

Advancing Manufacturing for Advanced Therapies

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CASSS Cell & Gene Therapy Symposium

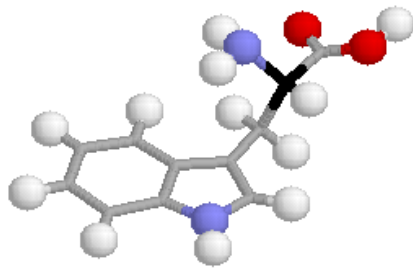
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Overview

Cell and gene therapy products hold the promise of transforming the treatment of many diseases

- Where have we come?
- Where are we going?
- How will we get there?

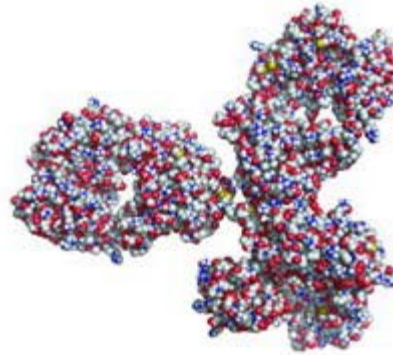
Relative Product Complexity



One subunit of a protein

10^2 Atoms

L-tryptophan
Small Molecule Drug



Protein composed of about
1100 subunits

10^5 Atoms

IgG antibody molecule
Protein Biologic



Cell composed of about
 3.6×10^6 proteins

10^{14} Atoms

Mesenchymal stem cell
Cellular Biologic

Examples of Cell and Gene Therapies



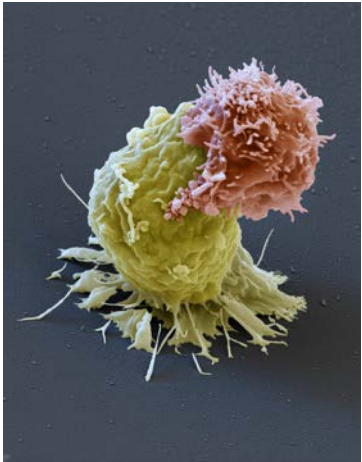
Bioengineered skin



Bioengineered blood vessel



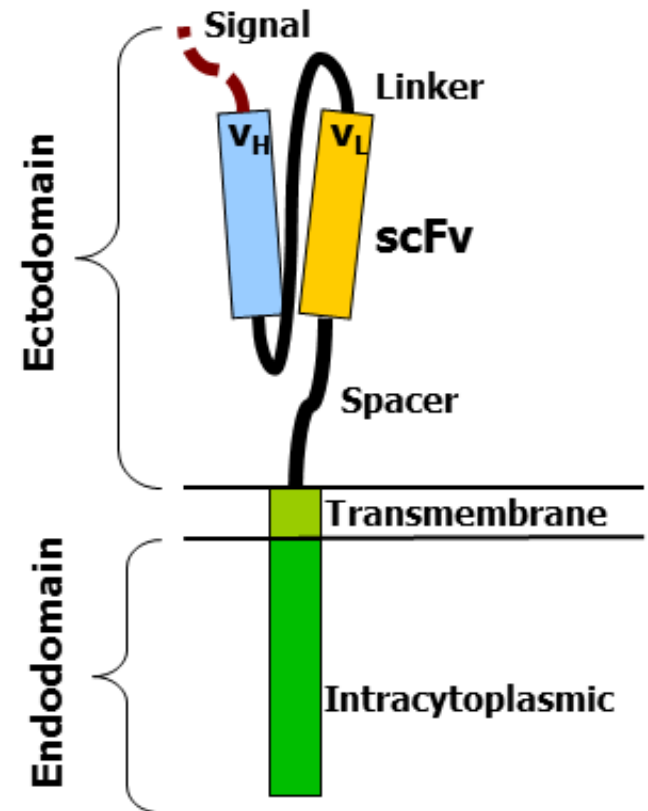
Bioengineered bladder



Chimeric antigen receptor-T cell (in red)
attacking a cancer cell (in yellow)

