Cell and Gene Therapy Market and Regulatory Trends

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bioMérieux

2023 PDA Asia Pacific Regulatory Conference

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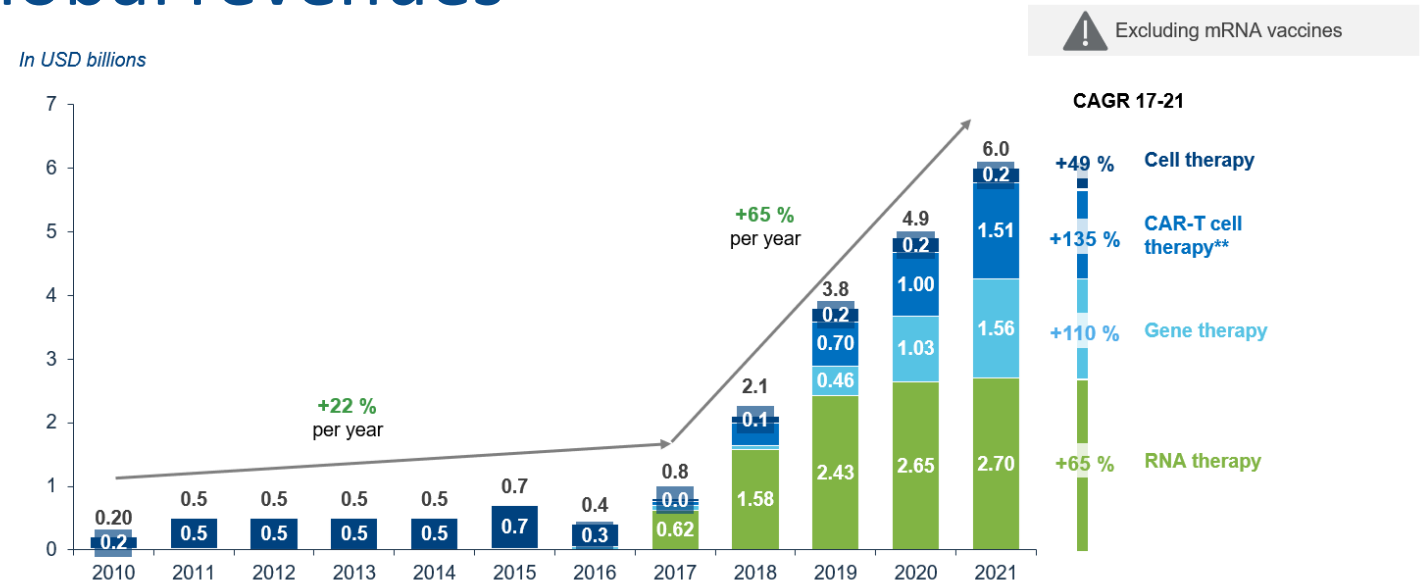
Global market trends

Global revenues



- C&GT market uptake has dramatically accelerated since 2017
- Within this landscape, CAR-T cell therapies have been the most dynamic segment

Values may not be exhaustive but are representative of the trends;
(**) excluding Abecma revenues.
Sources: bioMérieux market research partner

A booming market

	>1400 active developers	>2000 active clinical trials	$12.6 B raised in 2022
United States	686	964	$10.8B
Europe	244	403	$3.2B
Asia Pacific	492	848	$2.2B

2022 a year with many firsts

- First gene therapy treating **Hemophilia A** approved
- First gene therapy approval **beyond Rare Disease**
- First **Allogeneic T-Cell** approval
- First **2nd line** usage approved for several CAR-Ts

- North America and Asia Pacific together account for more than 75% of active clinical trials, while Europe is lagging
- China is a fast-growing market for C&GT development and ranks second in number of clinical trials
- CAR-T therapies continue to dominate pipeline
  - 98% of therapies in development are for cancer indications
- CAR-T therapies showed promise as an earlier-line treatment option
  - Gilead/Kite and Bristol Myers Squibb both reported clinical data showing favorable performance compared to the 2nd-line standard of care
  - Gilead/Kite shared positive data of Yescarta as a first-line treatment for high-risk patients

