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Early Recommendations for Promoting Future Cell and Gene Therapy Competition Through Biosimilars

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Introduction

Transformative cell and gene therapies (CGT) provide new and better treatment options for patients with conditions including genetic disorders and cancers by stopping or slowing disease progression. However, the introduction of CGTs has been complicated by high prices and other financial barriers, posing challenges to payers' budgets. Encouraging competition from biosimilars in the field of CGT in anticipation of the expiration of patents and other exclusivity rights holds promise for reducing the cost of these treatments, enhancing patient access, and ultimately improving outcomes. However, because CGTs are highly complex biologics, they may present considerable hurdles to effective competition through the process of "biosimilarization." This raises doubts about the practicality of fostering competition from CGT biosimilars. These challenges necessitate the development of strategies that would facilitate such competition in the CGT market through a supportive policy and regulatory environment.

Building on our detailed findings published here, in this document we describe the timely development of a set of policies to achieve such a competitive market. The policies will need to address a set of issues, including regulatory pathways, advanced manufacturing, and intellectual property (IP) protections. Ensuring robust competition, to the extent possible, will be critical to fulfilling CGTs' potential to improve the lives of patients living with serious conditions who have few or no other treatment options.

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Background

The U.S. Food and Drug Administration (FDA) has approved a variety of innovative CGTs thus far, marking a new era in medical interventions for genetic disorders and cancer: Abecma, Breyanzi, Carvykti, Casgevy, Elevidys, Hemgenix, Kymriah, Luxturna, Lyfgenia, Roctavian, Skysona, Tecartus, Yescarta, Zolgensma, and Zynteglo. Although cell therapies and gene therapies are often distinct categories, several of these are cell-based gene therapies (chimeric antigen receptor, or CAR-T-cell therapies, for the treatment of specific types of cancer). Cell-based gene therapies work by removing a patient's cells, modifying them with a standard vector and selected gene of interest, processing the modified cells, and finally inserting them back into the patient. They differ from non-cell-based gene therapies, which consist of standardized vectors and selected genes of interest that are directly administered to patients (in-vivo). The first approved durable CGT product was the CAR-T therapy Kymriah in 2017.[1]

The field of CGT continues to grow; by 2030, it is predicted that there will be between 50 and 75 new approvals for CGT,[2] and there are over 1,500 ongoing trials for CGT registered on ClinicalTrials.gov (the vast majority are in phases 1 and 2).[3] Of the currently active trials, about 60% are for cancer indications, with the next most common indications in cardiovascular diseases (6.2%)

[1] Vinay Prasad, *Tisagenlecleucel — the First Approved CAR-T-Cell Therapy: Implications for Payers and Policy Makers*, 15 NAT REV CLIN ONCOL 1, 11, 2 (2018) https://doi.org/10.1038/nrclinonc.2017.156.

[2] Sung Hee Choe et al., *Cell and Gene Therapies: Looking Ahead to 2022,* https://milkeninstitute.org/report/cell-gene-therapies-2022 (accessed Mar. 14, 2024).

[3] *2023's Market Outlook For Cell And Gene Therapies,* https://www.cellandgene.com/doc/s-market-outlook-for-cell-and-gene-therapies-0001 (accessed Jun. 7, 2023).

and immunology (5.7%).[4] For gene therapies alone, it is estimated that over 1 million US patients will receive gene therapy within the 15-year period from 2020 to 2034, and the total estimated spending over this period is $306 billion.[5] Other recent estimates of the US market predict annual sales of gene therapies reaching $8.4 billion in 2024 and annual revenues for durable cell and gene therapies reaching $24.4 billion in 2030.[6, 7] For cell therapies, the US currently holds a 53% share of the global market, and the global market is projected to grow to $60.7 billion annually by 2030.[8]

Although the currently approved CGT and many now in late-stage development are for rare diseases or relatively small indications, CGTs are increasingly being developed for more prevalent disease areas and expanding indications.[9,10] Additionally, existing CAR-T therapies are expanding indications and patient populations.[11] This trend could not only intensify the budget impact of CGTs but also contribute to more favorable conditions for future competition.

High upfront costs (ranging from hundreds of thousands of dollars to over three million dollars per treatment), patient pool variability, and the risk of loss of return on investment (either due to poor long-term effectiveness or patients changing insurance plans over time) are significant financial challenges facing payers across all sectors of the US health care system. Even though many of the CGTs currently on the market and in the pipeline target rare diseases with relatively small patient populations, their high list prices can still overwhelm payers' budgets, as there is a growing number of these CGTs to pay for across many diseases. In addition, smaller payers, including certain Medicaid state agencies, self-insured employers, and small plans, face greater actuarial risk than large payers due to the smaller number of lives they cover and can thus be the most impacted by the expanding range of CGTs.

These barriers could limit patients' access to treatment and impose substantial cost-sharing burdens. Cost issues around CGTs increase the urgency of preparing for and encouraging future competition. The two main paths for the possible introduction of follow-on or competitor CGT products are either through branded or biosimilar competition. Introducing branded competition would require that a developer create a new CGT within the same therapeutic class that is different enough that it does not infringe the innovator's patents. The alternative path is for developers to wait until the loss of exclusivity of an innovator product to produce a biosimilar product, which is the primary focus of the recommendations below.

There are many possible challenges to creating competitive biosimilar markets for CGT throughout the product lifecycle, described in great detail in our paper *"Introducing Biosimilar Competition for Cell and Gene Therapy Products."* Would-be competitors considering market entry may be deterred by regulatory uncertainty and ambiguity in the areas of CGT development, a regulatory environment that is still in its infancy even for novel products. For example, it is not yet known how the FDA will evaluate biosimilar CGTs because the two pathways have yet to interact, and there are meaningful differences between CGTs and the less complex biologic therapies the FDA had in mind when issuing various guidance documents for the biosimilar regulatory pathway enacted by Congress.