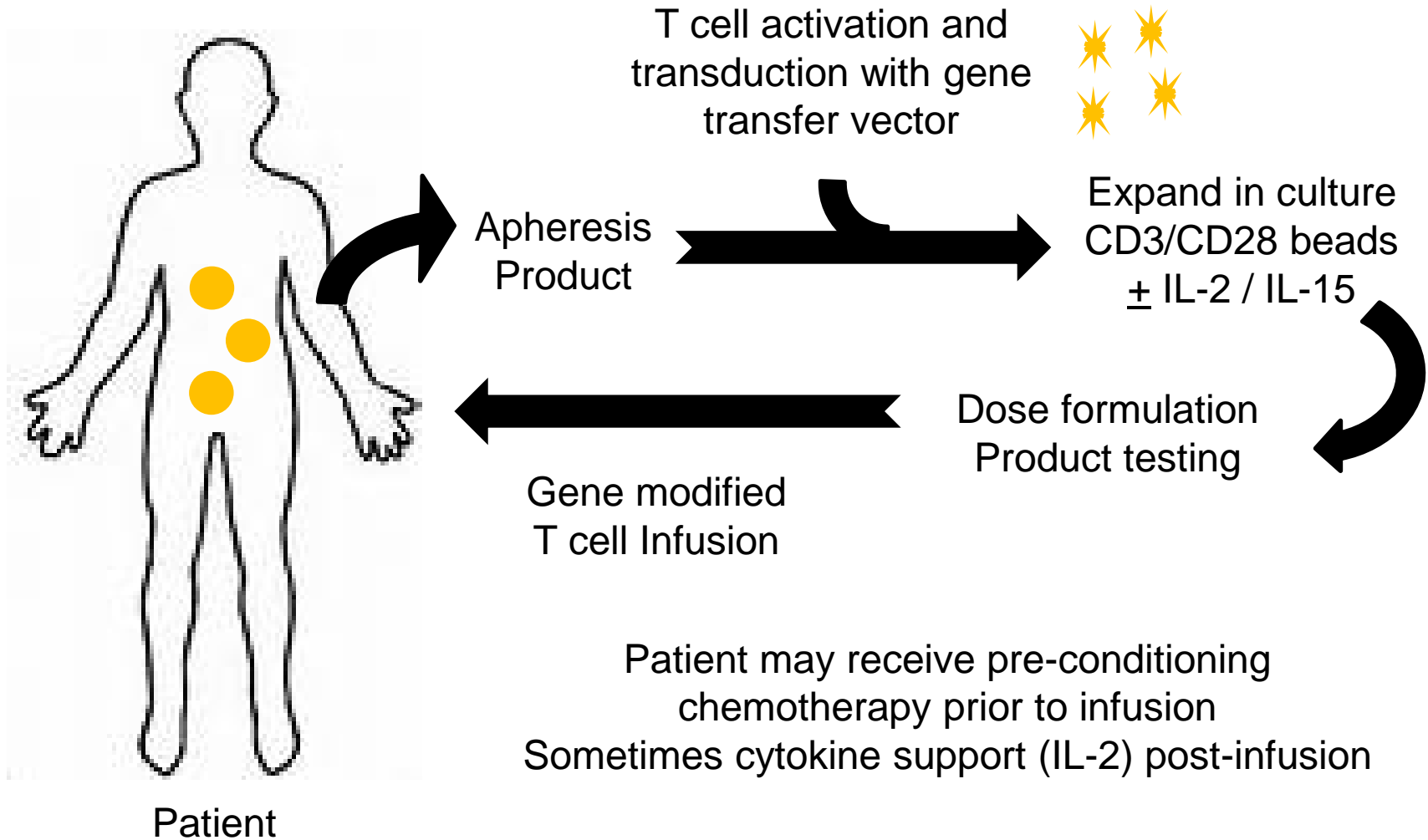
Genetic Modification: Introduction of Chimeric Antigen Receptor

