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Accelerating the development of genetically engineered cellular therapies: a framework for extrapolating data across related products

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ABSTRACT

Background: Significant advancements have been made in the field of cellular therapy as anti-cancer treatments, with the approval of chimeric antigen receptor (CAR)-T cell therapies and the development of other genetically engineered cellular therapies. CAR-T cell therapies have demonstrated remarkable clinical outcomes in various hematological malignancies, establishing their potential to change the current cancer treatment paradigm. Due to the increasing importance of genetically engineered cellular therapies in the oncology treatment landscape, implementing strategies to expedite development and evidence generation for the next generation of cellular therapy products can have a positive impact on patients.
Methods: We outline a risk-based methodology and assessment aid for the data extrapolation approach across related genetically engineered cellular therapy products. This systematic data extrapolation approach has applicability beyond CAR-T cells and can influence clinical development strategies for a variety of immune therapies such as T cell receptor (TCR) or genetically engineered and other cell-based therapies (e.g., tumor infiltrating lymphocytes, natural killer cells and macrophages).
Results: By analyzing commonalities in manufacturing processes, clinical trial designs, and regulatory considerations, key learnings were identified. These insights support optimization of the development and regulatory approval of novel cellular therapies.
Conclusions: The field of cellular therapy holds immense promise in safely and effectively treating cancer. The ability to extrapolate data across related products presents opportunities to streamline the development process and accelerate the delivery of novel therapies to patients.

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Introduction

Genetically engineered cellular therapies have emerged as a new treatment pillar and are poised to change the therapy landscape for patients with serious or life-threatening malignancies. To date, the U. S. Food and Drug Administration (FDA) has approved six autologous chimeric antigen receptor (CAR)-T cell-based immunotherapies, showing remarkable activity in certain hematologic malignancies. However, considerable scientific and operational obstacles must be overcome to enable broader application of this therapeutic modality in additional cancers, including solid tumors, and advance emerging technologies such as allogeneic and *in vivo* engineered cell therapies. Data extrapolation approaches that build on current products may reduce manufacturing costs and the time to develop next generation genetically engineered cellular therapies.

During the development of genetically engineered cellular therapies, sponsors investigating an autologous CAR-T cell product may also test different versions of the primary product (e.g., an altered CAR protein domain to enhance CAR-T cell activity, additional functional enhancements or co-stimulatory domains, a CAR-T cell derived from an alternative starting material, a more purified cell subtype) in parallel or in tandem [1]. As such, leveraging data from related product versions combined with prior platform technology knowledge are reasonably likely to make the drug development, manufacturing process and the regulatory review more efficient across related product versions. This concept is not exclusive to CAR-T cell products and the principles may apply to a variety of immune therapies such as T cell receptor (TCR) or other genetically engineered cell-based therapies (e.g. tumor infiltrating lymphocytes, natural killer cells and macrophages). Accordingly, adaptations of clinical development models and regulatory frameworks are needed to support more flexible development strategies and allow for product improvements based on empirical learnings. The Food and Drug Omnibus Reform Act of 2022 includes a provision for FDA to create a designation program for "platform technologies" that can be used with more than one drug and may be eligible for certain expedited development or review actions [2]. Within the platform technology program, sponsors may "reference or rely upon data and information" from a previous drug/biologics licensing application incorporating the same platform manufacturing technology. Data extrapolation strategies should consider the totality of evidence collected from preclinical research, clinical trials, and characterization of the manufactured product as well as any available published literature or post-marketing surveillance from related products to inform the safety and biological activity of iterative product versions. Ultimately, leveraging the data from the initial product can optimize the development of genetically engineered cellular therapies and may accelerate access to patients.