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[4] *2023's Market Outlook For Cell And Gene Therapies,* https://www.cellandgene.com/doc/s-market-outlook-for-cell-and-gene-therapies-0001 (accessed Jun. 7, 2023), Id.

[5] Chi Heem Wong et al., *Estimating the Financial Impact of Gene Therapy in the U.S.,* NBER (April 2021) https://www.nber.org/system/files/working_papers/w28628/w28628.pdf (unpublished manuscript).

[6] Tufts Health Plan, *Gene Therapy: Making Life-Changing Treatments Affordable | Why Choose Tufts Health Plan | Employer,* https://tuftshealthplan.com/employer/work-well,-live-well/technology/gene-therapy (accessed June 24, 2022).

[7] Colin M. Young, Casey Quinn, and Mark R. Trusheim, *Durable Cell and Gene Therapy Potential Patient and Financial Impact: US Projections of Product Approvals, Patients Treated, and Product Revenues,* 27 DDT 17, 13 (2022).

[8] GlobeNewswire News Room, *Cell Therapy Market Size to Surpass US$ 60.67 Billion by 2030,* https://www.globenewswire.com/en/news-release/2022/05/12/2442322/0/en/Cell-Therapy-Market-Size-to-Surpass-US-60-67-Billion-by-2030.html (accessed Mar. 14, 2024)

[9] Alliance for Regenerative Medicine, *Regenerative Medicine: Disrupting the Status Quo,* http://alliancerm.org/wp-content/uploads/2022/03/ARM_AR2021_FINAL-singles.pdf (accessed Mar. 14, 2024).

[10] IQVIA, *Piping Hot: A Look at the State of Cell, Gene and RNA Therapies in Early 2023,* https://www.iqvia.com/blogs/2023/04/piping-hot-a-look-at-the-state-of-cell-gene-and-rna-therapies-in-early-2023 (accessed Mar. 14, 2024).

[11] IQVIA, *Piping Hot: A Look at the State of Cell, Gene and RNA Therapies in Early 2023,* https://www.iqvia.com/blogs/2023/04/piping-hot-a-look-at-the-state-of-cell-gene-and-rna-therapies-in-early-2023 (accessed Mar. 14, 2024), Id.

Second, the manufacturing of CGT is complex and costly and faces significant capacity limitations. This will remain true for potential follow-on competition as well. Third, because the adage "the product is the process" applies squarely to CGT products, IP complications surrounding manufacturing processes may hinder future competition. In particular, extensive patent estates held by manufacturers of CGTs and the greater use of trade secrets around custom-made/bespoke manufacturing processes are likely to delay or prevent other developers from using their innovation to enter the market. At the same time, recent decisions by the US Supreme Court have limited the breadth of patent claims and could thus lower some barriers to future CGT competition. Lastly, because patient pools would be expected to shrink following treatment with innovator (and potentially curative) CGTs, it is expected that incentives for market entry by follow-on CGT will be constrained. These cross-cutting considerations must all be incorporated into the analysis for follow-on CGT.

Below, we propose recommendations that build on the findings from interviews with twenty-one relevant subject matter experts and reviews of white and grey literature described in our paper. We explore strategies to foster competition from potential CGT biosimilars while considering the main challenges mentioned above. Promoting future biosimilar competition in the CGT market, where feasible, in anticipation of patent and other exclusivity expiration for these products, should be explored to the greatest extent possible.

RECOMMENDATION 1

Issue guidance on CGT biosimilarity within the BPCIA pathway and promote regulatory flexibility for biologics to improve the development of follow-on CGT

Anticipating the regulatory landscape for CGT biosimilars requires a comprehensive understanding of the existing regulatory frameworks governing both CGTs and biosimilar products.

While the potential for CGTs to achieve durable or prolonged effectiveness can make them a preferred treatment option, the regulatory environment for novel CGTs is only in its infancy. Follow-on CGT product development is thus strained by the uncertainties present in the existing regulatory environment. Anticipating the regulatory landscape for CGT biosimilars requires a comprehensive understanding of the existing regulatory frameworks governing both CGTs and biosimilar products. The FDA regulates the approval of CGT products and the approval of biosimilar products. The Biologics Price Competition and Innovation Act (BPCIA), passed as part of the Patient Protection and Affordable Care Act, created an abbreviated pathway for follow-on biologic products that requires a demonstration of biosimilarity.[12] The statutory definition of biosimilarity may not need to be modified for products beyond therapeutic proteins to accommodate CGT biosimilars due to the flexible nature of the existing biosimilar pathway. However, because the FDA's current framework for biosimilar product approval has been developed scientifically with therapeutic proteins in mind, adaptation will likely be required to make it suitable for more complex biosimilar products. The manufacturing capability and capacity needed to ensure quality production of follow-on CGT also present new obstacles for manufacturers, regulators, and other stakeholders.

[12] Charles B. Rangel, H.R.3590 - *111th Congress (2009-2010): Patient Protection and Affordable Care Act,* (2010), https://www.congress.gov/bill/111th-congress/house-bill/3590 (last visited Aug 2, 2021).

[13] Center for Biologics Evaluation and Research, *Preclinical Assessment of Investigational Cellular and Gene Therapy Products,* U.S. FOOD AND DRUG ADMINISTRATION (2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preclinical-assessment-investigational-cellular-and-gene-therapy-products (last visited Jul 24, 2022).

Further FDA guidance on *novel* CGTs will be helpful in understanding how biosimilarity may be interpreted scientifically for these products. FDA has released existing guidance on the preclinical research program design for CGTs, providing specificity on particular cell types and vector types.[13] In addition, the agency has highlighted safety concerns and the lack of clinical experience for sponsors when designing early-phase clinical trials of CGTs.[14] Recent FDA guidance on post-approval reporting of manufacturing changes takes a lifecycle approach and offers recommendations for comparability assessments.[15] However, additional guidance is needed on relevant topics like manufacturing, testing, donor materials, stability of constructs for CGTs, and potentially distinct considerations for cell and gene therapy development. Further regulatory guidance and flexibility will allow sponsors to fully understand the reference products before engaging in biosimilar development, ultimately informing standards for biosimilar characterization and development in this space.

