Alliance for Regenerative Medicine

Tissue Engineering and Therapeutics: Takeaways from a Scientific Workshop

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INTRODUCTION

Tissue engineering seeks to restore, maintain, improve, or replace damaged tissues and organs via the combination of cells, scaffolds, and/or biologically active molecules. With wide-ranging indications and inherent complexities, tissue-engineering developers face both exciting possibilities and unique challenges. On September 6, 2023, ARM hosted their first workshop on Tissue Engineering and Therapeutics, aiming to provide this rapidly advancing field with a voice in the regenerative medicine sector. The workshop brought together developers, regulators, and other key stakeholders from across the tissue-engineering industry (see the Appendix for a full list of presenters and panelists). The goals of the workshop were to provide examples of the scientific advances in the field, obtain insights from developers and regulators on chemistry, manufacturing, and controls (CMC) considerations for the industry, and explore funding and market opportunities.

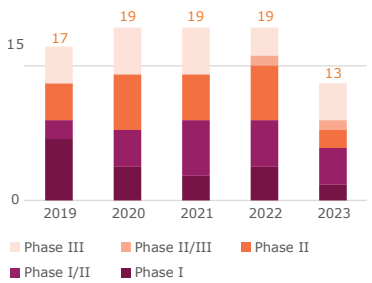
01 Tissue engineering: past, present, and future

In the early days of tissue engineering, efforts largely focused on biomaterial development and the use of engineering principles to mimic the structure and function of the extracellular matrix. Though these remain key areas of research today, the industry has incorporated concepts of gene editing, cell engineering, and advanced manufacturing, ultimately evolving into a field capable of making and scaling tissue-engineered therapies outside of a laboratory.

Though ARM is redefining how to characterize products as "tissue-engineered", it estimates that the number of clinical trials of such products remained fairly stable between 2019 and 2022, with strong representation in later-phase trials. A decline in 2023 may be attributed to 8 trials being completed in 2022. Many investigational and approved products are focused on wound care (e.g., burns and diabetic foot ulcers), but recent activities in the industry suggest that the mix of indications may change significantly over the next decade.

BOX 1. TISSUE ENGINEERING AND THERAPEUTICS—SECTOR OVERVIEW.

Clinical Trials by Year and Phase



2023 Q1 Clinical Trials by Region

Indication	Number of Trials (top 5; 2019-2023)
Diabetic Foot Ulcer	7
Burns	5
Crohn's Disease (Regional Enteritis)	4
Wounds	3
Articular Cartilage Defect	3

BOX 2. APPROVED TISSUE-ENGINEERED PRODUCTS.

Therapy	Type	Indication	Region
Aurix™ NUO THERAPEUTICS	Biodynamic hematogel composed of autologous platelet-rich plasma.	Treatment of wounds	USA
Apligraf™ ORGANOGENESIS, INC.& NOVARTIS AG	Bi-layered living skin substitute made from a dermal layer of human fibroblasts in bovine type I collagen and overlying cornified epidermal layer of living human keratinocytes.	Treatment of chronic venous leg ulcers and diabetic foot ulcer	USA
Dermagraft™ ORGANOGENESIS	Dermal substitute from human fibroblasts placed on a dissolvable mesh material	Chronic foot ulcers in patients with diabetes	USA
Epicel™ VERICEL	Autologous keratinocytes co-cultured with irradiated murine cells to form cultured epidermal autografts (CEA).	Deep dermal or full thickness burns	USA
Heart Sheet™ TERUMO BCT	Autologous skeletal myoblast preparation.	Treatment of patients with serious heart failure	Japan
Holoderm™ TEGO SCIENCES	Cultured epidermal autograft composed of autologous keratinocytes.	Treatment of skin disorders such as burns, vitiligo, nevi and scars	Republic of Korea
Hyalograft 3D™ CHA BIO & DIOSTECH CO LTD	Autologous skin fibroblasts in 3D scaffold formed of hyaluronic acid derivatives	Diabetic foot ulcers	Republic of Korea
JACC™ J-TEC	Combination product of autologous cultured chondrocytes and collagen gel.	Traumatic cartilage defect or osteochondritis disecans of the knee	Japan
JACE™ J-TEC	Epidermal cell sheet produced from keratinocytes isolated from a patient's own skin tissue.	Deep dermal and full-thickness burns covering 30% or more of the total body surface area; and treatment of giant congenital melanocytic nevi	Japan
KeraHeal™ BIOSOLUTIONS LTD.	KeraHeal™ is comprised of autologous cultured human epidermal kertinocytes, isolated from patient skin biopsies and propagated.	Deep 2nd and 3rd degree burns	Republic of Korea
MACI™ VERICEL	Autologous cultured chondrocytes on a porcine collagen membrane	Single or multiple symptomatic, full-thickness cartilage defects of the knee	USA
Rethymic™ ENZYVANT	Allogeneic processed thymus tissue-antigen-generating dendritic cells (agdc)	Immune reconstitution in patients with congenital athymia	USA
Stratagraft™ MALLINCKRODT	Allogeneic cultured keratinocytes and dermal fibroblast in murine collagen scaffold	Deep partial-thickness burns	USA

This Tissue Engineering and Therapeutics Workshop represents an effort to encourage multi-stakeholder engagement and collaboration on key issues and challenges facing the tissue-engineering industry. The workshop focused ***on four primary topic areas: current efforts in the sector, CMC considerations, regulatory perspectives, and funding/ market opportunities.***

CURRENT EFFORTS IN THE SECTOR

Developers provided examples of tissue-engineered products at various stages of development. The diversity of products and engineering approaches shared during their presentations aligns with the broad scope and promise of the industry.

01 Bioengineered transplantable organs

The CEO of Miromatrix described his company's goal of eliminating the organ transplant waiting list. Human-to-human transplantation is limited by organ availability and the possibility of organ rejection, whereas the safety of xenotransplantation (i.e., the process of transplanting organs between different species) remains a major regulatory concern. To develop fully bioengineered implantable livers and kidneys with superior safety profiles, Miromatrix uses a proprietary technology platform that involves sequential decellularization and recellularization (with human cells) of an organ scaffold.[1-3] Miromatrix is currently procuring human cells from organs that possess demonstrated safety profiles but that fail to meet transplantation criteria for various reasons (e.g., nicks/tears/trauma or long ischemia times). They have also developed a closed production system that will allow for rapid scale-up to meet patient demand.

BOX 3. AN OVERVIEW OF MIROMATRIX' PROPRIETARY PERFUSION TECHNOLOGY PLATFORM.

Decellularization + Recellularization = Bioengineered Organ

Pristine organ scaffold with intact functional structures derived from porcine organs

No Animal Cells Remain

We developed two acellular products that received FDA 510(k) clearance using our decellularization technology with thousands of patient implants

Scaffold seeded with living human cells (2- 4 weeks)

Human Cells

Living human cells are adaptive and when introduced into the decellularized scaffold display unique regenerative, plasticity, and adhesion properties

Targeting organ function and immune system tolerance

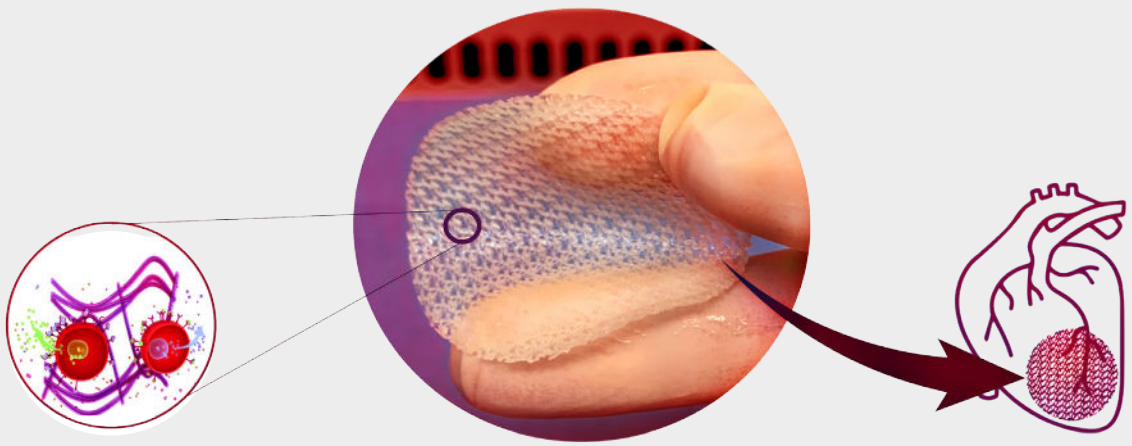
- No animal cells or porcine virus
- Highly scalable production technology
- Organs transplanted utilizing the same techniques and equipment as current organ transplantation

Miromatrix' development strategy has helped to de-risk their platform approach. Initially, decellularization technology was leveraged to develop and commercialize two acellular products, a hernia mesh (miromesh®) and a wound matrix (miroderm®).[4-6] Subsequently, their decellularization and recellularization processes have been integrated to yield miroliver*ELAP*™, an external liver-assist product that (in conjunction with a commercial delivery system) is designed to provide liver dialysis in the critical-care setting. Miromatrix' IND for miroliver*ELAP*™ is currently under a clinical hold with the FDA. In their response to the FDA, they plan to demonstrate that miroliver*ELAP* is safe and tolerable, yielding time- and dose-dependent changes in key biomarkers (e.g., ammonia clearance) and providing a survival signal. Miromatrix hopes that stablishing the safety and efficacy of miroliver*ELAP*™ will accelerate transplantation of bioengineered organs into humans.