The FDA continues to refine guidance to increase efficiencies and facilitate development of genetically engineered cellular therapies and released several guidance documents focused on informing development and streamlining regulatory processes for novel cellular and gene therapies [3–5]. Agency expectations around the types of data and necessary comparability studies required to enable process changes (e.g., changing serum-containing media to serum-free media, changing from adherent to suspension cell culture, or adding a new manufacturing site) by sponsors during the lifecycle of a cellular therapy product are becoming clearer [6–8]. However, agency expectations regarding product changes that sponsors may introduce (e.g., refining the cell source, modifying a CAR transgene, adding a second transgene) to enhance product safety and/or efficacy attributes are beginning to be explored. Specifically, FDA outlines an innovative trial design to investigate different versions of a cellular or gene therapy in a single "umbrella" trial using a single trial infrastructure, design, and master protocol during early clinical evaluation, rather than the traditional design of initiating individual trials for each product version. FDA provides several examples of changes that result in different versions, which would require separate investigational new drug applications (INDs) [5]. Within these different versions, one version would be the primary version with the "Primary IND" containing the clinical protocol, the chemistry, manufacturing, and controls (CMC), and pharmacology/toxicology information. Each of the "Secondary INDs" would cross-reference the clinical information in the Primary IND and contain additional CMC and pharmacology/toxicology information specific to each of the secondary versions (Figure 1).

As our experience with genetically engineered cellular therapies continues to improve and FDA's expectations for the types of data necessary to support product changes are clarified, Friends of Cancer Research convened an expert group of stakeholders and hosted a meeting on May 22, 2023 to develop specific strategies for leveraging data from product versions across the stages of development. Extending the concept of cross-referencing information from one product to a related product version could enable informed trial designs and refined data collection to improve operational activities, developmental efficiencies and streamline regulatory data packages. A risk-based data extrapolation approach is proposed to evaluate when, to what extent, and how data from one product can support development of another related product version. A conceptual, risk-based data extrapolation approach is described to leverage the totality of evidence e.g.—available manufacturing, product quality, analytical

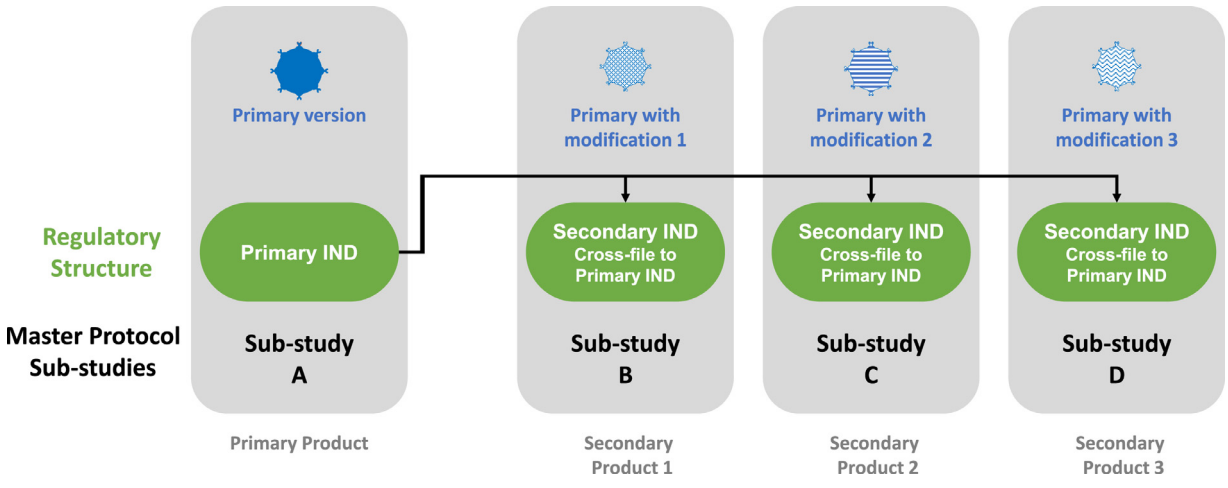

Fig. 1. Umbrella trial design for primary and secondary products. The proposed umbrella trial can simultaneously evaluate multiple product versions for a specific disease or condition using a single-trial infrastructure, design, and master protocol, allowing for more efficient product development.

characterization, non-clinical and clinical knowledge, to support development of multiple related product versions. This strategy minimizes redundant data collection, and optimize and accelerate the development of next generation genetically engineered cellular therapies. The data extrapolation concepts discussed draw upon drug development and regulatory processes in the United States, but the principles are congruent in other regions.