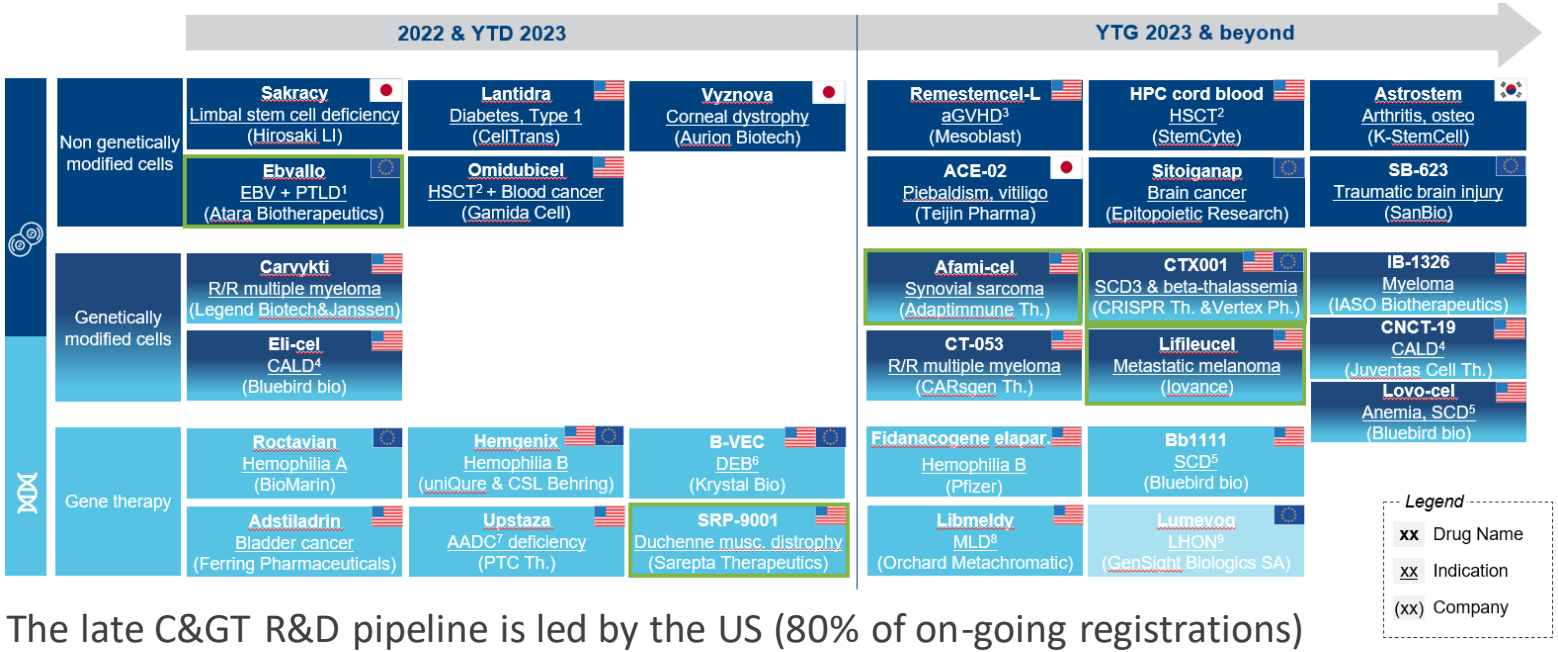
Approved car-T therapies*

	Kymriah	Yescarta	Carteyva	Breyanzi	Tecartus	Abecma	Carvykti	Fucaso	CNCT19
Diffuse Large B-Cell Lymphoma (DLBCL)	■	2nd line use US, EU, CN	■	2nd line use US, EU					
Follicular Lymphoma (FL)		■		■					
Relapsed/Refractory Multiple Myeloma (MM)						■	2nd line use approval pending	■	
Primary Mediastinal B-Cell Lymphoma (PMBCL)		■		■					
B-Cell Acute Lymphocytic Leukaemia (ALL)	■				■				■
Mantle Cell Lymphoma (MCL)					■				

