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Accelerating The Development of Engineered Cellular Therapies: A Framework for Extrapolating Data Across Related Products

Introduction

Engineered cellular therapies[a] 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 cell-based immunotherapies, each showing remarkable activity in certain hematologic malignancies. However, considerable scientific and operational obstacles must be overcome to enable broader application of this therapeutic approach in additional cancers, including solid tumors, and advance emerging approaches such as allogeneic and in vivo targeted cell engineering. Novel scientific approaches that build on current products and enhance product safety and efficacy, overcome biological limitations, and reduce manufacturing costs and time are necessary to develop the next generation of engineered cellular therapies.

During engineered cellular therapy development, sponsors investigating an autologous chimeric antigen receptor (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, a CAR-T cell derived from an alternative starting material, a more purified cell subtype) in parallel or in tandem. As such, leveraging data from related product versions combined with prior platform knowledge may support a more streamlined and effective development strategy across product versions and for future product versions. 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 approach 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, this strategy can optimize the development of these therapies and bring them to patients in a rapid, safe, and efficient manner.

[a]This document primarily focuses on genetically engineered cell-based gene therapies. The term engineered cell therapies includes a variety of immune therapies, such as T-cell receptor (TCR) or chimeric antigen receptor (CAR) based tumor infiltrating lymphocytes (TILs) and other T-cell based therapies.

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The FDA continues to refine guidance to increase efficiencies and facilitate development of engineered cellular therapies and has released several guidance documents focused on informing development and streamlining regulatory processes for novel cellular and gene therapies.[1,2,3] Specifically, FDA outlines an innovative approach to investigate different versions of a cellular or gene therapy in a single umbrella trial during early clinical evaluation, rather than the traditional approach of initiating individual trials for each product version. FDA provides several examples of changes that result in different versions (see Appendix), which would require separate investigational new drug applications (INDs). 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. The recent passage of the Food and Drug Omnibus Reform Act of 2022 also includes a provision for FDA to create a designation program for platform technologies that have the potential to be used with more than one drug and may be eligible for certain expedited development or review actions.[4] Within this program, sponsors may "reference or rely upon data and information" from a previous drug/biologics licensing application incorporating the same platform technology.

As our understanding of engineered cellular therapies continues to improve and FDA's expectations for the types of data necessary to support product changes are clarified, opportunities for leveraging data from product versions across the stages of development will likely increase. 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 and developmental efficiencies as well as streamline regulatory data packages. Because there is not a "one size fits all" approach for extrapolating data across product versions, a risk-based approach can help evaluate when, to what extent, and how data from one product can support development of another version. This white paper provides a conceptual, risk-based approach to leverage the totality of evidence—available manufacturing, product quality, analytical characterization, and non-clinical and clinical knowledge—to support development of multiple product versions, minimize redundant data collection, and optimize development of next generation engineered cellular therapies.

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 (Appendix Supplemental Table 1). 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 in engineered cellular therapies.

The extent to which data can be meaningfully extrapolated from a primary product to related engineered cellular therapy products 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 it may be considered the "same" therapeutic.[5] 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 post-market) and across product versions.

YESCARTA® and TECARTUS® provide an example of extrapolation in engineered cellular therapy products. The secondary product, TECARTUS®, shares the same anti-CD19 CAR construct, the vector used in the manufacturing, the final drug product composition, and cryopreservation method as YESCARTA®, the primary product. However, TECARTUS® has a modified manufacturing process, which includes a white blood cell enrichment process. Nonclinical, clinical, and certain CMC data were extrapolated from YESCARTA® to support development and approval of TECARTUS® **(Table 1)**. The concept of leveraging prior data and the totality of evidence seen in this example can be extended to other engineered cellular therapy products in development.

