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"What man has made of man?"

Anay Shukla & Dr. Milind Antani, Nishith Desai Associates

In April 2014, after a four yearlong investigation into stem cell therapy provided by an organization called Stamina Foundation in Italy, the public prosecutor concluded that the organization was "a criminal organization that has defrauded about a thousand patients since 2006 by administering a dangerous and unapproved treatment in exchange for money". The report identified a series of problem with the treatment, for instance, that the cells handled, processed and injected in non-sterile conditions. It also stated that "patients were turned into guinea pigs".

India has turned out to be a popular hub for stem cell therapy, arguably because of the lax regulations. In fact, some of the medical practitioners in India have heavily capitalized on the promise of stem cell therapy, and to some extent the desperation of patients, and are offering stem cell therapy for a range of diseases and conditions. New "stem cell clinics" have mushroomed in cosmopolitan cities of India over the past few years.

It is undisputable that stem cell therapy has the potential to grant a new lease of life to many patients. However, there are some valid concerns associated with use of stem cells at present in form of therapy. According to The Indian Council of Medical Research (ICMR), these concerns are: (i) Stem cells have the capacity for unlimited proliferation or tumorigenicity; (ii) risk of rejection of the new stem cells as "foreign body" by the recipient's own immune system, and (iii) and risk of contamination and/or alteration in the properties of cells.

Such concerns beget the question: Whether stem cell therapy is regulated so that a person is assured of its safety and efficacy?

The fact of the matter is that the science of stem cells is still in its nascent stage, and both basic and translational research is ongoing. There is not enough evidentiary proof available to conclusively establish that stem cell therapy is safe and efficacious to be used on humans in the form of

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standard therapy, except in cases of hematopoietic disorders (i.e. disorders of the blood connected to bone marrow). The Indian Council of Medical Research has categorically denounced stem cell therapy in as many words as follows:

"every use of stem cells in patients outside an approved clinical trial shall be considered as malpractice. It is hoped that this clear definition will serve to curb the malpractice of stem cell "therapy" being offered as a new tool for curing untreatable diseases"

The scientific and medical community is in need of clinical (i.e. patient) data through clinical trials (i.e. tests on real patients) so that safety and efficacy of stem cell therapy may be established. As stepping stones towards that end, the ICMR has notified certain standards and limitations which must be observed by researchers and practitioners who are conducting basic and translational research. The key areas ICMR has identified for regulation are:

1. PROCUREMENT
(i.e. Which biological material may be procured as a source of stem cells? What is the process to be followed?);

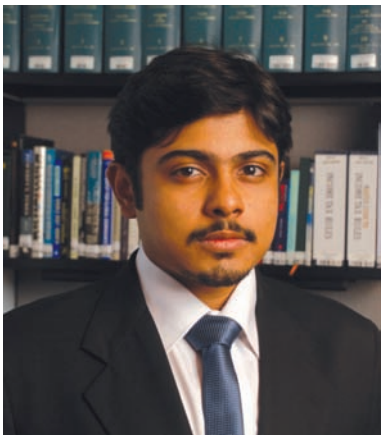
2. BANKING AND DISTRIBUTION
(i.e. What are the requirements for starting a cell bank or tissue bank? What is the process to be followed for obtaining and storing stem cell lines? What are the conditions to be satisfied before distribution of stem cells lines?);

3. RESEARCH
(i.e. Whether the research falls into the category of permitted research, restricted research or prohibited research); and

4. USE
(i.e What is the standard in terms of safety of process and end-product to be met by stem cells before they can be administered into patients? How should the study design of the clinical trial be? What is the format for the clinical trial protocol?)

In order to monitor those involved in the field of research, the ICMR has mandated establishment of an institutional committee called Institutional Committee for Stem Cell Research (IC-SCR) in each institution involved in stem cell research. The methodology of monitoring is described in the next paragraph. The composition of IC-SCR includes members of the institution and experts from the field of law, ethics and social-sciences, all of whom have no conflict of interest. The ICMR has also pushed for and established the National Apex Council for Stem Cell Research (NAC-SCR). The NAC-SCR has representation of all the government departments which deal with the subject of public health, notably the Drugs Controller General of India (Or DCGI, the executive body that controls standards and quality of medicines in Indian market), the Medical Council of India (which regulates professional and ethical standards in practice of medicine) and the Department of Biotechnology. All IC-SCRs have to be registered with NAC-SCRs.

Most of the research in the area of stem cells is self-regulated. Interested persons in all institutions have to take permission of the IC-SCR of their respective institution before commencing any significant activity in any of the areas outlined earlier. The role of IC-SCR before permitting any research activity is to ensure that such activity falls within the bounds set out by ICMR. The IC-SCR has the power to carry



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Any person who wishes to collect, process and store SCCP for the purpose of test and analysis must obtain a license. To obtain the license, the applicant must ensure that the research facility complies with the Good Manufacturing Practices norms under Part X D of Schedule F of the Drugs and Cosmetics Rules, 1945.

out periodic inspections of research being carried out at the respective institution. The role of NAC-SCR comes to light when a sensitive research activity such as genetic modification (major manipulation) of stem cells is proposed. In these cases, the researchers have to take permission of NAC-SCR. Where research is focused on commercial marketing of stem cell in future, the permission of DCGI is generally required.

