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Current global trends in regulations for stem cell therapy and the way ahead for India

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Abstract

In the last issue of this journal we had published an article 'The need to review the existing guidelines and proposed regulations for stem cell therapy in India based on published scientific facts, patient requirements, national priorities and global trends' on the need of new regulation for Stem Cell therapy in India. We had highlighted the deficiencies in the existing guidelines and suggested broad general principles on which new regulations should be framed. Worldwide countries have realized the need for newer regulations that are more permissive of stem cell therapy. Most progressive legislation is that of the USA (REGROW Act) and JAPAN (PMD Act and ASRM), which allows conditional, fast track marketing approval for stem cell products and separate monitoring systems for cell therapies based on their risk to human life and health. The Korean Regulations have excluded minimally manipulated cells from their 'Review and authorization of Biological products'. European medical agency (EMA) has also come up with the advanced therapy medical product (ATMP) laws, PRIME (PRIority MEdicines) act and Hospital Exceptions (HE) act that are also favourable to newer therapies such as regenerative medicines. New concepts and terms that are now becoming part of the more permissive regulations are Conditional marketing approval, Risk Stratification, Post-Hoc efficacy analysis, Presumed efficacy, Patients' right to seek treatment, Distinction between cellular therapies, Distinction between a stem cell product and medical service.

In sharp contrast to this, in India the latest guidelines made by Indian council of Medical Research (ICMR) are moving backward and are in the process of trying to implement policies that will completely destroy the stem cell therapy field in India. The Major limitation in the current guidelines is that the ICMR does not differentiate between a product and a medical service. The current regulatory policies which are in favor of corporates who can spend large amounts of money and which discourages or prevents those who cannot spend large amounts of money is not in the national interest of our country.

In this paper we elaborate on a road map that Indian regulators should take in order to facilitate easy availability of cellular therapies to patients suffering from incurable disease but ensuring at the same time that only safe therapies are provided. We suggest that there should be 3 categories; Researchers who would be regulated under ICMR guidelines, Corporate stem cell product manufacturers who would follow Central Drug Standard Control Organizaion (CDSCO)/ Drugs controller general (India) [DCG(I)] do therapy subject to IEC approval, Medium risk cell therapy providers such as more than minimally manipulated allogeneic would in addition need approval from IEC and CDSCO and those using high risk cell therapies such as embryonic and iPSCs would need IEC, CDSCO and ICMR approval.

We conclude that the ministry of health along with ICMR and CDSCO need to study the REGROW Act of USA as well as the Japanese and Korean legislations for regenerative medicine and come up with a definitive set of regulations which are permissive of medical practitioners offering safer forms of cellular therapies like autologous and minimally manipulated therapies and stricter regulations for more unsafe cellular therapies and corporates producing and selling stem cells as

a product. This will result in only safe treatments being available as therapy and at the same time ensure that patients suffering from serious medical conditions are not deprived of stem cell therapies that can help them.

Key words: *Stem cell therapy, cellular therapy, regulation, conditional marketing approval, presumed efficacy, compassionate use, Helsinki declaration, Japan regulations, Korea regulations, REGROW ACT.*

Introduction:

Over the last century in the field of medical practice there were two broad categories of regulations first for drugs and devices and second for medical procedures. Whereas drugs and devices have always been heavily regulated, medical procedures by and large did not come under the purview of regulators and it was left to individual physicians and surgeons to offer to their patients what in their view was the best medical practice. The evolution of stem cell therapy has created a peculiar problem because there are stem cell therapy related medical products as well as stem cell therapy that are offered as medical service. This has created a situation where it is difficult to have regulations for cellular therapy that are as strict as those for drugs and medical devices but at the same time give freedom and flexibility to medical practitioners to offer this as medical service. This difficulty has led to very strict regulations in countries where Stem Cells are considered as a biological product and therefore stem cell therapies are not available in such countries and on the other hand in some countries stem cell therapy are being offered without oversight.