Table 1. Use of Data Extrapolation between YESCARTA® and TECARTUS® 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.[6,7,8]

Data Type Extrapolated	Data Extrapolation Noted in FDA Review Documents
Non-Clinical Data	• Due to several identical features between YESCARTA® (axicabtagene ciloleucel) and TECARTUS® (brexucabtagene autoleucel)–the same anti-CD19 CAR construct, the vector used in the manufacturing, the final drug product composition and cryopreservation method—further safety pharmacology, pharmacokinetic, toxicology, tumorigenicity, and genotoxicity studies were not required for TECARTUS®.
Clinical Data	• The starting dose in the clinical study (ZUMA-2) to assess the safety and efficacy of TECARTUS® in subjects with relapsed/refractory (r/r) mantle cell lymphoma (MCL) was selected based on the prior explored dose of YESCARTA® in subjects with r/r MCL in the same clinical study. Therefore, the typical dose escalation cohorts, inter-patient intervals and stopping rules were minimized. • Due to several identical features existing across the two product versions, including the anti-CD19 CAR expressed, the vector used in manufacturing, and the similar safety profiles of cytokine release syndrome (CRS) and neurological toxicities, the FDA supported a combined risk evaluation and mitigation strategies (REMS) program for YESCARTA® and TECARTUS®.
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) of the two product versions, several relevant sections of CMC data were not generated for TECARTUS®, but rather FDA required the information be resubmitted in the TECARTUS® biologics license application (BLA). • Certain facility inspections were waived due to YESCARTA® and TECARTUS® sharing the same licensed manufacturing site, which could leverage overlaps in the planned cGMP/surveillance inspections. • For TECARTUS®, drug product batch analysis, stability and stability stress studies were conducted to confirm analytical methods, as well as container closure integrity testing was performed.

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

Extrapolating data across 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.[9,10] Extensive knowledge of critical process parameters, product quality attributes, and well-established, robust analytical methods are essential to justify extrapolation and support development of subsequent product versions. 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.

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 (process parameters and critical quality attributes [CQA]) and safety and efficacy using non-clinical or clinical data sets
While the initial assessment can be performed based on non-clinical and clinical data, as the product advances through later clinical development stages more robust information on the product efficacy and safety profile will enable a more meaningful determination of how a potential change can impact CQAs or product safety and efficacy. Thus, a stepwise approach will be necessary as multiple products advance through development: 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 to facilitate development 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, and 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 to support regulatory submission of a new product version
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, determine the appropriate actions. Such actions could include extrapolation of data from the primary product, generation of additional or new data or development of clinical risk mitigation strategies to facilitate clinical development of the secondary product. 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 be necessary to support the use of the new secondary products, etc.).

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 autologous products with variable incoming starting material, variability between final products can be expected, especially early in development, making extrapolations potentially more challenging. Furthermore, the sensitivity 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 impact only on product quality may require an analytical comparability assessment, while a moderate-risk impact that impacts 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 in thinking about risk and may lead to a shift in risk tolerance for a particular development program as well.

Classifying the impact of modifications and product changes as low- or high-risk may not be easily determined at the outset of development of the new product. The extent to which prior data can be extrapolated to inform development of a new product version will depend on several factors, including the intended development plan of the new product version and risk determination for the impact of the changes in the new product on safety and efficacy. In a risk evaluation, it will be 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 (**Table 3**). The analytical methods deployed will vary based on the type of 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 have an adequate level of sensitivity to identify expected differences between two product versions and support a risk-based extrapolation plan.

Table 3: Select Product Attributes, Analytical Assays, and Studies for Formulating an Extrapolation Strategy for Secondary Versions of Engineered Cellular Therapy Products

Parameter	Assessment Stage	Measure	Readout(s)	Actionable Output
Safety	Non-clinical/ Preclinical	Binder identity	• High-content proteomic screening • Tissue panel screening	Assess off-target binding potential (e.g., weak potential for off-target binding to non-essential and essential targets) vs. primary product
		In vivo pharmacology and toxicology and histopathology	• Tolerability • In-life parameters (e.g., body weight, physical appearance, behavior, etc.) • Tissue biodistribution • Deaths	Assess statistical differences vs. primary product
	CMC	Copies vector/cell	• Vector copy number	Assess average vector copy/cell vs. primary product
		Integration site and rearrangement analyses	• On- and off-target integration sites • Genomic rearrangement status	Identify and quantify frequency of on- and off-target genome editing sites and quantify genomic rearrangement events vs. primary product
		Cytokine production	• Cytokine profiling (e.g., basal, target dependent)	Assess statistical fold-change of effector cytokines values vs. primary product
		Proliferation potential	• Target dependent-rate, doublings • Antigen-/cytokine-independent proliferation	Assess statistical differences in proliferation rate and maximum proliferation vs. primary product
	Clinical	Immunogenicity assessment	• Anti-product antibody assay • Anti-transgene antibody assay	Assess titers and isotypes of anti-product antibodies vs. primary product
		Clinical measures	• Frequency and severity of adverse events • Clinical laboratory measurements • Product expansion kinetics	Identify statistically significant differences vs. primary product