- Using molecular genetics, novel protein receptors can be created that combine features of different proteins into one
- This allows one to both target and activate T cells to eliminate a cancerous or undesirable cell type



Drawing of chimeric antigen T cell (CAR-T) receptor construct

Overview of CAR-T Cell Therapy



Potential Advantages to Use of Genetically-Modified Cellular Therapies

- Appropriate methods can be used to address the issue of location of genomic integration
 - Ability to select appropriately transduced cells for administration to recipients
 - Use of newer technologies such as CRISPR possible
 - Control of effector function is possible, if necessary, through use of various approaches
- Possibility to provide therapeutic benefit with an extended duration of effect

Potential Challenges to Use of Genetically-Modified Cellular Therapies

- Process must be developed to consistently manufacture and characterize cells
- Logistics of manufacturing for autologous cells can be challenging
 - Though an allogeneic cell line (one product) may be preferable, there are developmental challenges
- Administration of therapies may be associated with various short and longer term side effects

Two Cell-Based Gene Therapies Approved in 2017

- **Tisagenlecleucel (KYMRIA[®])**: indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
- **Axicabtagene ciloleucel (YESCARTA[®])**: indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

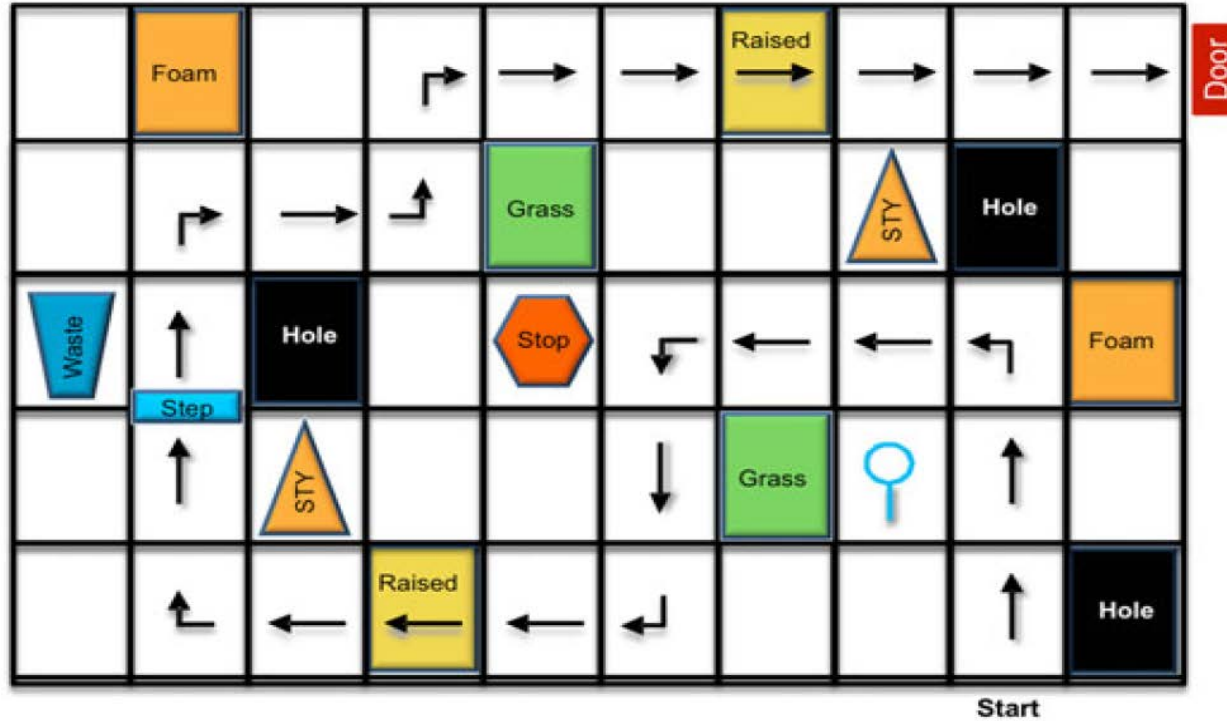


One Directly-Administered Gene Therapy Approved in 2017

- **Voretigene neparvovec-rzyl (LUXTURNA)**: indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the attending physician(s).
 - Novel endpoint used for approval developed by sponsor with input from FDA