In the last issue of this journal we had published an article 'The need to review the existing guidelines and proposed regulations for stem cell therapy in India based on published scientific facts, patient requirements, national priorities and global trends' on the need of new regulation for Stem Cell therapy in India.(1) We had highlighted the deficiencies in the existing guidelines and suggested broad general principles on which new regulations should be framed. We reviewed the regulations of different countries and compared it with the current regulations in India. Various dissimilarities were highlighted and suggestions for the changes in the Indian guidelines were made based on the regulations in other countries. In the current scenario countries worldwide have realized the need for newer regulations that are more permissive of stem cell therapy.

In the one year since we wrote the article, the most dramatic transformation is happening in the USA where a completely new law called the Reliable and Effective Growth for Regenerative Health Options that Improve Wellness Act (REGROW Act) is under consideration by their Senate.(2)

Evolution of regulatory framework for regenerative medicine in the United States of America (USA)

The original guidance regarding use of tissue products was drafted and approved in 1996. In the subsequent year (1997) a separate code of federal regulation (CFR) 1271 was drafted to regulate these products. (3) These were classified under Human cells and tissue and cellular and tissue based products HCT/Ps in this CFR which made a clear distinction between a 'drug' which is a chemical molecule from these biological products. The products were further classified as biological products or medical devices based on difference criteria and a separated set of regulations was drafted for both.These guidelines took into consideration the differences not only between the type of cells but also between the procurement procedures and routes of administration that may significantly alter the safety and efficacy profile of the cells. Although the classification was primitive and inadequate, it was based on the available body of evidence and existing trends and concepts for monitoring development of new therapeutic drugs. The products were classified into; minimally manipulated cells, defined as, cells that do not alter their relevant biological characteristics (due to the technique and/or chemicals used to procure them) and more than minimally manipulated cells. The regulations also differentiated between the route of

administration as homologous and non-homologous use. Homologous use was defined as the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

These products were regulated by 2 governing laws, first, Public health services act (PHS) which mandated that any new biological product for licensing will be required to produce the data from clinical study or studies that demonstrate the safety, purity and potency of the cells. (4) However, the guidelines did not define what type of studies or number of patients will be considered appropriate for demonstrating this.

The 21CFR 1271.15 clearly stated that minimally manipulated cells used for non-homologous use will be exempted from the regulatory requirements of FDA for marketing approval if the cells and procured and transplanted in the same surgical procedure. Another provision in the 21CFR 601.40 allowed for the accelerated approval for serious or life threatening illness. This was applicable to certain biological products that had been studied for safety, efficacy and provided meaningful therapeutic benefit to the patients over existing treatment. In accordance with these guidelines various autologous regenerative medicine products that were used for homologous use were approved and licensed in USA between1997 to 2011.

Between the years 2011 and 2015 in the view of growing clinical evidence for stem cell therapy, Right to try act was designed. Although the regulations prevented generalized marketing of regenerative medicine products up till 2015, after the introduction of Right to try act marketing of experimental drugs for the terminally ill patients was allowed on a case by case review basis.(5)

The act quoted, "Notwithstanding the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), the Controlled Substances Act (21 U.S.C. 801 et seq.), and any other provision of Federal law, the Federal Government shall not take any action to prohibit or restrict the production, manufacture, distribution, prescribing, dispensing, possession, or use of an experimental drug, biological product, or device that (1) is intended to treat a patient who has been diagnosed with a terminal illness; and (2) is authorized by, and in accordance with, State law."

Recently based on the growing clinical evidence for the use of cellular therapy for the treatment of various incurable disorders, Senator Mark Kirk introduced a bill to amend the Federal food, drug and cosmetic act; in front of committee on Health, Education, Labor and Pensions, in 114th congress of the American senate. The amendment was named Reliable and Effective Growth for Regenerative Health Options that Improve Wellness act, REGROW Act. (2)REGROW act alters the current regulatory framework to provide conditional marketing approval to minimally manipulated cells for non-homologous use and more than minimally manipulated cells without going through the formal procedure of approval as per section 351 (A) of part F of Title III of PHS law. Subsequently it is required that the licensing application be filed in the next 5 years, based on the post marketing research, as per section 351 (A) of part F of Title III of PHS law. The cells and products exempted under these conditions are described in detail in the REGROW act as, "

(1) Such cells or tissues are adult human cells or tissues.

