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A RACE FOR INNOVATION:

Regulatory Initiatives to Bolster Cell and Gene Therapy Development

AUTHORS

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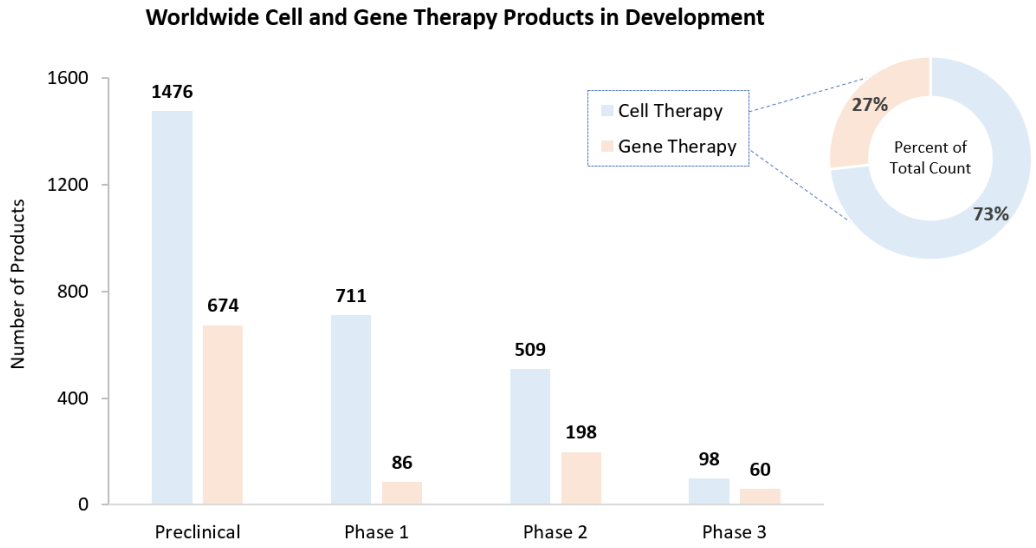
Executive Summary

Cell and gene therapies represent the cutting edge of biopharmaceutical development, leveraging innovative technologies to address medical conditions which often have no other existing disease-modifying therapeutic options. These groundbreaking assets garnered tremendous attention initially but have since seen sizeable slowdowns in funding due to cases of concerning adverse event profiles, high price tags, and macroeconomic trends. However, recent regulatory movements may generate renewed enthusiasm for these therapeutics due to published guidance that could ease the development and commercialization process.

In this white paper, we explore the implications of recently adopted regulatory policies on biopharma organizations that are developing cell and gene therapies. Specifically, we discuss recent FDA approvals and guidance to help streamline and accelerate the approval process for cell and gene therapies, CMS proposals for outcomes-based pricing, and the impact of the Inflation Reduction Act of 2022 (IRA) and implications for cell and gene therapy drug pricing. We conclude that these measures may create new opportunities for cell and gene therapy development, particularly in rare diseases and for programs with orphan drug designations.

Figure 1.



Worldwide Cell and Gene Therapy in Development. The cell and gene therapy pipeline features over 100 Phase 3 programs, with several hundred in early clinical and preclinical development[1].