Companies keep seeking extension of indications to treat more patients

(*) Matrix showing only approvals from the FDA, EMA, TGA and NMPA.
Other geographies have been approved but are not shown.
Sources: FDA, EMA, NMPA, TGA and corporate websites

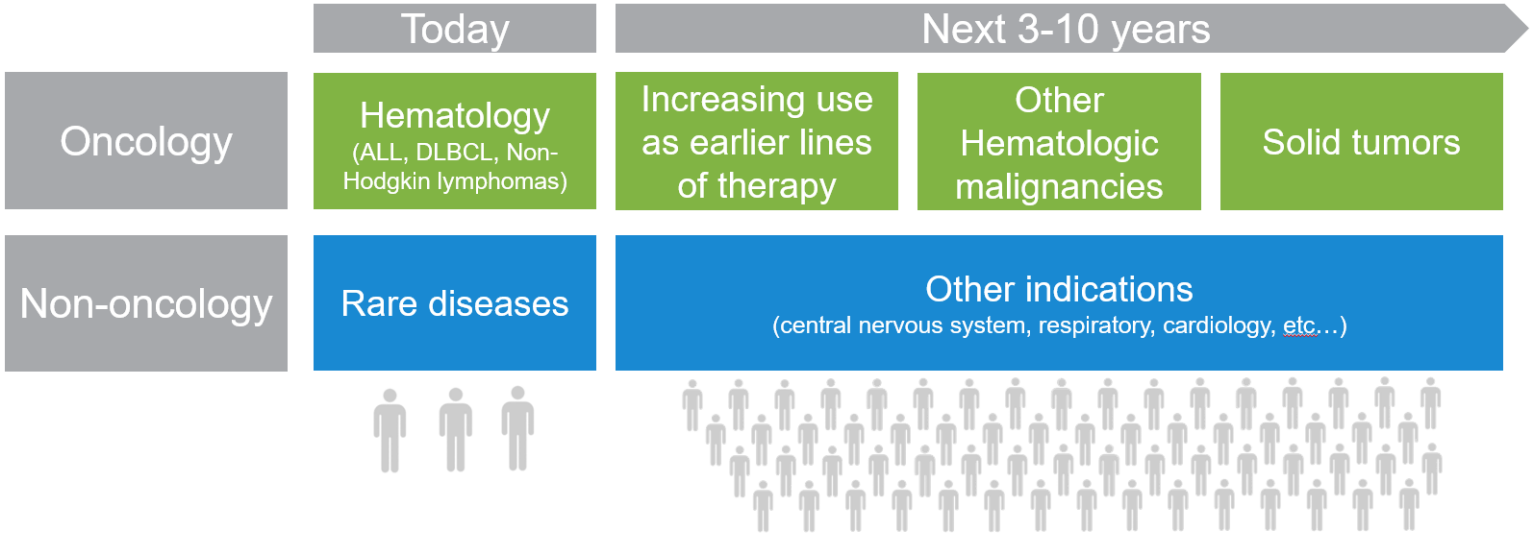
Expected approval for products that completed Phase III



- The late C&GT R&D pipeline is led by the US (80% of on-going registrations)
- The 2019 FDA prediction that it would approve 10-20 C&GT per year by 2025 looks possible

Notes: (1) EBV + PTLD= Epstein-Barr virus-associated post-transplant lymphoproliferative disorder; (2) HSCT = Unrelated Donor hematopoietic progenitor cell transplantation; (3) aGVHD= (4) CALD = Early active cerebral adrenoleukodystrophy; (5) SCD = Sickle cell disease; (6) DEB = Dystrophic epidermolysis bullosa; (7) AADC = Aromatic L-amino acid decarboxylase; (8) MLD = Metachromatic leukodystrophy; (9) LHON = Leber hereditary optic neuropathy.
Sources: Alliance for Regenerative Medicine, American Society of Gene + Cell Therapy, Citeline, United States Government Accountability Office

Market evolution

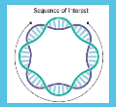


In 2021, Kymriah, Yescarta and Zolgensama were collectively administrated to less than 5000 patients