(2) Such cells or tissues have been evaluated to examine immunogenicity and do not provoke a significant unintended immune response in the recipient.

(3) Such cells or tissues are -

a. minimally manipulated for a non-homologous use; or

b. more-than-minimally manipulated for a homologous or non-homologous use, but are not genetically modified.

(4) Such cells or tissues are produced for a specific indication.

(5) Such cells or tissues are produced exclusively for a use that performs, or helps achieve or restore, the same, or similar, function in the recipient as in the donor.

(6) Within 5 years of the safety and effectiveness determination described in his section, the sponsor of the conditionally approved new

product prepares and submits an application for approval of a biological product under section 351(a), demonstrating potency, purity, safety, and efficacy of the use. The Secretary may permit continued use of such product until the Secretary completes the review of the application and makes a determination. Upon a determination by the Secretary not to approve the application, use of the cellular therapeutic shall not be permitted.

(7) During the conditional approval period and before approval of an application under section 351(a), the sponsor shall prepare and submit annual reports and adverse event reports to the Secretary containing all the information required for approved biological products.

(8) The sponsor has submitted an application under section 505(i) of the Federal Food, Drug, and Cosmetic Act for the treatment of the patients during the 5-year conditional use period.

(9) The sponsor has not previously received conditional approval for such product for the same indication."

Although REGROW Act is uniformly applicable to stem cell products as well as stem cell therapies the highlight of this act is A] Conditional marketing approval and B] Provision for post-hoc efficacy analysis. (2) This relieves the burden of the evidence from newer upcoming cellular therapies and products. It allows medical innovators and practitioners to develop promising therapies without having to go through phased approval process as before. The proposed law has created criteria to protect patients from unsafe therapies. This ensures easy and faster availability of promising cell therapies to patients that can benefit from them without any risk of adverse effects.

Once this law is implemented the principles of Conditional marketing approval and Provision for post-hoc efficacy analysis will become part of the regulations.

Evolution of regulatory framework in Japan

Japan took the first big step in 2014 when they modified their already existing medical law, Pharmaceuticals Affairs Law (PAL) through a partial amendment named as Pharmaceuticals and Medical Devices Act (PMD Act) under the act on promotion of regenerative medicine. (6) Till 2014 there was no statutory body in Japan for monitoring regenerative medicinal products. All the medicinal drugs and products were regulated under the general pharmaceutical regulations. In the same year another law that was formulated and implemented, Act on Safety of Regenerative Medicine (ASRM).(7) ASRM safeguarded the patients from unsafe cellular therapies. In these two laws they have made a clear distinction between the companies that make stem cell products, institutes that offer medical services and medical research. They have introduced the concept of conditional marketing for medical products and separate approval systems based on the risk stratification for the medical services. This for the first time ensured separate legislation for stem cell therapy products and medical devices and stem cell therapies offered as a treatment by individual practitioners and institutes.

When looking at the Japanese regulations, following points stand out

(A) Regulations for the product

(B) Regulations for the medical services and research (stem cell services)

(A) Regulations for the product:

Companies wishing to use Stem Cell products don't have to go through the earlier regulatory pathway of the phase I and phase II clinical trials.(6) Conditional approval process bypasses the conventional phased clinical trials before approval and requires only the preliminary safety studies that show the efficacy is likely. In a small number of patients the company can show presumed efficacy and definite safety after which a conditional marketing approval is given for seven years. Most important fact is that national insurance would now pay for these therapies. This provision allows for post market analysis of efficacy and early availability of promising cell therapy products.

(B) Regulations for the medical services and research (stem cell services): (Figure 1)

