National [illegible]
for Research, [illegible]
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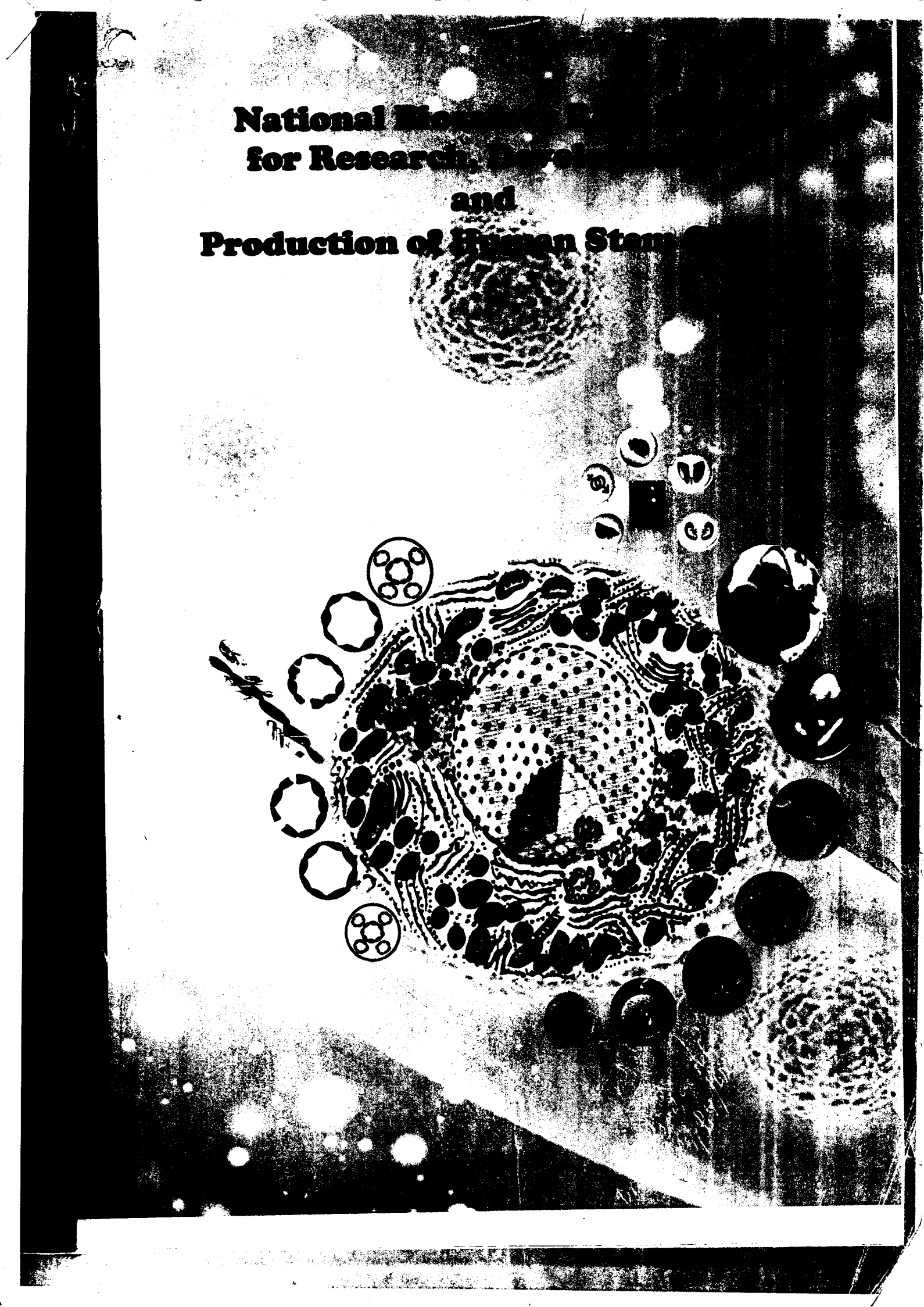