Technology evolution

Gene therapy

New biomolecular tools
- Improved plasmids
- New DNA formats



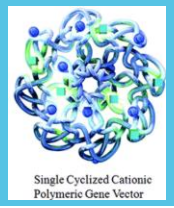
Better viral vector production
- Suspension bioreactors
- Improved transfection
- Stable cell lines
- Capsid engineering

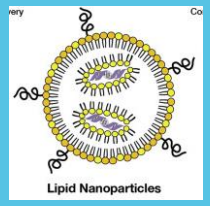
Viral vector analytics
- Digital PCR (dPCR)
- Automated Elisa
- Cryo-EM
- DLS/SLS/ UV-VIS
- Mass spectometry

Viral vector purification
- Improved chromatography
- Capture fusion protein

Automated manufacturing
- Enzymatic DNA synthesis
- LNP manufacturing

Non-viral gene delivery
- Electroporation
- Microfluidic cell squeezing
- Cationic polymers
- Lipid nanoparticles
- Exosomes


Single Cyclized Cationic Polymeric Gene Vector


Lipid Nanoparticles

Cell therapy

Sources: 2022 Sylvestre and Conti-Permanne. CGTI 8:11; 2022 Al-Haideri et al. Cancer Cell Int 22, 365; 2022 Xie et al. Cancers 30,14; 2023 Wang et al. J Nanobiotechnol 21, 272

Technology evolution

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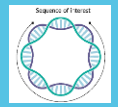

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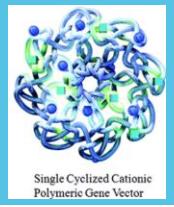
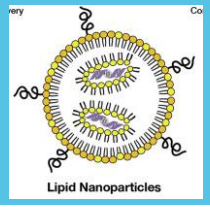




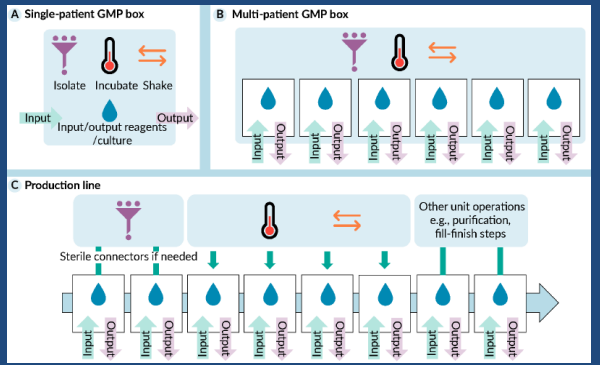
Cell therapy

New cultivation formats
- Microfluidics
- Encapsulation
- 3D matrix
- Small volume bioreactor

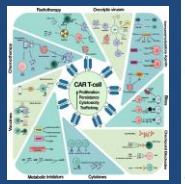
Cell therapy analytics
- Real-time culture media monitoring
- Live cell imaging
- Flow cytometry
- Mass spectrometry

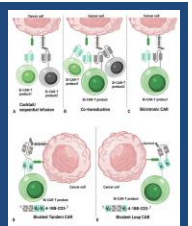
Cell separation and selection
- Magnetic sorting
- Debulk apheresis products
- Multiparameter cell sorting

Industrialization of production
- GMP boxes
- Transfection methods



New approaches for CAR-T
- Dual targeting
- Combination therapy
- *In situ* expansion
- *In vivo* CAR-T





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Global Regulatory Trends

A heterogeneous regulatory environment

- ✓ Minimum requirements for analytical methods are well defined, providing a foundation for early phase programs
- ✓ The US, EU, China, Japan and Korea have established specific regulatory processes for C&GT with several products already approved
- ◆ Emerging markets in the rest of the world have yet to develop specific regulatory oversight
- ◆ Different classification for C&GT means different controls and approval pathways
  - Challenging for manufacturers seeking approval in more than one country in parallel
- ➢ Harmonization is key for progress in the C&GT field
- ➢ Need best practices and lessons learned from previously commercialized products
- ➢ Early engagement of regulatory authorities to get early approval for the company's proposed strategy

