLBCL) in adults who have failed two or more prior lines of systemic therapy [9].

3.2. Yescarta® Axicabtagene ciloleucel

Axicabtagene ciloleucel (named Yescarta) is an advanced anti-CD19 CAR-T cell immunotherapy used to treat B-cell cancers, such as refractory Large B-cell Lymphoma (LBCL), which do not respond to conventional treatments. It genetically modifies the patient's own T cells to attack cancer, making it a highly complex treatment with risks such as Cytokine Release Syndrome (CRS). It is an immunotherapy with genetically modified autologous T cells directed towards CD19. Thus, the patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) composed of a variable murine single-chain anti-CD19 fragment linked to the CD28 co-stimulatory domain and the CD3-zeta signaling domain. Viable anti-CD19 positive CAR T cells are expanded in cell culture bottles, flasks or bioreactors, and perfused into the diseased donor, where they can recognize and eliminate target cells expressing CD19 [10].

3.3. Tecartus® Brexucabtagene autoleucel

Brexucabtagene autoleucel (named Tecartus) is an advanced autologous, genetically modified chimeric antigen receptor T-cell therapy approved to treat certain types of blood cancers in adults. Brexucabtagene autoleucel is approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor, and relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) [11].

3.4. Carvykti® Ciltacabtagene autoleucel

It is an advanced immunotherapy to treat multiple myeloma (MM) using the patient's own T cells, modified to recognize and destroy cancerous cells that express the BCMA antigen, being an option for patients who have not responded to previous treatments. This treatment is indicated for adult patients with relapsed or refractory multiple myeloma (RRMM) and patients who have already received at least three prior therapies (including immunomodulators, proteasome inhibitors, and anti-CD38 antibodies) and have progressed. This is an autologous drug based on genetically modified cells, containing T cells transduced ex vivo using a non-replicative/replicating lentiviral vector, which encodes a chimeric antigen receptor (CAR) against the B cell maturation antigen (BCMA), which includes two single-domain antibodies linked to a 4-1BB co-stimulatory domain and a CD3 zeta signaling domain [12].

4. Role of Isolators and RABs in Gene Therapy

4.1. Isolators

Isolators are crucial in gene therapy production, creating an aseptic (free of microorganisms), sterile, and contained environment (advanced HEPA filters, with glove compartments and controlled airflow, pressure, and filtration) essential for controlling the aseptic process. This allows for the handling of viral vectors and genetically modified cells, making it possible to prevent cross-contamination of the product, as well as protecting the operator's safety from

hazardous and highly potent substances by separating them from the external environment, thus ensuring safety and efficacy in the production of therapeutic products.

There are different types of isolators used for various applications in the pharmaceutical industry, such as containment isolators. These isolators focus on protecting the operator and the environment from hazardous materials, generally operating under negative pressure. On the other hand, we can cite as an example the aseptic processing or sterile filling isolator, which generally operates under positive pressure to maintain a sterile environment against contamination. Regardless of the type of isolator, safety and compliance with standards and regulatory agencies are crucial.

4.2. Restricted Access Barrier Systems (RABS)

RABS systems include safety-locking doors, a rigid machine frame, and glove compartments planned with an ergonomic design to be compatible with the main sterilization methods, significantly reducing the frequency of glove replacement and used in contamination control and product integrity. Open or closed restricted access barriers (oRABs/cRABs) provide an alternative to isolation technology. Product protection is achieved through a combination of a physical barrier and dynamic airflow. In aseptic processing, Restricted Access Barrier Systems (RABS) feature translucent rigid barriers that confine and separate the aseptic operating area from the surrounding cleanroom environment in a Grade A environment. The operator does not need to enter the aseptic area as they use glove ports installed in the rigid barrier. There are different types of RABS: passive and active. Passive refers to air filtration and ventilation through HEPA filters integrated into the cleanroom ceiling, and active refers to additional air filtration and ventilation through an independent and dedicated air handling unit (AHU). There are also open active and passive RABS and completely closed RABS. This last one, called Restricted Access Closed Barrier System (cRABS), is a state-of-the-art aseptic processing solution that creates a closed and highly controlled environment to protect the production of sterile products and can be equipped with an automated biodiscontamination system, such as hydrogen peroxide vapor [1,8].

Adding to this the RABS, which comprises a closed system, but not completely sealed from the external environment, there are isolators capable of providing continuous and complete isolation of the interior from the external environment, in which the doors are locked during the aseptic process. These are also divided into open and closed, depending on how material is transferred in and out through aseptic connections with auxiliary equipment. For both isolators and RABS, the materials used in glove systems must be defined in the Contamination Control Strategy (CCS).

5. Conclusion

There are regulatory differences that cross borders and can significantly impact the classification of advanced therapy products according to each regulatory agency. Among them, the following stand out: Australia - Therapeutic Goods Administration (TGA), Brazil - National Health Surveillance Agency (Anvisa), United States - Food and Drug Administration (FDA), European Union - European Medicines Agency (EMA) and Japan - Pharmaceuticals and Medical Devices Agency (PMDA). Moreover, there are some advanced therapy drugs that are in phase 3 of clinical trials and, after regulatory approval, may soon be approved as innovative new therapeutic alternatives.

For the development of these gene therapies, the use of sterile environments is essential to avoid contamination through the handling of cells and viral vectors. This forum highlights the use of isolators that allow the manipulation of cell cultures in a pharmaceutical context in accordance with Good Manufacturing Practice (GMP) guidelines, providing increased sterility by reducing the risks of contamination, with applicability for cell therapy and genetics, where high throughput is required as part of quality assurance, ensuring that products are consistently produced and controlled, with quality standards appropriate to the intended use. It is important to emphasize that laminar airflow systems for filling and packaging lines are used in aseptic environments with high requirements and offer the possibility of customized designs, such as including barriers for restricted access (glove chambers, safety glass, etc.).

Regardless of the viral vector platform selected for the development of cell and gene therapies, it is essential that pilot and commercial scale production comply with Good Manufacturing Practices (GMP). Although several types of viral vectors are used in gene therapy, such as adenovirus, MMLV, virus like particles (VLP), herpes simplex virus (HSV), and vesicular stomatitis virus (VSV), the approved products have widely used lentivirus and adeno-associated virus (AAV) vectors, as exemplified by the drugs mentioned. Both viruses share the common characteristics of parallel production in a standard biosafety level 2 laboratory and are produced in GMP-certified facilities. In terms of viral platform technology, two types of cell lines are generally used for viral vector production: the HEK 293 cell line with adherent cells and the sf9 insect suspension cell line using scalable bioreactors.

Optimizing the pharmacokinetics and pharmacodynamics of recombinant viral vectors is one of the crucial challenges regarding their efficacy and applicability in current treatments. In advanced therapy using viral vectors, laboratory steps such as vector amplification, cell transfection, transduction, purification, microfiltration/ultrafiltration, and transfer must be monitored to ensure good practices in aseptic processing. In this context, isolators and RABs act as a bridge between research and clinical application, being fundamental for the manipulation of vectors with genetically modified viruses that deliver therapeutic genes to target cells, ensuring quality through good manufacturing practices and proving the efficacy of the most advanced treatments.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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