OVERVIEW ON REGULATORY FRAMEWORK FOR CELLULAR, TISSUE AND GENE PRODUCTS IN EUROPE, US AND JAPAN

Aakashdeep Raval\(^1\) and Dr. Dilip Maheshwari\(^2\)*

\(^1\)Dept. of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad.

\(^2\)Head of the Department, Dept. of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad.

ABSTRACT

Purpose: In this modern era, diseases are developing in complex way and thus advanced therapies are essential to cure and prevent the diseases presently a day, because of nonexclusive rivalries and numerous issues center of pharma organizations has changed towards biological products, personalised medicines, targeted drugs especially cellular products, gene products and tissue engineered products. They are also known as advanced therapy medicinal products (ATMPs) or regenerative medicines. Method: Regenerative medicines are used to treat various diseases such as Alzheimer’s disease, Arthritis, Parkinson’s disease, nerve degeneration, cancers. They primarily derived from Biological creatures, animal tissues or modified human tissues. They may be of patients own cell or tissue or may be of diverse benefactors. So they are differing in their adverse reactions and their characteristics. They are not chemically synthesised molecule so regulations and quality controls tests for conventional medicines are not pertinent to them. Each nation has its own regulations of biologics in their own particular way as per their requirements. Mainly developed Countries designed regulations for their own country. Since it is extremely late strategy, harmonization for these regulations between all these nations has not been established yet. EMA, FDA and PMDA regulate these products respectively in EU, US and Japan. So database from their respective websites are used for this article. Result and Conclusion: This article will give overview of regulations and regulatory authorities, review committees and their regulatory framework for cellular, tissue and gene products in Europe, US and Japan.
KEYWORDS: Regulatory Framework, ATMP, HCT/Ps, Regenerative Medicines, Cellular Products, Gene Therapy, Tissue Engineered Products.

INTRODUCTION [1,2,3]
Medicines are constantly utilized since the people came in presence. From the most recent century, medicines are produced and/or blended artificially for the human and creature employments. Earlier, the medicines were utilized just to cure the sicknesses/diseases, which, now in present day period, are additionally used to keep the ailments and even to upgrade the life compass and in addition to enhance the life cycle. In this modern era, diseases are developing in complex way and thus advanced therapies are essential to cure and prevent the diseases. Now a day, a focus of pharma companies has changed towards Biological products.

Biologics have supplanted little particles as the overwhelming center of enormous pharma's pipeline. In 2012, around 40% of all biological products in clinical improvement were created by huge pharma, up from 15.2 % in 2000. Biotech items represented just 7% of income produced by the main ten medicines worldwide in 2001, yet made up 71% of that income in 2012. Over a comparative period, biotech products deals more than quadrupled, financing of biotech examination expanded tenfold, and the sum put resources into pharma-biotech research cooperation expanded six fold. Pharma has drastically moved its R&D technique from a very nearly particular concentrate on little particle tranquilizes in the early 1990s to a predominant concentrate on biotech items today. Driving the change are biological products novel systems of activity and capacity to charge high costs, joined with the declining patent lives of small conventional medicines. [4]

Patients over 65 years account for two-thirds of health care costs in Europe, U.S., and Japan. The aging patient is a chronic disease patient. Current treatments are just palliative and don’t address the basic disease state. Macular Degeneration, Arthritis, Hypertension, Nerve Degeneration these are some examples which can be treated by regenerative medicines which are the future of pharma for next 30 years. Allograft cell-based products generated more than $200 million in hospital purchases in 2013 only in US. More than one million U.S. patients have received allograft or autologous stem cell treatment last year. So the focus of the present study is to understand the regulation of Cellular Products, Gene Therapy and Tissue Engineered products in these countries.
Traditionally the medicines were being synthesized chemically and they were developed as small molecules, whereas, biologics are developed from living organisms or animal cells and tissues. Since the biologics are developed from humans and/or animals, the pharmacological actions are known and so they are designed to work according to our need. As the biologics are larger molecules, studies regarding to toxicity and impurity are difficult to carry out. Thus, the regulations have been developed for the traditional medicines cannot be implemented on the biologics.

