

Regenerative Medicine: Analysis, Forecast and Regulatory Requirements

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ABSTRACT

Regenerative medicine is a new and expanding field in biomedical research. Organ and tissue loss through disease and injury, propel the development of a treatment that can regenerate tissue and help for less relaying in organ transplantation. Regenerative medicine has the potential to heal tissue and damaged organ. Currently, a patient suffering from diseased and injured organs can be treated with transplantation organs, but there is a shortage of donor organs. Dermatology is estimated to have a larger share in the market for regenerative medicine as skin being an organ with great cell replicate characteristics. US and Japan play a major role in the market for regenerative medicine. Food and drug administration (FDA) regulations for a medical device used in regenerative medicine are covered here to support risk-based, flexible regulatory methods to help and support the potential to bring novel treatment possibilities to market further. But due to incorrect FDA regulations, it stands as a barrier for the marketing regenerative medicines. Better and clear guidance development or a clear regulatory framework for both regenerative medicine and medical device can leads the product a best fit clinical development and product access in the market.

Keywords: Regenerative medicine, regeneration, FDA guidance.

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INTRODUCTION

Regenerative medicine is an evolving field with the potential to provide a widespread enhancement in healthcare and patient comfort via the delivery of therapies that can regenerate or repair damaged organs and tissue, provoke the development of therapies and decrease reliance on transplantations. The current focus of regenerative medicine falls on somatic, adult stem cells or embryo-derived cells mutually known as pluripotent cells that of human cells. The objective of the present study is to comprehend the scenario of regenerative medicine, its future and the regulatory aspects of regenerative medicine in US and Japan.¹

DISCUSSION

In 2016, the turnover of regenerative medicine was \$17.03 billion. The contribution of North America in the global regenerative medicine market was about 39%. Recent advances and innovations have provided the pavement for the growth of the regenerative medicine market globally. The future scope of the regenerative medicine market is expected to cross \$50.55 billion by 2025. The speedy expansion of the technologies such as stem cells and gene therapy in US, Japan, Germany, and the U.K markets is the key driver for the development of the regenerative medicine market (Figure 1).²

The industry has been perceived to have a very solid growth with a year-over-year increase in the number of products gaining approval for clinical application as well as the number of products approved for investigational trials for potential analysis. Gene therapy is anticipated in research, owing to advances in gene sequencing and editing technology (CRISPR and CAS gene technology).¹ Moreover, advances in tissue engineering technology is expected to make higher donations towards market growth. But the growth is delimited due to regulatory and ethical issues in related fields such as stem cells, gene therapy and tissue engineering. In the therapeutic

UK regenerative medicine market revenue by product type, 2014 - 2025 (USD Million)

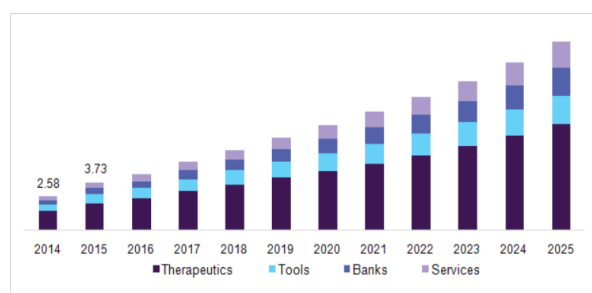


Figure 1: US Regenerative medicine revenue by product type, 2014 – 2024 (USD million)

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view of regenerative medicine, the dermatology section plays a vital role in the profit of regenerative medicine mainly through grafting techniques.³ Skin, being an organ with great cell replication features, provide various types of stem cells from its different layers. The other regenerative medicine products are carticel and demagraft, which are used for diabetic foot ulcer, celution which are used for the transfer of autologous stem cells.¹

In addition, a view to regulation of regenerative medicine in India imply the following

- India has no coherent national policy for regenerative medicine. To date, India has separate guidelines for few regenerative medicine subsectors such as stem cells, while other subsectors have no keen regulations (viz. nanotechnologies and 3D bioprinting)
- To fully apprehend the potential of regenerative medicine, a much stronger commitment in establishing a complete, clear, and, above all, an effective system of a regulatory framework is needed.