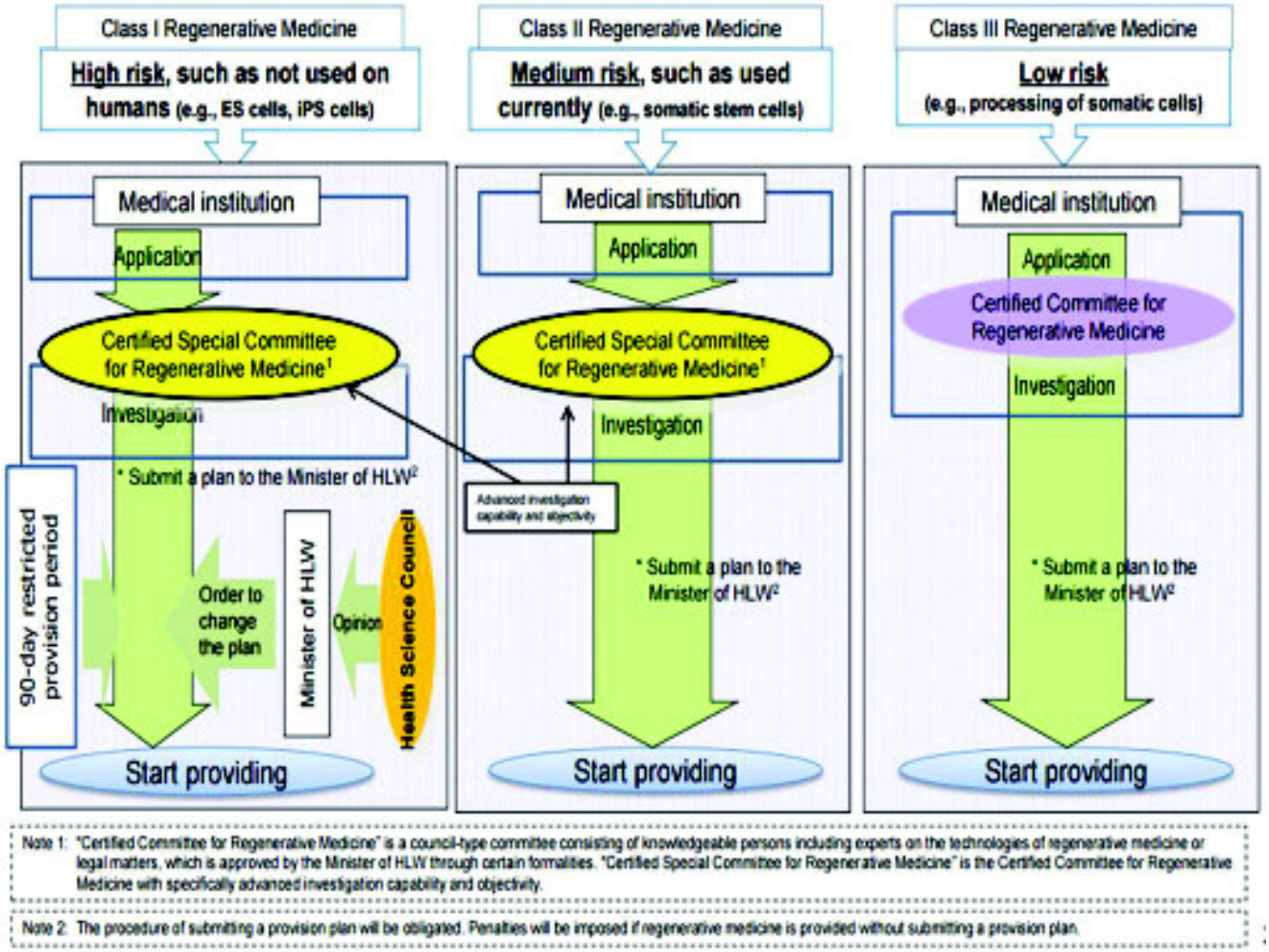
Here the Japanese regulators divide Stem Cell

Therapy in to the low risk, medium risk and high risk. Doctors practicing low risk therapy need permission only from their own institutional committee. Medium risk therapies need clearance from a committee outside the institute and High risk therapies are very heavily regulated. (7)

To elaborate, risk stratification is performed on the basis of risk to human life and health, Class III - Low risk, that is work involving processing of somatic cells, can be performed by taking approval from the institutional certified committee for regenerative medicine only. Class II - Medium risk therapies need approval of institutional certified committee of regenerative medicine as well as an external special committee for regenerative medicine. Class I - High risk that is Human IPCs, ESCs are regulated by a committee for regenerative medicine within the institute, special committee for regenerative medicine and the ministry of health, labor and welfare.