02 Biologic therapies for heart disease

The CEO of Avery Therapeutics described how his company is developing immunomodulatory biologic therapies to treat cardiovascular diseases, including heart failure. Avery Therapeutics' curative approach to heart failure involves targeted delivery of MyCardia, which combines a bioresorbable mesh with key cardiac cells and immunomodulatory factors, to the outside surface of the heart. MyCardia has demonstrated the ability to repair scarred and damaged heart tissue in murine, rat, and swine models.[7-12] In a preclinical swine study, it has also shown the novel ability to restore cardiac function through the improvement of left ventricular contractility and filling.[10]

BOX 4. MYCARDIA, AN ADAPTIVE BIOLOGIC PLATFORM TO REPAIR INJURED HEART TISSUE.



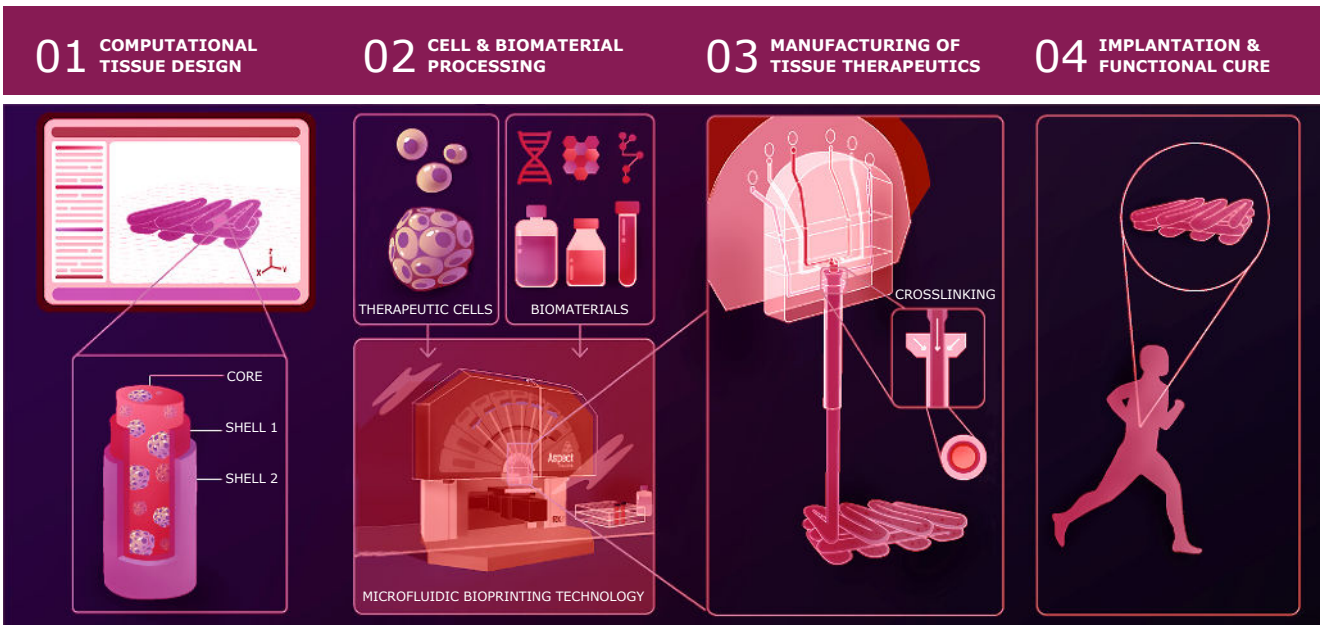
Biologically-derived therapeutic	MyCardia	Targeted application
Bioresorbable mesh, fibroblasts, cardiomyocytes and associated cytokines & chemokines	Single entity combination product	Minimally invasive, precision delivery

Though in late-stage preclinical development and some time off from filing an IND, the company is utilizing a forward-thinking strategy, considering factors related to production (e.g., sourcing of biomaterials and manufacturing), logistics (e.g., storage and distribution), as well as treatment (e.g., dosing at the clinical site). At present, they are using a relatively manual process to create roughly 100 doses at a time, but they have had early success with an automated, closed, bioreactor-style system capable of enabling significant scale-up. The company has always focused on getting their product into the hands of implanting surgeons, which has helped to refine structure and handling characteristics that will ensure the easiest, quickest, and most precise delivery to the patient. Ideally, delivery of MyCardia will be possible via minimally invasive approaches (e.g., laparoscopic) or open-chest surgeries.

03 Bioprinted tissue therapeutics for Type 1 diabetes and liver disease

The CBDO of Aspect Biosystems discussed how his company is bioengineering allogeneic tissue therapeutics by combining proprietary microfluidic bioprinting technology, computational tissue design, therapeutic cells, and biomaterials. Using a bespoke bioprinter, they can control the micro- and macro-architecture of the bioprinted tissue. On a micro level, the cell-containing core is surrounded by one shell that serves as a barrier to the adaptive immune response and a second shell that enhances vascularization and integration with host tissue. On a macro level, the tissue architecture (e.g., shape, size, and fiber spacing/patterning) can also be controlled.

BOX 5. ASPECT BIOSYSTEMS' PROPRIETARY FULL-STACK TISSUE THERAPEUTIC PLATFORM.