Leveraging Data Across Product Versions to Support Clinical Development

Data extrapolation to advance new versions of investigational products has occurred for several decades across therapeutic classes due to an understanding of the biology, mechanism of action, and manufacturing processes (Supplementary Table S1). Lessons learned from leveraging the totality of evidence in other therapeutic classes to support inferences for new product versions or indications provide a basis for data extrapolation for genetically engineered cellular therapies.

The extent to which data can be meaningfully extrapolated from a primary product to related genetically engineered cellular therapy product(s) depends on the type of modification (including prior knowledge of its impact on related constructs) and phase of development of the primary and secondary products, as well as how "similar" the two versions are to each other. Notably, a case-by-case assessment should be done to determine if a version may be considered the "same" therapeutic [9]. The appropriateness of data extrapolation between two product versions may vary throughout the product lifecycle (e.g., first-in-human studies, early phase, late phase, and postmarket) and across product versions.

Axicabtagene ciloleucel and brexucabtagene autoleucel provide an example of extrapolation in genetically engineered cellular therapy products. The secondary product, brexucabtagene autoleucel, shares the same anti-CD19 CAR construct, vector used in the manufacturing, drug product composition, and similar safety profiles of cytokine release syndrome (CRS) and neurological toxicities as axicabtagene ciloleucel, the primary product. However, brexucabtagene autoleucel has a modified manufacturing process, which includes a white blood cell enrichment process. Nonclinical, clinical, and certain CMC data were extrapolated from axicabtagene ciloleucel to support development and approval of brexucabtagene autoleucel (Table 1). Further, data extrapolation strategies using letetresgene autoleucel (autologous T cell receptor [TCR] T cell therapy targeting NY-ESO-1 and/or LAGE-1a) have been deployed to clinically evaluate next generation versions in a master protocol [10]. The concept of leveraging prior data and the totality of evidence can be extended to other genetically engineered cellular therapy products.

Table 1
Use of data extrapolation between axicabtagene ciloleucel and brexucabtagene autoleucel CAR-T cell therapies targeting CD19. Publicly available FDA review documents include examples where data extrapolation has been used in the development and approval of CAR-T cell therapies [11–13].

Data type extrapolated	Data extrapolation noted in FDA review documents
Non-Clinical Data	• Due to several identical features between axicabtagene ciloleucel and brexucabtagene autoleucel, –further safety pharmacology, pharmacokinetic, toxicology, tumorigenicity, and genotoxicity studies were not required for brexucabtagene autoleucel.
Clinical Data	• Starting dose in the clinical study to assess the safety and efficacy of brexucabtagene autoleucel in subjects with relapsed/refractory (r/r) mantle cell lymphoma (MCL) was selected on the prior dose of axicabtagene ciloleucel in subjects with r/r MCL in the same clinical study. The typical dose escalation cohorts, inter-patient intervals and stopping rules were minimized. • Due to several identical features existing across the two product versions and similar safety profiles of cytokine release syndrome (CRS) and neurological toxicities, the FDA supported a combined risk evaluation and mitigation strategies (REMS) program for axicabtagene ciloleucel and brexucabtagene autoleucel.
CMC Data	• Due to several similarities in the manufacture (vector construct, vector manufacturing process, product manufacturing process, controls, formulation, container closure system validation, storage, equipment, and same manufacturing sites), several sections of CMC data were not generated for brexucabtagene autoleucel, but information resubmitted in the brexucabtagene autoleucel biologics license application (BLA). • Certain facility inspections were waived due to axicabtagene ciloleucel and brexucabtagene autoleucel sharing the same licensed manufacturing site.