Since the implementation of these laws, two new products have been given conditional marketing approval and over 100 Stem Cell Therapy centers have opened up in Japan.

Figure 1: Risk stratification and Separate regulatory oversight for different categories according to risk stratification



Korean regulations for stem cell therapy:

The Korean guidelines, in their definition of cell therapy product, exclude cases where a medical doctor performs minimal manipulation of autologous or allogeneic cells. (8)

The regulations state that, "Cell therapy product" means a medicinal product manufactured through physical chemical, and/or biological manipulation , such as in vitro culture of autologous, allogeneic, or xenogeneic cells. However, this definition does not apply to the case where a medical doctor performs

minimal manipulation which does not cause safety problems of autologous or allogeneic cells in the course of surgical operation or treatment at a medical center (simple separation, washing, freezing, thawing, and other manipulations, while maintaining biological properties).”

Therefore by their regulations treatments done at a medical center using minimally manipulated cells are excluded from the regulatory framework of cell therapy products.

Regulatory framework in Europe:

European medical agency (EMA) has drafted a separate legislation for regenerative medicine products which is known as act on advanced therapy medicinal product (ATMP).(9) Various regenerative medicine products are put into this newly designed category for such products. This legislation recognizes the difference between the drugs and stem cell products. Another law formulated by EMA, called Hospital Exemptions act (HE) allows a practitioner or an institute to offer stem cell therapy as a form of treatment for terminally ill patients. (10) The law states that,

"Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined."

Recently in the year 2016 EMA also formulated a PRIority Medicines (PRIME) program to support development of medicines for unmet medical needs. (11) Under this scheme promising therapies and medicines that are important for public health will be given additional support and accelerated regulatory approval. The products that are in the stage before Phase II as well as Phase III trials can be a part of this scheme.

These schemes highlight patient's right to seek treatment for a disease that has no cure. If there is no treatment available, then regulatory bodies should not prevent patients from taking benefit of safe but unproven therapies. This concept was known as compassionate use in Europe earlier which has now evolved in the legislation explained above. In Australia and Canada as well such laws exists which allow marketing and provision of safe but unproven therapies and drugs to patients that suffer from incurable disorders after taking their informed consent and by reporting any possible adverse events noted. In Australia this is known as Special access scheme and in Canada it is known as special access program. (12,13)

New concepts that have emerged from the recent regulations (Figure. 2)

1. Conditional marketing approval
2. Risk Stratification
3. Post-Hoc efficacy analysis
4. Presumed efficacy
5. Patients right to seek treatment
6. Distinction between cellular therapies
7. Distinction between a stem cell product and medical service
8. Non-homologous use

Figure 2: New concepts emerging from the recent regulations

Conditional approval

Conditional approval first introduced by Japan and later also implemented by USA is revolutionary concept that allows for faster marketing of promising stem cell therapy products. In the last century the most promising medical research was done by individual doctors in their field of practice who kept patient care at the center of their research. But industrialization of pharmaceutical sciences and stricter regulations implemented for getting marketing approval made it impossible for individual practitioners to develop promising therapies and medicines. Conditional approval allows for promising therapies to be marketed for a stipulated time at an earlier stage of Phase I or pilot trials which are sufficient to prove the safety of the therapy and suggest efficacy of the same.

The concept of conditional approval has shifted the control of medical innovation back in the

hands of individual doctors practicing and researching to provide better patient care.

Risk Stratification

Risk stratification means grouping the stem cell therapies and products based on their risk to human life and health. Such stratification helps to differentiate between less harmful and more harmful cellular therapy products.

A) Using this principle Korea has excluded the safer forms of therapies from their regulatory framework.

B) Japanese guidelines have based their regulatory requirements on risk stratification. With low risk needing only institutional clearance, medium risk needing outside institutional clearenace and high risk requiring clearance from MHLW.

C) The new proposed American law REGROW Act, using this principle has proposed more permissive regulatory pathway for safe cell therapies such as cells or tissues that are minimally manipulated for a non-homologous use; or more-than-minimally manipulated for a homologous or non-homologous use, but are not genetically modified.