Potency	Preclinical	*In vivo* efficacy studies	• Tumor growth	Quantify statistical differences in dose required to achieve complete response vs. primary product
	CMC	Functional response	• Target-specific cytokine production/ cytolysis	Quantify statistical differences in target-dependent cytolysis and effector cytokine activity vs. primary product
		Transgene expression	• % transgene-positive cells • Mean fluorescence index of transgene on engineered cells	Assess statistical differences in engineering efficiency and transgene expression vs. primary product
		Phenotypic/ genotypic assessment	• Flow cytometry-based T-cell immunophenotyping	Compare immune activation, memory, exhaustion phenotype and genetic evaluation vs. primary product
	Clinical	*In vivo* dose/ response evaluation	• Expansion kinetics and persistence • Minimum efficacious dose	Assess statistical differences in rate of expansion, maximal expansion, 30-day area under the curve (AUC), 30-, 60-, and 90-day persistence vs. primary product
Identity	CMC	Transgene cassette sequence	• Full sequencing of transgene cassettes and regulatory elements	Identify any changes in protein sequence vs. primary product

This table provides examples for how product attributes, analytical assays, and studies can help evaluate the impact of a modification on product biology including potential safety and efficacy. Not all measures are relevant for each type of engineered cellular therapy.

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. A few example strategies are also noted below.

1) **Early Phase Clinical Development**

Early phase safety and efficacy data from the primary product could support an understanding of the preliminary safety and efficacy profile, the context to establish 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 approaches to reduce or mitigate symptomatic adverse events.

2) Late Phase Clinical Development

In instances where a primary product is in late phase development or is 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 to justify a reduced clinical dataset for the secondary product 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 to support registration of the secondary product. This could dramatically improve patient access to improved variations of products which have already demonstrated robust safety and efficacy (i.e., via Phase 3 RCT).

3) 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 clinical 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 for a secondary product in late-stage development or reduce the 15-year long-term follow-up period in the post-market setting to decrease costs, resources, and patient burden.

Table 4: 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 to support process qualification • Use stability data from primary product to support initial stability for secondary product • Implement reduced stability programs leveraging previous programs and/or matrixing beyond initial stability studies • Include only 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 • Use a risk-based microbiology control strategy based on experience with the primary product to minimize redundant safety testing requirements • Use same analytical methods including potency assays (qualified or validated as appropriate) • Use orthogonal assays to support similar characteristics of potency with the secondary product • Extrapolate residual control strategy as applicable, and apply to new product • Leverage specifications development of primary product to enable more refined set CQAs

Non-clinical/ Preclinical	• Use 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 data generated with the primary product • Use potency data from primary and secondary product 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 required to assess long-term safety • Extrapolate potency data to determine potential support for or differentiation of the safety profile for the secondary product as a supplement of secondary drug safety data with supportive key safety data (or conclusions) from the primary drug data • Extrapolate safety data from the primary product for the secondary product in a regulatory filing(s)
Clinical Efficacy	• Support the starting dose and number of dose levels needed to be tested in early clinical studies, where appropriate • Extrapolate certain clinical data from one indication to support development of other clinical indications with the secondary product using the primary drug product efficacy as supportive or primary evidence to support the secondary drug clinical development and regulatory filings • Pending the nature of the modification and stage of development, the clinical trial may require fewer patients treated with the new product version for clinical comparability • Consider whether shortened follow up time for the patients treated with the new product version may be appropriate • Extrapolate biomarkers/assays for measuring clinical efficacy based on similarity to primary product or to support clinical cutoff for patient selection

