Chapter 12
Commercialization, IPR, and Market of Stem Cell Products

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Abstract Stem cells and their derivatives stem cell products have broad and diverse applications in regenerative medicine. Specific stem cell lines are used as potential targets for the study of several diseases in pharmaceutical applications. Recently, stem cell products combined with an engineering approach are novel targets for replacing damaged and degenerated tissues for the numerous applications of recent tissue engineering applications. The emerging cellular therapeutics manufacturing unit is also dependent on an intricate array of stem cell products. The wide range of stem cell products is dynamically burgeoning with accelerating demand in the market due to their contribution as potential therapeutic effectors. The scientists and researchers involved in biotechnology companies, pharmaceutical companies, and academic platforms leverage stem cell products for a wide range of essential and functional applications. The chapter reviews the brief introduction of stem cell products, market availability, market-based competition for various stem cell products, and funding. Besides, topics such as the commercial status of stem cell products of particular reference to the clinical therapeutic application and intellectual property rights associated with regulatory policies of stem cell products and research are also discussed.

Keywords Stem cell products · Commercialization · IPR

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Introduction to Stem Cell Products

Introduction to Broad Categories of Stem Cell Research Products and Regulations Associated with Stem Cell Research Products

In the current scenario, stem cells are one of the most promising entities that can be used for medicinal and research-based purposes as they aid in the regeneration and replacement of disease and damage organs and tissues. Several life-threatening diseases such as cardiomyopathy, spinal cord injury, Parkinson's, liver disease, tumor, and myocardial infarction can be benefitted from cell-based therapy. However, the translation of stem cell research and their respective benefits for their application as therapeutics is a sequential multi-step complicated and complex procedure. Also, the stem cell-derived products are different from the pharmaceutical-based origin, and therefore, the issues of stem cell-based product efficacy, consistency, and safety require addressable attention. Therefore, it necessitates experimenting on relevant issues related to the management of therapeutic outcomes and the potential risks with the fulfillment of existing guidelines and regulations attached to stem cell product development and their marketing. In the developing countries for "stem cell-based products (SCBP)," there is an immediate and high requirement of well-structured and well-defined rules and regulatory frame work like the regulations developed countries such as European Union (EU), Japan, and USA (US) which have well-defined and functional regulatory frame work (George, 2011).

"Stem cell-based products (SCBP)" term refers to the products which are descendants and derivative of stem cells and, further, these derived and developed products need to be administered into a patient and that contain or are derived from stem cells (Halme & Kessler, 2006). Globally, the commercial availability of stem cell-based products is very high in the market in form therapeutics but, still, these products and therapeutics do not fulfill the safety guidelines as most of them do not fall under formal clinical trial inspection which may intend to the detrimental effect on the physical health of the patient and also the financial exploitation remain extremely high. The clinical test should be performed with utmost safety guidelines and attention before delivering the market product (Giuseppe et al., 2010). Thus, there is a requirement for the appropriate well-structured and well-regulated system for the commercial supplies of SCBP to safeguard public health safety and trust issues. However, this situation and requirement impose presents numerous regulatory challenges.

Currently, scientists promote the use of stem cell research products as therapeutics for a wide range of applied applications. In contrast, clinical researchers support the concept by integrating both stem cells and their application in regenerative medicine for the treatment of diseases. Further, the pharmaceutical industry plays a significant role in the regulated use of stem cell products to conduct pharmacological testing on cell-specific tissues. Furthermore, tissue engineering scientists and researchers

are intensively working upon replacement and repairing damaged tissues and organs by developing new techniques to combine bioengineering techniques and stem cell-based products.

The broad categories of stem cells research products available in market for the expedition of research are explained below:

- Stem cell lines which includes different types of cell lines. Example: iPSCs, MSCs, HSCs, NSCs, and ESCs.
- Stem cell culture media with and without supplements.
- Instruments related to stem cells culture and maintenance.
- Stem cell culture reagents.
- Stem cell-specific cytokines and growth factors.
- Primary antibodies against specific stem cell antigens.
- Bead-based stem cell separation systems.
- Fluorescent-based labeling and detection.
- Stem cell protein purification and analysis tools.
- Tools for DNA and RNA-based characterization of stem cells.
- Isolation/characterization services for stem cells and cell-based specific cell lines.
- Molecular tools for stem cell gene regulation.
- Mechanisms for in vivo and in vitro stem cell tracking.
- Expansion/differentiation medium for stem cell media.
- RNAi products.