Developing a Risk-Based Approach to Support Data Extrapolation Between Product Versions

Extrapolating data across genetically engineered cellular therapy product versions necessitates a fundamental understanding of the primary product and its functional and biophysical properties (Table 2), which in turn requires sufficient non-clinical, CMC, and clinical data, and adequate scientific justification for extrapolation. A framework for evaluating risk in pharmaceutical development is well established in the International Council for Harmonization (ICH) Q9 (R1) and Q8(R2) guidelines on Quality Risk Management and Product Development [14,15]. Extensive knowledge of critical process parameters, product quality attributes, and well-established, robust analytical methods are essential to allow for data comparability and justify extrapolation to support development of subsequent product versions [16–18].

To support this, qualified and fit-for-purpose analytical methods that characterize quality attributes are necessary for a variety of critical parameters (e.g., safety, purity, potency, and identity) to define risk categories. Based on the magnitude of difference in assay outputs relative to the original product version and other data governing the modification that may exist, a risk assessment can demonstrate the probability and severity of risk to patients due to a product modification. Of note, especially for products with highly variable incoming starting material, variability between final products can be expected, especially early in development, making extrapolations potentially more challenging. Furthermore, the sensitivity and degree of qualification of the assays utilized for in-process controls and final product release must be considered. Consequently, evaluating the totality of the manufacturing, characterization, and release data as well as clinical data are critical when extrapolating between product versions.

The type and amount of required additional data for extrapolation will vary and depend on whether a change has a minor or major impact on product quality, efficacy, or safety. A modification that results in a low-risk impact may allow for data extrapolation across products with targeted data collection to address data gaps and support regulatory requirements, whereas a modification that results in a high-risk impact may require more extensive studies. For example, a low-risk impact that has a minor bearing only on product quality may require an analytical comparability assessment, while a moderate-risk impact that involves patient safety/efficacy may require a clinical bridging study, and a high-risk impact may require a larger clinical trial to confirm safety and efficacy in accordance with the degree of expected similarities. The patient population and magnitude of unmet need should also be considered and may lead to a shift in risk tolerance for a particular development program. An assessment aid-like tool (Table 3) could support a systematic approach for

Table 2
Proposed best practices in process and product development to support data extrapolation.

1. Generate comprehensive product knowledge
Gather appropriate non-clinical, clinical, and CMC knowledge based on the stage of drug development.

2. Evaluate the relationship between product attributes
While initial assessments can be performed based on non-clinical and clinical data, as the product advances through clinical development, more robust information on the product efficacy and safety profile will enable a more meaningful determination of how a potential change can impact critical quality attributes (CQAs) or product safety and efficacy. A stepwise approach is necessary to:
1) Assess the relationship between manufacturing process parameters and CQAs (e.g., identity, purity, potency, and safety).
2) Assess the impact of each CQA on product safety and efficacy (i.e., clinical activity).

3. Develop parameters to define risk and perform risk assessment of secondary products
Based on the defined relationships between any changes in quality attributes and safety and efficacy profiles between the primary and secondary product, define:
1) The relative risk of a change on product safety and efficacy
2) Appropriate action(s) to be taken based on the assigned risk.

4. Develop data packages based on identified risk and actions to mitigate risk in regulatory submissions
Determine the appropriate actions based on the totality of evidence from the primary and secondary products and assigned level of risk of the change(s) on safety and efficacy of the secondary product. Such actions could include:
- Extrapolation of data from the primary product
- Generation of additional or new data
- Develop clinical risk mitigation strategies to facilitate clinical development.

There should be frequent and early discussions with FDA particularly when there are uncertainties regarding regulatory and clinical pathways (i.e., will the data extrapolation package be acceptable, will safety run in data or additional data necessary to support the secondary products etc.).

determining the appropriateness of data extrapolation within clinical development programs of secondary products and serve as a summary for FDA submissions.