Introduction and Background

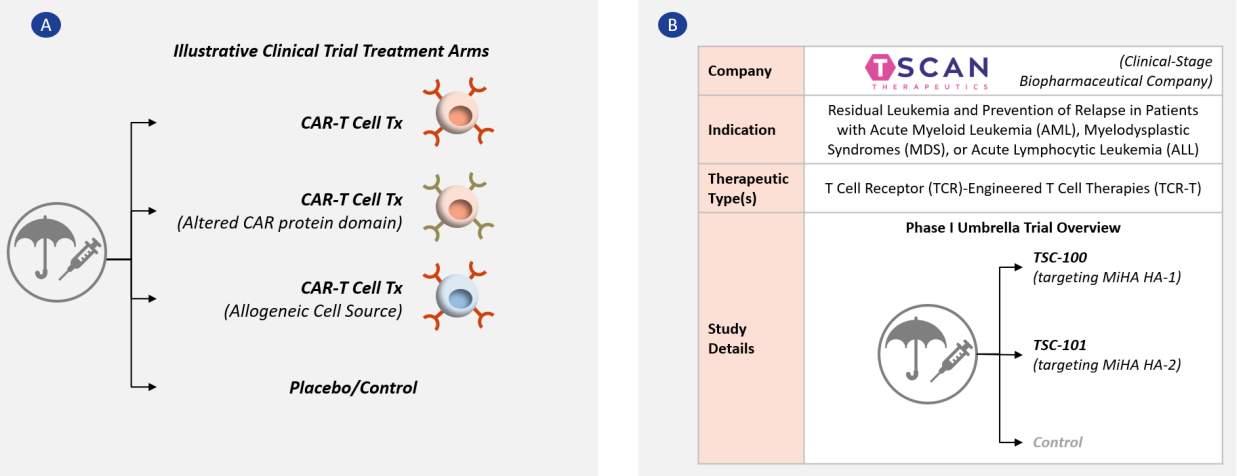
Investor enthusiasm in biotech has waned in recent years, and the cell and gene therapy sector is no exception. Currently, a significant portion of the cell and gene therapy pipeline sits at the preclinical stage, but more programs than ever before are in later phases of development (see Figure 1). While the investment stagnation continues to pervade the industry, several recently developed government policies, with particular relevance to cell and gene therapies, have the potential to accelerate development and commercialization and potentially renew interest in the space. In 2022, the FDA released guidance to cell and gene therapy innovators to streamline the development and approval processes. Additionally, the FDA has dedicated increased levels of attention and commitment of resources to support these programs early and throughout the development process. The CMS Center for Medicare and Medicaid Innovation has also announced it will test a model for biotherapeutics which will pool bargain and base pricing expectations based on measurable outcomes (i.e., outcomes-based payment arrangements); an approach which may reduce the friction of securing coverage for novel biotherapeutics. Finally, while the IRA contains measures that allow the Centers for Medicare Services (CMS) to negotiate down the list prices of particular drugs after a set duration of time and to cap drug prices, several of these pricing controls are expected to have lesser impacts on biotherapeutics for rare diseases, which should mitigate the impact on most cell and gene therapies in development today.

Collectively, these governmental activities and policy changes may have net positive implications for future development and commercialization of cell and gene therapy products.

FDA Emphasis on Streamlined Biotherapeutic Approvals

In 2022, the FDA published two new guidance documents aimed at improving the agility of cell and gene therapy development. The first guidance, titled "Studying Multiple Versions of a Cellular or Gene Therapy Product in Early-Phase Clinical Trial," provides recommendations on how to structure investigational new drug applications (INDs) and submit new information for sponsors seeking to gather preliminary evidence of safety and activity using multiple versions of a cell or gene therapy product in a single clinical trial[2]. This guidance could streamline early clinical development by expeditiously identifying alternative versions of a product that may be safer or more effective.

Figure 2.