Common Types of Stem Cell Product and Supply

There are various facilities, products, and supplies provided by the stem cell products industry. Stem cells were discovered before 30 years; therefore, there is a vast availability of stem cell-derived products, related services, and their market. There is a diverse market for stem cell products because of their complexity and technologies required to maintain and supply stem cell-based products. The standard type of stem cell products which are used in stem cell research is stem cell lines, differentiated type of stem cells, stem cell cultures, stem cell maintenance products such as growth factors and cytokines, primary antibodies, molecular and analytical tools for stem cells cloning, tools for gene expression and regulation such RNA and protein purification kits, imaging and tracking systems. Such stem cells, stem cell-derived products, and their maintenance and research stem cell products can be sold as an individual product or in bundles or as complete functional kits for the characterization and research studies in the field of stem cells. Currently, therapies which include mesenchymal stem cell (MSC), iinduced pluripotent cells (iPSCs) and embryonic stem cells (ESC) are used as therapy for the treatment of human diseases and are under pre-clinical development.

These stem cell-based products are bought by different researchers in diverse fields in academics, biotechnology companies, clinical institutions, and pharmaceutical companies-based researchers to develop new formulation and therapies for different diseases. The stem cell industry has been heavily driven and boosted by developing and manufacturing stem cell therapeutics and their products. The large-scale production of stem cell-based products is mediated by the use of a wide range of bioreactors, biofermentors, and 3D manufacturing systems through different industries.

Market Competition with Perception to Stem Cell Products

As per market perspective, the major focus of investors is on stem cell products as these are highly promising entities in the treatment of a wide range of genetic diseases and the development of new artificial organs and tissues that cannot be cured by non-cell products. Currently, adult stem cells (ASCs) market, which includes ESCs and cord cells derived from fetus placenta, is the largest commissioned market with huge market potential. There are around 180 companies which are involved in the marketing of stem cell products. The developed nations as USA are one of the leading master followed by the European and Asia–Pacific regions in stem cell and stem cell products market. Stem cell research is presumed to boost rapidly in the upcoming years because of the regulatory amendments in several countries in the next few years. For developing countries like India, a market share of about $540 million with an annual growth rate of 15% is expected. This indicates that there could be an enormous possible investment from pharmaceutical, biotechnology, and bioengineering companies of different developed and developing countries in the market to develop stem cell-based products (Korde, 2008). The process of development of stem cell therapy and its flow to the market is explained in Fig. 12.1.

Different companies in the market supply the tools for the isolation, differentiation, expansion, culture, and characterization of stem cells, along with the technologies based enabled the production of these products at a small to large scale. These companies' versatile function includes stem cell research applications, the satisfaction of relative demand for stem cell products, analysis of stem cell manufacturing technologies, analysis of market trends including opportunities and threats related to the stem cell-based products. With market competition growing increasingly fierce, leading competitors within the sector include the companies in the market involved in the global competition are listed in Table 12.1.

With the increase in demand for stem cell-based products as therapeutics, there are high possibilities for rising stem cell-based production in the market. There are various emerging market opportunities for developing new products as per requirement or demand in the market depending upon increased acceptance of stem cell technologies and recognition of regenerative medicine's potential to reduce globally accelerating healthcare costs. In the current scenario, increasing health costing