Classifying the risk impact of modifications may not be easily determined at the outset of development of the related product. The extent to which prior data can be extrapolated will depend on several factors, including the intended development plan of the new product version and risk determination for the impact of the changes on safety and efficacy. In a risk evaluation, it is important to assess the robustness and types of existing data available from the primary product such as information from analytical and *in vitro* studies, non-clinical *in vivo* studies, clinical pharmacokinetic/dynamic (PK/PD) studies (i.e., biomarker correlates, product correlates of response), and clinical efficacy and safety studies (Supplementary Table S2). The analytical methods deployed will vary based on the type of genetically engineered cellular therapy product (e.g., autologous, allogeneic, CAR, TCR, etc.) as well as the types and extent of modifications introduced. Methods to analyze risk should be defined early in development and an adequate level of sensitivity to identify expected differences between two product versions and support a risk-based extrapolation plan.

Leveraging the Totality of Evidence to Support Product Development at Specific Stages of Clinical Development

As products progress through development, the amount of data available to determine risk and extrapolate across versions increases (e.g., extrapolating data from a primary product in early phase, a primary product in late phase, or an already approved product). Table 4 provides examples of how, when justified, data extrapolation can streamline evidence generation, assist in a more seamless transition from one phase of development to another (i.e., academic to industry, early- to mid-phase, and late-phase to post-market), minimize repetitive data collection, and potentially shorten clinical development timelines. The transition from early to later phase clinical development often aligns with a transition from the academic to biopharmaceutical setting and a pivotal step where the product manufacturing process might be modified to support commercialization [19]. Assessment of the impact for such process modifications is captured under more mature FDA guidance; [6–8] however, it is possible that modifications may impact product attributes and thus be informed by the herein proposals. Some example scenarios that might support an accelerated transition of a secondary product through various stages of clinical development are presented below.

Early clinical development

Early phase safety and efficacy data from the primary product could support an understanding of the preliminary safety and efficacy profile, to establish the dosing and schedule, and an approach to data collection in later-phase studies for the secondary product. For example, if appropriately justified, sponsors could propose a similar starting dose for a secondary product as the recommended phase 2 dose for the primary product and/or use the primary product profile to inform more targeted dose limiting toxicity (DLT) criteria to advance a secondary product through early phase studies more efficiently. In early and late phase trials, prior product knowledge could help prepare for expected toxicities and/or inform monitoring strategies to reduce or mitigate symptomatic adverse events.

Late phase clinical development

In instances where a primary product is in late phase development or approved, the totality of data from the primary product may allow a secondary version to move straight into a Phase 2/3 clinical trial. Additionally, data extrapolation may be appropriate and generation of a reduced clinical dataset for the secondary product may be justified based on the similarities with the primary product. For instance, a Phase 3 randomized controlled trial (RCT) readout of the primary product paired with a single-arm clinical bridging study of the secondary product in the same indication may be used to support registration of the secondary product, which could dramatically accelerate patient access to improved product variations.

Post-market phase

Prior product knowledge and the totality of evidence could aid in identification of potential longer-term treatment effects, inform safety surveillance activities, and support patient management in clinical practice for a secondary product. Additionally, post-market data from a related product may justify a shorter duration of patient safety follow-up and reduce the 15-year long-term follow-up period for a secondary product in development or postmarket to decrease costs, resources, and patient burden [20].

Mechanisms for Exploring Data Extrapolation Opportunities and Engaging with FDA

Considerable progress is being made in the development and use of genetically engineered cellular therapies and the field is still evolving. The conceptual framework herein outlined, intends to accelerate investigation and development of the next generation of genetically engineered cellular therapy products and may act as a guide when expanding to other indications and patient populations. As data extrapolation across product versions becomes more common in development programs for genetically engineered cellular therapies,

Table 3
Data extrapolation assessment aid prototype. This document could be submitted as part of an initial IND and/or subsequent IND amendments for a secondary product or as justification to support amendments to a protocol based on learnings from a related product version for FDA meetings. Part A and Part B describe supportive information and data to justify and evaluate data extrapolation in the clinical development of secondary products.