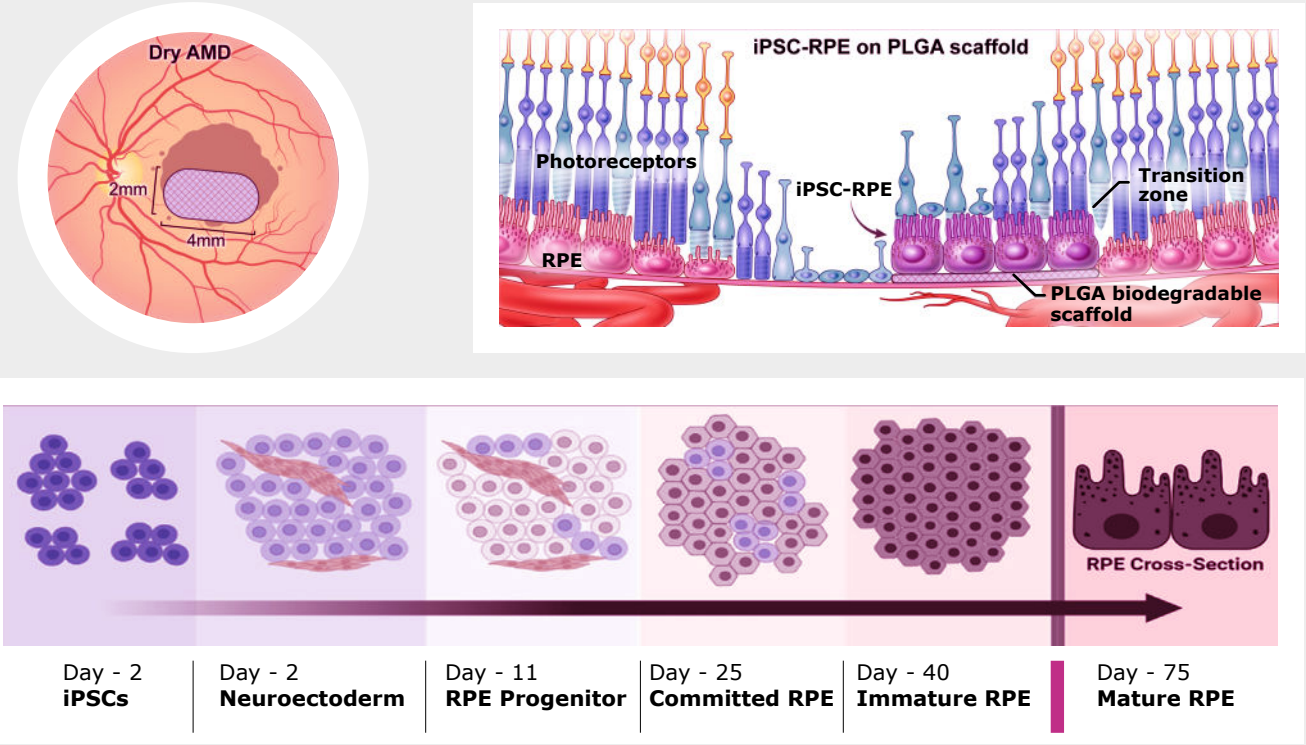


With a pipeline currently focused on metabolic indications, Aspect Biosystems has demonstrated that their islet tissue implants can control hyperglycemia in both xenogeneic and allogeneic models of Type 1 Diabetes.[13,14] Based on these promising data, they've entered into a strategic partnership with a large pharmaceutical company to develop bioprinted tissue therapeutics for diabetes and obesity. Aspect Biosystems is also working to expand the applications of their tissue therapeutics. Their bioprinted human hepatocyte tissue, implanted intraperitoneally or subcutaneously, can increase survival by up to 70% in immune-competent murine models of liver failure, without the need for immunosuppression.[15] Detoxification and replacement of lost enzyme functions of this tissue are being explored,[16] with the goal of eventually being able to address multiple types of liver disease.

04 Bioprinted vascularized eye tissue

The Director of the Intramural Research Program for the National Eye Institute (NEI) at the NIH described their approach to bioprinting vascularized eye tissue, with the goal of treating age-related macular degeneration (AMD). The pathology of AMD centers around the death of retinal pigment epithelial (RPE) cells, which supply nutrients to photoreceptors in the retina. Their first product, a 2D autologous iPSC-derived RPE patch,[17] has received IND approval from the FDA and is currently being tested in a Phase 1/2a clinical trial.[18] Their autologous GMP manufacturing process takes about 6 months.

BOX 6. NEI APPROACH TO TRANSPLANTING AN AUTOLOGOUS IPSC-RPE PATCH.



ADAPTED FROM: SHARMA R, ET AL. ANNU REV PHARMACOL TOXICOL. 2020;60:553-572.

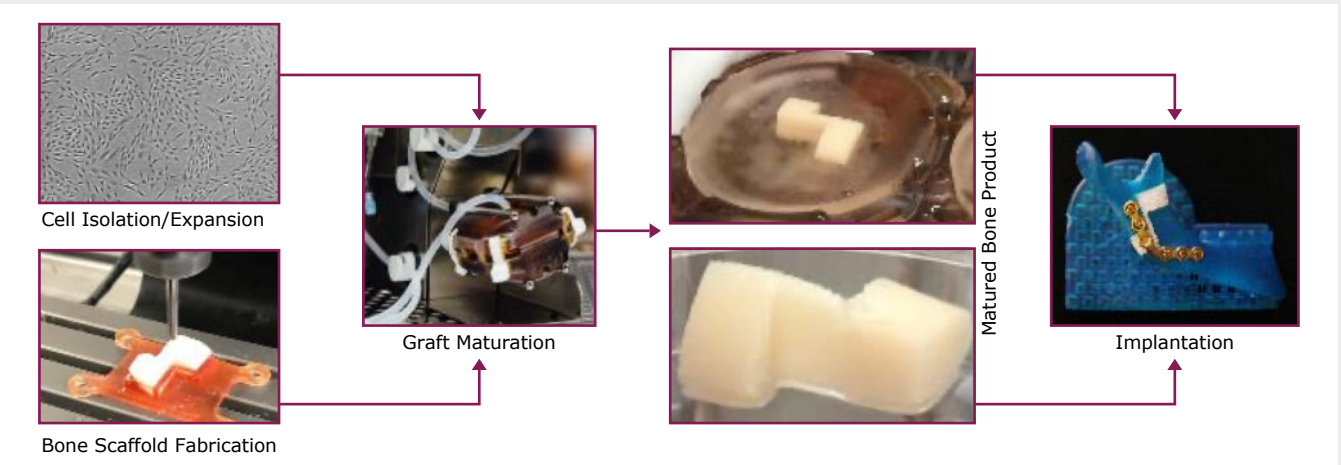
A limitation of the iPSC-RPE patch is that it will only protect photoreceptors that are about to die. As such, the NEI is trying to develop a product that treats the broader AMD disease process, which extends into the choroidal capillaries that supply blood to the RPE. Their approach is to recreate the entire back of the eye via 3D bioprinting, which involves applying their "bioink" (a fibrin-based hydrogel that contains a mixture of endothelial cells, pericytes, fibroblasts, and a key growth factor) to the same biodegradable scaffold being used to produce their 2D RPE patch.[19] In preclinical models, they've shown that their 3D RPE/"Choroid" tissue has the same structural and functional properties of native eye tissue, with key interactions occurring between the RPE cells and choroid capillaries.[19] Thinking ahead to preliminary in vivo efficacy studies for this more complex product, they are expanding their CMC operations and considering how to best address key quality control and regulatory challenges.

05 Bioengineered regenerative medicines for musculoskeletal repair

The CEO of EpiBone described how her company is pioneering the next generation of tissue repair and replacement. By combining stem cells, cell culture media, and scaffolds within a proprietary bioreactor, EpiBone is able to emulate natural conditions for bone and cartilage development, thus creating fully differentiated tissues, relative to PRP treatments that are unregulated, and the only existing cellular treatment available today. Their bone products utilize a scaffold of decellularized bovine bone that has been machined to mimic anatomical shapes. They've partnered with other companies to extract 3D data from CT scans and to procure the stem cells used during product development. EpiBone can engineer bone in 3 weeks and cartilage in 4 weeks, producing a graft that is alive and can participate in normal growth functions. In theory, their platform technology should allow them to engineer any bone or joint in the human body.

EpiBone's EB-CMF product, which has just completed its Phase I/II clinical trial,[20] is a tissue-engineered autologous bone graft intended for complex reconstruction of the mandible.[21,22] Six months post-implantation, fully vascularized, integrated tissues were seen in all six of the patients in the study who suffered from congenital defects, trauma, or sleep apnea (unpublished data).

BOX 7. EPIBONE'S PROCESS FOR EB-CMF, A TISSUE-ENGINEERED AUTOLOGOUS BONE GRAFT.