Currently, given that the CGT development environment is still in its infancy for novel products, there has not been an attempt by CGT developers to use the regulatory pathway for biosimilar products. As CGT developers begin to contemplate biosimilars, they will need to address a number of regulatory considerations. Understanding what the FDA considers to be "highly similar" with "no clinically meaningful differences" for CGT will be key. Given the broad language of the BPCIA standard, the statutory definition of biosimilarity probably does not need to be modified to accommodate CGT biosimilars. However, the regulatory standards for, and scientific framework around, biosimilarity will need to evolve as we learn more about novel CGTs, and FDA could explore and introduce modified standards for establishing biosimilarity in this unique space.

Specifically, in setting out standards for biosimilarity for CGT products, further clarity is needed from FDA on what the agency would consider a reference product for developing a potential biosimilar CGT. Several factors will help address this question—namely the primary mode of action for the product, answering aforementioned knowledge gaps within the existing CGT landscape, and greater technical knowledge around manufacturing components. The primary mode of action maps directly to the quantity and complexity of the CGT's functional elements. Variability among therapies ranges from in-vivo gene therapies—with standardized vectors and selected genes of interest—to cell-based gene therapies, which may have determinations of product biosimilarity informed by the processed cellular material and the vector administered to introduce the genetic material into the cells.

Evidence standards for CGT biosimilars should encompass both the product specifics and the production process. The correct critical quality attributes and parameters for analytical comparability exercises will need to be established to meet the analytical similarity piece of the biosimilarity paradigm. This is similar to the process that has occurred for therapeutic proteins, as scientific research permitted advanced characterization of protein structure and function. Manufacturing and process standards will also need to align, including the harvesting method, how cells are expanded and transfected, and cell characteristics as transfected cells are formulated. In terms of evidence collection, demonstrating proof of concept and long-term safety and effectiveness of products will be the most important considerations for CGT biosimilars. Proving treatment durability will require long-term data collection to understand the functional response and safety and collect novel data packages.

Finally, further FDA guidance for different product classes, accounting for differences within product classes, may provide more clarity to developers and manufacturing facilities on the necessary and best practices for production and testing processes.

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[13] Center for Biologics Evaluation and Research, *Preclinical Assessment of Investigational Cellular and Gene Therapy Products,* U.S. FOOD AND DRUG ADMINISTRATION (2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preclinical-assessment-investigational-cellular-and-gene-therapy-products (last visited Jul 24, 2022).

[14] Center for Biologics Evaluation and Research, *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products,* US Food and Drug Administration (FDA, February 10, 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-early-phase-clinical-trials-cellular-and-gene-therapy-products.

[15] Center for Biologics Evaluation and Research, *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products.* U.S. FOOD AND DRUG ADMINISTRATION (2023), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-changes-and-comparability-human-cellular-and-gene-therapy-products.

Following current good manufacturing practice (cGMP) standards for CGTs is often challenging as manufacturers must collect sufficient compliant starting materials while standards are lacking for therapeutic areas like regenerative medicine, leading to a variety of different protocols.[16] For example, in autologous cell therapy products, the source cell quality of diseased patients will not meet cGMP standards for production.[17] Developers and manufacturing facilities must also account for the differences in clinical and commercial manufacturing standards—GMP for commercial production for example may require more viable cells than in clinical trial production.[18] As further guidance is issued and knowledge on CGTs is increased, the feasibility of the current pathway for biosimilar approval for potential CGT products will become more apparent.

In addition to advancing novel and biosimilar developments, the FDA could also take steps to promote regulatory flexibility. Biologic product development lacks the equivalent of the 505(b)(2) provision in the Federal Food, Drug, and Cosmetic Act, a pathway that reduces the need for redundant data collection in the development of small molecule drugs by using data from previously approved products. Current follow-on biologic development is constrained by the existing regulatory framework that does not acknowledge innovation outside of products that meet the requirements of the 351(k) pathway for biosimilar biologics license applications.[19] A middle-ground pathway equivalent to the 505(b)(2) used for follow-on drug development, may be part of further incentives for prospective CGT developers to prioritize biologics research. The creation of a middle-ground pathway equivalent would require legislative action by Congress.

Congress has taken recent action through the enactment of the Federal Drug Omnibus Reform Act (FDORA), passed as part of the 2023 Consolidated Appropriations Act, to authorize a provision for FDA to establish a designation

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for platform technologies, to improve the efficiency of the development of technologies that potentially encompass more than one product by making drug applications that incorporate these platform technologies potentially eligible for expedited review.[20] However, this benefit is only conferred to the drug sponsor or an authorized designate of the sponsor, and only if the platform technology used is identical to the one previously approved. In contrast, a 505(b)(2) pathway equivalent for biologics would go further, by allowing applicants not authorized by the sponsor to rely on existing data (including biosimilar developers, to take advantage of the expedited review available for the use of the platform technology) and for applicants to expand on the existing data, for example, by creating new-generation platform technologies. In the absence of legislation to create such a pathway, FDA may promote follow-on biologic development by providing increased flexibility in the 351 (a) pathway for stand-alone biologics license applications. Further guidance and rulemaking could allow greater data availability and encourage reliance on existing, approved biologics license applications.[21]

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[16] Kris Elverum and Maria Whitman, *Delivering Cellular and Gene Therapies to Patients: Solutions for Realizing the Potential of the next Generation of Medicine,* 27 GENE THER 537, 7 (2020) https://doi.org/10.1038/s41434-019-0074-7.

[17] P. Moutsatsou et al., *Automation in Cell and Gene Therapy Manufacturing: From Past to Future,* 41 BIOTECHNOL LETT 1245 (2019).