Overview of the Regulatory Framework covering Regenerative Medicine in Japan

- Japan instigated two new acts, the Act on the Safety of Regenerative Medicine Act (RM Act) and Pharmaceuticals and Medical Devices Act (PMD Act).
- The RM Act includes the clinical research, medical practice with the help of processed cells and licensing scheme.

While the PMD Act, sets a certain regulatory structure for regenerative medicine products.

- PMD Act also includes the clinical trials which is essential for approval of the regenerative medicines. Pharmaceuticals and Medical Devices Agency (PMDA) reviews the regenerative medicinal products.
- The approved regenerative medicine products are accepted for the National Health Insurance (NHI) coverage in case of medical treatment.⁴

Process for Approval of Regenerative Medicine in Japan

PMDA reviews the complete data first and the report is submitted for the approval process of the product. This report is sent to MHLW for further reviewing process. An advisory committee is appointed to support MHLW for the reviewing process. The conditional approval process is time-limited and should include all the further requirements for the safety and efficiency studies of the regenerative medicinal products in the course of the conditional approval period. The conditional approval period has period as 7 years or lesser as fixed by the Japanese regulators. Reapplication has to be submitted during the conditional approval period to carry on marketing the regenerative medicinal products. The review and decision process of PMD/MHLW will be frequent throughout the conditional approval period. The marketing authorization will be rejected if there is adequate information about the safety and efficacy studies is not included (Figure 2).⁵