It will come as a surprise to many that ICMR has not laid down any punishment for violation of the regulatory framework drawn by it. The reason for this is that the ICMR has not been bestowed by the legislature with a power to punish those who default. At present, the enforcement of the standards set by ICMR is done indirectly. For example, if a medical practitioner is found administering stem cell in form of therapy, it would not be ICMR who will punish the medical practitioner, but the Medical Council of India (or appropriate State Medical Council) who will initiate action against the medical practitioner for "professional misconduct". This long-arm approach has been criticized for being ineffective. However, the government is hopeful of stringent enforcement as from the beginning of December 2013, a nominee of each MCI and DCGI has been given a permanent position in NAC-SCR with the intention of improving co-ordination amongst the government institutions.

The regulatory framework published by ICMR suffers from another serious limitation. It does not extend to commercial use of stem cells because the mandate of ICMR is limited to regulation of research. In fact, there is no regulatory guidance at all available at present for commercialization of stem cells.

Perhaps, to fill this void, the Central Drugs Standards Control Organization (CDSCO), the parent organization of DCGI and apex drug standard control body in India, has recently published draft guidelines for regulatory approval of commercial use of stem cell and cell based products (SCCPs). In effect, the draft guidelines propose to regulate all practices related to the use of stem cells as well as other cells for therapeutic purposes in India. They require that all SCCPs and all activities related to their usage i.e. manufacture/isolation/ collection, storage and transplantation into patients must be done only under a license or permission that would be granted by the DCGI. Some of the highlights of the draft guidelines are as follows:

- Any person who wishes to collect, process and store SCCP for the purpose of test and analysis must obtain a license (Category 1 License). To obtain the license, the applicant must ensure that the research facility complies with the Good Manufacturing Practices norms under Part X D of Schedule F of the Drugs and Cosmetics Rules, 1945 (D&C Rules). Further, all clinical and cell storage areas must conform to the requirements laid down in Schedule L of the D&C Rules.
- To conduct a clinical trial, a separate license will be required (Category 2 License). Category 2 license will be issued only to those institutions which have a Category 1 License.
- Import or manufacture of SCCP will require another license (Category 3 License), which will be issued to those institutions which have Category 1 and 2 Licenses. The license will be granted after satisfaction of quality controls; establishment of characterization, cell identity, purity, impurity and potency; stability testing; proof of adequate container and closure systems; proper labeling and product tracking and few other requirements.
- Sale of SCCPs at whole sale or retail level will also require a license (Category 4 License). A Category 4 license applicant must have already received all the previous Category licenses.

The draft guidelines by themselves, however, seem to be extremely controversial and bereft from the commercial realities of the day. The "tying-in" of licenses means that the research institution has to necessarily conduct

clinical trials, establish a commercial scale manufacturing facility and eventually set up a retail outlet from where stem cells may be sold. There is no scope for market players to don roles of just a manufacturer or just a retailer. The draft guidelines also completely negate the possibility of setting up commercial cell repositories in remote areas of the country because a commercial repository would not be able to obtain Category 1, 2 and 3 licenses required for end consumer sale.

The draft guidelines, even if finalized, will be ineffective without supporting amendments to the Drugs and Cosmetics Act, 1940 and Rules, 1945. It is expected that such amendments will be introduced soon.

The absence of a clear regulatory pathway to commercialization of stem cell therapy in the present day has done a lot of harm to the industry. While the less ethical minority has profiteered from the absence of enforcement, the majority feels it has "burnt holes" in its pockets by investing in the science. This sentiment of the majority has to be understood in a context. Research and development requires substantial capital investment and continuous financial support. The cost of developing a viable SCCP must also include cost of research that failed. Hence, the institutions involved in research and development are almost always looking out for cash-rich investors/partners. At present, there is little clarity on regulatory framework for commercialization of stem cells. If a SCCP, or for that matter a product of any research, does not get commercialized within reasonable time, those who were involved in doing research and those who financially supported it end up making a loss. Hence, it is natural that investors are hesitant to commit a substantial sum for research and development of SCCPs. Institutions then are left with no option but self-financing through loans or diverting profits from its portfolio. However, there is a limit up to which they can support themselves after which there is no option left but to discontinue the effort.

In light of the above, most research and development institutions are understandably eager to get returns on its investment. While the less ethical have started administering stem cells as therapy, a lot of institutions are generating revenue by supporting clinical trials by supplying clinical grade stem cells for use in trials or conducting clinical trials themselves. Many patients are willing to enroll in clinical trials to take a chance with stem cell therapy and are ready to pay. However, acceptance of money for enrolment in clinical trials is unethical and prohibited by Indian Good Clinical Practices. Realizing this, many such institutions have devised innovative ways to plough in some revenues in order to off-set the cost of research.

The Industry is also upset with the surprise inspection that state-level drug regulatory authorities conduct on research and development facilities. The Drugs and Cosmetics Act, 1940 and Rules, 1945 regulate manufacturing carried out for sale or distribution only. Thus, if an institution is engaged in research and development of stem cells is processing stem cells for that purpose, it is not carrying out illegal activity and any state drug regulatory authority is not legally equipped to take any adverse action against such institutions for said activity.

One can only hope that an effective regulatory framework for commercialization is introduced soon which is able to balance the regulators' apprehensions and the industry's commercial interest in a way that provides maximum benefit to the public! The need of the hour is to have sensible regulations which may be enforced, in absence of which patients will continue to be victims, not being able to benefit from a potentially curative therapy.

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