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(RESEARCH ARTICLE)

The commercialization of tissue engineered medical products: Challenges and recommendations

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Abstract

Tissue engineering merges engineering and life sciences to create biological constructs that restore or enhance tissue function. Since its inception in 1993, it has drawn significant interest for its potential to address donor tissue shortages and overcome limitations of mechanical replacements. Tissue engineering utilizes two main approaches: in situ regeneration with cell-free matrices and in vitro growth with cell-seeded matrices. Despite progress, the commercialization of tissue-engineered medical products (TEMPs) lags behind other biomedical innovations like cell and gene therapies.

A literature review was conducted to analyze challenges in FDA regulations, funding, manufacturing, and storage for TEMPs. Key issues identified include regulatory hurdles, manufacturing limitations, and preservation challenges. The FDA's unclear classification of tissue-engineered products creates legal barriers, while high costs and specialized processes hinder manufacturing scalability. Additionally, current storage technologies and the need for rapid sterility testing complicate tissue preservation and distribution.

To overcome these challenges, the paper recommends companies collaborate with the FDA, clearly define product benefits, and reference similar approved products. For funding and manufacturing, securing investments, early automation collaboration, and planning for large-scale production are essential. Early selection of hypothermic or cryogenic preservation methods is also crucial for maintaining tissue viability.

In conclusion, the paper consolidates current strategies, challenges, and recommendations for advancing tissue engineering.

Keywords: Tissue Engineering; Tissue Engineered Medical Products; Medical Treatment; FDA Approval process

1. Introduction

1.1. The Current State of Tissue Engineering

Tissue engineering innovative field holds promise in revolutionizing medical treatments through tailor-made biological constructs. It merges engineering and life sciences to craft biological replacements enhancing tissue function (Langer and Vacanti, 1993) [17]. It pioneers interdisciplinary approaches, striving to restore, maintain, or elevate tissue capabilities. The field has gained great momentum and interest within the past few decades due to its potential to address the shortage of available donor tissue as well as its potential to solve many of the shortcomings of current mechanical replacements (Belleghem et al., 2020) [5]

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There are two distinct, but closely related approaches to tissue engineering. The first is based on utilizing cell-free matrices in order to promote guided tissue regeneration within the body (in situ regeneration). In the second approach, a cell matrix construct is produced by seeding cells onto a matrix (tissue is grown in vitro). Common cell types utilized are stem cells and differentiated mature cells. Cell sources can be autologous (from the patient), allogenic (from other humans), or xenogeneic (from other species). Both cell-free and cell-seeded tissue engineering approaches can be enhanced with the incorporation of growth factors and other biomolecules which can be optimized to promote ideal tissue growth (Belleghem et al., 2020 [5]; Walles & Walles, 2011 [27]).

The manufacturing process of tissue engineered products is lengthy and requires knowledgeable personnel for proper production. For technologies which include cells, the initial tissue source of the cells must be acquired before the cells are isolated from the tissue, expanded in culture, and seeded on the applicable scaffold (Hunsberger et al., 2015 [16]). There are several distinctive manufacturing processes utilized to produce three-dimensional scaffolds or matrices for tissue engineering. These processes include decellularization, electrospinning, crosslinking, and bioprinting. After cells are seeded onto the scaffold, mechanical conditioning may need to be implemented based on the specific product being produced. Additionally, quality control testing, storage, and shipping logistics need to be sorted (Hunsberger et al., 2015). [16].

Despite the large amount of research and published literature with a focus on tissue engineering, the number of tissue engineered medical products (TEMPs) available on the market is remarkably low. This statement holds true when comparing the commercialization of other biomedical products such as cell and gene therapies, whose market presence far surmount that of tissue engineering-based products as indicated in the figure below (Gerlovin et al., 2020) [13].