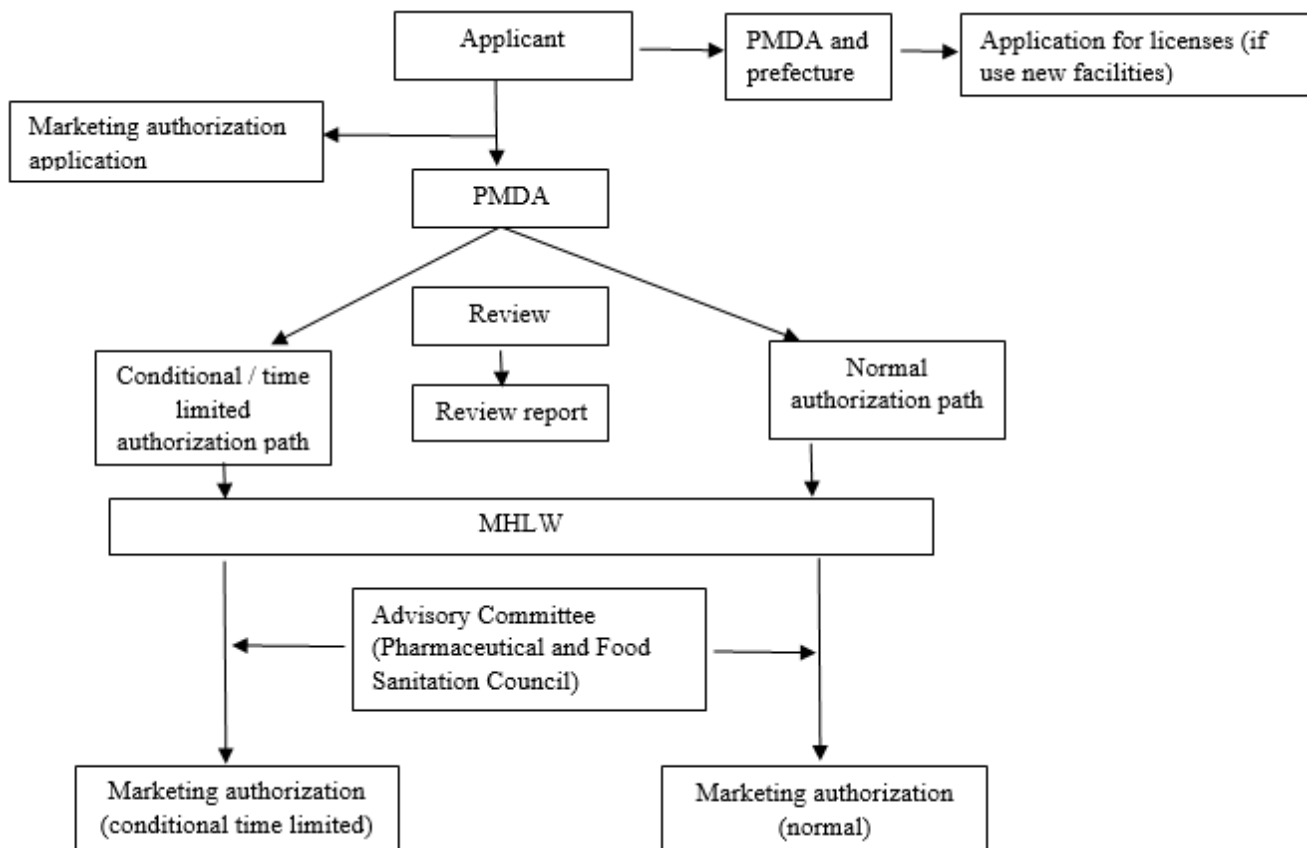


Figure 2: Process for the regenerative medicine approval in Japan⁵

Further, the use of regenerative medicinal products is restricted only to those physicians or institution that has the knowledge and enough training in the use of regenerative medicinal products.

Regulatory Framework for Regenerative Medicine in the United States

FDA has a policy framework for regenerative medicine to support access in establishing safe and effective treatment. Four guidance documents aids in regulating the products into drugs, devices or biologics with appropriate information using a risk-based method:

1. Minimal Manipulation and Homologous use for regenerative medicine.
2. Same Surgical Procedure.
3. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions.
4. Evaluation of Devices used with RMAT.⁶
 - Human cells, tissues, and cellular and tissue-based products (HCT/P) includes human cells that are expected to implant, transplant, infuse or transmission of HCT/P into a human receiver as defined in 21 CFR 1271.
 - Due to their unique nature and risk-based approach, FDA implemented HCT/P regulation and so tissues are regulated under the public health service act of section 361.
 - According to Section 361, the product has to be regulated to avoid the spread of transmissible diseases; as per 21 CFR 1271, the HCT/P's need not require pre-market approval, and has to identify the manufacturing, reporting, and registration process.
 - Product which does not fall under 21 CFR 1271.10 OR qualified for an exception under 21 CFR 1271.15 are regulated under Section 361 and Section 351 of the Public Health Service Act as well as Part 1270 and Part 1271 of the FD&C Act.⁷

FIRST GUIDANCE: Regulatory Considerations for HCT/P: Minimal Manipulation and Homologous use.

The guidance aims to determine whether the HCT/P justifies the various criteria which have to be regulated under or as section 361 or not. The “Regulatory considerations for human cells, tissues, cellular and tissue-based products: Minimal manipulation and homologous use” guidance talks the use of various criteria which is listed in 21 CFR 1271.10 (a)(1) and 21 CFR 1271.10(a)(2). Under Sec 361 of the Public Health Service (PHS) Act the 21 CFR 1271.10 gives various criteria on what the HCT/P is regulated and 21 CFR 1271 are (Figure 3):

1. HCT/P are slightly changed.
2. HCT/P which is meant only for homologous usage, the manufacturer's objective intent has to be indicated on the labeling, advertising, or other indications.
3. The HCT/P manufacturer should not combine with the cells or tissues with another article with exception to the water, crystalloids, sterilizing agent, preserving agent, or a

storage agent. In case, such that the other articles wouldn't rise any new clinical safety outcomes.

4. Moreover:
 - HCT/P shouldn't have any systemic outcome and shouldn't hook onto the functional action of the cells for its major functions.
 - HCT/P have a systemic outcome or it is hooked on the functional activity of the cells for its major function,
 - » it is aimed only for the autologous usage
 - » it is only aimed only for the allogeneic usage in a 1st degree blood relative or 2nd degree blood relative disorder
 - » it is meant only for the reproductive usage⁽⁷⁾

SECOND GUIDANCE: Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and answers regarding the scope of the exception.

This guidance provide FDA's recent idea on the “Same surgical procedure exception” which is mentioned in 21 CFR 1271.15(b) Q/A set up and should not mention any added exemptions.

The criteria to apply for the exemption are:

1. Process of implantation has to be steered in the same surgical method.
2. HCT/P are removed and also it has to be implanted into the same person.
3. The HCT/P should be in its original form.