Mechanisms for Exploring Data Extrapolation Opportunities and Engaging with FDA

Considerable progress is being made in the development and use of engineered cellular therapies and the field is still evolving. The conceptual framework outlined in this white paper intends to accelerate investigation and development of the next generation of engineered cellular therapy products and may also act as a guide when expanding to other indications and patient populations. As the use of data extrapolation across product versions becomes more commonly explored in development programs for engineered cellular therapies, optimal approaches 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. An assessment aid-like tool (see prototype in **Appendix Supplemental Table 2**) could support a more systematic approach for determining the appropriateness of data extrapolation within clinical development programs of secondary products and serve as a vehicle for transparent information exchange when meeting with the FDA.

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. A systematic approach for determining the appropriateness for extrapolating data should include the following elements:

- An extrapolation concept that leverages available data (i.e., non-clinical, CMC, preclinical and clinical) to develop a hypothesis regarding the similarity in safety and efficacy between product versions.
- A data extrapolation plan that proposes a set of supportive studies in accordance with the extrapolation concept.
- A validation approach for the extrapolation plan by relevant emerging data (i.e., non-clinical, CMC, preclinical and clinical).
- An approach for interpreting the data from the secondary product in the context of information extrapolated from the primary product.

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. 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 serve as mechanisms to introduce the data extrapolation plan, available data and risk assessment for a secondary product, 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 be considered for discussions on data extrapolation. This may also be available without having an IND in place.
- **Regenerative medicine advanced therapy (RMAT)/Breakthrough Therapy Designation (BTD) products:** Eligible for further meetings to garner feedback from the FDA 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. This pilot will enable additional interactions with FDA

during product development and, if applicable, warrant the use of science- and risk-based regulatory approaches allowing streamlining of CMC development activities, so that clinical benefits of earlier patient access to these products can be realized.

- **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 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 able to be successfully 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 engineered cellular therapies, opportunities for continued dialogue in 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 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 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 in this white paper hold promise in streamlining data requirements, while still adequately and robustly assessing products, and ultimately shortening the timelines for bringing these transformative therapies to patients.

The field continues to progress, and numerous developers are investigating engineered cellular therapies to not only expand into new disease areas and lines of therapy, but also to improve upon available engineered cellular therapies. For innovation to reach patients in a meaningful timeframe, leveraging available data and extrapolation from related product versions is one mechanism to accelerate development. Additional approaches for accelerating investigation and development of the next generation of engineered cellular therapy products should also be explored. Specifically, in addition to extrapolation, trial design considerations, alternative study designs, real-world data sources, novel endpoints, and use of bioinformatic approaches may accelerate investigation and will require thoughtful discussion among key stakeholders, including regulators, investigators, patient advocacy groups and sponsors.

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Appendix

Examples of Changes that Result in Different Versions of an Engineered Cellular or Gene Therapy Product

FDA provides several examples of changes that result in different versions of an engineered cellular or gene therapy product[1]:

- Changing a cellular product from bulk tumor-infiltrating lymphocytes (TILs) to purified CD8+ TILs.
- Changing from dendritic cells (DCs) pulsed with a recombinant tumor antigen to DCs pulsed with immunodominant peptides from the same antigen.
- Altering the differentiation state of a stem cell product to a more mature cell type along the same lineage (e.g., neural progenitor cells vs. neurons).
- Changing the cell source (e.g., allogeneic vs. autologous, or cord blood vs. bone marrow) for a mesenchymal stromal cell product.
- Changing from an embryonic stem cell bank to an induced pluripotent stem cell (iPSC) bank to produce the same cell type (e.g., retinal pigment epithelial cells).
- Replacing the CAR transgene of a CAR T cell product with a new CAR transgene.
- Modifying a CAR T cell product by adding a second transgene that expresses a costimulatory protein.
- Modifying a gene therapy vector to express the same transgene with a different codon usage, promoter, enhancer, microRNA (miRNA) target or other control element.
- Deleting one or more genes from a viral-based or bacterial-based gene therapy vector.
- Modifying the transgene sequence in a gene therapy vector, resulting in a change to the amino acid sequence of the encoded protein.
- Changing a capsid protein of a viral-based gene therapy vector.