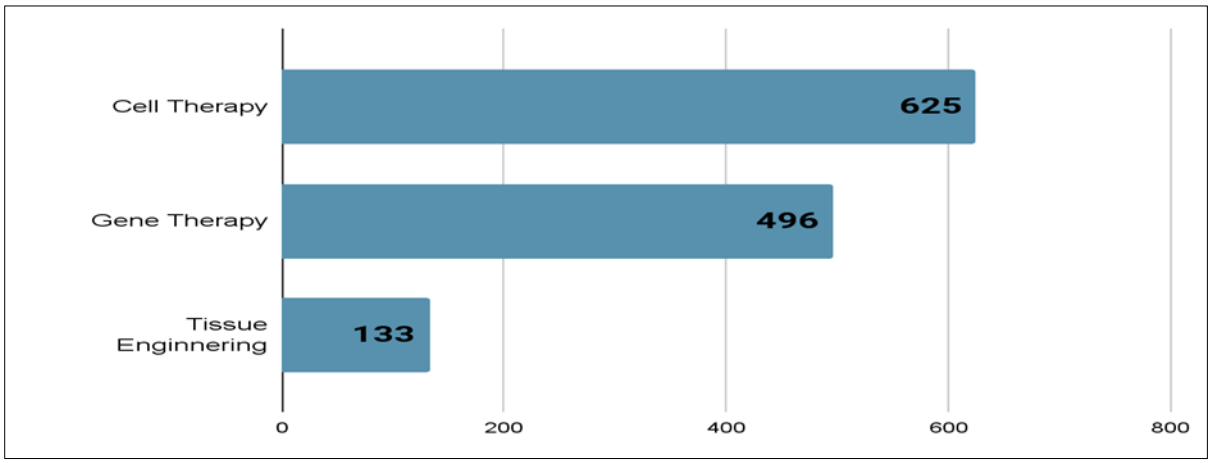

Figure 1 Number of Companies in three biomedical sectors as of 2020 (Gerlovin et al., 2020) [13]

2. Material and methods

The methodology for this paper involved a comprehensive literature review to identify challenges in tissue engineering, specifically focusing on FDA regulations, funding and manufacturing, and storage methods for tissue-engineered medical products (TEMPs). The review process began with an extensive search of academic databases, including PubMed, Google Scholar, and specialized journals in biomedical engineering and regulatory science. Keywords such as 'FDA regulations', 'tissue engineering', guided the search.

Selected articles and studies were analysed to identify common themes and recurring challenges faced by the field. The review included both historical and recent publications to ensure a broad perspective on the evolution of tissue engineering and its current state. Key criteria for inclusion were relevance to the topic of interest and the credibility of the sources.

Data from the reviewed literature were synthesized to highlight major issues, such as regulatory ambiguities, high manufacturing costs, and preservation difficulties. This synthesis allowed for the formulation of actionable recommendations. The paper also compared findings across various sources to ensure a comprehensive understanding of the challenges and to propose effective strategies for overcoming them. This methodology aimed to provide a clear, evidence-based analysis of the current barriers and solutions in tissue engineering.

3. Results and discussion

3.1. Challenges in Commercialization of Tissue Engineering

The following section will outline three identified areas in which the innovation of tissue engineering has been limited or constricted by either legal or logistical standardization. The purpose of this section is to distinguish the setbacks of the innovation, leading into how it can develop as a large-scale operation such as modern drug and medical device development. The first challenge covers FDA regulations as a primary legal inhibitor. As new medical innovations are brought forth, the FDA has a unique responsibility to assess and ensure the safety of newly approved products. As seen in the section to follow, drug and medical devices are well referenced for their long-term relevance in the FDA approval process, though tissue engineered products (as a new category of their own) have come forth for their demand in medical improvement. Challenge two and challenge three discuss the logistical setbacks of tissue engineered medical innovations as the ability to effectively manufacture, store, and distribute living cells and tissue is difficult. The ability to not only create the product but make them effective when needed for the patient is a setback in the development and scale of these innovations. Finally, this section reviewed the ability to effectively produce and manufacture tissue engineered products at scale and at high rates of reliability.

3.1.1. Challenge 1: Lack of clear regulatory pathway for FDA approval.

The FDA is the federal organization which is responsible for the ethical safety of Food and Drugs. FDA approval (particular to medical approval) is a term which reflects that a particular medical product has been reviewed and is allowed to be publicly marketed in the US commerce. While this approval rating is bothersome for companies to achieve due to highly regulated and strict market standardization, passing through the process allows them to promote themselves as a reliable or reputable product. Particularly with medical goods, such as drugs and medical devices, approval is required before public consumption of the product. The purpose of the organization and its approval process is to protect consumers in the free market of products; intended to ensure that there is a known level of risk, assessing the product for what is promoted as. In general, the regulations for food, drugs, and other products which filter through the FDA are all very different and this analysis will focus on medical approval for its relevance to tissue engineered products.