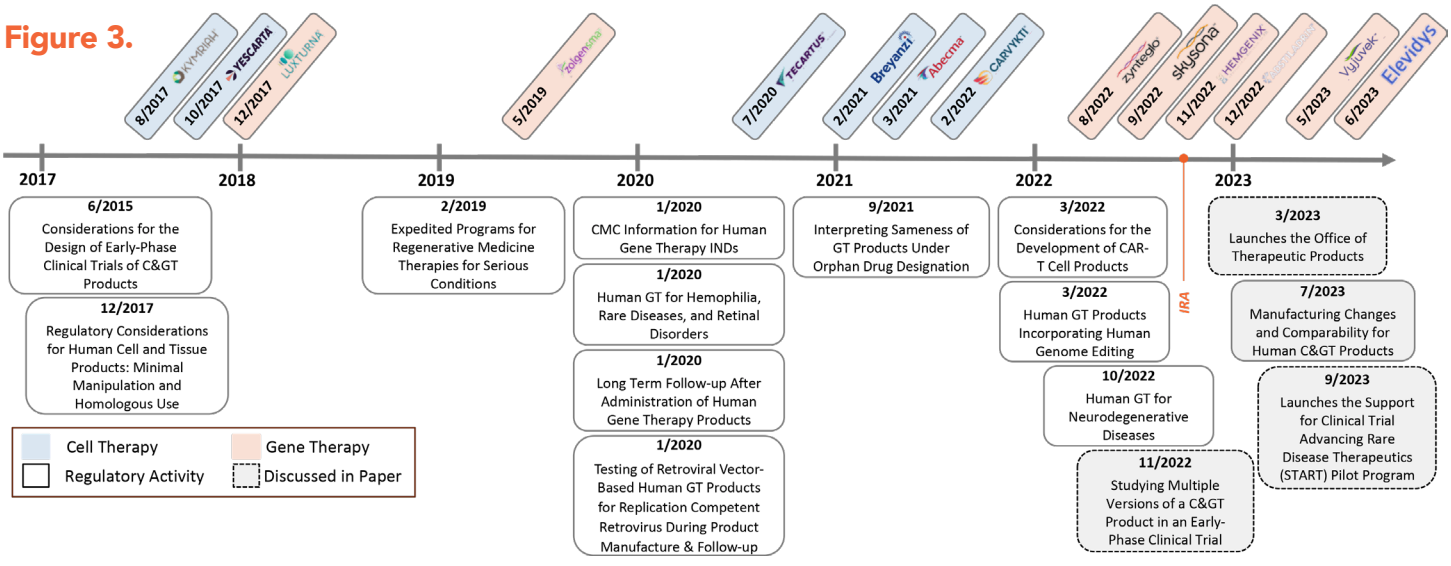
Illustrative and Representative Examples of Sponsors Studying Multiple CAR-Ts or TCR-Ts in Early-Phase Clinical Trials.
(A) Illustrative clinical trial design, enabling multiple versions of a cell or gene therapy (CAR-T) to be studied within a single, multi-armed, clinical trial. (B) Cell therapy developers have already begun capitalizing on FDA guidances enabling study of multiple product forms in early-stage trials, demonstrated by T Scan Theraputics TCR-T for residual Leukemia[3].

For example, a sponsor investigating a CAR-T cell therapy may wish to investigate a different version of the asset with an altered CAR protein domain or a new cell source such as an allogeneic donor (see Figure 2). By studying multiple versions of an asset in a single clinical trial, sponsors can more efficiently identify the most promising candidates for further development, potentially shortening the time it takes to bring a product to market. Coupling this new provision and the addition of surrogate biomarkers to clinical trial designs, cell and gene therapy innovators could expedite the development process of a new therapeutic significantly.

A second guidance document, titled "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products," details the CMC manufacturing changes which would require a new IND filing versus changes which would only require amendments to an existing IND application[4]. Generally, the document highlights that CMC manufacturing changes which result in acceptable quality where safety and efficacy can be tested by analytical comparability assessment would be submitted as an amendment or in an annual report to the IND rather than requiring a brand-new IND application filing with the FDA. Thus, this guidance helps to support continued acceleration of cell and gene therapy product development if manufacturing changes were to occur at different phases of development. Furthermore, the document also recommends proactive communication with the FDA's CBER on topics such as study design feedback and statistical approaches for the comparability assessment if a developer expects to encounter any manufacturing changes, particularly those which would need to be implemented later in the product lifecycle. By more clearly outlining the implications of specific manufacturing changes, and opening communication channels with regulatory bodies, the FDA is enabling cell and gene therapy developers to plan and adjust manufacturing needs in a manner that avoids major delays such as complete response letters (CRLs) or requirements for new IND applications.

Both of the aforementioned guidance documents are aimed at improving the agility of cell and gene therapy development, given the current backlog of FDA review. By providing clearer and more concise guidance, these documents could support shortened development timelines and quicker product launches for successful development programs. For manufacturers, this means increased efficiency, more predictable pre-approval inspection, faster product launches and strengthened commercial opportunities. Additionally, these documents supplement previous guidance seemingly focused on later-stage development and launch of new cell and gene therapies, underscoring increased FDA support within this field earlier in development (see Figure 3; see Supplementary Table 1 for a more detailed overview for each draft guidance).

Figure 3.