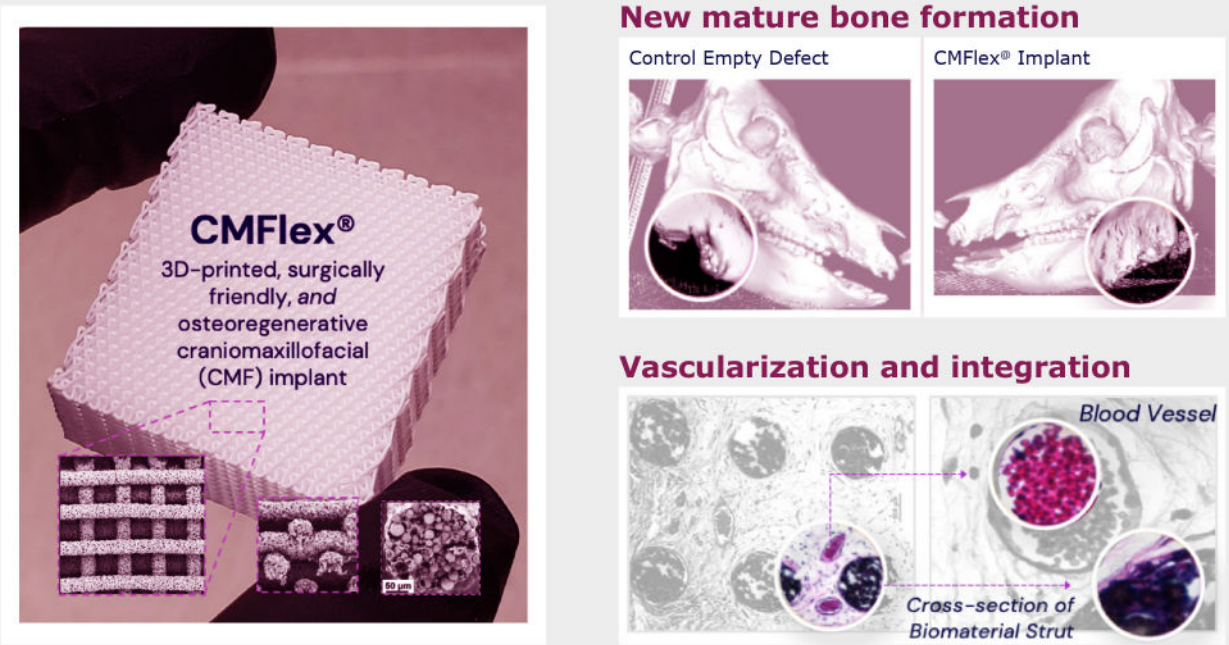


EpiBone has leveraged this process for EB-CMF development to produce an allogeneic tissue-engineered osteochondral graft (EB-OC) intended for full-thickness cartilage repair.[23] This product has shown excellent results in an equine model and was IND-approved by the FDA for Phase I/II clinical trials in July 2023.[24] With funding from the Department of Defense, they are also working to develop an injectable allogeneic cartilage filler suitable for field administration.

06 Bioengineered microenvironments that restore healthy cellular function

The CEO of Dimension Inx discussed how her company is combining a proprietary biomaterials and 3D printing manufacturing platform to design, develop, and manufacture therapeutic products that restore tissue and organ function. Recognizing that cells alone aren't enough to solve a biologic problem, they focus on using biomaterials to create optimized 3D microenvironments that direct cell behavior. These microenvironments are made of different materials depending on the application, and their features (e.g., intra-fiber topography and porosity) can be tailored to promote cell functions such as adhesion and proliferation. Dimension Inx is developing an ex vivo system for the growth and maturation of human egg follicles within a synthetic, dynamic ovary microenvironment, with the goal of providing an alternative to the hormone stimulation required during traditional in vitro fertilization.[25] In addition, their CMFlex® product, an acellular, 3D-printed, flexible osteoregenerative craniomaxillofacial implant, received 510(k) device clearance from the FDA in late 2022 and is being shipped to surgeons in preparation for initial clinical cases. CMFlex® is made primarily of hydroxyapatite, and its intrafiber micro and nano features create a high-degree of surface tension and wickability.[26] After implantation, the product quickly draws in surrounding cells and fluids, initiating cascades that ultimately lead to bone formation.[26] It is a ready-to-use product with shelf stability of 1 year that can be readily shaped by surgeons to match a patient's particular defect.

BOX 8. DIMENSION INX' CMFLEX® CRANIOMAXILLOFACIAL IMPLANT.



07 Takeaways from industry presentations

Industry presenters described multiple approaches to bioengineering tissue therapeutics, yet many common themes emerged. Tissue therapeutics are being designed to address significant unmet medical needs, their development generally requires significant funding and/or industry partnerships, and significant consideration needs to be given to the end-user (i.e., the surgeon). Though developers often leverage similar technologies or biomaterials, current manufacturing platforms tend to be proprietary and bespoke, with minimal (if any) involvement of CROs or CDMOs. Scaling of production and the ultimate delivery of these products to patients may require alternative cell sources, advances in technology (e.g., perfusion, cryopreservation) to maximize shelf life, and creative means of setting up a value proposition and achieving insurance reimbursement. Given complex MOAs that may span both cell therapy and device spaces, tissue therapeutics can also face unique regulatory challenges. As such, many developers employ a de-risking strategy, where they may start with a simple (but still potentially lucrative) product that transitions into more complex products designed to meet broader needs. This strategy of having "multiple shots on goal" can allow developers to move forward with certain products when others might be on an IND hold. The remaining sections of this whitepaper will delve into some of the key considerations and challenges facing the industry.

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC) CONSIDERATIONS

Developing a tissue-engineered therapeutic requires careful consideration of multiple factors, ranging from obtaining critical reagents to ensuring safe and feasible delivery to the patient.

BOX 9. KEY CONSIDERATIONS FOR DEVELOPING A TISSUE-ENGINEERED PRODUCT.

Many of these considerations center on how to meet CMC requirements for demonstrating product safety, identity, quality, purity, and strength (including potency) as the product moves through its development lifecycle. Expert panels were convened to discuss CMC issues related to both the scaling of manufacturing and to the potency, stability, and delivery of tissue therapeutics.

01 Scaling of manufacturing

Panelists discussed what they feel is needed to scale and make tissue-engineered products a reality. Solving the blood/material interface and achieving long-term perfusability of implanted therapeutics is critical. Analytical capabilities must also grow to increase product and process understanding. From a product standpoint, the "homework assignment" for developers is to build assays that can predict how a tissue therapy will perform in vivo (e.g., assays that measure metabolic and functional parameters of organ performance). Assays should ideally be non-destructive and focus on data that are critical to the product's safety or efficacy. Because of the inherent complexity of tissue-engineered products, multiple release assays may be required.

> **"The more complex the product, the more time you have to spend thinking about the minimal set of assays you need for release. It's hard to narrow it down to the key assays, and nothing more. We have a relatively simple product and have been able to narrow release testing to 6-7 assays, but that number will be higher for more complex products."**
>
> CEO of Theradaptive, Inc.

From a process standpoint, biosensors may enable functional testing of cell health and cell expression throughout the manufacturing process, which could allow for upstream detection of process control (or lack of control) and ultimately help developers to minimize costs. However, building a biosensor requires a thorough understanding of what factors impart clinical success and/or clinical risk, and achieving that level of understanding is challenging with tissue therapeutics. Ultimately, analytical infrastructure for in-process controls must expand so that developers can utilize systemic resources (e.g., CROs) rather than in-house, bespoke assays.

Imaging technology could be leveraged to better assess and understand tissue therapeutics. Traditional microscopy-based approaches may be suitable for small therapeutics but may not allow developers of larger products (e.g., organ or cartilage implants) to view their products at sufficient depth. Radiologic imaging could yield more robust information. In either case, imaging would be subject to the same rigor expected of commercial manufacturing processes (e.g., demonstration of consistent control and lack of drift). Finding imaging technology that offers both the standardized process and reproducible output expected by regulators may be difficult.

For scale-up, manufacturers will need to have developed systems that demonstrate the rigor of their process and commercial-readiness of their product. This will require a diverse workforce of not only scientists, physicians, surgeons, and biomedical engineers, but also of people with basic training in manufacturing. Automation (e.g., modular platforms, robotics) may play an important role in tissue engineering. With the advantage of high reproducibility, automation may be best-suited for manufacturing steps that are subject to high levels of variability or error. Though expensive to introduce, automation can help to control costs in the long-run and set manufacturers up for success in later phases of scale-up. As such, the correct time for pursuing funding for automation (i.e., before or after proof-of-concept) should be weighed into decisions. Whether manual or automated, panelists suspect that centralized manufacturing is most practical for tissue-engineered therapies. Moving to point-of-care manufacturing may jeopardize quality control and is unlikely to be economically feasible.

> **"In the early clinical phase, our manufacturing was mostly manual, but we had a core modular platform that allowed us to quickly automate once we reached commercial-scale manufacturing. Setting yourself up for success in later phases of scale-up is really important."**
>
> Director of manufacturing at Humacyte

Panelists encouraged developers to have early foundational conversations with regulators. Rather than viewing IND holds or other FDA requirements as regulatory hurdles, such interventions should be viewed simply as developmental milestones that haven't been met. Ultimately, the FDA is an instructive resource with significant brain power. When no precedent has been set for how to monitor a specific function of a product, regulators may be able to draw from past experience and provide ideas for how to best develop CMC plans.

In addition to early discussions with regulators, it is also important to involve the end-consumer (i.e., the surgeon or clinician) early in the process. The surgical community appears excited about the potential of tissue-based therapeutics, and the success of an individual product may ultimately be determined by the comfort level of the end-user. Packaging, thawing requirements, "hand-feel", and implantation procedures may be critical to achieving uptake and success of the product.

Panelists offered some closing advice for developers of tissue-engineered products:

Explore translational and industry relationships early—this accelerates the process of bringing the product to clinic

Seek community input on regulatory advice/experience

Think about suppliers and processes in early phases—choose suppliers that you can grow with, audit your suppliers regularly, and set up modular manufacturing processes that will allow you to scale

Persevere and embrace the journey and learnings as you go!