Multi-Luminance Mobility Test

Negotiating a path with obstacles at different light levels

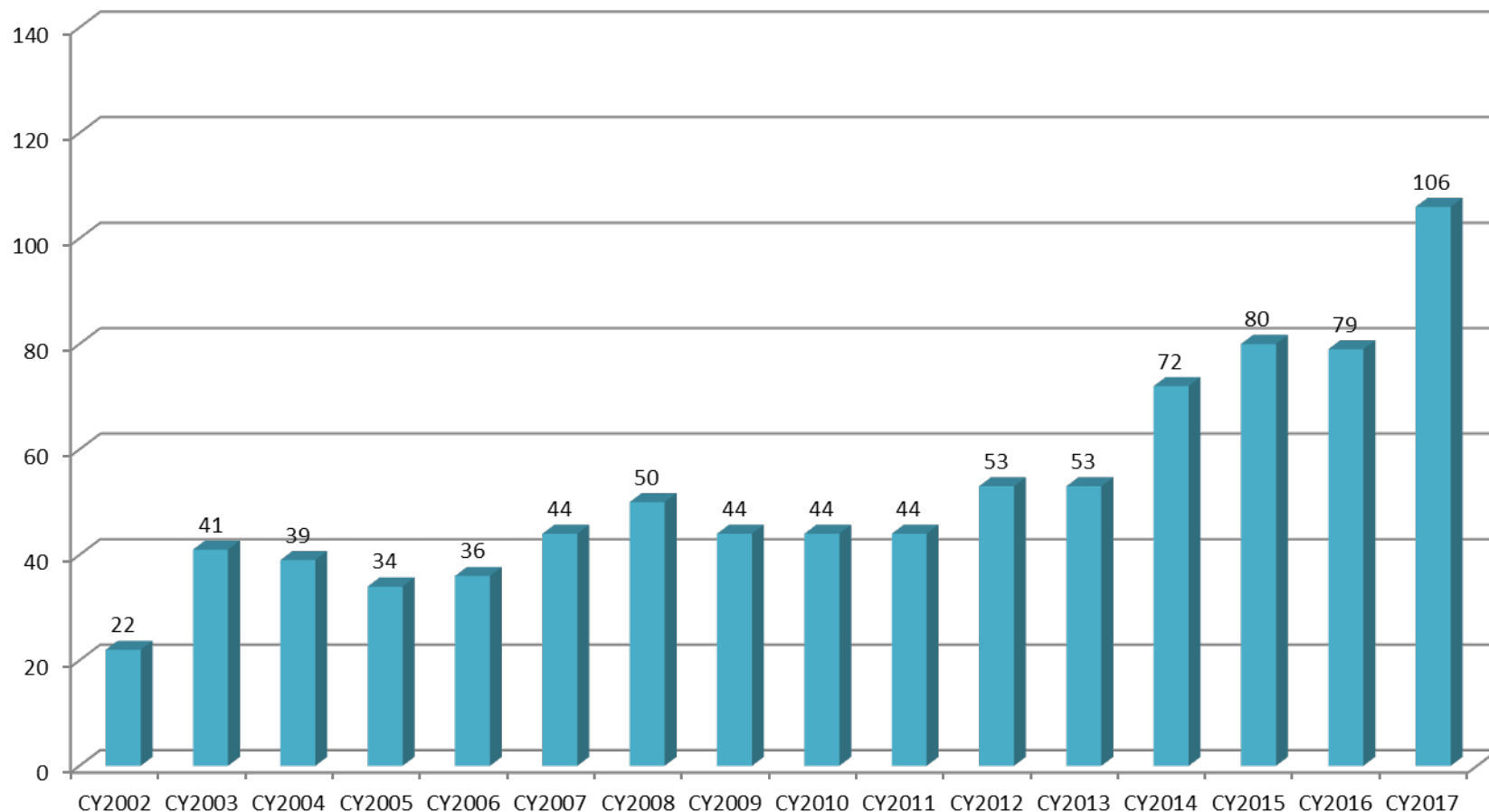


Scoring based on time and accuracy

Illuminance (lux)	Luminance (cd/m ²)	Corresponding environment
1	0.32 mesopic vision	Moonless summer night; or indoor nightlight
4	1.3 mesopic vision	Cloudless summer night with half moon; or outdoor parking lot at night
10	3.2 mesopic vision	60 min after sunset in a city setting; or a bus stop at night
50	15.9 photopic vision	Outdoor train station at night; or inside of illuminated office building stairwell
125 [†]	39.8 photopic vision	30 min before cloudless sunrise; or interior of shopping mall, train or bus at night
250 [‡]	79.6 photopic vision	Interior of elevator, library or office hallway
400	127.3 photopic vision	Office environment; or food court



All Investigational New Drug Applications for Gene Therapy Products, CY 2002-2017



Yearly submissions to the Center for Biologics Evaluation and Research