Though biologics is a tremendous field, the fundamental concentrate in creating the pharmaceuticals are hereditary qualities (genetics), cell items and tissue designed products which are continuously delivered by modifying/adjusting qualities, cells and tissues of humans and animals. Each nation has made regulations of biologics in their own particular way. Since it is extremely late strategy, harmonization between all the nations has not been established yet.

DEFINITIONS [5]

**Gene Therapies**
Gene therapy alludes to products acquired through a set of manufacturing processes aimed for the exchange, to be performed either ex vivo or in vivo, of a prophylactic, diagnostic or therapeutic gene, to human / animal cells and its resulting articulation in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral or non-viral origin. The vector can likewise be incorporated in a human or animal cell.

**Somatic Cell therapies**
Somatic cell therapy incorporate the utilization in humans of autologous (originating from the patient himself), allogeneic (originating from alternative individual) or xenogeneic (originating from animals) somatic living cells, the biological attributes of which have been significantly changed as a consequence of their manipulation to obtain a therapeutic, diagnostic or preventive impact through metabolic, immunological and pharmacological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo, the utilization of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo.
Tissue Engineered Products

Tissue Engineered Products will be products that contain or comprise of engineered cells or tissues, and is displayed as having properties for, or is utilized as part of or administered to human beings with a perspective to regenerating, repairing or supplanting a human tissue. A tissue product may contain cells or tissues of human or animal origin. The tissue or cells may be viable or may be non-viable. It might likewise contain additional substances, for example cellular products, bio-molecules, biomaterials, synthetic substances, matrices or scaffolds.

Table 1: Examples of Approved Products under Cellular, Tissue and Gene Therapy

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Product</th>
<th>Class of product</th>
<th>Use of Product</th>
<th>Approved Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>MACI[^8]</td>
<td>Combined ATMP</td>
<td>Knee cartilage defects</td>
<td>EU</td>
</tr>
<tr>
<td>3</td>
<td>Proveenge[^9]</td>
<td>Somatic Cell</td>
<td>For Prostate cancer</td>
<td>EU, US</td>
</tr>
<tr>
<td>4</td>
<td>Carticel[^10]</td>
<td>Cellular Product</td>
<td>Knee Cartilage defects</td>
<td>US</td>
</tr>
<tr>
<td>6</td>
<td>JACC[^12]</td>
<td>Tissue Product</td>
<td>For cartilage defect</td>
<td>Japan</td>
</tr>
<tr>
<td>7</td>
<td>JACE[^13]</td>
<td>Cultured Epidermis</td>
<td>Burn Treatments</td>
<td>Japan</td>
</tr>
</tbody>
</table>

METHOD AND MATERIAL (WORKDONE)

REGULATIONS OF BIOTECH PRODUCTS IN EUROPE

The European Union (EU) is a politico-monetary union of 28 part expresses that are fundamentally placed in Europe. The EU works through a system of supranational independent institutions and intergovernmental negotiated decisions by the member states. The European Medicines Agency is a decentralized office of the European Union, spotted in London. It was first named in 1993 as the European Agency for the Evaluation of Medicinal Products (truncated to European Medicines Evaluation Agency, or EMEA). It renamed in 2004 as the European Medicines Agency, however held the acronym EMEA. Toward the end of 2009, changed the acronym to EMA. The Agency is in charge of the investigative assessment of medicines created by pharmaceutical organizations for utilization in the European Union. It started working in 1995.^[14]
The cellular, Tissue and Gene products are overseen in EU as advanced therapy medicinal products (abbreviated as ATMPs). The regulatory framework for ATMPs is established in Regulation (EC) No 1394/2007. The unlucky deficiency of a broad managerial structure in the past provoked unique national methodologies which thwarted patients' right to gain entrance to products hampered the development of this emerging industry and eventually affected EU competitiveness in a key biotechnology area. The EU institutions are agreed on a Regulation on advanced therapies designed to ensure the free movement of advanced therapy products within Europe, to encourage access to the EU market and to cultivate the aggressiveness of European organizations in the field, while ensuring the largest amount of health protection for patients.