02 Potency, stability, and delivery

Panelists discussed approaches to defining and measuring the potency and stability of tissue-engineered products and optimizing delivery to the patient. From a potency standpoint, a quantitative assay seems to be the ultimate expectation of regulators. One developer described how the FDA accepted a semiquantitative histological potency assay during BLA filing but is now requiring a more quantitative assay under a post-marketing agreement. His company is working with their CMC review team at the FDA to strike a balance between what is desired and what is actually feasible. Ultimately, their quantitative assay will be used during process characterization and comparability studies rather than as a release assay.

An early-stage developer is using an advanced bioinformatics tool as their potency candidate, performing RNA sequencing of their cell product and comparing it to a reference set of genes in cells with known efficacy. Many panelists are prioritizing the development of functional potency assays that demonstrate a product's ability to process specific analytes (e.g., to reduce ammonia) or produce key substances (e.g., albumin). Cell viability assays and measurements of structure (i.e., examining cell morphology and histology via imaging) may also be used to demonstrate potency. Given the complexity of tissue-engineered products, developers may start with a potency matrix that is ideally pruned as more is learned about their process and product. Because every tissue therapeutic will possess a unique MOA, a standard potency assay is unlikely to be feasible.

> **"We prioritize functional assays to guide us through development. We look at functions related to our disease indication—the processing of specific analytes, production of specific proteins, and biomarkers to monitor for engraftment. We're using a wide array of potency assays right now."**
>
> Chief Technology Officer at Satellite Bio, regarding their preclinical program

The inherent nature of tissue-based products can make it difficult to measure potency and, ultimately, to validate a potency assay. Some products contain precursor cells that are expected to mature after implantation, meaning that a potency assay must try to hit a moving target in the maturation process. Similarly, it can be difficult to stabilize tissue-based products for long enough to measure their potency. Trying to normalize a quantitative potency assay can be difficult when starting material varies (e.g., when it is donated tissue coming from different sources). Panelists agreed that an incredible amount of development will be needed to achieve consensus on appropriate, feasible, and meaningful potency assays.

Potency assays are regarded as the key outreads and indicators of stability. Stability times vary widely depending on technology and storage requirements. One developer's product is stable for only 3.5 hours from the time of release to implantation. This is feasible when manufacturing occurs near the implanting hospital, but stability time will need to be significantly lengthened as distribution is extended to regional centers of excellence. As such, they are developing shipping containers that can maintain temperature, sterility, and quality, aiming for stability times of 96 hours. For products like this with short half-lives, ship studies may be done as part of an IND filing. Other companies have developed cryopreservation methods to achieve significantly longer stability. With any product, in-use stability studies (e.g., hours on the surgical floor spent preparing and/or thawing) need to be considered. The FDA may request details on how individual hospitals handle logistics once a product arrives. Ultimately, weaving potency (along with viability and identity) into stability studies is necessary.

> **"There is an opportunity as an industry to think about what stability means, how to define it, and how to share experiences."**
>
> Co-founder and CEO of Stemson Therapeutics

Panelists discussed challenges related to the delivery of tissue-based therapies (i.e., the process of taking a product and putting it into a patient). For some products, the manufacturer is part of the delivery process on-site. In such cases, coordinating personnel to clinical sites can be challenging. As far as delivery techniques, tissue-based products may be implanted surgically (e.g., as an organ or a graft) or delivered via an infusion. Surgical procedures may be simple and straightforward or may require the development of bespoke technology (e.g., an MRI-capable syringe that allows slow delivery of the product during brain surgery).

Moving forward, panelists shared some ideas of what might be needed to make tissue-engineered solutions a reality for patients:

Models for thinking about MOA need to evolve—tissue-based products are impacting whole body systems rather than just one discrete target

The industry may benefit from being more proactive (vs reactive) about regulatory expectations

Approaches to stabilization (e.g., hypothermic storage, cryopreservation, formulation matrices) could be standardized, perhaps first across individual niches (e.g., liver), aiming for long-term shelf life

A more holistic view of variability will be needed—some degree of variability may be unavoidable, and variability doesn't necessarily mean that a product is of poor-quality

Methods for demonstrating efficacy in patients will need to be defined, and manufacturers should work to better understand how product potency correlates with clinical activity

> **"When it came down to actually getting the license, everything revolved around CMC. My advice is to think about CMC earlier in the process and also to ensure that your quality systems are robust enough to work on understanding how everything comes together."**
>
> Senior VP of CMC Manufacturing at Sumitomo Pharma America, Inc.

REGULATORY PERSPECTIVES ON TISSUE ENGINEERING

The Director of the Division of Cell Therapy 2 within the Office of Cellular Therapy and Human Tissue CMC, Office of Therapeutic Products (OTP) at the FDA Center for Biologics Evaluation and Research presented regulatory considerations for the field of tissue engineering. The OTP regulates a diverse set of products that include cellular products, tissue-based products, and combination products (e.g., engineered tissues/organs) that span designations. Following her presentation, a panel of experts with vast regulatory experience (most being either current or former reviewers at the FDA) convened to delve further into regulatory considerations facing the industry. Their insights have been incorporated into the ensuing sections.

01 Regulatory framework for tissue-engineered products

Most tissue-engineered products are considered Human Cells, Tissues & Cellular and Tissue-Based Products (HCT/Ps) and, therefore, must follow regulations outlined in 21 CFR 1271.[27]

Depending on the exact type of product, it may also be subject to other regulations:

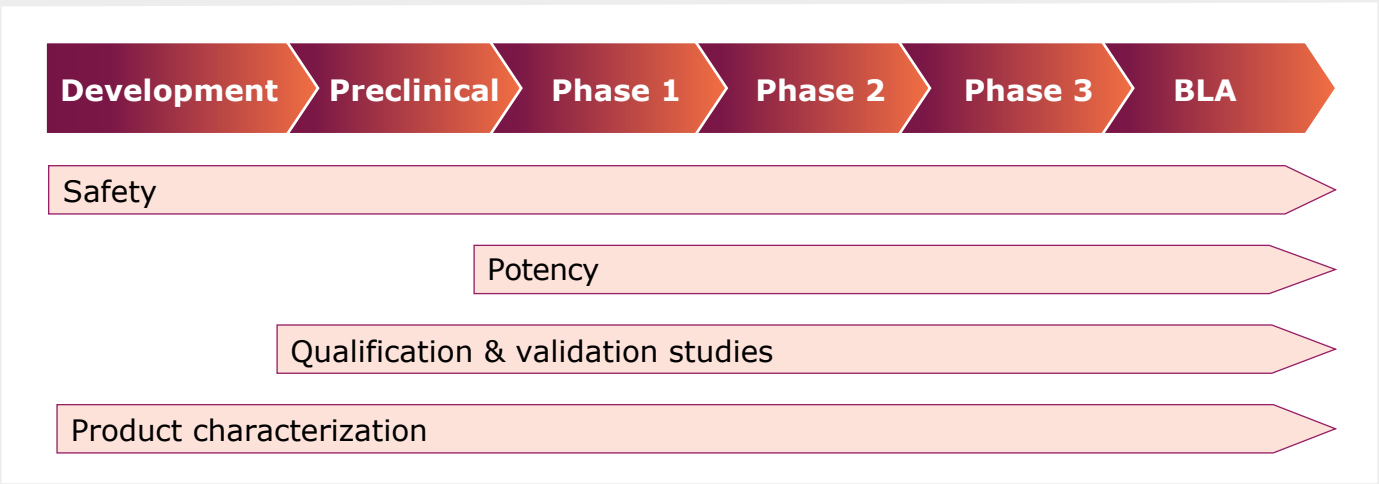
01	02	03	04
Biologics: 21 CFR 600s[28]	**Drugs**: 21 CFR Part 312 Investigational New Drug (IND)[29]; 21 CFR Parts 210/211 Current Good Manufacturing Practices[30,31]	**Devices**: (e.g., when a structural scaffold is used in combination with cells or when a delivery device is used): 21 CFR 800s[32]	**Combination Products**: 21 CFR Parts 3 and 4[33,34]

For combination products, the lead center within the FDA must be determined. Sponsors may elect to submit informal jurisdictional inquiries and/or a Request for Designation with the Office of Combination Products. Ultimately, the lead review center will be designated based on the primary mode of action, inter-center agreements, the center with the most relevant expertise, and any precedents set for similar products. Though sponsors may associate a "combination product" designation with heightened regulatory requirements, their associated regulations are designed to help streamline GMP requirements and may ultimately be less burdensome than following full sets of individual regulations (i.e., those for biologics, drugs, and devices).