Expected Growth in C&GT filings

- Less than 30 C&GT have so far been approved by the FDA
- 2,500 active investigational new drug (IND) applications pending
  - 1,300 active IND applications for gene therapies
  - 1,200 active IND applications for cell therapies
  - Increase in Breakthrough and Regenerative Medicine Advanced Therapy designation requests
- Expansion of INTERACT meetings and new type D meetings
  - INTERACT meetings: input on novel questions and unique challenges that need to be addressed prior to a pre-IND meeting
  - Type D meetings: focused on a narrow set of issues
- Increased regulatory burden in EU with genetically modified organism (GMO) assessment
  - GMO regulations have been developed for agricultural use to protect consumers against genetically modified crops
  - CAR-T therapies, being genetically modified cells, fall under the GMO definition
  - ARM, EFPIA and Europabio have called for this to change

ARM: Alliance for Regenerative Medicine; EFPIA: European Federation of Pharmaceutical Industries and Associations; Europabio: European Association of Bioindustries

More objections from regulatory bodies than biologics

Analytical methods

- Potency assays are often considered inaccurate and/or not completely fulfilling their purpose
- Challenging due to variability of starting material, heterogenous product composition, lack of reference standards, incomplete understanding of MOA, multiple active ingredients, limited stability, etc…
- The FDA issued two new guidelines in 2022, one for CAR-T cell products and one for Gene Therapy products Incorporation Genome Editing; both address potency testing of such products

Clinical studies

- Designs are raising doubts about trial outcomes leading to narrower indications
- Randomized clinical trials (RCT) may not always be feasible
- Patient populations are small for target indications
    - Lack of agreement on surrogate endpoints between regulators and sponsors has been an issue

Sources: bioMérieux market research partner

Regulatory updates: Annex 1

PICS PE009 Guide to GMP for medicinal products

- Annex 1 Manufacture of sterile medicinal products → Revised to include EU GMP Annex 1
- Annex 2 is now split into two separate annexes:
  - Annex 2A provides GMP guidance for manufacturers producing ATMPs
    - PQS/QRM requirements to reduce contamination risks, cross-contamination risks, and to minimize product variability
    - Contamination Controls Strategy (CCS)
    - Requirements for non-routine production and dedicated vs shared facilities
    - Product-specific guidance for ATMPs
- Annex 2B provides GMP guidance for manufacturers of biological medicines

Regulatory updates: Rapid Microbial Detection

RMM are “one of the top priority areas” for USP’s new Microbiology Expert Committee

- **USP <72> Respiration**-Based Microbial Methods for the Detection of Contamination in Short Life Products
- **USP <73> ATP Bioluminescence**-Based Microbial Methods for the Detection of Contamination in Short Life Products
- **USP <74> Solid-phase Cytometry**-Based Microbial Method for Detection of Contamination in Short Life Products
- **USP <77> Mycoplasma Nucleic Acid Amplification Tests**

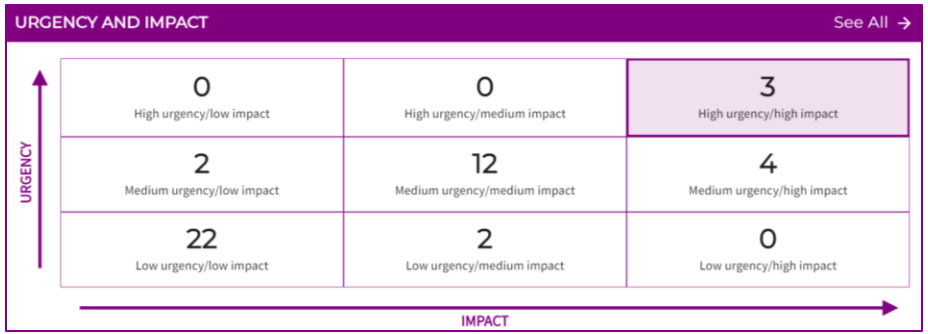
PDA - future update of the TR No. 33, Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods,