Table 1 Clarifies some of the existing criteria for analyzing all products seeking FDA approval

	Name:	**Application**
Criterion 1:	Analysis of conditions and treatments	FDA determines if the foreseeable benefits of a drug outweigh the potential risks. How many people are at risk, and how lethal is it
Criterion 2:	Benefits vs. Risk	Clinical assessment of these factors compared to the historically/ currently similar medications
Criterion 3:	Managing risk	Can the foreseeable risks of the medication be reduced by doctors, manufacturers or patients?

FDA self-defines its approval as a process in which benefits of a drug are analyzed to determine if they outweigh the potential risks. The extent of this process is to consider the benefits of newly approved drugs, and the implications of its availability to the population. While this definition leaves lots of ambiguity as to why or when a drug would be approved; it remains to be the most sought out approval methodology. The FDA employs a comprehensive approach in evaluating medication approval, focusing on three primary categories. Firstly, thorough analysis of the target condition and existing treatments is conducted. This involves assessing the medical necessity, efficacy, and safety of the proposed medication in comparison to established therapeutic options, ensuring optimal patient care and public health outcomes. Their criterion established a base of knowledge for the target illness or condition, determining the severity to the population based on the amount of people who have the target illness, people at risk and condition lethality. These metrics are functionally given a score or rank, and then compared to the potential benefits of the medication and its effectiveness in treating them. Additional considerations such as symptoms are considered and factored into the cost/benefit comparison. The second criterion looks into clinical data and analyzes the feasibility of the drug and its current uncertainties. The term ‘clinical trials' is a broad term which defines a process in which a medical or drug is taken through various phases of testing to show effectiveness and reliability. The third criterion to achieve FDA approval is detailed and effective strategies for mitigating or reducing these identified risks (FDA Approval, 2022).

As seen in recent years in COVID-19 virus, this risk mitigation strategy is fluid, and can be expedited to accelerate availability to the population. The most typical example of an accelerated pathway is seen in surrogate medication, where there is temporary or conditional drug approval pending additional long-term research affirming the currently known information. The FDA, when examining a new medication for approval may categorize applicants into one of three categories which are: fast track, breakthrough therapy and priority. These distinctions are used to accelerate or accentuate a specific part of the process based on known and relevant information about the applicant. Fast track typically is used for a completely unmet or significantly under-represented clinical need (Drug Development, FDA, 2022). For example, a medication with extremely well documented and convincing clinical trials that treats a common lethal illness may be fast tracked because the potential risks are already greatly overwhelmed by the potential benefit. Breakthrough therapies typically exhibit a significantly new approach to any other available product; even if the drug has significant risks, it may still be approved so that there is something available for patients with that particular illness. Priority review simply accelerates the entire process from 10 months to 6 months based on a current and relevant social need. Applicants can apply for multiple of these designations at once based on need, and proof of concept. (FDA Approval, 2022)

The general format for an FDA approved medication takes about 10 months, often lasts many years but has some variables based on the medical classification the product is placed within. Medications are categorized into one of three classes, determined by the risk tiers discussed earlier. Class 3 poses the highest risk, while Class 1 presents the lowest. This classification system guides regulatory decisions, ensuring appropriate management of risks associated with each medication for the safety and well-being of patient. Of course, products such as pacemakers are almost always placed into the greatest risk categories not because they are less effective, but rather as a result of the sheer reliance of their effectiveness. Here, the greatest factor in determining if a medical device is approved and at which tier is determinant on familiarity with the product, similar products and the known risk factors. (Norman, 2016) [21].