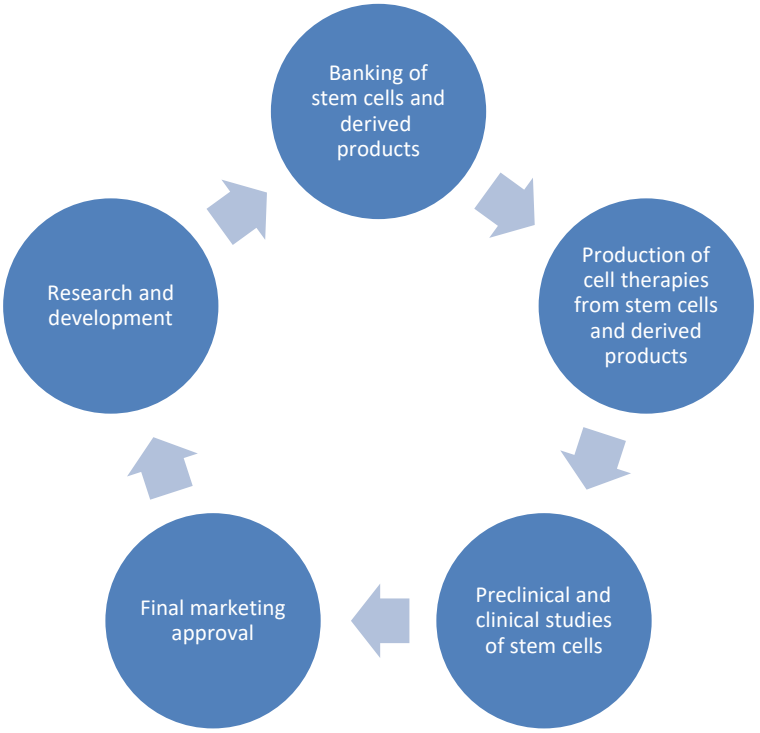

Fig. 12.1 Workflow of stem cell product therapy to market approval

services may drive essential factor costs for the investment into stem cell products and therapies on a global scale.

Funding for Stem Cell Research

The federal funding of stem cell research in developing counties such as the USA, from the National Institutes of Health (NIH), made an investment of $1.495 billion into stem cell research projects, with the pharmaceutical industry and private sources contribution of over 1.7 billion dollars annually (NIH Categorical Spending -NIH Research Portfolio Online Reporting Tools (Report). N.p., 2016. Web. 26 Jan. 2016; $40 Million to Support Future Stem Cell Scientists. CA Institute of Regenerative Medicine, Press Release. Available at: http://www.cirm.ca.gov/PressRelease_061809. Accessed Jan 24, 2016).

Table 12.1 Companies in the market involved in production and supply of stem cells and stem products at global level

S. No.	Specialization of company	Name of company	Product supply
1	Stem cell therapy	Mesoblast, Cynata Therapeutics, and Steminent Biotherapeutics	Stem cells
2	Industrial-scale production and manufacturing of stem cells and differentiated cells	Cellular Dynamics, Fujifilm CDI, Rooster Bio, ReproCELL and Ncardia	IPSCs and MSCs
3	Stem cell research tools	STEMCELL Technologie, Thermo Fisher Scientific, BD Biosciences, and Miltenyi Biotec	All stem cell-derived research products
4	Stem cell products	Corning (specializes in Matrigel®)	Products to support pluripotent stem cell culture and culture ware
5	Stem cells culture and maintenance products and instruments	Thermo Fisher Scientific, BD Biosciences, a Division of Becton Dickinson (BD), Merck KGaA, Miltenyi Biotec, Lonza Group, Takara Bio, GE Healthcare Life Sciences, Sigma Aldrich	Products to support stem cell culture and maintenance in vivo and in vitro

Current Regulatory Challenges in Stem Cell Product Development

In this section, the regulatory changes related to safety, efficacy, and quality are encountered in stem cell-based product (SCBPs) developments.

These issues are related to the preparation of cell therapies and tissue-based therapies at the clinical level as well as the commercial supply of SCBPs. The testing to ensure the safety of the products for administration in patients includes the examination and assay of product for any microbial and toxin contamination, followed by in vitro functional assays for the assessment of its clinical effectiveness and pervasiveness, including standards and controls to satisfy regulatory framework (Collins, 2009; Rayment & Williams, 2010). However, it is observed that all the model organisms used for experimental purposes during assays for pre-clinical and clinical studies have inherent limitations (Bianco & Robey, 2008). Also, the pre-clinical data needs to be studied before conducting the relevant examinations (George, 2011).

Commercialization

Stem Cell Therapy and Its Inclusion at Global Level in Clinical Research

Stem cell therapy and SCBPs are the best resources for the treatment of various diseases such cardiovascular diseases, diabetes, neurological disorders, spinal, orthopedic injuries, and regenerative medicine for the replacement of damaged tissues and organs through the clinical approval of a number of optimized techniques (Ghasroldasht et al., 2014; Lavoie & Rosu-Myles, 2013; Naderi-Meshkin et al., 2015). As previously reported till 2014, 4776, studies are registered on the US registry for clinical trials 2014. According to global research data, hematopoietic and bone marrow stem cells are top cells used in stem cell therapy, accounting 36 and 34% of total studies, respectively, followed by neural stem cells (14%), mesenchymal stem cells (11%), adipose-derived stem cells (4%), and embryonic stem cells (1%) as shown in Fig. 12.2. There was a remarkable growth discerned in one last decade with an emphasis on MSCs. In previous last ten years, a remarkable improvement has been observed in the increase in stem cell research and techniques to overcome such challenges (Naderi et al., 2011). The current challenges that the researchers still need to address in stem cell therapy are summarized in Fig. 12.3.