Post-Hoc efficacy analysis

Concept of Post-Hoc efficacy analysis means that true efficacy of the product or therapy can be determined post marketing. This is the most dramatic shift in the current medical regulations that do not permit marketing of unproven drugs and therapies. However based on this principle therapy or product can be permitted for marketing based on studies showing definite safety but preliminary efficacy analysis. The roots

of this concept are in the basic principle of compassionate use, facilitating early availability of potentially lifesaving experimental medication which are safe but unproven.

This is a revolutionary concept that has already been implemented in Japan since November 2014 and 2 products have already received approval under this legislation. Recently, based on this concept REGROW Act has also been put forth in the USA.

The basis of post - hoc efficacy analysis lies in the concept of Practice based evidence which allows for gathering information regarding efficacy of a particular therapy after using it clinically as a form of treatment and recording the clinical outcomes in the patients treated. Unlike evidence based medicine, the concept of practice based evidence gives the flexibility to offer a treatment after the safety is established and offer it as a treatment while simultaneously studying the effects on clinical outcome.

Presumed efficacy

It has been debated earlier that the modern standards for efficacy testing are too idealistic and may in turn slow down the progress of medical science. Although the regulations are for safe guarding the patients they fail to determine when a therapy will be considered as proven. The current regulations ask for Phased clinical trials that take up to 6 to 8 years before a new product can come in the market and have a cost estimate of about 5 million dollars. Current research and statistical methods are more suited for a drug or a molecule that has finite chemical reactions in the body, however in biological products there are infinite possibilities for interactions and therefore it may take decades before a conclusive efficacy analysis can be done.

Japan in their regenerative medicine regulations for the first time proposed a concept of 'Presumed efficacy'. This means that the preliminary trials that lack statistical rigor but are suggestive of beneficial clinical outcome can be considered as the evidence for efficacy of the treatment. Simply put, it means that it can be reasonably assumed that therapy will be effective in larger population based on a finding with a smaller population.

It was earlier considered unethical to charge for therapies that have shown efficacy in smaller populations. Japan in their recent regulations allowed for marketing of such therapies under a conditional approval and these therapies were also covered under Japan's national health insurance schemes. In the recently proposed REGROW act, USA; similar suggestions have been made for allowing safe therapies to be marketed based on their presumed efficacy.

Patient's right to seek treatment

Up till the last century availability of the clinical treatments was solely based on decisions of regulatory bodies. If a treatment did not fit the criteria laid out in the regulations then it was not allowed in the market, thereby denied to the patients. Although this was to safeguard patients from adverse effects of under investigated therapies, terminally ill patients were losing out on promising therapies due to strict demands for proving efficacy.

Most of the patients with progressive fatal disorders do not have enough time for an experimental drug which has proven safety and has shown efficacy in smaller trials to be tested in the statistical rigor of bigger trials. These drugs could be potentially lifesaving for these patients. There were many efforts lead by patients and non-profit organizations, which demanded access to such experimental drugs for patients with terminal illnesses.

The origin of compassionate use is in the World Medical Association's Declaration of Helsinki on ethical principles for medical research involving human subjects. The declaration in their clause on unproven intervention in clinical practice states that, 'In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available'. (14)

The concept of patient's right to seek treatment is highlighted in the White paper published by the International society of Cellular Therapy which states that "Patients seeking medical treatment for cellular therapies have the following rights that must be respected by healthcare providers and all associated with their care. The right to seek treatment: patients and their families/partners have the right to seek treatments for their diseases. No entity should withhold this fundamental right unless there is a high probability of harm to the patients."(15)

Efforts made by the patients in accordance with this ethical principle led to changes in the legislation for USA, Europe and several other countries in the world. In USA this was implemented as Treatment/Emergency IND initially and later as Right to try Act in 2015. (5) In Europe this was implemented as Compassionate use Act and recently a program was launched to support to development of priority medicines for unmet medical needs, PRIME. In addition other Acts like Hospital Exemption Act in Europe (10), Special access program in Australia (12) and special access scheme in Canada (13) are based on this principle.

These compassionate use programs highlight patient's right for seeking unproven but safe experimental drugs and allows access to such medicines and therapies at the personal recommendation and responsibility of the treating physician. Such use is deemed ethical and can be charged for after receiving an informed consent from the patient, explaining the possible adverse effects if any and informing the patient about the experimental nature of the therapy.