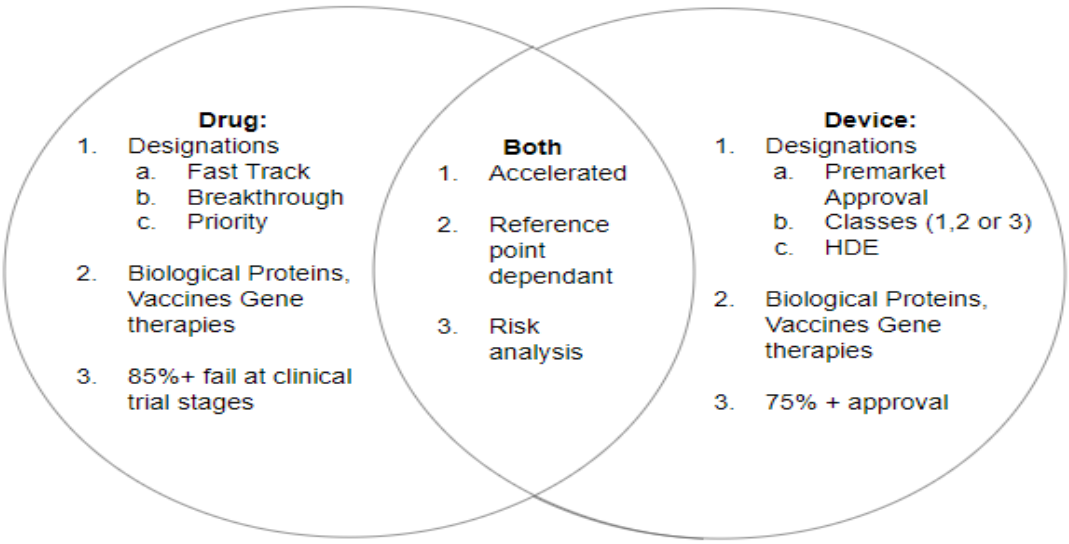

Figure 2 Venn Diagram comparing significant differences between Device and Drug pathway. Not the approval rate and designations during this process. Modern problem is effectively categorizing Tissue Engineered products into either of these and regulating such pathways (Norman, 2016)[21]

As seen in Figure 2., there are some minor semantic differences between the 'device' and 'drug' pathway. Determining, mitigating, and assessing risk is linear. Products which are considered drugs are classified and accelerated, while devices are tiered into need-based sections. Devices encompass instruments, implements, machines, implants, or in vitro reagents, while drugs are substances intended for diagnosing, curing, mitigating, treating, or preventing diseases (Human Drugs, FDA, 2021). Since tissue engineered products do not effectively fit into either of these categories there is lots of ambiguity as to which pathway they should continue through. Looking at the products through the FDA's definition, TEMPs could be considered a drug, this poses greater legal hoops for companies as the approval process is more strict when considering the approval of a drug. A staggering 86% of clinical trials fail to secure approval from the Federal Drug Administration (FDA), imposing substantial economic burdens (O'Donnell et al., 2019). As a result, companies vouch for their products to be considered devices as they are often mechanically implemented apparatuses. This results in misinformation about TEMPs which have been FDA approved, or makes it nearly impossible to find a linear direction to seek FDA approval. (Human Drugs, FDA, 2021). The definition of new medications becomes ambiguous due to the complexity and evolving science of TEMPs. Variations between cellular therapies, drugs, biologics

(e.g., monoclonal antibodies), and medical devices pose challenges in organizing these treatments within existing regulatory guidance and application frameworks, as noted by Belsky & Smiell (2020).

3.1.2. Challenge 2: Funding and Operational Limitations in Manufacturing

With any technological innovation, the acquisition of sufficient funding is crucial for bringing a product to the market. This is especially true for tissue engineered medical products. In fact, a major challenge contributing to the slow translation of tissue engineering products to the market is a lack of funding to support early-stage products. There is an intricate relationship between research personnel and investors. Funding early-stage tissue-based products is considered a high-risk investment due to the uncertainty regarding their success in the market. A 2012 study which interviewed individuals from governmental, private, and public investors sectors regarding their willingness to invest in tissue engineering-based products, reported, "limited interest in early-stage start-up companies" across all of the sectors (Ta et al., 2012) [26]. While hesitation in funding a higher risk project is warranted, this provides a major barrier to tissue engineering advancement as sufficient funding for long-term translational products is particularly challenging to acquire. Moreover, the scientific inclination towards uncovering new discoveries, coupled with this funding approach, often prompts many researchers to prioritize refining basic research projects over advancing findings towards translational applications (Madry et al., 2014) [18]. Discouraging scientists from pursuing the commercialization of a product has certainly hindered the number of tissue engineering based technologies that have made it to the market.