[18] BioPharmaReporter, *CAR-T Concerns for Novartis as Kymriah Identified out of Spec,* https://www.biopharma-reporter.com/Article/2018/07/25/CAR-T-concerns-for-Novartis-as-Kymriah-identified-out-of-spec (accessed Jul. 26, 2022)

[19] Temkin, Eva, and Jessica Greenbaum, *Approval Regs Must Change To Keep Up With Biologics Tech - Law360* https://www.law360.com/articles/1720940/approval-regs-must-change-to-keep-up-with-biologics-tech (accessed Nov. 17, 2023)

[20] Gerald Connolly, HR 2617, *Consolidated Appropriations Act,* 2023, (2022), https://www.congress.gov/bill/117th-congress/house-bill/2617.

[21] Temkin, Eva, and Jessica Greenbaum, *Approval Regs Must Change To Keep Up With Biologics Tech - Law360* https://www.law360.com/articles/1720940/approval-regs-must-change-to-keep-up-with-biologics-tech (accessed Nov. 17, 2023).

RECOMMENDATION 2

Prioritize gene therapy biosimilars and address regulatory gaps for both gene and cell therapies

Our findings suggest that gene therapies would be substantially more feasible to "biosimilarize" than their cell therapy counterparts.

Because their functional elements are different, there are unique considerations for examining potential biosimilarity between gene and cell therapy products. Our findings suggest that gene therapies would be substantially more feasible to "biosimilarize" than their cell therapy counterparts. Gene therapies are defined by genetic sequencing corresponding to introduced genetic material. The nature of the introduced genetic material is usually in the form of a transgene, a nucleic acid sequence encoding for the gene of therapeutic interest.[22] The vehicle for delivering the introduced genetic material into the cell, the vector, is typically derived from viruses (adeno-associated viral, adenoviral, lentiviral, or retroviral).[23] The delivery mechanism for the gene therapy product is impacted by the choice of vector.

As the major functional element of the product will be the transgene itself, one can establish the identity of what is being produced in the follow-on product, and its biosimilarity to the reference product by examining the genetic sequence—in other words, the genetic sequence of interest can be substituted into the viral vector. It will also be important to examine how the genetic sequence is delivered via vector, and FDA should clarify what level of flexibility in vector variability will be permissible from a regulatory standpoint to demonstrate biosimilarity.

In 2021, FDA issued final guidance on the regulatory "sameness" criteria for gene therapies in the context of orphan drug regulations. According to FDA, two gene therapies that use different vectors are different drugs for purposes of the orphan drug program but *variants* of a vector from the same viral group (e.g., AAV2 vs. a variant of AAV2) would be assessed for sameness on a case-by-case basis. While "highly similar" is not the same standard as "same," clarity from FDA is needed on whether considerations of sameness for gene therapy vectors might intersect with the criteria used to demonstrate biosimilarity for CGT products. If the "sameness" and "high similarity" standards for the orphan drug regulations and the BPCIA, respectively, are interpreted in a strictly parallel fashion, then the stakes for competitive entry do not change. But if FDA deems a potential biosimilar sufficiently "different" that it falls outside the originator's orphan drug exclusivity but nonetheless "highly similar" for the purpose of FDA approval under the BPCIA, then FDA significantly weakens the orphan drug exclusivity and streamlines the entry of the biosimilar into the market. Given the potentially significant competitive implications, clarity from the FDA regarding the interpretation of these two concepts within the CGT context and their potential intersection is needed.

The exact differences in the vectors will need to be well characterized for any functional or analytical differences. Given the centrality of manufacturing to the therapy itself, even if the viral vector is the same variant, it will still be important to display biosimilarity within the manufacturing process using purity markers like the level of capsids filled and DNA contamination. The viral vector also includes sequences encoding proteins responsible for creating the protein shell of a virus (a capsid), as well as other proteins needed for replication. For the assembly of certain vector types, e.g., adenovirus and adeno-associated viral vectors, additional materials including an inert, helper virus or shuttle vector can be used to create the engineered viral vector. Manufacturers then use certain cell types to host the vector and allow it to reproduce so that there is a large enough quantity to harvest.

[22] FDA, *Long Term Follow-Up After Administration of Human Gene Therapy Products, Guidance for Industry,* https://www.fda.gov/media/113768/download (accessed Mar. 14, 2024).

[23] Jote T. Bulcha et al., *Viral Vector Platforms within the Gene Therapy Landscape*, 6 SIG TRANSDUCT TARGET THER 1 (2021).

Additionally, clinical trials for comparative immunogenicity are more easily performed with gene therapies than for cell therapies but the exact immunogenicity considerations, if needed, for gene therapy clinical trials would still need to be defined by FDA.

Cell therapies present additional complexities for demonstrating biosimilarity. Such challenges include the functional elements of the cellular starting material and final product formulation. The cellular starting material for cell therapies can be derived from either the patient's own body, known as autologous treatment, or from a donor or donated cells or tissue, known as an allogeneic treatment.[24] The final product formulation for cell therapy is either infused shortly after formation into the patient or cryopreserved for later infusion.[25] Analytical and functional characterizations for cell therapies, needed to ascertain biosimilarity, would need to be carefully designed to not destroy the final cell-based product.

Further clarity is needed on whether the different categories of cell therapy products would lend themselves to different criteria for proving biosimilarity. Autologous cell therapies will have to show that the vector is identical or highly similar and leads to no clinically meaningful differences compared to the reference cell therapy's product. Further support for biosimilarity would likely stem from undefined critical quality attributes, including characterization of the vector-transduced starting cell material leading to cell characterization after transduction alignment.

Conversely, allogeneic "off the shelf" products with a larger patient population might better lend themselves to biosimilarity as an economic matter because the same product can be manufactured over and over again (i.e. more than once as with an autologous product). However, identifying the reference product will be difficult because the starting material of the cell is so vast, despite well-standardized procedures for harvesting. The raw and donor cell materials used in allogeneic products would need to meet a high standard of consistency. Demonstration of the same level of efficacy would also be difficult given the differences in sources and the intrinsic heterogeneity of donor cells.