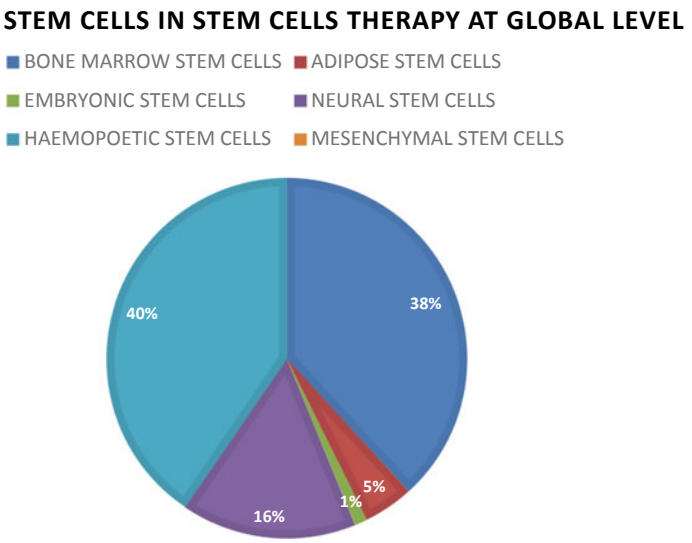

Fig. 12.2 Involvement of stem cells in stem cell therapy at global level

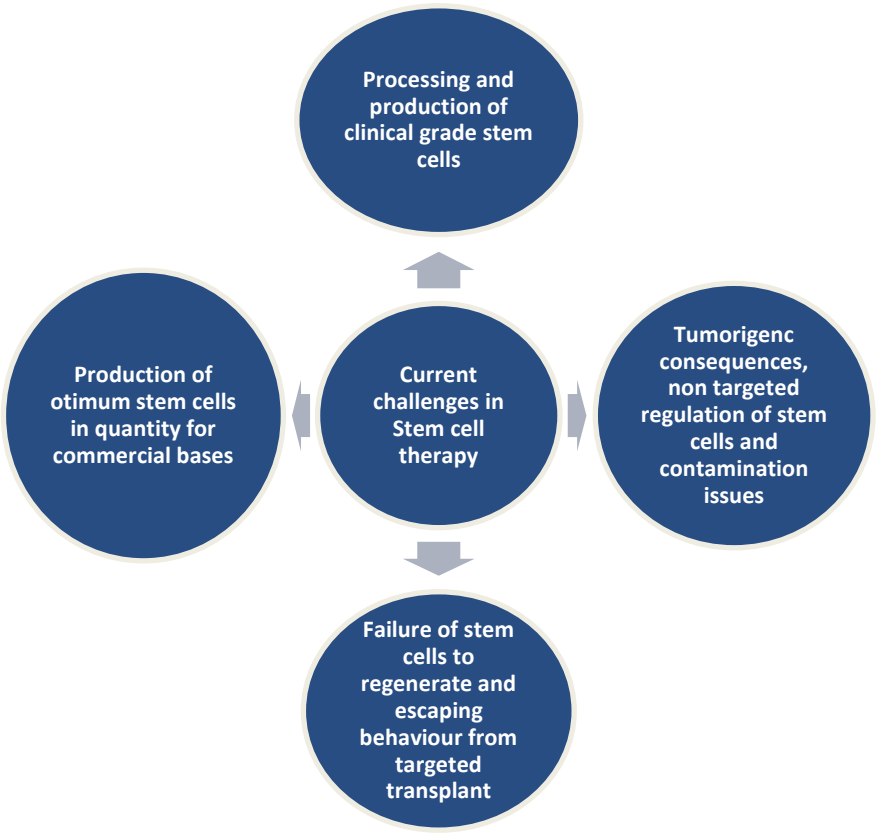

Fig. 12.3 Current challenges in stem cell therapies

Stem Cell Production at Clinical Dimension and cGMP Protocol

As per current reports, researchers are not aware of the cGMP protocol. The initial step for clinical-grade production is testing their regenerative potential as pre-clinical studies on animal models with efficacy evaluation through both in vivo and in vitro assays. Following initial assessment and promising pre-clinical data, follow-up of cGMP protocol for phase I and II monitoring is performed. Further, following the results obtained from Phase I and Phase II, the trials of phase III clinical trials, which shows 99% efficacy, can be finalized for commercial production. In case the data is conceded concerning phase I and II, results may be requested to be tried and reproduced again for trials to the researchers of the Research and Development Department of the respective company for further clinical-grade productions (Sensebe, 2008; Sensebe et al., 2011). The flow chart of cGMP protocol is summarized in Fig. 12.4.

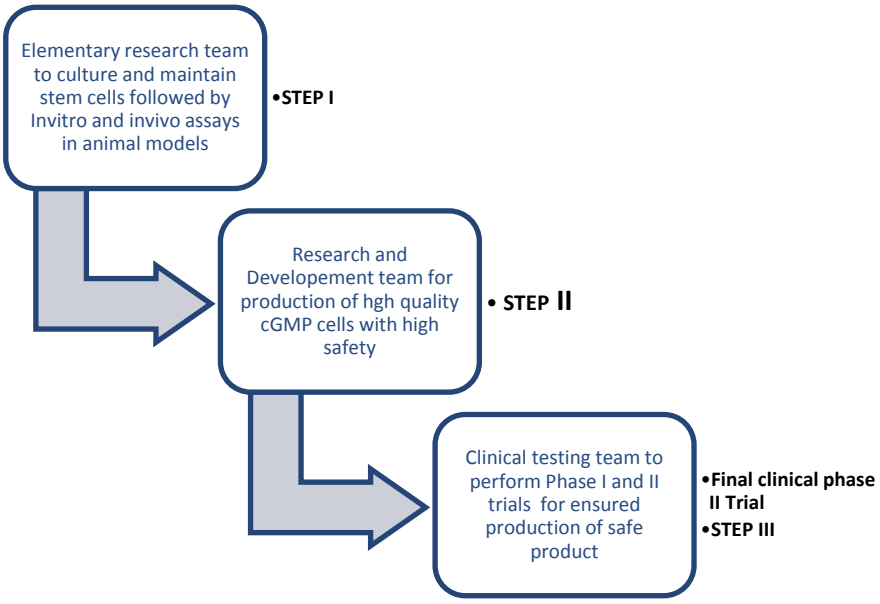

Fig. 12.4 Flow chart of cGMP protocol

Stem Cell Commercialization Establishment

Stem cell commercialization requires the transformation of stem cell research into the health industry with direct implementation into clinical studies to develop stem cell product-based therapeutics (Cuende & Izeta, 2010). It requires investment to gain skills expertise by the researchers to develop cell-based therapies with good manufacturing practice (cGMP) before applications and commercial supply of products. Robust coordination and dedication are required