Table 2 Major Barriers to Manufacturing Scale-Up in Tissue Engineering

	Benefits	**Challenges to Implementation**
Acquisition of Funding	Funding is required to purchase technologies to support the scaling of production (Martin et al, 2009[19] & Doulgkeroglou et al., 2020) [11]	investors are hesitant to invest in early-stage research (Ta et al., 2012) [26]
Bioreactors	Provides controlled environment for cell/tissue maintenance which supports scalable manufacturing Reduces contamination risk (Martin et al, 2009) [19]	High initial investment cost Requires specialized training of laboratory personnel (Martin et al, 2009) [19]
Automation Processes	Decreases manual workload Decreases product variability Reduces contamination risk (Doulgkeroglou et al., 2020) [11]	High initial investment cost (Doulgkeroglou et al., 2020) [11]

The effect of limited funding goes further than just discouraging scientists from pursuing commercialization. In many cases it also serves as a barrier, stopping innovation in its tracks. Although difficult to acquire, funding is essential for moving early-stage research projects to the commercial stage, especially due to complexity associated with scaling up the production of engineered tissue products. Tissue engineered products are composed of living tissue and thus have very precise production processes which need to be supported by specialized technology. For example, bioreactors are required for the production of the majority of these products. In order for the biological construct to remain viable through all stages of the production process, a controlled environment which mimics the physiological conditions of the body is essential. Without a doubt, bioreactors play a pivotal role in the automated, standardized, traceable, cost-effective, safe, and regulatory-compliant production of cell-based products or engineered grafts for clinical applications (Martin et al, 2009)[19]. Unfortunately, the initial investment cost of bioreactors serves as a major barrier for smaller start-up companies with limited funding as the installation of a single bioreactor can cost over $10,000. The cost of the cell media and other reagents required for production are also significant. In addition to monetary costs, the implementation of bioreactors also requires specialized training of laboratory personnel to ensure proper operation of the technology.

Another hurdle to the scale-up of tissue-based products is the high cost associated with implementing automated production processes. In the early development stages of tissue-based products, essentially all production work is done manually in a laboratory setting. While this initial production method is essential for establishing a proof of concept, it is not sustainable for large-scale manufacturing of the product due to the large amount of manual labor required as well as increased risk of variability between final products (Chapekar et al., 2000). For instance, automated pipetting techniques can increase the accuracy of measurements, and automated screening technologies (ex. automated calculation of cell morphology/confluency) can reduce inconsistencies due to subjective human judgment

(Doulgkeroglou et al., 2020)[11]. Again, however high initial investment cost minimizes the implementation of automated technologies, which then prevents tissue-based products from reaching the commercial market.

Finally, the sheer volume of equipment and space required to produce the number of products required to meet market demand is another major challenge. If scaffolds are produced by bioprinting methods, numerous bioprinters will be needed. Likewise, the quantity of bioreactors required correlates with the volume of cells needed for specific applications. Limited funding poses a significant barrier for numerous start-up ventures to progress to the commercialization stage, hindering their ability to finance large-scale manufacturing. Table 2 underscores the obstacles linked with scaling up tissue engineering manufacturing processes

3.1.3. Challenge 3: The Need for the Preservation of Tissue Engineered Products

Preservation is a crucial part of every transplant surgery. In tissue engineering, where the creation of cells and tissues are handled outside the body, its significance is not diminished. The National Institute of Standards and Technology (NIST) has pinpointed four research domains necessitating substantial technical innovation for the advancement of manufacturing processes. These areas encompass automation and scale-up, sterilization techniques, product storage solutions, and product transportation methodologies.

The main issue of preservation and storage of live biomaterials is the problems related to the transfer from the laboratory to the market. Manufacturers and distributors understand the need to keep a stable supply of their products in stock. Still, the erratic clinical demand for certain tissues will force the establishment of tissue banks at hospitals. The source of cells and the finished tissue constructions or implantation devices require effective preservation techniques. The technology for tissue preservation uses cryopreservation for long-term archiving and hypothermic (above-freezing) procedures for short-term storage.

Living tissue equivalent are cultured tissues employed for reconstructing bodily structures (EDQM, 2015)[12]. These may comprise ex vivo expanded cells and an extracellular matrix. The tissue's origin, like epidermis, dermis, cartilage, or muscle, should be specified in product details when relevant (EDQM, 2015}[12]. Allogeneic and autologous cells were uniformly distributed across various pharmaceutical dosage forms and delivery methods. It's essential for cells to remain in suspension or solution to ensure adequate oxygenation and nutrient supply through diffusion gradients.

Another crucial point is that fresh tissue engineered products rather than frozen ones are frequently required. As a result, the shelf life, indicating the period suitable for long-term storage, tends to be relatively short, typically ranging from 12 to 72 hours, which primarily encompasses the duration of shipping. Approved tissue-engineered medical products (TEMPs) typically have a maximum shelf-life of approximately four days. Beyond this, shelf-life varies considerably, leading to cellular degradation and loss of function. According to the product European Public Assessment Report (EPAR), Spherox can be stored between 1°C and 10°C for 72 hours, while ChondroCelect and MACI have suggested shelf lives of 48 hours and six days (notably long), respectively. Holoclar should be maintained between 15°C and 25°C for a maximum of 36 hours.