Cell and Gene Therapy Regulatory Guidances and Approvals. Increased regulatory guidance coincides with increased cadence of cell and gene therapy approvals in recent years5.

In addition to streamlining processes, the FDA has taken additional efforts to reduce the biotherapeutic review backlog by aiming to hire over 100 managers in cell and gene therapy roles[6] and launching the Office of Therapeutic Products (OTP) in March 2023 which it has been described as the new "super office" for the Center of Biologics Evaluation and Research (CBER)[7].In September 2023, the FDA launched the Support for Clinical Trial Advancing Rare Disease Therapeutics (START) Pilot Program to further support clinical trial study design for rare diseases that is similar to Operation Warp Speed during the COVID-19 pandemic[8]. The program will aim to bring cell and gene therapies for rare diseases to the market as quickly as possible while maintaining the thorough evaluation of their safety and efficacy. The program will be housed within the OTP and will enroll up to three sponsors each from two groups of applicants with one group being sponsors whose product is a cell or gene therapy regulated by CBER that is directed at an unmet medical need in a rare disease. Sponsors will benefit from frequent advice and regular ad-hoc communication with FDA staff to address product-specific development issues, such as clinical study design, choice of control group, and fine-tuning the choice of patient population. The increased rate of formal and informal communication during Operation Warp Speed in 2020 was critical for developing safe, effective COVID-19 vaccines and making them available to the public in record time, despite the existence of several unknowns with the disease and the novel vaccines.

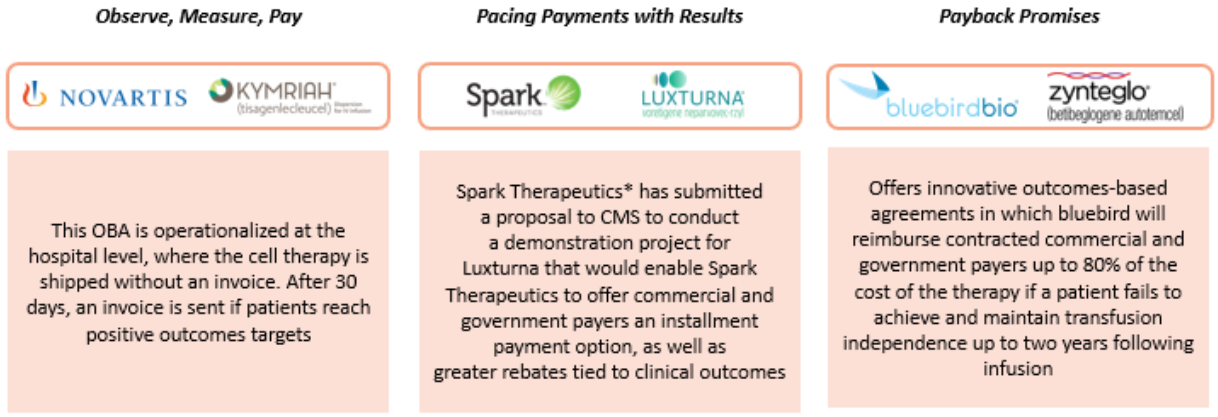
Taken together, these recent efforts by the FDA serve as indicators of heightened opportunity for cell and gene therapies to reach the market quicker than they have historically, which may bring renewed interest to the sector from both innovators and investors.

Outcomes-Based Pricing Opportunity Augmented by Biomarker Utilization

Another regulatory movement comes from the CMS Innovation Center, which is introducing new pricing models designed to reduce program expenditures while enhancing the quality of care provided to its beneficiaries. The Cell & Gene Therapy Access Model, one of three models selected for testing by the CMS Innovation Center, provides state Medicaid agencies with the option to direct CMS to coordinate and administer multistate, outcomes-based agreements (OBAs) with manufacturers for certain cell and gene therapies.[9] CMS would be responsible for implementing, monitoring, reconciling, and evaluating the financial and clinical outcomes outlined in the OBAs.

The model is designed to allow CMS to pool bargaining power to obtain discounted pricing, condition the cost of cell and gene therapies on measurable outcomes, and shift the burden of administering complex outcomes-based agreements from state Medicaid agencies to CMS. By tying payment to outcomes, this model incentivizes manufacturers to produce therapies that are both clinically- and cost-effective, which may in turn facilitate quicker and more widespread access to cell and gene therapies.