The main elements of the Regulation are. [15]

- A centralised marketing authorisation approach, to benefit from the pooling of expertise at European level and direct access to the EU market.
- Committee for Advanced Therapies (CAT) was established to assess advanced therapy products and follow scientific developments in the field.
- Technical prerequisites adjusted to the specific attributes of these items.
- Special incentives in fees of processing for small and medium-sized enterprises.

This Regulation additionally denotes the distinction that various advanced therapy products actually combine biological materials, for example tissues or cells, and chemical structures for example metal implants or polymer scaffolds. These combination products lie at the fringe of the traditional pharmaceutical territory and different fields (e.g. medical devices). They therefore cannot be regulated as 'conventional' drugs and need adjusted
prerequisites. In addition, it should be borne in mind that a significant share of economic operators involved in this field are not large pharmaceutical companies, but small and medium-sized enterprises or hospitals.

The ATMP Regulation engaged the Commission to receive particular prerequisites in regards to the, good manufacturing practices, marketing authorisation applications, good clinical practice, and the traceability of ATMPs. Furthermore, an amended Guideline on good manufacturing practice containing specific adaptions for ATMPs applies since 31 January 2013. Notwithstanding, the selection of particular necessities with respect to good clinical practice and traceability is as of now pending as extra experience was esteemed important to better comprehend the kind of adjustments needed.

Table 2: Key Regulations in EU [16]

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC No 1394/2007</td>
<td>Regulation for Advanced Therapy Medicinal Products, i.e. rules regarding authorisation, supervision and pharmacovigilance</td>
</tr>
<tr>
<td>EU 2004/23/EC</td>
<td>Human Tissue and Cells Directive. This applies where the ATMP contains human cells and covers donation, procurement and testing of stem cells.</td>
</tr>
<tr>
<td>EU 2003/94/EC</td>
<td>Good Manufacturing Practice for Medicinal Products. Products must comply with this directive and also with the European Commission’s new GMP guidelines for ATMPs, which take into account their specific manufacturing processes.</td>
</tr>
<tr>
<td>EU 2001/20/EC</td>
<td>Clinical Trials Directive, to implement Good Clinical Practice.</td>
</tr>
<tr>
<td>EU 2001/28/EC</td>
<td>Good Clinical Practice for Medicinal Products</td>
</tr>
<tr>
<td>EU 2001/83/EC</td>
<td>Medicinal Products for human use (includes 2003/63/EC, 2004/27/EC and Advanced Therapy Regulation). This includes the patient’s right to know the origin of the ATMP cells but at the same time respect donor anonymity.</td>
</tr>
<tr>
<td>93/42 OR 90/385</td>
<td>If the ATMP is a combination product it must include a description of the product’s physical characteristics, performance and design methods</td>
</tr>
</tbody>
</table>

Another Review and direction council was created as per Regulation (EC) No 1394/2007 on ATMPs. The Committee for Advanced Therapies (CAT) is the panel at the European Medicines Agency that is in charge of surveying the quality, security and adequacy of cutting edge help restorative items (ATMPs) and taking after exploratory advancements in the field.
It is a multidisciplinary advisory group, assembling a percentage of the best accessible masters in Europe.

The principal commitment of the CAT is to situated up a draft assumption on every ATMP application submitted to the European Medicines Agency, before the Committee for Medicinal Products for Human Use (CHMP) receives a last assessment on the conceding, variation, suspension or renouncement of an marketing authorisation for the drug concerned. At the sales of the EMA Executive Director or of the European Commission, a conclusion is similarly drawn up on any investigative matter relating to ATMPs. \[^{17}\]

**REGULATIONS OF BIOTECH PRODUCTS IN US**

The Food and Drug Administration (FDA or USFDA) is a government organization of the United States Department of Health and Human Services, one of the United States elected official divisions. The FDA is in charge of securing and advancing general wellbeing through the regulation and supervision of food products safety tobacco items, dietary supplements, solution and over-the-counter pharmaceutical medications, antibodies, blood transfusions, biopharmaceuticals, electromagnetic radiation radiating devices (ERED), Medical Devices, beauty care products, animal nourishments & food and veterinary medicines. \[^{18}\]

FDA regulates biologics as per the following.