Regenerative Medicine Advanced Therapy Designation (RMAT)

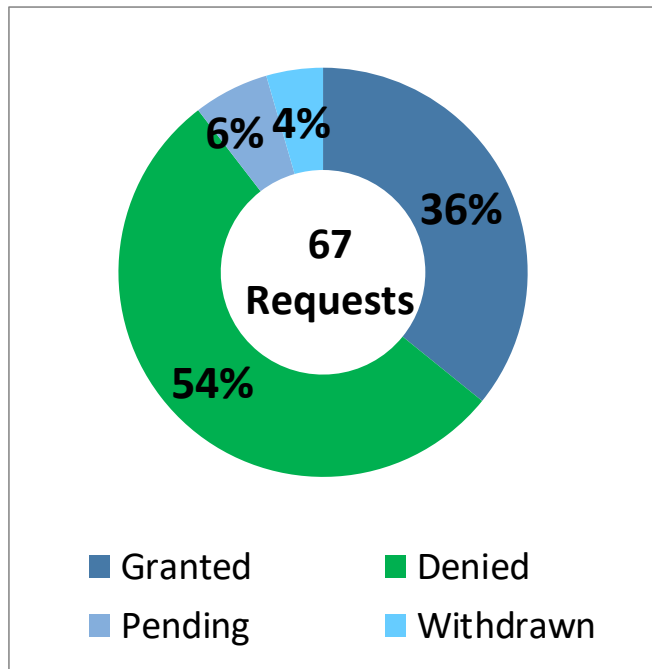
- To expedite the development and review of regenerative medicine advanced therapies
 - Applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products
 - Genetically modified cell therapies and gene therapies producing durable effects included



Regenerative Medicine Advanced Therapy Designation (RMAT)

- Products must be intended for serious or life-threatening diseases or conditions
- Preliminary clinical evidence must indicate potential to address unmet medical needs
- Designated products are eligible as appropriate for priority review and accelerated approval
- Expanded range of options for fulfilling post approval requirements of accelerated approval

RMAT Designations Granted



Data as of June 30, 2018

- 24 products granted designation
- 15/24 products have Orphan Product designation
- Most are cellular therapy products or cell-based gene therapy products