02 Regulatory considerations across the product development lifecycle

As a tissue-engineered product advances through various stages of development, the focus of regulatory reviews also evolves. Importantly, safety remains the primary concern at all stages.

BOX 10. CONSIDERATIONS ACROSS THE PRODUCT DEVELOPMENT LIFECYCLE.



Within an IND submission (prior to Phase 1 studies), regulators expect to see details of the planned clinical study, available pharmacology/toxicology data, and full CMC information for the product. CMC requirements include the following:

- Describe composition, manufacture, and control of the investigational product
- Describe testing conducted to assure identity, quality, purity, and potency (biological activity) of the investigational product
- Demonstrate capability to consistently and reproducibly manufacture the investigational product
- Provide information on product stability, storage and shelf life
- Provide information on container, label, and tracking information

The FDA expects and encourages sponsors to refine specifications and improve their manufacturing process throughout product development. Product consistency must be maintained throughout, and preclinical testing must be representative of the eventual clinical lots. During later stages of development, the FDA expects to see a controlled manufacturing process and sufficient process knowledge to determine CPPs, set in-process quality criteria, and plan for future scaling of production. Sponsors are expected to have refined product acceptance criteria and to show evidence of qualified/validated analytical assays. The FDA recognizes that it may not be possible to narrow specifications for tissue-engineered products, at least not to the extent expected for cell and gene therapies. Nevertheless, sponsors should be able to demonstrate that they can produce a quality, consistent product with specifications that are set wide. The FDA and sponsor may also come to an agreement that specifications will be further adjusted post-licensure.

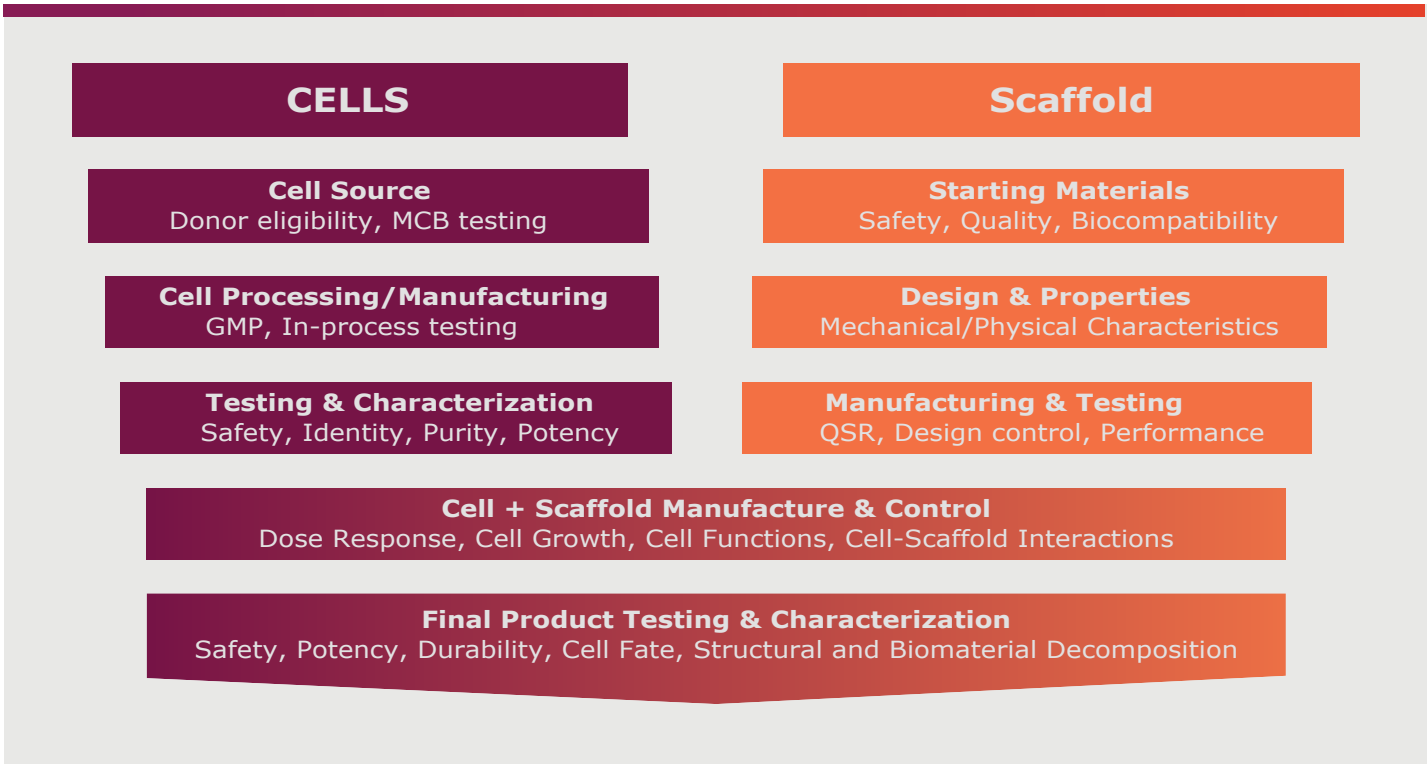
Importantly, a biologically relevant potency assay must be in place prior to any study intended to provide the primary evidence of efficacy to support licensure. In products designed for orphan indications, especially extremely rare diseases, a Phase I study can easily morph into a registrational study. In addition, potency can be particularly difficult to establish with tissue-engineered products, as they often possess multiple modes of action. Given these considerations, the agency recommends that developers start investigating potency-assay candidates very early-on. Ideally (though not required and sometimes not possible), potency will align with clinical outcome. This alignment makes a thorough understanding of CQAs and the setting of clinically meaningful specifications more feasible. Sponsors should remember that reviewer determinations rely heavily on the results of CQAs, including potency assays and clinical outcomes seen during later-phase studies.

The agency recognizes that the understanding of this nascent industry is incomplete, both for developers and regulators, and that it can be particularly difficult to demonstrate manufacturing comparability and consistency for tissue-engineered products. Because product types can vary significantly, regulatory review is highly specific to individual products and does not take a “one-size-fits-all” approach. Many factors are considered during review, including the scale of the product, manufacturing procedures, amount of material available for testing, the risk imparted by source/starting materials, and the inherent variability of certain product types.

03 Manufacturing considerations

When manufacturing a tissue-engineered product, considerations must be made for individual components of a product (e.g., cells and scaffold) as well as for the resultant combination of these components.

BOX 11. MANUFACTURING CONSIDERATIONS FOR TISSUE-ENGINEERED PRODUCTS.



For these complex products, characterization methods are not well-defined because it can be uncertain how much each component contributes to the overall function and performance of an engineered tissue construct being developed. Acceptable characterization methods may include testing a surrogate sample (i.e., one made using identical materials and manufacturing methods as for the clinical product) or testing an unused/extra portion of the clinical product itself. In either case, the sponsor must demonstrate that the sample/portion is representative of the final/whole clinical product. Sponsors may also choose to utilize the entire product for lot-release testing (e.g., sterility, potency, endoxtoxin, identity, etc.), which should be performed after all manufacturing steps have been completed. This approach may be most feasible when testing is nondestructive and/or when the lot size is large. In the case of a cell + scaffold product, sponsors can consider separating cells from the scaffold to evaluate cell characteristics (e.g., viability, identity, potency) and scaffold characteristics (e.g., porosity, strength, degradation). Importantly, consideration must also be given to how the dissociation of cells from the scaffold (and the persistence or reabsorption of the scaffold) may impact the product. Similarly, when the scaffold takes the form of a hydrogel, it may be considered an excipient, which conveys unique considerations for characterization.

The FDA recognizes the manufacturing challenges associated with tissue-engineered products, many stemming from their structural complexity, heterogeneity in composition, potential for small lot sizes, and likelihood that the product will remodel post-implantation. It can be difficult to define potency and performance requirements when multiple modes of action are present. In addition, because these products are not designed to be "stable", final specifications from in vitro testing may not be predictive of clinical safety and/or efficacy. Furthermore, tissue-engineered products may have special considerations for the "pooling" of materials (e.g., combining iPSC clones from the same vs different donors). The FDA may consider pooling exemptions on a product-specific basis. Finally, comparability should be ever-present in sponsors' minds, as the agency will want to see that the final product is not affected by changes made to the manufacturing process. The ability to assess and demonstrate comparability will likely rely on a thorough understanding of the CQAs of the product.