In addition, cell lines shift in characteristics over time, complicating the already complex quality parameters needed for the establishment of biosimilarity. These products will need to demonstrate consistency in manufacturing, and developers will need standard practices for harvesting donor and raw materials. However, reaching standardization in manufacturing will be burdensome for developers and may require navigating legal and resource-driven barriers.

Given the knowledge gaps in applying the existing biosimilar framework for cell therapies, FDA may consider prioritizing this topic for its regulatory science research program. The third authorization[26] of the Biosimilar User Fee Act (BsUFA) provided FDA the opportunity to pilot a regulatory science research program to improve decision-making and science-based recommendations to underlie the basis for biosimilar development. The current research roadmap[27] outlines two aims for this pilot program, which are to advance the development of interchangeable products and improve the efficiency of biosimilar product development. The future goals of the pilot program could include an additional objective: supporting the conceptualization of emerging biosimilar products, using cell therapies as a prime example.

[24] *Allogeneic vs. Autologous Treatments: Definitions and Differences,* BIOINFORMANT (2022), http://https%253A%252F%252Fbioinformant.com%252Fallogeneic-versus-autologous%252F (last visited Jul 21, 2022).

[25] Center for Biologics Evaluation and Research, *Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products,* U.S. FOOD AND DRUG ADMINISTRATION (2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products (last visited Jul 26, 2022).

[26] US Food and Drug Administration, *BsUFA III: Fiscal Years 2023-2027,* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products (last accessed March 2024).

[27] US Food and Drug Administration, *BsUFA III Regulatory Research Pilot Program: Research Roadmap,* https://www.fda.gov/media/164751/download (last accessed Mar. 14, 2024).

RECOMMENDATION 3

Enhance regulatory review and the distribution of expertise within FDA to accommodate CGT biosimilars

CGTs are reviewed by multiple divisions within the newly formed Office of Therapeutics (OTP) within the Center for Biologics Research (CBER). In addition, CBER has established an interdisciplinary center team to promote engagement with prospective innovators, developers, and sponsors regarding advanced manufacturing technologies, the CBER Advanced Technologies Team (CATT).[28] For potential CGT biosimilar sponsors that use advanced manufacturing technologies, coordination between CATT and review divisions within CBER can help address perceived regulatory barriers that may prevent the adoption of advanced manufacturing technologies and ultimately entry into the CGT biosimilar market.

The Center for Drug Evaluation and Research (CDER) at FDA has wide-ranging expertise in both rare disease and biosimilar research and review. The Accelerating Rare Disease Cures (ARC) Program is scoped to speed the development of rare disease treatments and coordinate all work that could affect rare disease development, such as novel clinical trial designs and endpoints and stakeholder outreach.[29] ARC will *"address challenges with well-established trial designs, endpoint selection with a limited understanding of the natural history of the disease, and give advice on performing and interpreting rare disease clinical trials with small patient populations."*[30] It serves as "connective tissue" throughout the agency rather than a discrete center of excellence, to spread expertise.[31] Biosimilar expertise at FDA is confined within CDER's Office of Therapeutic Biologics and Biosimilars (OTBB). Typically, the review of biosimilar products is coordinated with the same clinical review division that reviewed the reference product. CGT biosimilar reviews will thus likely present a need for coordination across CBER reference product review divisions within the OTP and CDER staff experienced with rare diseases and biosimilar research.

Further support for CGT biosimilar development can be provided by FDA, building off of existing early engagement opportunities. For example, the Biosimilar Initial Advisory Meeting serves as a checkpoint for FDA to meet with sponsors on whether an investigational product will meet expectations for the 351(k) biosimilar pathway. The INitial Targeted Engagement for Regulatory Advice on CBER/CDER Products allows for discussion on product development with only preliminary proof-of-concept studies.

The importance of facilitating early interactions is paramount for smaller companies that may lack the regulatory experience or expertise in biosimilars and/or in CGTs; this issue was noted as a regulatory challenge in a recent Government Accountability Office report on regenerative medicine.[32] FDA could work with sponsors, and other leading stakeholders, to formulate private-public partnerships that share emerging best practices and lessons learned to enhance the development of CGT biosimilars.

Any pathway or initiative for CGT biosimilar approval will require clear communication and frequent meetings with sponsors so that they understand the feasibility of their product while being provided with sufficient guidance. With limited FDA capacity to process all the CGT applications received, the increased OTP staff designed to respond to CGT development under the Prescription Drug User Fee Act (PDUFA) VII could provide the needed resources for current CGT approvals, and future BsUFA reauthorizations could include staffing for future CGT biosimilar development.

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[28] Steven Oh, *Facilitating Advanced Technologies in Cell and Gene Therapies,* Presentation at CASSS, (June 7 2021) https://www.casss.org/docs/default-source/cgtp/2021-cgtp-speaker-presentations/speaker-presentation-oh-steven-cber-fda-2021.pdf?sfvrsn=193414c_6.

[29] Rachel Sher, *A Focal Point for FDA's Rare Diseases Efforts: CDER's New ARC Program,* https://advance.lexis.com/document/?pdmfid=1516831&crid=fab0a4fb-40c1-4757-b250-b4d9905d340f&pddocfullpath=%2Fshared%2Fdocument%2Fnews%2Furn%3AcontentItem%3A65GJ-9N41-F03R-N1M9-00000-00&pdcontentcomponentid=299488&pdteaserkey=sr1&pditab=allpods&ecomp=rz2yk&earg=sr1&prid=098bf71f-975b-4d70-939e-e44e2cb8b98b h (last visited Jul 21, 2022).

[30] CITI Program, *FDA Announces New Accelerating Rare Disease Cures (ARC) Program | CITI Program,* HTTPS://ABOUT.CITIPROGRAM.ORG/, https://about.citiprogram.org/blog/fda-announces-new-accelerating-rare-disease-cures-arc-program/ (last visited Jul 21, 2022).