Issues in the Manufacture of Cell and Gene Therapies

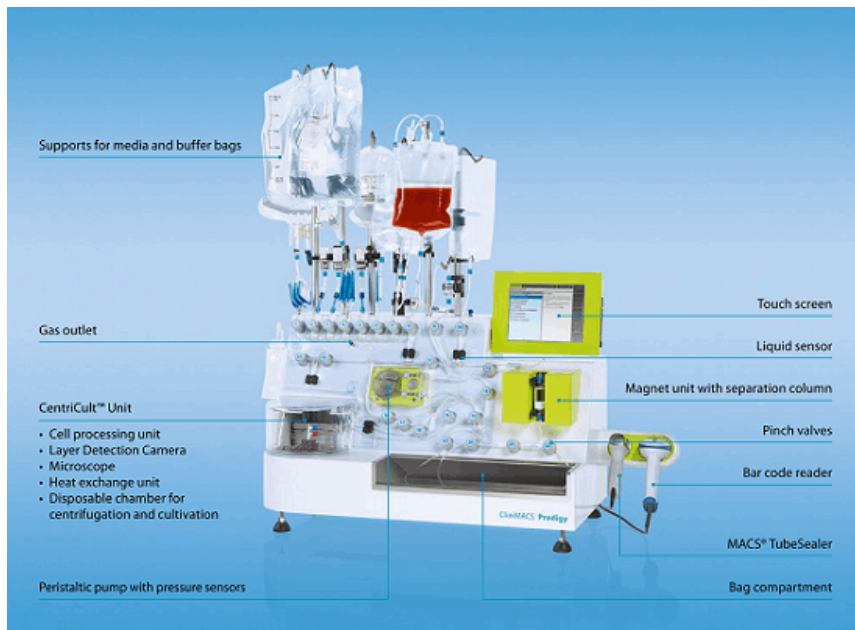
- Challenges of developing and validating manufacturing processes for autologous cell therapies
- Need for standards for the reproducible production of regenerative medicine products such as cellular therapies

Issues in the Manufacture of Cell and Gene Therapies

- Lack of capacity for manufacture of lentiviral and adeno-associated virus (AAV) vectors is limiting clinical development
- Process of production in current cell lines is still not able to meet demand despite some improvement over past few years

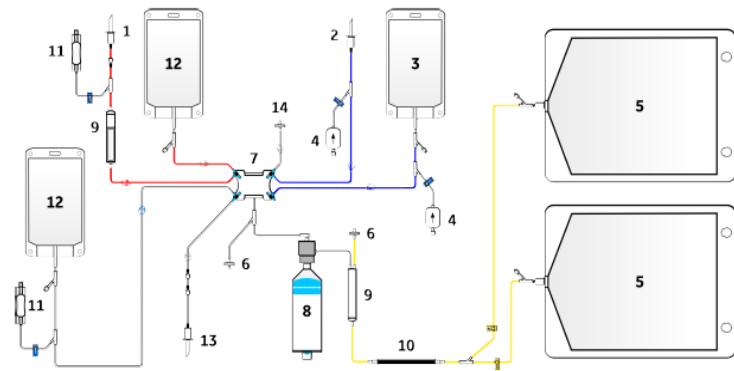
Solutions on the Horizon for Cell and Gene Therapy Manufacturing

- Partially automated closed manufacturing systems



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Solutions on the Horizon for Cell and Gene Therapy Manufacturing

- Modular manufacturing facilities
 - Scalable pre-built biotechnology



- Continuous manufacturing applied to biologics

Improving the Manufacture of Cell and Gene Therapies

- CBER is working with NIH and National Institute of Standards and Technology (NIST) and others to facilitate the development of standards for use in regenerative medicine
- Plans for CBER laboratory research programs and collaborations with academic and public private partners to advance field
 - Improved cell lines for vector production
- FDA guidance suite to be issued in FY2018



Simplifying Agency Interactions for Gene Therapy Products

- Gene therapy protocol sponsors interact with both the Recombinant DNA Advisory Committee (RAC) at NIH and the FDA for approval and reporting of adverse events
- Given recent advances in gene therapy, FDA and NIH reviewed the utility of the existing framework
- FDA and NIH are collaborating on a proposal to reduce regulatory burden while enhancing the value added provided by the RAC



INTERACT Program

Initial Targeted Engagement for Regulatory Advice on CBER products

- To further encourage interaction with sponsors and replace the pre-pre-IND meeting process across the Center
- Anticipate ultimately having an external-facing web page describing the program in detail

The Path Toward Progress

- Keep pace with advancing technology
- Refine regulatory framework as necessary
- Overcome limitations in manufacturing
- Facilitate optimal product development