The agency suggests aligning clinical development with product development, offering several key pieces of advice to developers:

01

Do not begin studies intended to support licensure if there is indecision on the manufacturing process or without established CQAs

02

Do not underestimate the time and resources needed to bring manufacturing up to the level of Phase 3 and commercial production

03

Recognize that the establishment of quality attributes, measurement of potency, and demonstration of product stability can be particularly challenging

04

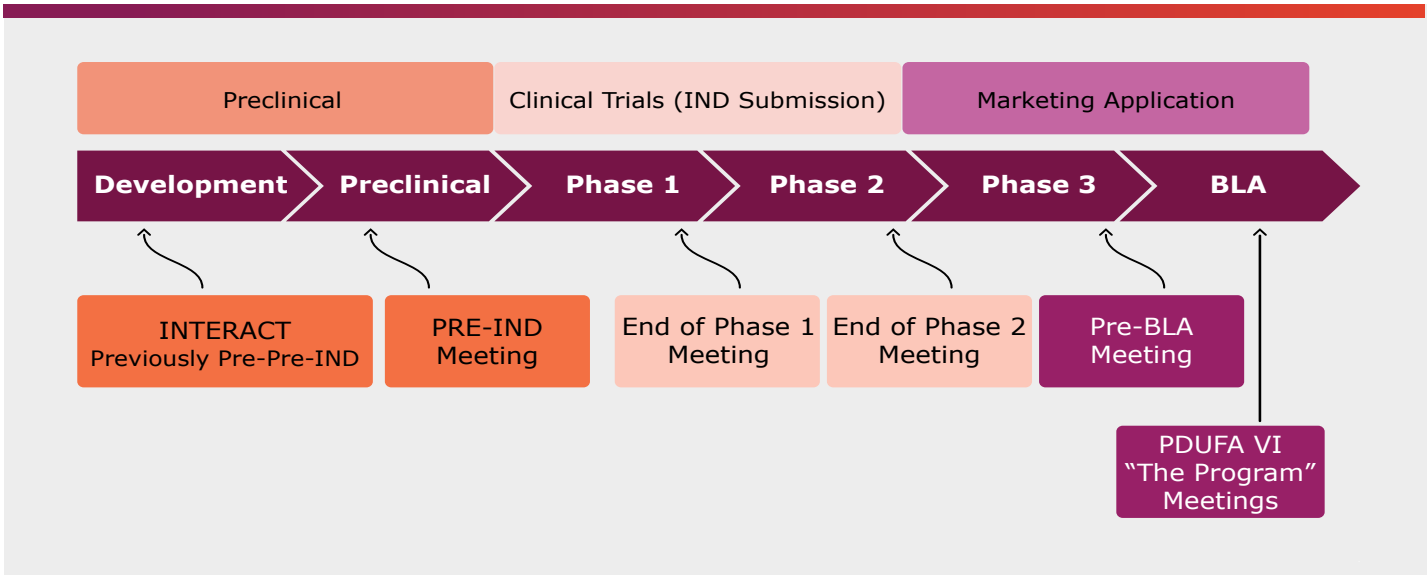
Understand that to receive BLA approval, all assays and methods must be validated and the facility must be ready for commercial production

Early alignment is particularly crucial for products under expedited development (i.e., accelerated approval, priority review, fast-track designation, breakthrough therapy designation, or regenerative medicine advanced therapy), as timelines from early to late development may be compressed.

04 Interacting with the FDA

Many opportunities exist for interacting with the FDA during product development,[35] and sponsors may lack a full understanding of opportunities available during preclinical stages.

BOX 12. OPPORTUNITIES FOR INTERACTION DURING PRODUCT DEVELOPMENT.



The goal of an INTERACT (INitial Targeted Engagement for Regulatory Advice on CBER producTs) meeting is to allow sponsors to obtain early feedback on a product development program for a novel investigational agent via nonbinding, targeted scientific discussion with reviewers. Only one INTERACT meeting is allowed, and it should be scheduled when sponsors have generated preliminary preclinical data (i.e., proof-of concept and some safety data) but are not yet ready to conduct definitive preclinical safety studies. Similar to the INTERACT meeting, only one pre-IND meeting is granted. The goal of the pre-IND meeting is to help sponsors achieve a successful IND submission. During comprehensive communication of their product/clinical development plan, sponsors can seek feedback on questions related to product characterization, the preclinical testing program, and the scope and design of their planned clinical trial. The pre-IND meeting should be requested prior to conducting definitive preclinical safety studies.

When manufactures are struggling to come up with appropriate testing or characterization methods for their product, early conversations with the FDA become critical. To get the most out of one-shot interactions with the agency, INTERACT and pre-IND packages should be well thought-out and should ask clear, specific questions. If certain methods or approaches are not feasible for an individual product (e.g., cell viability cannot be measured because of engraftment), the agency will want to hear justification for why this is the case. In exchange, they may be able to offer ideas that can lead to a solution.

Under a unique FDA initiative, sponsors of products with expedited clinical development timelines may be granted additional opportunities to discuss CMC readiness with reviewers. Within the CMC Development Readiness Pilot (CDRP),[36] up to nine applicants per year (between both CBER and CDER) from 2023 to 2027 will be granted two dedicated CMC meetings (in addition to existing meetings) as well as follow-up discussions. To promote innovation and understanding of CMC aspects of expedited development, lessons learned through this pilot program may be presented by the FDA as case studies and will be incorporated into a strategy document that the agency intends to issue.

FUNDING AND MARKET OPPORTUNITIES

01 Grants and venture-capital

Earlier discussions highlighted the need for tissue-engineering developers to secure funding and industry partnerships. To this end, a panel consisting of representatives from federally or state-funded institutions and venture capital (VC) firms discussed how developers can approach opportunities for nondilutive capital (e.g., grants) and dilutive capital (i.e., that provided in exchange for equity or ownership in a company).

Both nondilutive and dilutive funding are important sources of capital. Though one source may predominate at certain stages of development, it is also possible for them to overlap. At the earliest stages of product development (e.g., mechanism of action or working principles), funding tends to come from traditional NIH Research Program (R01) grants, which are the flagship academic grants. Many academic investigators are forward-thinking and may be increasingly interested in spinning out a company capable of bringing a product to market. In the initial phases, angel investors help a company launch based on an initial proof-of-concept or, if a company has already been formed, a Phase I Small Business Innovation Research (SBIR) grant may be available. Next-stage funding may come from follow-on Phase II SBIR grants that have longer-term (e.g., 2-3 year) commitments, disease foundations, as well as private equity and VC firms. This may present an opportunity for co-funding of projects (e.g., between the NIH and a VC firm), which is generally positive for all involved. Industry, often known as "strategic investors", may get involved either in the form of project funding through their business development groups or in the form of equity investment through their VC groups. It was noted that in the current financial climate, industry seems to be investing at later, more de-risked stages than was historically the case and wants to see large animal, if not human, data prior to investing.