- Cellular & Gene Therapy Products
- Tissue & Tissue Products
- Vaccines
- Blood & Blood Products
- Allergenics
- Xenotransplantation

**The Centre for Biologics Evaluation and Research (CBER) \[^{19}\]**

CBER is the Centre inside FDA that controls biological products for human use under appropriate government laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. CBER secures and propels the public health by guaranteeing that biological products are sheltered and effective and accessible to the individuals who need them. CBER additionally gives general society data to advance the sheltered and suitable utilization of natural items. CBER has an office particularly for these sorts of items which is known as "Office of Cellular, Tissue, and Gene Therapies (OCTGT)" There are three survey
divisions in OCTGT. The Division of Cell and Gene Therapies is by a wide margin the biggest. This division contains both review and research/review scientists. The research center part leads mission-important research and additionally audit of administrative records.

Products regulated by Office of Cellular, Tissue, and Gene Therapies \[^{20}\]
- Gene therapies
- Cellular therapies
- Tissue and tissue based products
- Combination products
- Anti-idiotype antibodies
- Tumor vaccines
- Devices used for cells/tissues
- Xenotransplantation products

**Cell & gene therapy regulation \[^{21}\]**
The Center for Biologics Evaluation and Research (CBER) steers cell help items, human quality treatment items, and certain gadgets identified with cell and quality help. CBER used both the Public Health Service Act and the Federal Food Drug and Cosmetic Act as enabling statutes for oversight. Cellular products incorporate cell immunotherapies, and different sorts of both autologous and allogeneic cells for certain therapeutic signs, including grown-up and embryonic immature cells.

Human gene therapy help alludes to products that bring hereditary material into an individual's DNA to supplant broken or missing innate material, along these lines treating a sickness or atypical therapeutic condition. Albeit some cellular therapy products have been endorsed, the amount of cellular and gene therapy-related research and development occurring in the United States continues to grow at a fast rate. CBER has gotten numerous solicitations from restorative specialists and makers to study cellular and gene therapy and to create cellular and gene therapy products. Notwithstanding administrative oversight of clinical studies, CBER gives proactive experimental and administrative guidance to therapeutic researchers and producers in the zone of novel products advancement.

**Tissue Engineered Products \[^{22}\]**
Human cells or tissue planned for implantation, transplantation, mixture, or move into a human beneficiary is controlled as a human cell, tissue, and cell and tissue-based products or
HCT/P. The Center for Biologics Evaluation and Research (CBER) directs HCT/Ps under 21 CFR Parts 1270 and 1271. Illustrations of such tissues are bone, tendons, skin, heart valves, cornea, dura mater, ligaments hematopoietic stem/begetter cells got from fringe and cord blood, oocytes and semen. CBER does not direct the transplantation of vascularized human organ transplants like kidney, liver, heart, lung or pancreas.

The Health Resources Services Administration (HRSA) supervises the transplantation of vascularized human organs. Parts 1270 and 1271 oblige tissue foundations to screen and test benefactors, to get ready and take after composed methods for the anticipation of the spread of transmittable malady, and to keep up records.

FDA has distributed three last controls to widen the extent of items subject to regulation and to incorporate more far reaching prerequisites to keep the presentation, transmission and spread of transmittable infection. One last lead obliges firms to enlist and rundown their HCT/Ps with FDA. The second lead obliges tissue foundations to assess givers, through screening and testing, to diminish the transmission of irresistible ailments through tissue transplantation. The third last lead secures current great tissue hones for HCT/Ps. FDA’s re-examined regulations are contained in Part 1271 and apply to tissues recuperated after May 25, 2005. The new prerequisites are proposed to enhance assurance of the general wellbeing while minimizing administrative trouble.