Unfortunately, in India there are no laws or regulations for compassionate use. Indian regulators and guideline formulators have not taken into consideration the right's of these patients to seek treatments that may potentially save their lives.

Distinction between different types of cellular therapies

Earlier the guidelines did not make distinction between different types of cells, processes of procurement and routes of administration. However the recent guidelines have made various distinctions and have made separate regulations and guidelines accordingly.

In USA the REGROW Act makes distinction between minimally manipulated cells and more than minimally manipulated cells.(2) Minimally manipulated cells are defined as, "cells procured using technologies when there is no intended alteration in the biological characteristics of the cell population relevant to its claimed utility, performed by a medical doctor at a medical center during the same surgical procedure without compromising the safety of the cells; this may include separation of mononuclear cells, washing, centrifugation and suspension in acceptable medium." All the other cell types are characterized as more than minimally manipulated cells.

In Japan, there is a separate law designed only for the classification of the regenerative medicine products based on their safety profile.(7) These products are divided into 3 separate classes as, class I - High risk, Class II - Medium risk and Class III - Low risk products (Figure).

In European guidelines, the products are divided into minimally and more than manipulated as well. Minimal manipulation is defined as cells procured through simple technologies like cutting, grinding, shaping, centrifugation, soaking in antibiotics of antibiotic solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation and vitrification. However there are no separate guidelines for the use of these products as allowed in Japanese and USA laws.

Distinction between a cellular therapy product and cellular therapy medical service

Advent of cellular therapy has given rise to a huge dilemma for regulators whether to regulate these as a product or a medical service. Therefore most of the guidelines are too restrictive where it is considered as a product or too liberal where it is considered a therapy. Although burden of evidence lies on both therapy and product; the criteria for marketing approval have been traditionally very different for both. Every new product is regulated separately and the evidence for one is usually not applicable to the other

therefore companies designing different products need to seek different approvals. The guidelines for these are also very strict. However a therapy once proven safe and effective can be used by multiple practitioners and they individually do not need to seek approval for the same. This is a basic distinction in the product and therapy which most of the guidelines in the world including Indian guidelines fail to understand.

Japanese guidelines however have been very progressive and they have designed 2 separate laws for products and therapies. These two laws have also been very progressive in their field of application allowing fast track conditional approval for products and mandatory approval from MHLW only for high risk therapies. USA has taken a step ahead in not only allowing a fast track conditional approval for products but also allowing different companies to get faster marketing approval based on exhibited biosimilarity with an already existing approved product.

Non-homologous use

The proposed REGROW Act 2016 has for the first time made a provision for conditional approval of therapies and products using minimally and more than minimally manipulated cells for non-homologous use i.e. not in the same body system as that of the source of the cells. (2)

Current Indian Scenario:

In sharp contrast to this, in India the latest guidelines made by Indian council of Medical Research (ICMR) in 2013 are moving backward and are in the process of trying to implement policies that will completely destroy the stem cell therapy field in India.(16) The Major problem is that the ICMR does not seem to understand that there is a difference between a product and a medical service. They refuse to accept that there is something like stem cell 'therapy'.

The regulations were quiet progressive in their earlier versions (2002 and 2006) allowing co-existence of research and therapy based on the risk stratification of cells.(17) In addition to already existing institutional oversight by Institutional Ethics Committee (IEC), ICMR added another layer of oversight at an institutional level called Institutional committee of stem cell research and therapy (IC - SCRT) and at a national level called National Apex Committee for stem cell research and therapy (NAC - SCRT). Indian innovators and doctors have collected a huge amount of clinical evidence in this field and are ahead of doctors from any other country in the world. Since 2002 there are a total of 80 published clinical studies from India in various different neurological, musculoskeletal and cardiovascular disorders which is amongst the largest published clinical evidence from a single country. Most of these disorders are incurable and fatal. All of these publications unanimously document the safety of cellular therapy and potential benefits. All of this development was led by individual doctors and practitioners who innovated the stem cell therapies for incurable disorders keeping the patient at the center of their research. This is becoming increasingly difficult now since the evolution of latest ICMR and CDSCO guidelines.