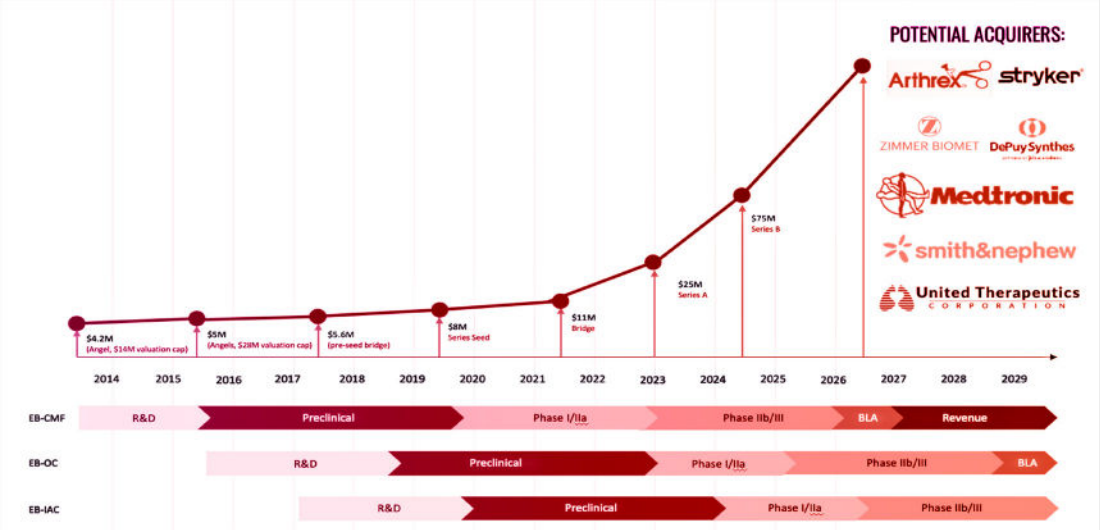
From the moment VC is taken, the timeclock for building commercial value of a company starts. Raising a Series A traditionally means that a company will need to triple in commercial value over the following 18-24 months. This timeframe might be slightly longer for developers of tissue-engineered products because of the novelty, complexity, and potential for high-reward, but founders will need to show that they are making progress toward commercialization with reasonable momentum. Regardless of the exact timeframe, the expectation for value increase is underwritten by the investor. As such, it may be most appropriate to seek VC during later stages of development, whereas grants may be a more reasonable source of capital during data-generation stages, especially when trying to establish proof-of-concept for high-risk programs. Grant-funding agencies tend to have more flexibility than VC firms in terms of time allowed, though more specialized programs may incorporate milestones to release funding at appropriate development points as outlined in the funding agreement. Regardless of the source of capital, the onus lies on company founders to de-risk their pitched idea and demonstrate how their science and strategic plan will ultimately deliver their product to patients.

> **"This is an incredibly high-risk, high-reward, worthwhile space of development. The timeline (for increasing value) may be different, but ideally, you're at least showing progress of a product towards market. It really comes down to the relationship you build with your investor."**
>
> Venture capitalist with KdT Ventures

Both dilutive and nondilutive funding share the problem of noncontinuity of capital. All funding comes from different buckets, often creating gaps in capital that can make it difficult for developers to continue rigorous investigations into complex products. To that end, investors not only provide a source of money, but many also try to make sure that awardees make important industry connections. Grant-funding institutions or foundations may leverage relationships with academic centers or government agencies to ensure awardees have the resources they need to succeed. Venture capital firms may hire government relations specialists, people with regulatory experience or manufacturing connections, and/or heads of talent to provide added value to the companies they're funding. They may also connect companies with potential sources for next stages of funding (e.g., Series B or C). Companies should seek interest from, and relationships with, investors that provide these types of strategic perspectives.

Earlier in the day's discussions, one developer shared an example of her company's path to value creation, which sums up several points made during the panel discussion. She showed how value-inflection points at regulatory milestones can create optionality for licensing, spin-outs, IPO, or acquisition.

BOX 13. THE PATH TO VALUE CREATION: AN EXAMPLE SCENARIO FROM EPIBONE.



02 Increasing the "fundability" of tissue engineering

Panelists were asked about key advances, perhaps in science, technology, or within the regulatory landscape, that could make the tissue-engineering industry more attractive to investors.

They shared the following ideas:

01
Increasing patient accessibility to therapies in a cost-effective manner

02
Availability of fully redifferentiable stem cells

03
Gaining a better understanding of how tissues function in vivo in real-time

04
A paradigm shift in how pharma thinks about drug development, away from the traditional model of a single drug having a single target

05
Improvements in cell sourcing and maturation protocols, which will rely on heightened understanding of developmental biology

06
Strengthening bioinformatics, perhaps via AI, to help with optimization and prediction

CONCLUSIONS

This workshop brought together stakeholders from across the tissue-engineering industry to share exciting advances in the field and begin discussing manufacturing challenges, regulatory considerations, and funding/partnership opportunities. Tissue engineering is a nascent field, involving complex products that span a wide array of both intended indications and regulatory frameworks. Most tissue-based therapeutics are attempting to address a significant unmet medical need, and the hope is that collective efforts such as this workshop will help to bridge the gap between concept creation and clinical reality.

Several clear needs arose from the workshop, including heightened means for understanding mechanisms of action, advances in analytical technologies and infrastructure, greater availability of standards and reference materials, and ways to extend shelf-life and optimize delivery. Presenters and panelists shared strategies for exploring funding opportunities, building translational relationships, and connecting with industry partners. Valuable regulatory advice was offered, conveying consistent themes: 1) tissue-engineered products possess a level of inherent complexity that may be unprecedented; 2) developers must align clinical development and product development efforts early-on, with a keen focus on CMC; and 3) sponsors should engage with regulators as early and often as possible, taking full advantage of meeting opportunities by preparing well-thought-out packages that ask clear and specific questions.

APPENDIX

01 Workshop Presenters and Panelists

- **Michael Lehmicke**, Senior Vice President, Science & Industry Affairs, Alliance for Regenerative Medicine
- **Jeff Ross**, Chief Executive Officer, Miromatrix Medical Inc.
- **Jordan Lancaster**, Chief Executive Officer, Avery Therapeutics
- **Eric Roos**, Chief Business Development Officer, Aspect Biosystems
- **Kapil Bharti**, Director, Intramural Research Program, National Eye Institute, National Institutes of Health
- **Nina Tandon**, Co-Founder and Chief Executive Officer & Co-Founder, EpiBone
- **Caralynn Nowinski Collens**, Chief Executive Officer, Dimension Inx
- **Jane Lebkowski**, President of Research and Development, Regenerative Patch Technologies
- **Matt Panning**, Director of Manufacturing, Humacyte
- **Luis Alvarez**, Chief Executive Officer, Theradaptive, Inc.
- **Richard McFarland**, Chief Regulatory Officer, Advanced Regenerative Manufacturing Institute
- **Harald Ott**, Chief Executive Officer, Iviva Medical
- **Geoff Hamilton**, Co-Founder & Chief Executive Officer, Stemson Therapeutics
- **Blair McNeill**, Senior Vice President of CMC Manufacturing, Sumitomo Pharma America, Inc.
- **Carl Simon**, National Institute of Standards and Technology
- **Tom Lowery**, Chief Technology Officer, Satellite Bio
- **Kim Raineri**, Chief Technology Officer, Aspen Neuroscience
- **Tina Rausch**, Senior Director of Quality, Miromatrix Inc.
- **Brock Reeve**, Chief Executive Officer and Co-Founder, Eos BioInnovation
- **Justin Briggs**, Prime Movers Lab
- **Rima Chakrabarti**, KdT Ventures
- **Ruchika Nijhara**, Executive Director, Maryland Stem Cell Research Fund
- **Rahul Thakar**, Program Director, Advanced Technology and Surgery Branch, National Heart, Lung, and Blood Institute
- **Laura Ricles**, Director of the Division of Cell Therapy 2, Office of Cellular Therapy and Human Tissue CMC, Office of Therapeutic Products, Center for Biologics Evaluation and Research, US Food and Drug Administration
- **Deborah Hursh**, Principal, Hursh Cell Therapy Consulting, LLC
- **Heather Lombardi**, Director of the Office of Cellular Therapy and Human Tissue CMC, US Food and Drug Administration
- **Don Fink**, Master Practice Expert / Regulatory at Dark Horse Consulting Group
- **Mason Macenski**, Vice President of Clinical and Regulatory Affairs, Miromatrix
- **Debra Webster**, Vice President Regulatory Affairs, Aditum Bio

02 Term key

2D: 2-dimensional

3D: 3-dimensional

AMD: age-related macular degeneration

ARM: Alliance for Regenerative Medicine

BLA: Biologics License Applications

CBDO: Chief Business Development Officer

CBER: Center for Biologics Evaluation and Research

CDER: Center for Drug Evaluation and Research

CDMO: Contract development and manufacturing organization

CEO: Chief Executive Officer

CFR: Code of Federal Regulations

CMC: Chemistry, Manufacturing, and Controls

CPP: critical process parameter

CQA: critical quality attribute

CRO: contract research organization

CT: computed tomography

FDA: United States Food and Drug Administration

GMP: Good Manufacturing Practices

HCT/P: Human cells, tissues, and cellular-based products

IND: Investigational new drug

IPO: initial public offering

iPSC: induced pluripotent stem cells

MOA: mechanism of action

MRI: magnetic resonance imaging

NEI: National Eye Institute

NIH: National Institutes of Health

OTP: Office of Therapeutic Products

RPE: retinal pigment epithelial

SBIR: Small Business Innovation Research

VC: Venture capital

VP: Vice President

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