as several small biotech incorporations have shown their potential to commercialize cell therapeutic research (Lysaght et al., 2008). The developed nations such as Japan, the Republic of Korea, Germany, the USA, and Brazil have raised and supported public funds to perform stem cell clinical trials on a human to reduce the gap between basic and clinical research and their connectivity with the general public (Daniels et al., 2006).

- Commercialization of cell therapeutic research should maintain a strong pipeline, along with a planned growth of intellectual property (Hourd et al., 2008). The steps for the commercialization of therapeutic sciences are explained. The measurement of efficacy of pre-clinical trials in suitable and reliable validated animal models.
- Validation of safety measures for effective production of pre-clinical therapeutic products.
- Confirmation to attain FDA regulatory approval safe and effective pre-clinical products to performing prior to human clinical trials.

Commercial Perspective of Stem Cell Products

The process of transformation of research-based stem cell-based products into clinical practice requires immense and intensive coordination among academic institutions, hospitals with associations of patient and research organizations such as pharmaceutical and biotechnology-based companies followed by ethical and moral regulations for clinical commercialization. If these regulatory issues do not need to be addressed, they may account for the adverse effects on developing final products at the later stages before commercialization (Feigal, 2014). Companies require investment in the last stages of product development because of the low growth in the first initial years, which can be compensated by the following options mentioned.