While freezing requires a dependable cold-chain delivery system, entailing significant financial implications and transportation complexities, it proves advantageous by extending shelf life and allowing ample time for comprehensive release testing of the product (Quick International Courier, 2021)[25]. For example, the inability to freeze tissue-engineered medical product (TEMP) items requires modifications in sterility testing procedures. This poses the risk that the product received by a patient might be contaminated with microbes at the time of release.

There is a growing emphasis on the advancement and implementation of rapid sterility testing methods. Additionally, alternative strategies are being devised for situations where products must remain fresh or unfrozen. These include options like cell banking or readily available donor databases for cell sourcing, as well as starting materials or intermediates that can be frozen, such as peripheral blood mononuclear cells or mesenchymal stem cells (MSCs), facilitating on-demand manufacturing to produce fresh products. The advantages of developing allogeneic products rather than autologous ones are increased because these alternatives can be more effectively implemented with allogeneic TEMPs.

The biophysical impacts of hypothermic and cryogenic storage differ significantly depending on the size and composition of tissues and their unique structural arrangements. In recent years, extensive endeavors have focused on devising and evaluating preservation protocols and solutions, as well as examining the effects of hypothermic and cryogenic temperatures on various tissue-engineered products, such as neural tissue, cartilage, mucosa, skin, and

vascular grafts (Day et al., 2017[10]; Nover et al., 2016) [22]. However, there is still a need for further studies on the subject.

3. Recommendations for Early-Stage Tissue Engineering Companies & Researchers

3.2. Recommendations Based on Challenge 1: FDA Regulations

In order for an effective resolution of tissue engineering innovation to come to pass, there are several strategies currently employed by companies to improve or clarify the FDA approval process. In order to be successful throughout the FDA approval process, companies must reduce their likelihood of being recycled or restarted to an earlier part of the process. Since the process typically takes a minimum of 6 months even for well documented and known medications, the process can become rigorously cyclic if careful revision is not taken prior. Presenting this requires an acute understanding of how specific products will be classified by the FDA. This understanding can be obtained by working with the FDA throughout clinical trials, working with FDA professionals during the process in order to make the approval more streamlines. The strongest piece of evidence that a company can provide in addition to clinical trials is referencing similar products which have proven relevant success. For example, when looking at something like name brand pain reducing medication compared to generic brands, both products must be individually approved. Although a nearly identical product has already been approved, follow-on approval processes are simplified and streamlined. Companies that can provide such reinforcing studies, or historical reference points have the best chance of being successful in the FDA process. In general, companies do not have control over the FDA approval, and are somewhat at the mercy of the institution's assessment of the product. The following points summarize the best actions to take in improving success

- Working closely with the FDA during clinical trials and approval
- Clearly stating and understanding the products potential benefits vs risks
- roving the product has a relevant need in the medical industry
- Using relevant and similar products as reference points for reinforcement

3.3. Recommendations Based on Challenge 2: Funding & Manufacturing

In order for a smaller company to overcome the manufacturing challenges of tissue engineering, the issue of limited funding must first be addressed. In order for a research project to be viewed favorably by investors, the researchers must have a firm understanding of how their product intends to solve a need in the medical industry as well as how the product will interact with different customer sectors (clinicians, surgeons, patients, insurance companies, etc.). Undoubtedly, conducting a thorough market assessment is crucial for new products, and collaborating with industry partners is vital to ensure realistic guidance for potential products (Mandy et al., 2014)[18]. Collaboration with individuals from each of the applicable market sectors should start early on in the research project and continue throughout the entire development process as these individuals will be able to provide valuable insight on the need and general feedback on initial prototypes of the product. It is important to remember that each sector has different wants and needs that must be considered. For instance, surgeons will want the implantation procedure to be simple and with low failure risk, whereas patients may be more concerned with the lifespan of the product. A product which has the support from different customer sectors and shows promise in meeting a verifiable unmet clinical need is far more likely to get investment funding than one that does not.