[31] Rachel Sher, *A Focal Point for FDA's Rare Diseases Efforts: CDER's New ARC Program,* https://advance.lexis.com/document/?pdmfid=1516831&crid=fab0a4fb-40c1-4757-b250-b4d9905d340f&pddocfullpath=%2Fshared%2Fdocument%2Fnews%2Furn%3AcontentItem%3A65GJ-9N41-F03R-N1M9-00000-00&pdcontentcomponentid=299488&pdteaserkey=sr1&pditab=allpods&ecomp=rz2yk&earg=sr1&prid=098bf71f-975b-4d70-939e-e44e2cb8b98b h (last visited Jul 21, 2022).

[32] United States Government Accountability Office, *Regenerative Medicine: Therapeutic Applications, Challenges, and Policy Options* : report to congressional committees, https://www.gao.gov/assets/gao-23-105430.pdf (last accessed Mar. 14, 2024).

RECOMMENDATION 4

Promote the standardization of manufacturing platforms to address the high costs and complexity in CGT manufacturing and foster more entry into the CGT space

CGTs are largely manufactured through bespoke processes that are not efficient or cost-effective.

Unlike other drug products on the market that benefit from "plug-and-play" manufacturing platforms (such as commonly-used bioreactors or modular fillers), CGTs are largely manufactured through bespoke processes that are not efficient or cost-effective and that require knowledge that may not be easily transferable through normal scientific exchange and market channels. The lack of more cost-effective development opportunities and process standardization may hamper the ability of both innovator and biosimilar developers to enter the market and hinder the creation of competing products that meet biosimilarity thresholds. Addressing these concerns may foster initial interest and investment in both current CGT manufacturing and future biosimilar development opportunities.

Several features of CGT manufacturing platforms can reduce the cost of production. Platforms that allow for easy scaling-up of production, such as through larger batch sizes and/or higher volumes after commercialization can lower the cost-of-goods-sold (COGS) and the price per therapeutic dose. Centralized manufacturing is a more traditional manufacturing method and can lower manufacturing costs by reaching economies of scale. It could be adapted with lessons learned from the blood supply chain model utilized by blood banks—particularly the high-speed and high-volume management of procurement in the blood supply chain, administration with track and trace capacity, and segregation of lots with embedded quality control (QC).[33] Decentralized manufacturing can also present unique opportunities for scaling up CGT manufacturing and lowering the cost of production by increasing development capacity and more rapidly identifying and addressing consumer needs. It can also streamline manufacturing with the use of cloud-based systems that allow for the implementation of the same protocols, in-process and batch release assays, and quality attributes across sites.[34] However, decentralized manufacturing has its complexities, and may entail fewer economies of scale, expensive distribution of raw materials, higher automation requirements between sites, and partnerships between sites to share pre-competitive information.[35] Similarly, a point-of-care manufacturing approach allows for manufacturing at various, smaller facilities, and at the patient's site of clinical care. If stakeholders can build and operate these facilities, point-of-care care manufacturing can eliminate some parts of the manufacturing process, like the cryopreservation of materials for distribution.[36]

To achieve scale-up, manufacturers may also develop or utilize platforms that can start with small-scale production to take advantage of existing innovations for this level of production and then move towards commercial-scale manufacturing as needed.[37] Importantly, this move towards commercial-scale manufacturing may require rethinking the production processes used in early development to keep costs consistently low and the use of different, larger-scale innovations that lend themselves better to commercial production.

Platforms that utilize automation can also lower the cost of production by providing an alternative to the time and labor costs of CGT production, and variability in manufacturing that may lead to errors in the development process or lead to variability in the products themselves that pose challenges to demonstrating biosimilarity. While

[33] Richard P. Harrison et al., *Decentralised Manufacturing of Cell and Gene Therapy Products: Learning from Other Healthcare Sectors,* 36 BIOTECHNOLOGY ADVANCES 345 (2018).

[34] Karoline Hahn, *Decentralized Manufacturing: A Path towards Smart Cell and Gene Therapy Manufacturing,* MassBio, https://www.massbio.org/news/recent-news/decentralized-manufacturing-a-path-towards-smart-cell-and-gene-therapy-manufacturing/ (2022).

[35] Richard P. Harrison et al., *Decentralised Manufacturing of Cell and Gene Therapy Products: Learning from Other Healthcare Sectors,* 36 BIOTECHNOLOGY ADVANCES 345 (2018).

[36] Xiuyan Wang & Isabelle Rivière, Clinical Manufacturing of CAR T Cells: Foundation of a Promising Therapy, 3 MOL THER ONCOLYTICS 16015 (2016).

[37] R. Lee Buckler et al., *Technological Developments for Small-Scale Downstream Processing of Cell Therapies,* 18 CYTOTHERAPY 301 (2016).

there are currently first-generation automated platforms on the market that integrate several manufacturing steps into one machine, second-generation platforms are in development that can fully automate the manufacturing process and eliminate the need for manual labor at any point in production—including the transfer of materials from one unit of operation to another.[38]

With the development and increased use of manufacturing platforms that can reduce COGS and encourage developer participation in the market, platform standardization will be crucial to their widespread adoption and can encompass the processes and equipment used for critical stages such as hosting, processing, and purifying viral vectors, as well as cell collection, isolation, transfection, culturing, and washing. Furthermore, standardizing quality checks could enhance both the reliability and scalability of CGT production, facilitating a more streamlined pathway from development to delivery. Standardization can also further decrease costs as it allows manufacturers to better pinpoint the most cost-effective raw materials and labor necessary prior to production and reduce time to production. When CGT biosimilar development begins, standardization can also facilitate meeting the biosimilarity standard in the manufacturing process.

However, there are several barriers to reaching widespread standardization. Developing these platforms across companies will require GMP oversight and prior knowledge of platform utilization that many companies may not have. It will also be difficult to standardize platforms across cell therapy types and even within specific products—for example, CAR-T chimeric antigen receptors may differ by company cell materials and make it difficult to apply a standardized platform for manufacturing and testing.