(1) Institutions support in the form of grants and funds through public and private institutes.
(2) Outsourcing of research by different companies.
(3) Mutual collaborations among universities in a joint venture to exchange research facilities and ideas among researchers with expertise in respective areas.

Intellectual Property Rights and Stem Cell Products

Intellectual Property Rights and Stem Cell Products

Stem cells and their derived stem cell-based products have remarkable attributes to serve as commercial entities in the global market. Conceivably, making SCBPs readily available to the general public and common man as patients for the treatment of various diseases and organ transplantation or tissue replacement for a therapeutic application requires manufacturers' particular interest to commercialize the product and gain some profit. On a contradictory basis, if there is the least prospect for gaining profit, it is unlikely that the companies will manufacture the product. Regardless of considerable investments in research and development secured by numerous biotechnology industries to generate stem cell products, the simultaneous risk factors are very high, including zero guarantees of meeting the regulatory requirements imposed by different nations (Mummery et al., 2014).

Regulatory Intellectual Properties and Laws of Stem Cell Research in Different Developed Nations

The regulatory policies are followed by different well-developed nations such as the USA, Europe, and Canada (Zachariades, 2013). As shown in Fig. 12.5, the regulations of different nations such as USA, intellectual property (IP) regulations support the

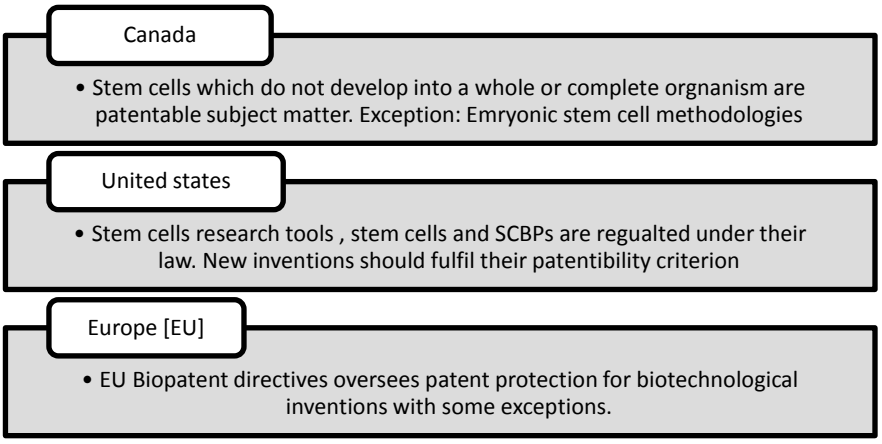

Fig. 12.5 Regulatory intellectual properties and laws of stem cell research in different developed nation

human embryonic stem cells (hESCs) and pluripotent stem cells and methods to develop such cells patentable in the USA. However, it is wholly inhibited in Europe EU. Thus, different research organizations, academic institutions, biotechnology, and pharmaceutical companies may collaborate at this point. They should reexamine their IP, regulatory, and commercial strategies based on jurisdictional laws and regulations. They must strictly comply with the current patent law regulations. The summary of intellectual properties and laws followed in different nations is explained in Fig. 12.5.

Market of Stem Cells Products

Global Stem Cell-Based Products and Stem Cell Therapy Market

The stem cell therapy and SCBPs market at a global level with its market size is predicted to reach USD 214.5 million by 2024. This market is expected to be primarily driven by enhancement of awareness among the general public about the therapeutic potency and application of stem cells, banking of stem cells and SCBPs, and their processing for future applications.

Market Segmentation

The market is segmented on the on bases of type of cells, therapeutic applications, and sources of cell. Each section is explained below.

Type of Cells

Stem cell therapies are classified into two types—autologous stem cell therapies and allogeneic stem cell therapies. Among two, the allogeneic stem cell therapies market has a larger share because of its intensive therapeutic applications, promotion in a clinical trial for developments of allogenic products, and finally cumulative commercialization of allogeneic products, which can quickly be produced through scale-up process. This suggests their rapid demand in the market in the upcoming future.

Type of Therapeutic Application

The stem cell-based products and stem cell therapy market have been various therapeutic applications in treating cardiovascular diseases, muscular diseases, skeletal diseases such as bone or joint related diseases, spinal and neural surgeries, gastrointestinal diseases, and skin diseases as burns, injuries, and wounds. It was reported that the musculoskeletal disorders category contributed to the most considerable revenue in the market for the treatment of musculoskeletal disorders and growing patient preference for effective and early treatment strategies.