Supportive data	Key information	Guidance for providing information
	Part A- Background/Overview	
Overview of the Primary Product	• What is the stage of development of the primary product? • Summary of product characteristics (e.g., type of genetically engineered cellular therapy, mechanism of action, target, CMC overview) • Summary of data related to safety, efficacy and pharmacologic properties (e.g., safety summary, efficacy summary, dosing, dose/response relationships, any correlations or association between CQAs and clinical data, PK characteristics, clinical studies)	Articulate key non-clinical, CMC, preclinical and clinical safety, and efficacy data set.
Overview of the Secondary Product	• What is the stage of development of the secondary product? • Summary of shared characteristics and differences between product versions • Summary of data from secondary product [*if applicable*] • Summary of known information gaps	Articulate similarities and differences between product versions with a focus on patient safety and pharmacologic properties.
Summary of Development Plan for Primary and Secondary Product	• Summary of development strategy (i.e., will both products be developed in parallel, or will the secondary product replace the primary product?) • Timeline of development strategy	Describe development strategy for product versions. Outline anticipated timelines for data readouts and how this informs development decisions for the secondary product.
	Part B- Extrapolation strategy	
Data Extrapolation Details	• What data are being extrapolated? • How will the extrapolated data from the primary product be used in the development of the secondary product?	Information collected in this section could be presented in a tabulated format: • Data being extrapolated
Justification for Data Extrapolation	• What is the rationale and justification for data extrapolation (i.e., risk assessment)?	• Sponsor assessment of associated risk
Risk Mitigation	• How will known information gaps and risks be mitigated?	• Mitigation strategy

optimal methods to analyze, interpret, and present data in a rigorous and standardized manner will be critical. As product and process knowledge increases within individual development programs and within the field, adaptive regulatory processes that adjust based on the potential risks associated with the modification or stage of development should be in place and support data extrapolation in development of iterative product versions.

Sponsors should consider engaging the FDA early in the clinical development lifecycle when they are interested in justifying the use of prior product knowledge and data extrapolation to inform a specific program and establish pre-specified parameters for risk tolerance. Sponsors should have adequate product quality data or published data to demonstrate that distinct product versions are "similar" in a manner that mitigates concerns about product safety and efficacy when engaging with the FDA and can use the data extrapolation assessment aid prototype (Table 3). Since much of the data to support these assessments will not be publicly available, these assessments will be considered individually by each sponsor. However, public information available could be leveraged by sponsors as has been observed with industry coalescing around published data supporting starting doses for CAR-T cell therapies.

If the relationship between product attributes and patient safety and/or efficacy is not yet fully established (e.g., if the development of both primary and secondary products are in early stages), it is important to identify the uncertainties and knowledge gaps and have a plan for continued assessment of the relationship (e.g., setting milestones after a predetermined number of patients are treated or at the end-of-phase 1 or end-of-phase 2 studies). Pre-defined opportunities for meetings between sponsors and the FDA can be used to address issues relating to product development and to propose mechanisms for data extrapolation to align the core components of such a data package. FDA guidance is available that describes the various FDA meetings, meeting formats, how to submit a request, meeting package requirements, and the different timings for such meetings [22,23]. Ultimately, meetings can help ensure aspects of manufacturing, data capture, and trial designs are sufficient to support a data package for new INDs and BLAs for the next generation versions. Several regulatory opportunities exist that may be particularly advantageous to present the data extrapolation plan and propose the study design for clinical development:

- **Type B Meetings:** Pre-IND, end-of-phase 1, end-of-phase 2, pre-phase 3 meetings, or pre-biologics license application (BLA) can introduce the data extrapolation plan, available data and risk assessment, and how data extrapolation will support the development of a secondary product.
- **Type D Meetings:** Meeting to discuss a narrow set of issues (i.e., not more than 2 focused topics) and should not require input from more than 3 disciplines or Divisions, which may also consider discussion on data extrapolation. Type D meetings may also be available without having an IND.
- **Regenerative Medicine Advanced Therapy (RMAT)/Breakthrough Therapy Designation (BTD) products:** Products that receive these designations signal an organizational commitment by the FDA that involves senior managers. Additionally, products that leverage expedited development programs have shorter clinical development timelines [24]. Designated products are eligible for further FDA meetings that can include data extrapolation for new product version(s).
- **CMC Development and Readiness Pilot (CDRP):** Under the pilot, FDA will provide product-specific CMC advice during product development for products with RMAT/BTD designation, including two additional CMC-focused Type B meetings, as well as a limited number of additional CMC-focused discussions. The pilot will enable additional interactions with FDA during product development and, if applicable, warrant the use of science- and risk-based regulatory frameworks allowing streamlining of CMC development activities to provide earlier clinical access to patients.
- **Designation Program for Platform Technologies:** This is a designation program for platform technologies that have the potential to increase efficiencies in drug development. Applications for drugs or biologics that use or incorporate platform technologies may be eligible for certain expedited development or review actions. The intent of this designation program is to bring significant efficiencies to the drug development or manufacturing

Table 4
Potential opportunities for data extrapolation from a primary product.

Data	Opportunities
CMC	• Extrapolate viral vector/gene editing tools/cell engineering product information, and product/process characterization data • Extrapolate drug product presentation information including container and closure systems, fill volumes and cell concentration • Use stability data from primary product to support initial stability for secondary product • Reduced stability programs leveraging prior programs • Include representative engineering batches in the initial IND of a secondary product and commit to provide certificate of analysis from good manufacturing practice (GMP) batch prior to initiating patient dosing • Reuse gene editing safety data (i.e., translocation information, on and off target editing data) if same edits are used with different CAR • Risk-based microbiology control strategy based on primary product to minimize redundant safety testing requirements • Same analytical methods including potency assays • Orthogonal assays to support similar characteristics of potency • Extrapolate residual control strategy as applicable, and apply to new product • Leverage specifications of primary product
Pre-clinical	• Same relevant animal model and, if not available, justify not conducting toxicity studies • Potential to reduce/waive *in vivo* studies and use *in vitro* studies for proof of concept by referencing primary product data • Use comparative potency data to support *in vivo* study design for secondary product (i.e., dose)
Clinical safety	• Inform starting dose using primary product data • Extrapolate safety data from primary product to optimize, reduce testing (i.e., replication competent lentivirus [RCL]/ replication competent retrovirus [RCR]), and timepoints for long-term safety • Extrapolate potency data to determine potential support for or differentiation of the safety profile for the secondary product • Extrapolate safety data from the primary product • Modified or combined REMS programs for products and use operational efficiencies as proposed by the American Society for Transplantation and Cellular Therapy (ASTCT) 80/20 Task Force [21]
Clinical efficacy	• Support the starting dose and minimize the number of dose levels needed to be tested in early clinical studies, where appropriate • Extrapolate certain clinical data from one indication to support other indications with the secondary product • Potential for fewer clinical trial patients to be treated subject to clinical comparability • Potential short follow up time for the patients treated with the new version, as appropriate • Extrapolate biomarkers/assays for measuring clinical efficacy based on product similarity or support clinical cutoff for patient selection

process as well as to the review process for products across the platform. Many of the concepts and areas for data extrapolation outlined above may be within scope of cell therapy platforms and thus leveraged in subsequent platform products.

In addition to the meeting types and mechanisms noted above, the Initial Targeted Engagement for Regulatory Advice on CBER/CDER Products (INTERACT) and CBER Advanced Technology Team (CATT) may be appropriate to discuss data extrapolation plans or use of new technology/methods to enable data extrapolation.