“Same surgical procedure,” says the removal and implantation of HCT/P inside the same patient. This process is also known as the autologous process. In addition, at some situations the removal and implantation process of HCT/P takes place after some days, and also the same association must deal with the implantation procedure as during the transportation it can lead to contamination. FDA has implemented the guidance for those procedures. HCT/P guidelines in the third criteria, HCT/P manipulations clearly state the process such as washing, cleansing, reducing, and structural changes. In case the manipulation observed to be minimum which comes under 21 CFR 1271.10(a) result in a way that HCT/P is never again considered as “such HCT/P” this renders, the exception unacceptable.⁷

THIRD GUIDANCE: Expedited Programs for Regenerative Medicine Advanced Therapy (RMAT).

FDA has published the RMAT under 21st Century Cures Act under sections 3033 – 3036

- “Section 3033” Designation for regenerative medicine advanced treatments
- “Section 3034” Guidance for the device which is used in the retrieval process, separation method, or transfer of regenerative medicine advanced treatments.
- “Section 3035” Compulsory yearly FDA report on regenerative medicine advanced treatment Department of Health and Human Services (HHS) in coordination with the
- “Section 3036” Guides in the advancement of standards for regenerative medicine therapies by the National Institute of Standards and Technology (NIST) and sponsors

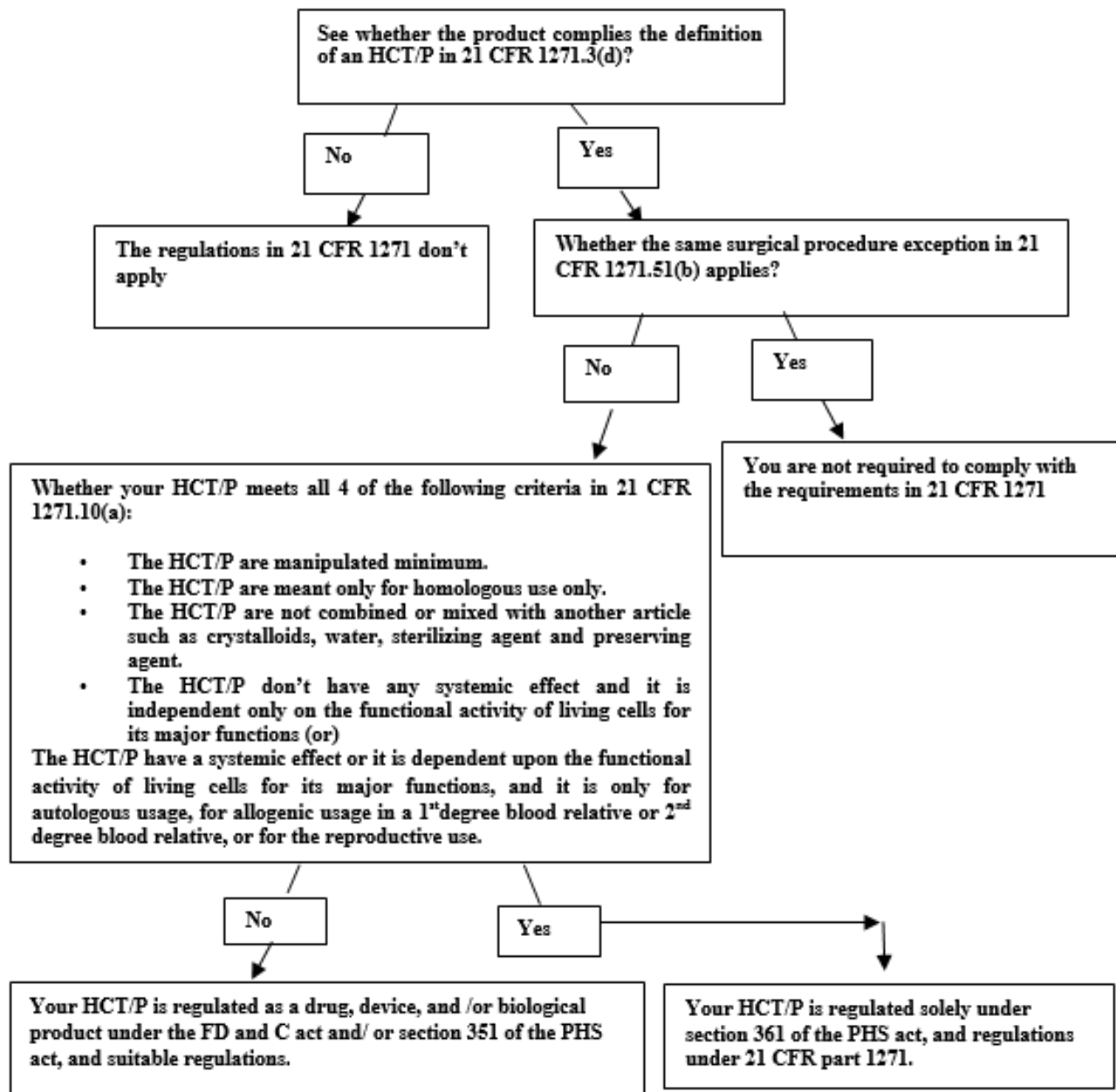


Figure 3: Flowchart demonstrating the Application of the Criteria in 21 CFR 1271.15 and 1271.107

Expedited Programs for RMAT's, "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions" includes five programs such as,

1. Even with preliminary evidence for the investigational products which is meant for serious conditions, facilitates the faster review process and submission process and that is known as the fast track designation process (FTDP).
2. A treatment which is intended for treating a severe condition which only has preliminary clinical evidence over the existing treatments, at least any one clinical endpoint will be eligible for the fast track designation process and that process is known as Breakthrough Therapy Designation.
3. According to the 21st Century Cures Act under Section 3033, the Regenerative Medicine Advanced Therapy designation was instigated, which talks about that the RMAT which is used for the treatment, modification, therapy for a serious problem with available scientific report to talk about the medical needs. The advantage of getting the designation has all provisions those of FTDP, Breakthrough Therapy Designation process, in addition to the post-approval requirements alternative options, and faster review and approval process.
4. The product which has FTDP, Breakthrough Therapy Designation process with valid clinical evidence is given with Primacy review designation. This Primacy review designation shortens the time frame of the Centre for Biologics Evaluation and Research (CBER) to 6 months.