Table 3: Key US regulations [23]

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA FORM 3674</td>
<td>New provisions require additional information to be submitted to Clinical Trials. Gov. and the application must be accompanied by a certification that all applicable requirements of section 402(j) of the Public Health Service Act has been met.</td>
</tr>
<tr>
<td>21 CFR 1270</td>
<td>Human tissue intended for transplantation.</td>
</tr>
<tr>
<td>21 CFR 1271</td>
<td>Human cells, tissues, and cellular and tissue-based products.</td>
</tr>
<tr>
<td>21 CFR 210</td>
<td>Current Good Manufacturing Practice in Manufacturing, Processing, Packaging or Holding of Drugs.</td>
</tr>
<tr>
<td>21 CFR 211</td>
<td>Current Good Manufacturing Practice for Finished Pharmaceuticals.</td>
</tr>
<tr>
<td>21 CFR 58</td>
<td>Good Laboratory Practices for Nonclinical Laboratory studies.</td>
</tr>
</tbody>
</table>

REGULATIONS FOR BIOTECH PRODUCTS IN JAPAN

Japan has two administrative powers, one is MHLW-Ministry of Health, Labor and welfare and another is PMDA- Pharmaceuticals and Medical Devices Agency. The Ministry of Health, Labor, and Welfare (MHLW) was created by a merger of the Ministry of Health and
Welfare (MHW) and the Ministry of Labor, on January 6, 2001 as a major aspect of the legislature program or rearranging government services. The MHLW, which was initially settled in 1938, has been accountable for the change and advancement of social welfare, standardized savings and general wellbeing, and the new association has the same undertakings. It comprises of the service fitting, associated foundations, boards, nearby extensions, and an outside association. The part of the PMDA is to give meetings concerning the clinical trials of new medications and therapeutic gadgets, and to lead approbation surveys and studies of the dependability of use information. MHLW is for arranging essential arrangement, regulatory measures while PMDA is for audit examination and information investigation. PMDA has an office of Cellular and Tissue based items which are focus and Bio-item subcommittee for item assessment for CTBPs- Cellular and Tissue-based Products.

Cell, Tissue and Gene products are managed as Orphan drugs and therapeutic gadgets till 2012 in Japan. Presently, Japan has built new regulations and law name as the regenerative medicines law in 2013 suitable for cell tissue and organic items which is implemented to secure their safety and to quicken their advertising. It likewise settled another dynamic regard pathway for these products.

![Fig. 2: New Approval Process of Regenerative Medicines in Japan [25]](image)

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly approved main Regulation</td>
<td>The Regenerative Medicine Law 2013</td>
</tr>
<tr>
<td>Notification No.0208003</td>
<td>Guideline on Ensuring Quality and Safety of Products Derived from Processing Human (Autologous) Cells/Tissue</td>
</tr>
<tr>
<td>Notification No.0912006</td>
<td>Guideline on Ensuring Quality and Safety of Products Derived from Processing Human (Allogeneic) Cells/Tissue</td>
</tr>
</tbody>
</table>
RESULT

From above all database study following can be concluded.

Table 5: Comparisons of Regulatory Framework for Cellular, Tissue and Gene Products in EU, US and Japan.

<table>
<thead>
<tr>
<th>Regulatory authority</th>
<th>EUROPE</th>
<th>US</th>
<th>JAPAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review committee</td>
<td>CAT</td>
<td>CBER</td>
<td>PMDA</td>
</tr>
<tr>
<td>Classification</td>
<td>ATMP</td>
<td>HCT/Ps</td>
<td>Regenerative Medicines</td>
</tr>
<tr>
<td>Regulations</td>
<td>EC regulation 1394/2007</td>
<td>21 CFR Part 1270</td>
<td>The Regenerative Medicines Law</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 CFR Part 1271</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

Cellular Products, Gene Therapy and Tissue Engineered Products are same in creation and their use still every country has its own particular regulations with a few differentiations and a similitudes. Every one of them is covered however not blended. The advancement course for ATMPs for regenerative treatments infrequently takes after an established pharmaceutical track. One eccentricity is the unlucky deficiency of concentrate on particular evidences at the start. Rather, starting innovative work has a tendency to be centred on the foundation and characterization of 'practical, organically dynamic units' that are fit for producing or repairing tissue. Developers will consequently at first focus on tissue-related capacity and afterward on quality and wellbeing. For these novel methodologies 'proof of concept' preclinical work will frequently be performed, whilst keeping evidence choices open. Controllers can assume a major role in controlling and supporting improvement of ATMPs to guarantee that the field survives. So Harmonization or Guidance or a center approach to satisfy necessities of controllers is required.

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