Supplemental Table 1. Examples of Data Extrapolation in Drug Development. A review of publicly available FDA summary documents[11,12] includes examples where data extrapolation has been appropriately used in drug development.

Therapeutic Class	Data Type Extrapolated	Select Examples	Examples from Review Documents
Small molecule drugs	Clinical pharmacology and exposure-response data	COREG®/ COREG CR®	**Clinical Pharmacology/Pharmacodynamics:** Based on equivalencies in PK and PD data in COREG CR® compared to COREG the conclusion was drawn that the indications for which the immediate-release (IR) formulation had been approved can be inferred and claimed for the controlled-release (CR) formulation.
Peptide products (synthetic)	Non-clinical and clinical for rDNA derived peptides	Liraglutide/ future liraglutide ANDAs	**Non-clinical Pharmacology/Toxicology**: Safety margins for toxicities calculated using steady state systemic exposure in healthy adults were similar based on plasma liraglutide area under the curve (AUC) supporting the basis for inclusion of boxed warning and REMS on the risk of thyroid C-cell tumors observed in rodents. **Clinical Pharmacology/Pharmacodynamics:** Exposure results VICTOZA® in the thorough QTc trial were compared with exposures (Cmax) following SAXENDA® in weight management trials and found to be largely overlapping supporting extrapolation of results from VICTOZA®'s QTc trial to support approval of SAXENDA® for weight management.

Therapeutic Class	Data Type Extrapolated	Select Examples	Examples from Review Documents
Antibody-based biologic agents	Manufacturing/ CMC and clinical data	HERCEPTIN®/ HERCEPTIN HYLECTA® RITUXAN®/ RITUXAN HYCELA®	**HERCEPTIN®/HERCEPTIN HYLECTA®** **Clinical Data:** Data extrapolation possible due to the same drug substance and only a formulation change and comparable PK profiles of IV trastuzumab across the neoadjuvant-adjuvant/adjuvant treatment settings in patients with early breast cancer and metastatic breast cancer. **Manufacturing and CMC data**: Due to the same manufacturing processes and drug substances, cross referencing to the BLA was possible. **RITUXAN®/RITUXAN HYCELA®** **Manufacturing/CMC:** Manufacturing processes cross referenced in product quality review. **Pharmacology/Toxicology:** PK Bridging studies used as primary source to support approval/comparable benefit of RITUXAN® and RITUXAN HYCELA®.
Vaccines	Manufacturing/ CMC and clinical primary immunogenicity leverages parent profile as a control (PVN 13 vs PVN20)	PREVNAR 13® (PVN13)/ PREVNAR 20® (PVN20)	**Manufacturing/CMC:** P20VN and PVN13 vaccines have nearly identical manufacturing processes for the 13 common serotypes. **Clinical/Primary Immunogenicity:** Vaccine induced opsonophagocytic activity (OPA) activity was used in the licensure of PVN13 by comparing the OPA titers induced by PVN13 with the licensed 7-valent pneumococcal conjugate vaccine.

Supplemental Table 2. 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 for subsequent amendments to a protocol based on new learnings from another product version to aid in discussion with FDA. 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 in? • Summary of product characteristics (e.g., type of engineered cellular therapy, mechanism of action, target, CMC overview) • Summary of data related to safety and efficacy data 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 in? • Summary of shared characteristics and differences between secondary and primary product • Summary of data from secondary product [*if applicable*] • Summary of known information gaps	Articulate similarities and differences between primary and secondary product with a focus on impact to patient safety and pharmacologic properties.
Summary of Development Plan for Primary and Secondary Product	• Summary of development strategy for primary and secondary product (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 the primary and secondary product. Outline anticipated/expected timelines for data readouts and how this will inform 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 • Sponsor assessment of associated risk • Mitigation strategy
Justification for Data Extrapolation	• What is the rationale and justification for data extrapolation (i.e., risk assessment)?	
Risk Mitigation	• How will known information gaps and risks be mitigated?	