Figure 4.



Examples of Outcomes Based Agreements for Cell and Gene Therapies. Manufacturers have begun to implement outcomes-based agreements to increase patient access across multiple cell and gene therapy products[10].

While at face value this appears as a hurdle to cell and gene therapy manufacturers, outcomes-based reimbursement is already becoming a strategic approach to reduce the friction with payers for obtaining reimbursement for novel products following approval. Manufacturers of currently approved gene therapies have begun to offer outcomes-based contracts, innovative contracting models, and pay-over-time options. For example, with Luxturna, Spark Therapeutics reached an outcome-based agreement with certain health insurers (e.g., Harvard Pilgrim which provides health benefit plans, services, and programs to over 3 million customers) to risk-share by paying rebates if a patient fails to meet specific outcome thresholds, therefore linking short-term efficacy (30-90 days) and longer-term durability (30 months) to the gene therapy costs. Similarly, Bluebird Bio will reimburse commercial and government payers up to 80% of the cost of Zynteglo if a patient fails to achieve and maintain transfusion independence up to two years following the infusion (see Figure 4). Additional payment models include pay-over-time options, which are currently offered for Luxturna and Zolgensma. The CMS pricing model extends this approach to CMS patients and may also remove some of the burden from the manufacturers, as CMS has indicated it will be responsible for the monitoring, reconciling, and evaluation of the outlined outcomes.

Additionally, this pricing model may be supported by programs that are increasingly including measurable biomarkers that are correlated to functional outcomes within clinical trial design. Such biomarkers can provide a fast, efficient means to obtaining a quantitative measurement of the biological response to the therapy and help determine whether the therapy is having the intended clinical effect. Correlative biomarkers could potentially be used to determine reimbursement for the therapy and are particularly useful for outcomes-based pricing models. By incorporating biomarkers into clinical trial design, manufacturers may be able to accurately predict the clinical outcomes of their therapies and negotiate more favorable pricing agreements with CMS. Inclusion of biomarkers in clinical trials has recently demonstrated additional upside, as multiple programs (e.g., Biogen's Leqembi and Sarepta's gene therapy Elevidys) have been granted accelerated approvals by the FDA using biomarkers as surrogate endpoints, as discussed in our previous white paper: "The Biomarker Breakthrough: Sarepta's Path to Approval via Surrogate Endpoint Signals a Positive Outlook for Gene Therapy Developers".[11]

Historically, the list price of cell and gene therapies has contributed to some access inertia, but increasingly there are mechanisms to onboard these products faster through various forms of risk-sharing. CMS and other payers want to make these products available to patients, and OBAs are presenting as an effective method to enable this access. Inclusion of measurable biomarkers in trials and OBAs for cell and gene therapies may provide opportunity for both streamlined development timelines and a greater appetite for broader reimbursement.

Protections Against Drug Pricing Controls

The IRA of 2022, specifically in the context of healthcare, was enacted to improve drug affordability and access to millions of Americans who have Medicare Part D. More specifically, the IRA contains several measures to limit the prices of drugs, particularly by allowing Medicare to negotiate prices with drug companies, putting an inflation cap on drug prices, and lowering out-of-pocket expenses for Medicare recipients. The drug price negotiation will take effect 9 years post-approval for small molecules and 13 years for biologics.[12] The industry has pointed to the fact that because there was no floor price in the bill, CMS may demand generic-like pricing, which will effectively truncate these products' revenue-generating years, even if they still hold marketing exclusivity. Companies will likely not be able to refuse to sell products to Medicare patients if they disagree with the negotiated CMS price, and since the penalty for not accepting CMS's price is a sizeable tax, they may essentially be forced to use the CMS-determined price across channels.

Given there is higher commercial upside in the later years of exclusivity post-launch, this shortening of the revenue trajectory for small molecules may push sponsors and investors to prioritize biologics and biotherapeutics, which are less impacted by the provisions in the IRA due to the longer time horizon for price negotiations being in-line with typical exclusivity timelines. Additionally, the IRA legislature exempts drugs from this price negotiation when they have orphan drug designation for only one approved disease or condition, further de-risking investment in many gene therapy programs where the only focus is on a single rare genetic disease.