Standards coordinating bodies will play a key role in developing and facilitating the use of standardized technical approaches. National standards bodies are currently developing standards for specific products or procedures. The United States Pharmacopeia (USP) is developing new standards for specific elements of CGT manufacturing, and currently relying on existing USP publications that provide best practices guidance for CGT products.[39] As USP produces additional standards for CGTs, these will be incorporated into FDA regulation, which will play a large role in encouraging standardization across the industry. Other stakeholders like the Standards Coordinating Body (SCB) can play a central role by coordinating community efforts for standards development, which may facilitate the incorporation of standards with widespread stakeholder support into regulatory guidelines for submission. FDA could further encourage the use of standardized platforms to facilitate the development process, leveraging the Advanced Manufacturing Technologies Designation Program. This program, created by the Consolidated Appropriations Act of 2023, enables expedited regulatory review of drugs and biologics made with designated advanced manufacturing technologies. CATT could identify some standardized scale-up and automation platforms that, if employed by innovator companies, could be eligible for receiving the Advanced Manufacturing Technologies Designation.[40] In addition, biosimilars utilizing designated platforms under the Advanced Manufacturing Technologies Designation Program should also benefit from an expedited review process.

In June 2023, Duke-Margolis convened stakeholders to discuss this program and other efforts to advance the utilization and implementation of innovative manufacturing techniques. When promoting manufacturing platform standardization, USP, FDA, and other standards setters will need to find a careful balance between fostering innovation on new products and enabling biosimilar development. Over time, standard-setting priorities and advanced manufacturing platform selection should shift towards enabling biosimilar development and considering the unique role that the manufacturing process plays in displaying biosimilarity.

[38] P. Moutsatsou et al., *Automation in Cell and Gene Therapy Manufacturing: From Past to Future,* 41 BIOTECHNOL LETT 1245 (2019).

[39] US Pharmacopeia, *US Pharmacopeia Standards for Cell and Gene Therapy,* https://www.usp.org/sites/default/files/usp/document/our-work/biologics/asgct-poster.pdf (accessed Oct. 23, 2023).

[40] Joanne Eglovitch, *Omnibus Brings New Advanced Manufacturing Programs to FDA,* https://www.raps.org/news-and-articles/news-articles/2023/1/omnibus-brings-new-advanced-manufacturing-programs (last accessed Mar. 14, 2024).

RECOMMENDATION 5

Facilitate the development of CGT biosimilars through knowledge transfer, disclosure incentives, and greater patent law clarity

The manufacturing process is central to biologic products, and especially to CGTs. One indication of this importance is the large number of manufacturing process patents filed on CGTs. However, current patent disclosure practices might not always meet patent law's "enablement" and "written description" requirements, as these requirements are not necessarily enforced rigorously by the United States Patent and Trademark Office (USPTO). Crucial manufacturing techniques and know-how are also often held as trade secrets. While patent law requires adequate disclosure in exchange for the 20-year period of exclusivity (an exclusivity that also protects against independent invention), trade secrecy requires no disclosure and confers exclusivity until the secret information is independently invented or reverse-engineered. Manufacturers may thus pursue patents for aspects of the manufacturing process that competitors might quickly uncover and opt for trade secrecy to protect elements less likely to be independently discovered or reverse-engineered. In such cases, trade secrets can offer protection from competition for durations surpassing the 20 years provided by patents. Consequently, sponsors may face challenges in creating therapeutically equivalent biosimilars, leading to prolonged periods without competition.

Insufficient disclosure in manufacturing patents and/or critical information held as trade secrets may also make it difficult for coordinating bodies and other stakeholder groups to select and share appropriate platforms. Traditional biosimilar companies have acquired crucial information on manufacturing practices from knowledge that was shared as experts moved around different companies. Ensuring an adequately sized and trained workforce with knowledge of CGT production is necessary for knowledge transfer amongst companies to occur and for the successful production of CGTs. CDMOs may also house the manufacturing know-how for CGT manufacturing, which smaller generic and biosimilar developers can utilize through manufacturing contracts.

Insufficient disclosure in manufacturing patents and/or critical information held as trade secrets may also make it difficult for coordinating bodies and other stakeholder groups to select and share appropriate platforms.

To utilize the role of CDMOs and promote long-term knowledge transfers, stakeholders can further invest in CDMO manufacturing capabilities for CGTs.

Standardization efforts can play a large role in advancing knowledge transfer as this will encourage or require developers to move away from bespoke processes. Within companies, data extrapolation between product versions can also speed up knowledge transfer, which will be supported by further FDA guidance on their use of extrapolation between CGT products.[41]

Additionally, legislative or regulatory efforts to encourage the sharing of manufacturing process knowledge could accelerate knowledge transfer between developers. For example, Congress could provide a pathway for the disclosure of certain critical manufacturing information in return for expedited FDA approval (based on the various tracks that FDA already has) and for incorporating the originator manufacturer's process information into an FDA-blessed standard. While other entities could potentially replicate the information once it becomes a standard, the disclosing party would hold an advantage due to their deeper familiarity with meeting its requirements. This pathway could apply to both information covered by trade secrets that should have been disclosed in the patent (for purposes of complying with the disclosure requirements of patent law) and to information covered by trade secrets that is necessary to create the biosimilar but is outside the scope of patent claims. In the case of the first category, the failure to disclose the information should render the patent

[41] Friends of Cancer Research, *Accelerating The Development of Engineered Cellular Therapies: A Framework for Extrapolating Data Across Related Products,* https://friendsofcancerresearch.org/wp-content/uploads/Accelerating_The_Development_of_Engineered_Cellular_Therapies.pdf?eType=EmailBlastContent&eId=f76efe17-9ea8-46e2-aa4b-977d2d19127b (last accessed Mar. 14, 2024).

invalid. Thus, in addition to Congressional intervention, the USPTO could do a "second review" to determine that disclosure requirements are complied with.