Moving Forward

Given the uniqueness of genetically engineered cellular therapies, opportunities for continued dialogue beyond the post-approval setting with the FDA, including the Office of Therapeutic Products (OTP), will be important to encourage continued innovation. Additional data and evidence generation, as well as learnings from leveraging safety data across different versions of products, should inform risk-based approaches to defining the optimal safety follow-up period as the field of genetically engineered cellular therapies continues to grow and evolve. FDA workshops could help inform updated guidance on, for example, generating long-term follow-up data for genetically engineered cellular therapy products and clarifying opportunities to streamline data or compress development timelines based on known or expected safety events. Additionally, workshops and other mechanisms should be explored to capture and disseminate best practices and case studies of data extrapolation in clinical development as well as learning from pilot projects like CDRP, which will help educate sponsors in exploring adequate development pathways. A question-and-answer resource could provide timely answers to questions that are commonly asked and applicable across development programs. The concepts and proposals put forward hold promise in streamlining data requirements, while still adequately and robustly assessing products, and ultimately accelerate timelines for patients to access these transformative therapies.

As the field progresses, developers are investigating genetically engineered cellular therapies to not only expand into new disease areas (e.g., CD19-CAR-T cell therapy trials in autoimmune diseases, gene-modified stem cells for genetic disorders) and lines of therapy, but also to improve upon available genetically engineered cellular therapies. For innovation to reach patients in a meaningful timeframe, leveraging available data and extrapolation from s related product version is one mechanism to accelerate development. Additional strategies for accelerating the development of the next generation of genetically engineered cellular therapy products should be explored. In addition to data extrapolation, trial design considerations, alternative and adaptive study designs, real-world data sources, novel endpoints, and use of bioinformatics may accelerate development and require thoughtful discussion among key stakeholders, including regulators, investigators, patient advocacy groups and sponsors.

Declaration of competing interest

M.K. holds IP related to cell therapy, assigned to the University of Pennsylvania and licensed to Novartis, board memberships with IMVinc, Nanocell therapeutics, and is on scientific advisory boards for AdicetBio, Annoca AG, cTRL-therapeutics, Cue Biopharma, Lykan Bioscience, Senti Biosciences, Vittoria Therapeutics. J.J is an employee of Kite, A Gilead Company. J.Y. is an employee of Janssen R&D, LLC. M.F is an employee of Novartis. S.G. is an employee of Allogene Therapeutics. C.G. is an employee of GSK. P.J.H. is a Scientific Advisor or Advisory Board for Cellenkos, Cellevolve, Discovery Life Sciences, Microfluidx, Autolomous, Capsida and is co-founder, board of directors of Mana Therapeutics. J.H. is an employee of Merck & Co. Inc. W. L. is an employee of Lyell Immunopharma. L.P. is an employee of the Canadian Cancer Trials Group and past employee of GSK, and holds shares in GSK. S.P.T reports that Moffitt Cancer Center has licensed Intellectual Property (IP) related to the proliferation and expansion of tumor infiltrating lymphocytes (TILs) to Iovance Biotherapeutics. Moffitt has also licensed IP to Tuhura Biopharma. S.P.T. is an inventor on such Intellectual Property. SPT has received consulting fees from Seagen Inc., Morphogenesis Inc., and KSQ Therapeutics. M.V. is an employee of Genentech, Inc. J.V. is an employee of A2 Biotherapeutics, Inc. S.W. is an employee of Bristol Myers Squibb. All other authors report no potential conflicts.

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Author Contributions

Conception and design of the study: MDS, BAM, HSA, JDA, MK, VC, MB, JJ. Analysis and interpretation of data: MDS, MK, VC, MB, JJ, JY, JJ, MF, SG, CG, PH, JH, WL, BAM, LP, SPT, HSA, MV, JV, SPW, JDA. Drafting or revising the manuscript: MDS, MK, VC, MB, JJ, JY, JJ, MF, SG, CG, PH, JH, WL, BAM, LP, SPT, HSA, MV, JV, SPW, JDA. All authors have approved the final article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcyt.2024.03.009.

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