EDQM is updating several chapters to reflect the latest advancements in the field of pharmaceutical microbiology

- **Ph. Eur. 2.6.7 Mycoplasmas:** will include changes to guidelines for the validation of NAT
- **Ph. Eur. 5.1.6 Alternative:** will reflect the techniques currently in use and update the validation guidance
- **Ph. Eur. 5.1.9 Guidelines for using the test for sterility:** will reflect the use of alternative sterility methods

Regulatory updates: standards development

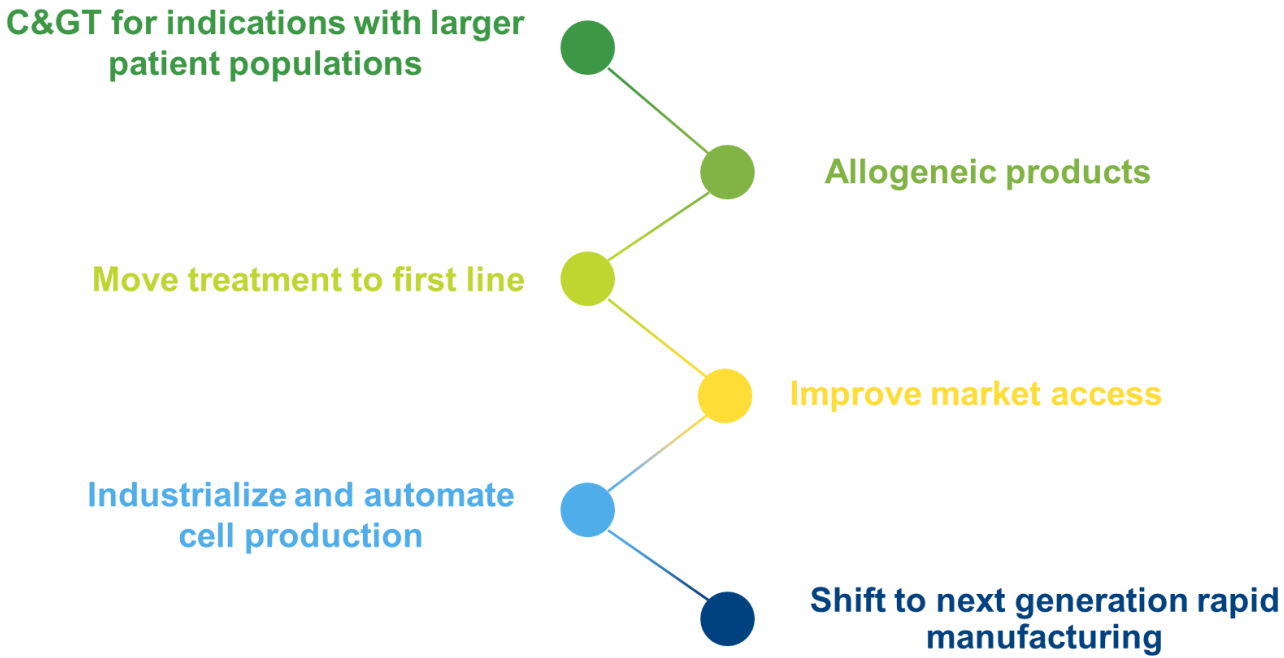
- FDA guidance: Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies
  - Designed to identify and recognize VCS
  - Opportunity for manufacturers to request the recognition of a specific VCS
- SCB's interactive database: current landscape, standards published and in-development and community-identified areas of need



1. Ancillary Materials
2. Cell Collection Procedures
3. Product Potency and Functionality Measurement Methods

Source: FDA Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies 2023; Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery (SCB) https://portal.standardscoordinatingbody.org/

A look to the future



Thank you

2023 PDA Asia Pacific Regulatory Conference

28 - 29 November 2023

8:45AM - 5:30PM, JUNIOR BALLROOM

Session III: Challenges with ATMP Manufacturing Amongst Differing Global Regulatory Requirements

Pauline Deng
CSL Behring
Moderator

Janet Macpherson
Cytiva

Richard Denk
SKAN

Juliana Gutierrez
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