To further tackle the challenge of manufacturing scale-up, researchers should consider how automation technologies can play into their product design at an early-stage. While manual proof of concept manufacturing will be the main production method while optimizing the design, communication with automation experts at early development phases will help support the transition into large-scale manufacturing. In particular, the automation program should be viewed as integral to the entire product life cycle, seamlessly integrated into the overall product development plan and commercial manufacturing process. Every possible implication of automation on the final product should be thoroughly examined (Doulgkeroglou et al., 2020) [11]. Early consideration of automation processes gives the product the best possible chance of being able to succeed at the large-scale production required for commercialization.

3.4. Recommendations based on challenge 2 (Storage)

To improve TEMPs and facilitate the effective distribution of these products, there is a need to change a majority of the currently utilized medical practices (Brockbank, 2000) [7]. Crucial manufacturing constraints are essential for facilitating the transition from laboratory development to clinical application and the commercialization of tissue-engineered products. Ensuring optimal transportation and storage of engineered tissues is fundamental for enabling

their banking or distribution. The objective of preservation is to retain tissue viability, extracellular matrix integrity, and composition while slowing cellular processes to a hypometabolic state. Cells, tissues, and organs have been preserved at hypothermic or cryogenic temperatures for both short and extended durations, utilizing specialized media and cryoprotectants. These substances mitigate the biophysical effects linked to the cooling, freezing, and thawing processes (Pegg, 2007 [24]; Baust et al., 2009) [4]. It is recommended that an early stage company determine which storage method is suitable for their product as early as possible, such that proper associated testing can be conducted in a timely manner. Two possible storage techniques: hypothermic and cryogenic, are outlined below for reference.

3.4.1. Hypothermic Storage

Hypothermic storage operates on the premise that biochemical processes decelerate at low temperatures, inhibiting the accumulation of molecular damage. This preservation method is relatively cost-effective, making it an attractive option (Acker, 2007) [1]. However, the metabolic processes are only partially repressed at hypothermic temperatures, leading to cell and tissue deterioration. Cell damage brought on by hypothermic preservation includes deactivation of the membrane pump, disturbance of the calcium homeostasis, cell swelling, and apoptosis brought on by free radicals (Giwa et al., 2017[14]; Armitage, 2011[3]). As a result, hypothermic preservation is typically utilized solely to prolong the shelf life of biological materials for a short duration during delivery and distribution.

3.4.2. Cryogenic Preservation

Cryogenic preservation is indispensable for long-term storage and banking purposes. Cryoinjuries occur due to the formation of ice crystals inside and outside cells, osmotic imbalances, and the toxicity of cryoprotectants. At extremely low temperatures, cellular metabolic activity comes to a near-complete halt (Best, 2015) [6]. Because of their heightened biological complexity, reduced heat transmission, and limited diffusion of cryoprotectants, both natural and engineered tissues and organs frequently experience more pronounced biophysical effects during preservation compared to individual cells (Xu et al., 2010) [28]. The specific outcomes of preserving tissues generated from induced pluripotent stem cells (iPSCs) at hypothermic and cryogenic temperatures are yet to be established.

Although there is a clear reduction in the metabolic activity of tissue-engineered medical products (TEMPs) when exposed to cryoprotectant-containing solutions, the findings of several studies remain consistent. They demonstrate a persistent decline of 25% or more in tissue viability and the count of viable cells after reconstitution. This number increases after 24 hours, indicating that storage-induced damage worsens after revitalization (Costa et al., 2012) [9].

The biophysical impacts of hypothermic and cryogenic storage significantly vary depending on the size and type of tissue, along with their distinctive structural organization. In recent years, extensive endeavors have been dedicated to developing and testing preservation protocols and solutions, as well as researching the impacts of hypothermic and cryogenic temperatures on various tissue-engineered products, encompassing neural tissue, cartilage, mucosa, skin, vascular grafts, and more (Day et al., 2017 [10]; Nover et al., 2016 [22]). However, there is still a need for further studies on the subject.

4. Conclusion

The business landscape of TEMPs is certainly difficult to navigate due to the challenges of FDA regulations, manufacturing complexities, and storage and distribution logistics. However, with careful planning and a thorough understanding of the market and the factors that influence the market, successful companies and researchers can overcome these challenges and bring their TEMPs through the commercialization process. With proper early-stage support through the collaboration of individuals of different expertise, these technologies have the potential to make a positive impact on millions of lives.

Compliance with ethical standards

Disclosure of Conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

The study did not involve individual, hence, no informed consent was necessary

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