5. Treatment which has a meaningful advantage over the current existing therapy for a serious condition even with preliminary clinical data accelerated approval is given but post-approval studies are done.^{3,7}

FOURTH GUIDANCE: Evaluation of Medical Devices used with RMAT.

- According to the 21st Century Cures Act under Section 3034 recommends to all the manufacturers of medical devices which is used in the regenerative medicine advanced therapy such as for “recovery, isolation or delivery of regenerative medicine advanced therapies” has to be evaluated.
- Based on the technology used in the medical devices and the devices intended use in the regenerative medicine advanced therapy the regulatory pathway varies.
- According to section 513 of FD&C Act, the pre-market pathway differs according to the classification of certain medical device and are:

Class I	General controls
Class II	General and special controls
Class III	Premarket approval of medical devices

- With the threat of the medical devices, valid safety and effectiveness assurance is provided.
- This guidance helps to understand the regulatory pathways to get marketing authorization of the medical devices and premarket notification (510 k).
- Possibility of fast approval procedure of a medical device used in the regenerative medicine advanced therapy, and so for the first time the medical devices used for the regenerative medicine advanced therapy is accepted. It also raises the question that the accelerated approval of medical devices only apply to the same manufacturer who created regenerative medicine advanced therapy or whether FDA is planning to launch certain information or guidelines that can support for the subsequent applicant.⁽⁷⁾

CLINICAL TRIAL PROCESS:

- In US and EU, the clinical trial process is much different.
- In EU, to conduct clinical studies the manufacturer or applicant has to submit the application to their respective regulatory authority in each member state, to get permission to conduct clinical studies.
- In US, the manufacturer has to get approval from FDA and also from the Institutional Review Board (IRB) before a clinical studies is conducted that involves HCT/P.⁸

US market grows faster because of the growing demand for tissue-engineered and stem cells products for the prevention of various diseases. The potential of regenerative medicine in the diseased organ is one of the major factors that drive the market in US. The other factor is US has more vendors and sponsors. Growth is restricted due to regulatory and ethical issues in the related fields such as stem cells, gene therapy and tissue engineering. So, the introduction of changes in

regulatory is projected to reduce the impact of these barriers over the forecast period.⁽²⁾

CONCLUSION

Over the years, the advancement in the cutting-edge therapies has strengthened and various new products are in developing stages but there is a regulatory barrier. Thus a better and clear guidance or a clear regulatory framework for both regenerative medicine and medical device in regenerative medicine can lead to the development of an effective product with the best clinical fit and product access in the market.

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