Courts,[42,43] including the Supreme Court, have recently been applying stricter standards for patent disclosures, ruling in favor of robust disclosure in patent claims to satisfy the legal requirements for enablement and written description. This could mean that CGT manufacturers may need to pursue narrower patent claims, for example, claiming the product by structure rather than seeking a broad claim on function. While recent case law does not address patent litigation by biosimilar competitors, it could have implications for future competition from biosimilars by limiting the breadth of patent claims that might otherwise block biosimilar entry. Going forward, there could be opportunities for the development of biosimilars with different designs that steer clear of reference product patent infringement. This possibility hinges on the condition that such biosimilars meet the FDA's criteria for high similarity, ensuring there are no clinically meaningful differences compared to the reference CGT. As discussed above, as loss of exclusivity draws closer, FDA should provide CGT-specific guidance on meeting the biosimiarity requirements under the BPCIA.

Finally, further clarity may be needed to ensure that the Bolar exception, created to promote the entry of generics and biosimilars by allowing their manufacturers to prepare these products before the expiration of the originators' patents,[44] can accommodate CGT biosimilars by extending to different patented manufacturing processes. The Bolar exception is particularly important for CGT biosimilars because of the complexity of the processes covered by patents, for example, the process of culturing the cell for making a viral vector for gene therapy. A recent ruling in a district court has raised uncertainties regarding this extent of protection within the context of CGT. The court determined that the patent-protected cells used in gene therapy, which are not themselves subject to FDA approval (as opposed to the gene therapy itself), are ineligible for the protection of the safe harbor.[45] Additional legal developments over the scope of the Bolar exception are anticipated considering that this interpretation by the lower court may be in conflict with the broader interpretation provided by the US Supreme Court in the 2005 case *Merck v. Integra*[46] and could help facilitate future biosimilar entry in the space.

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[42] Juno Therapeutics, Inc. v. Kite Pharma, Inc., No. 20-1758 (Fed. Cir. 2021) 2:17-cv-07639-PSGKS, (C.D. Cal. April 8, 2020), ECF 728.

[43] Amgen Inc. v. Sanofi Aventisub LL et al., Petition for a Writ of Certiorari, https://www.supremecourt.gov/DocketPDF/21/21-757/200548/20211118155938529_PCSK9%20Cert%20Petition%20-%20For%20Filing.pdf.

[44] Viviana Munoz Tellez, *Bolar Exception,* SPRINGER ACCESS TO MEDICINES AND VACCINES 135-49 (2021).

[45] Regenx Inc. v. Sarepta Therapeutics, Inc., No. 20-1226-RGA (D. Del. Jan. 4, 2022).

[46] 545 U.S. 193 (2005)

RECOMMENDATION 6

Prioritize a CGT biosimilar development demonstration program to identify key gaps in knowledge, technology, and other areas that could inform future policy steps to promote the development of CGT biosimilars

The efforts described above to improve the availability of necessary manufacturing know-how for the successful development and production of CGT can be complemented by a Congressionally-funded demonstration program to replicate the existing manufacturing process for one or several approved CGTs. This program could utilize relevant information that is protected by patent or trade secret through the pathway for the disclosure of critical manufacturing information described in Recommendation 5 and other publicly available resources that a biosimilar company would have access to. This program could be coordinated and implemented through a joint effort between stakeholders including academia, FDA, NIH, standards-setting bodies such as USP and the SCB, and CGT manufacturers. Consideration should be given to potential collaboration and shared objectives between this program and the newly-established National Centers of Excellence in Advanced and Continuous Manufacturing, which were authorized by FDORA.[47]

The goals of the program could include the following: identifying current and developing new, analytical testing methods that could be used to demonstrate that there will be no meaningful clinical difference between originator CGT products and their biosimilar counterparts (with the eventual goal of moving the focus of biosimilar approval at the FDA away from a focus on the manufacturing process); providing a perspective regarding whether existing patent disclosures are robust enough to allow replication of the manufacturing process and further supporting the above-described legislative and regulatory efforts to strengthen disclosure in patents and other critical manufacturing information, and; identifying and describing other challenges and roadblocks encountered in CGT biosimilar manufacturing. Such a program would set the stage for potential reforms that may be necessary to foster CGT biosimilar development ahead of originator patent expirations and could also serve as an incubator for smaller firms that may not otherwise be able to participate in CGT biosimilarization.

Consideration should be given to potential collaboration and shared objectives between this program and the newly-established National Centers of Excellence in Advanced and Continuous Manufacturing,

Activities undertaken by the participants in the demonstration program might include manufacturing site selection, raw material selection, analytical test method development, regulatory body engagement, IP reviews, and workforce training. To encourage industry participation, certain assets developed during the demonstration could potentially be granted to the manufacturers that participate for possible future commercialization, with certain stipulations included--for example, that key findings from the program be shared publicly. Of course, if the assets are shared publicly regardless of participation in the program, that diminishes incentives to participate. On the other hand, public release of the assets would, of course, foster their dissemination more quickly. The demonstration program may also provide insights into the feasibility of creating a future CGT biosimilar Center of Excellence, centered around particular universities and biosimilar development companies, which could develop the expertise and manufacturing know-how required to tackle the biosimilarization of increasingly complex therapies.

[47] Gerald Connolly, HR 2617, *Consolidated Appropriations Act,* 2023, (2022), https://www.congress.gov/bill/117th-congress/house-bill/2617..

Conclusion

Our research and analysis for fostering future competition for CGT products through biosimilars underscores the necessity for detailed regulatory guidance, standardized manufacturing practices, addressing IP complexities, and mechanisms to foster disclosures. These recommendations aim to navigate the complexities of biosimilar CGT development and introduction, in order to enable the health care system to benefit from both novel treatments and cost-effective biosimilar alternatives when the innovator products lose their exclusivity. As the CGT field advances, collaboration between Congress, regulators, industry, and other key stakeholders will be paramount in clarifying the path forward, ensuring that the promise of CGTs is accessible to all patients in need.