Types of Cell Source

The primary cell resources in stem cell therapy and stem cell-based products are comprised of mesenchymal stem cells (MSCs), bone marrow-derived mesenchymal stem cells, placenta or cord blood cells from the fetal origin, and adipose tissue-derived mesenchymal stem cell. Among all these categories, the bone marrow-derived mesenchymal stem cells are the major market shareholders for increasing demand in the market due to diversified therapeutic applications.

Market Dynamics

Growth drivers, challenges, forecast parameters, data validation.

The industry experts should conduct the primary research in the market to understand the market dynamics, followed by valid market data validation. For market

research, consumer-based surveys, which are comprised of consumer feedback and requirement, can also be conducted to understand and know consumer behavior and demand. Different growth driver regulates the market dynamics explained below:

Growth Drivers

1. **Awareness**: The emerging awareness in the general public about their health driven by the knowledge of the therapeutic potency of stem cells and its application in the future is one of the significant growth drivers for the market development. This envisages the customer or client to invest in the development of research for the promotion of advanced genome-based cell analysis techniques in the development infrastructure related to stem cell banking and processing. It eventually encourages customers to invest in the development of stem cell therapies for their upcoming future generations for longevity and healthy life. As per the World Health Organization (WHO) information, more than 50,000 transplants are carried out annually globally.
2. **Increasing risk of acute and chronic diseases**: The increasing risk of several acute and chronic diseases such as multiple sclerosis, cardiac arrest, heart failure, cerebral palsy, Parkinson's diseases, and hearing loss has promoted the interest of the general public toward the stem cell therapies-based treatments.
3. **Transplantation substituted by organ regeneration-based treatments**: Currently, there are several restrictions on traditional organ transplantation because of the dependency of patients on organ donor, transplanted organ rejection, and suppression of the immune system. These factors are also boosting the growth of the stem cell therapy market.

Challenges

1. **Technical limitations**: The limitation related to production during the scale-up, socio-ethical issues related to the use of stem cells in disease treatment. Another high possibility is in the systematic follow-up of the regulatory guidelines for product development and commercialization for the stem cell therapy market's growth.
2. **Socio-ethical issues**: This involves the religious briefs among the ordinary people in society.
3. **Economic perspective**: The investment of capital in research, poorly developed research infrastructure, and facilities for the development of stem cell therapeutics, stem cell-based product, and their preservation are also some of the challenges in the stem cell therapy market.

Forecast Parameters

The parameters which help in the identification of variables that may influence the establishment of the stem cell-based product in the market are as follows:

1. Adoption, production, import, export, and follow-up of regulatory frame work for product development.
2. Uniform of the establishment of the market according to the region.
3. Analyses of market penetration and respective opportunities according to understanding product commercialization, regional expansion.
4. Analyses and study of the historical background of the product to be launched.
5. Analyses of demand and supply trends and making alternations in industry dynamics to establish future growth.
6. Analyses of prolonged sustainability strategies abide by market partakers to determine the future course of the market.

Data Validation

Data validation is required to smooth the marketing of stem cell therapy and stem cell-based product supply in the market. The method responsible for data validation in the sustenance of the market is summarized in Fig. 12.6.

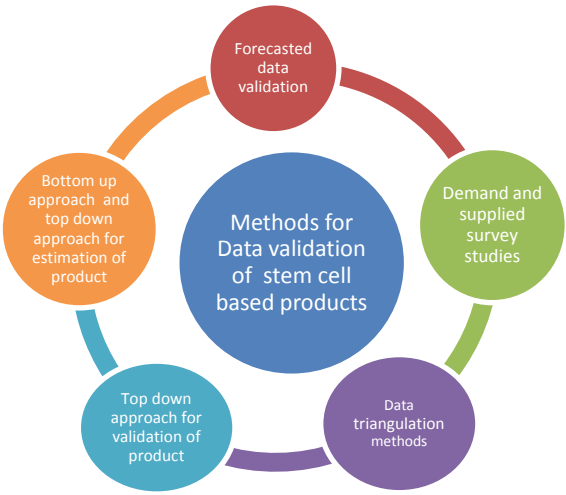

Fig. 12.6 Methods for data validation in sustenance of stem cell therapy and stem cell-based product market

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