As time progressed the guidelines regressed from liberal guidelines that were permissive of cellular therapies in India to the most recent restrictive guidelines that suggest all stem cell related work can only be performed as research. These restrictive policies are completely destroying the field of stem cell therapy in India. A peculiar thing to note is that by changing the guidelines the progress of the field of stem cell therapy in India is now controlled by the corporate who have large funds. Current policies of ICMR which insist on having an IC-SCR registered with NAC-SCRT, registration with CTRI, having a data safety monitoring board and a DCG(I) license for GMP facility means that only heavily funded private corporates can fulfill their criteria. The current policy ensures that government/ semi government institutions, smaller private hospitals and individual doctors can never fulfill their criteria. Even if institutions want to work in accordance with ICMR regulations, NAC-SCRT makes it extremely difficult for them to even begin the process. This is evidenced by the fact that out of 107 institutes that have applied for NAC-SCRT registration only 24 i.e 22% have actually got the NAC-SCRT registration. Also the process is extremely long and can take several months to years to complete. The result of this is a real life example in recent months wherein a semi

government hospital in Gujarat doing wonderful limb salvage stem cell therapy free of cost was made to stop their work whereas a private corporate was given permission to charge patients (US $2200) for similar type of indication. Any regulatory policy that favors only those who can spend large amounts of money and discourages or prevents those who cannot spend large amounts of money is not in the national interest of our country.

Indian regulators fail to understand the 1] distinction between drug and stem cell therapy 2] distinction between stem cell therapy product and stem cell therapy. The current Indian guidelines do not incorporate any of the new concepts that have emerged in the recent progressive guidelines of other countries.

Proposed changes in the Indian regulations:

We would like to propose a road map for regulating stem cell work in India in such a manner that the safer forms of therapies are easily available to patients with incurable diseases whereas less safer forms of therapies are regulated more strictly.

(A) For this we propose that there should be 3 different sets of guidelines for,

1) Researchers - Those who are doing basic laboratory research and clinical trials in patients.
2) Corporate Manufacturers - companies that are manufacturing stem cells and stem cell related products on a large scale
3) Clinical stem cell therapists - doctors and institutes that offer cellular therapy as a treatment.

Separate rules and regulations should be formulated for these. The researchers should follow ICMR guidelines. Corporate manufacturers should follow CDSCO / DCG(I) guidelines.

Clinical stem cell therapies should further be categorized into

Low risk: Therapies using autologous and minimally manipulated stem cells. These therapies could be permitted under the oversight from the IEC.

Medium risk: Therapies using more than minimally manipulated allogeneic cells of non-embryonic origin. These therapies would need oversight of IEC and approval from CDSCO/ DCG(I).

High risk: Embryonic/ Fetal stem cells and iPSCs. Therapies using these cells would require oversight of IEC and approval from CDSCO and ICMR.

A key aspect of debate between clinicians and regulatory bodies is what new clinical indications should be considered as approved to offer stem cell therapy. We believe that if there are publications, that document safety and presumed efficacy of stem cell therapy in a particular indication from any part of the world, then this should be considered as an accepted indication.

(B) The membership of NAC-SCRT should be expanded to include more members from the clinical side having experience and expertise in Stem cell therapy so that a more balanced view is taken. The Chairmanship of NAC-SCRT should be changed by rotation every year so that fresh insights are available to the committee.

Conclusion:

We conclude that the Ministry of Health along with ICMR and CDSCO need to study the REGROW Act of USA as well as the Japanese and Korean legislations for regenerative medicine and come up with a definitive set of regulations which are permissive of medical practitioners offering safer forms of cellular therapies like autologous and minimally manipulated therapies and stricter regulations for more unsafe cellular therapies and corporate producing and selling stem cells as a product. The Indian guidelines should also incorporate principles of risk stratification, post-hoc efficacy analysis, conditional marketing approval, distinction between stem cell therapies and stem cell products and patients right to seek treatment. This will result in only safe treatments being available as therapy and at the same time ensure that patients suffering from serious medical conditions are not deprived of stem cell therapies that can help them.

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