The implications of the IRA pricing measures may ultimately be significant for drug developers, but some of the most consequential provisions may be mitigated or avoided entirely for cell and gene therapies, particularly those pursuing treatment of rare, orphan indications.

Opportunity Upswing for Cell & Gene Therapy Development

Regulatory and legislative actions in the past two years have alleviated many development and commercialization barriers for cell and gene therapy manufacturers, with the hope of spurring additional innovation in the sector. As investors place their next round of bets in the current funding environment, cell and gene therapy manufacturers should emphasize the recent regulatory policies that could give their programs the edge needed to secure funding and move innovation forward.

Supplementary Materials

Table 1.

FDA Guidance Title	Effective Date	Guidance Summary
Manufacturing Changes and Comparability for Human C&GT Products	7/2023	• Provides guidance on CMC manufacturing changes that would require a new IND filing versus changes that would only require amendments to an existing IND application through comparability assessments
Studying Multiple Versions of a C&GT Product in an Early-Phase Clinical Trial	11/2022	• Provides recommendations on how to structure and design INDs that allows for investigating multiple versions of a cell or gene therapy product in early phase of development (i.e., basket trial)
Human Gene Therapy for Neurodegenerative Diseases	10/2022	• Provides considerations for product development, testing, and trial design and outlines how product critical quality attributes (CQAs) may also influence CMC considerations and final formulation parameters
Human Gene Therapy Products Incorporating Human Genome Editing	3/2022	• Provides guidance on information that should be provided (e.g., preclinical safety assessment, product and clinical trial design, and manufacturing) in an IND application that will ensure appropriate safety and quality assessment of the gene therapy product
Considerations for the Development of CAR-T Cell Products		• Provides recommendations on product development such as CMC, pharmacology and toxicology, and clinical trial design as well as considerations specific to autologous and allogeneic CAR-T products and analytical comparability studies
Interpreting Sameness of Gene Therapy Products Under Orphan Drug Designation	9/2021	• Provides guidance to assist sponsors who are seeking orphan-drug designation and orphan-drug exclusivity (i.e., factors to consider when determining sameness such as the principal molecular structural features (e.g., transgenes or vectors) of the GT product), in the development of gene therapies for rare diseases
Human Gene Therapy for Hemophilia, Rare Diseases, and Retinal Disorders *(3 separate guidances published in unison)*	1/2020	• Each guidance provides considerations for product development, preclinical studies, clinical trial design, and manufacturing within each respective disease/therapeutic area
CMC Information for Human Gene Therapy INDs		• Provides CMC considerations to ensure sponsors have sufficient information on a product's safety, identity, strength, purity, and quality
Long Term Follow-up After Administration of Human Gene Therapy Products		• Provides recommendations regarding the design of long-term follow-up studies for the collection of data on delayed adverse events following administration of a GT product
Testing of Retroviral Vector-Based Human GT Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up		• Provides guidance on testing for replication competent (RCR) during the manufacturing of retroviral vector-based GT products as well as recommendations for monitoring patients for evidence of retroviral infection post administration
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions	2/2019	• Describes expedited programs available to sponsors of regenerative medicine therapies designated as RMAT (Regenerative Medicine Advanced Therapy), considerations for clinical development, and opportunities to interact with CBER
Regulatory Considerations for Human Cell and Tissue Products: Minimal Manipulation and Homologous Use	12/2017	• Outlines agency definitions of minimal manipulation for cell therapies designed for homologous use, and therapeutics applications in which additional scrutiny may be required for these biotherapeutics
Considerations for the Design of Early-Phase Clinical Trials of C&GT Products	6/2015	• Provides agency recommendations regarding trial design and key product features impacting trial design for phase I and II trials investigating safety, tolerability, and administration for C&GTs

Discussed in Paper

Additional FDA Guidances to Cell and Gene Therapy Innovators. Additional guidances in recent years have clarified specific questions related to various therapeutic areas, biotherapeutic modalities, and manufacturing, thus enabling more successful development and commercialization.

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