Contents

Skip not what must be done

and

Repeat not what is firmly established and documented

FOREWORD

Biology has been harnessed since antiquity to fulfill humanity's most fundamental needs – from increasing food supplies to improving health care. The availability of new and novel methodologies has greatly expanded the scope of its applications. For the first time in the history of mankind, it seems within reach of human endeavors to design new customized drugs to fight against cancer, hepatitis, leprosy, AIDS and cardiovascular diseases; eliminate viral and parasitic diseases; diagnose and cure human genetic disorders even before birth. The recent discovery that human genes can be expressed in fast growing microbes has enabled commercial production of once scarce bio-materials, the presence of which could only be felt from their action but never visible to the naked eye (such substances include human growth hormone, cytokines and blood clotting factor). Another breakthrough discovery is that human stem cells can develop into many different lineages such as skin cells, brain cells, lung cells and so on. This has opened new avenues in medicine called **"regenerative medicine"** — a game-changer with the potential to fully heal damaged tissues and organs, raising aspirations of people suffering from incurable diseases. Production of clinical grade stem cells and human pharmaceutical proteins (through cloning of human genes in fast-growing microbes), is a rapidly expanding venture and presently the most profitable industry in the world. The market for prescription drugs in the US has doubled in the last ten years and is expected to quadruple in the next ten years. Additionally, health care is emerging as a political and social issue in developing countries.

As the global landscape for health and medicine is changing, new strategies are being developed that involve combining basic laboratory research with clinical practices. This is not happening in Pakistan because we have neither recognized the impact of the changing international scenario nor taken measures to develop laboratory infrastructure required to take new initiatives. In 2006, Centre of Excellence in Molecular Biology (CEMB) proposed to set-up an interferon purification facility to exploit the revolutionary potential of cloning of human pharmaceutical protein genes in *E.coli* which would also act as a breeding ground for the generation of a cadre of specially trained manpower. The project was approved in the pre-Central Development Working Party pre-(CDWP) meeting but withdrawn before it was even discussed (for approval) in the CDWP meeting. Regrettably, as of to-date, there is no USFDA (United States Food and Drug Administration) approved or EMA (Europe Medicine Agency) approved pharmaceutical protein purification /stem cell production facility in Pakistan, neither in the public sector nor in the private sector. The world's leading countries have established cGMP compliance facilities as well as formulated national regulations to regulate all new biotechnologies. During 2000-2010, through an initiative of the Indian President at the time, Dr. A P J Abdul Kalam, India's largest biopharmaceutical protein purification set-up, with six dedicated, production units in a row, designed according to US FDA standards, was established at Wockhardt Biotech Park, in Aurangabad, India. Since then establishment of such facilities have proliferated from coast to coast in India forming a sound base for the production of clinical grade pharmaceutical proteins/stem cells.

While the proposal to establish a cGMP compliance protein purification facility at CEMB, was not accepted, the institute succeeded in obtaining approval of the Ministry of Health for the formulation of a small amount (1gm) of indigenously purified interferon into one lac 3miu interferon injections, at M/s Cirin Pharmaceuticals, Hattar Industrial Estate, Haripur, Khyber Pakhtunkhwa (KPK) strictly for

human trials to be carried out at Sheikh Zayed Hospital, Lahore under the supervision of Dr Huma Qureshi Chairperson, Pakistan Medical Research Council (PMRC) at the time and Dr. Anwar ul Haq, Chairman Sheikh Zayed Hospital, Lahore. Regrettably, PMRC never secured the necessary funds to conduct human trial studies and the entire stock of one lac injections was wasted as "expired medicine" as was the remaining stock of ten grams of indigenously purified interferon. To further aggravate the situation, the Ministry of Science and Technology (MoST) ordered several inquiries into a set of frivolous and fabricated allegations of financial embezzlement against the Principal Investigator in these studies, Dr. Riazuddin. Though, the inquiries by Federal Investigation Agency (FIA), completely exonerated him from all charges of embezzlement/corruption, the enquiries dragged on, long enough to completely shatter the interferon production laboratory infrastructure at CEMB and that it has since been impossible to revive local production of pharmaceutical proteins. The FIA reports were placed before the Federal Public Accounts Committee (PAC) which critically evaluated the outcome of FIA reports and issued Dr. Riazuddin a letter of "commendation".

To place Pakistan on a firm footing with regard to the uses of new molecular and cellular technologies, Prof. Riazuddin's research groups at CEMB and Allama Iqbal Medical College (AIMC) have been working to clone human pharmaceutical protein genes in fast growing microbes. Further, his laboratory has been studying differentiation of adult stem cells, progenitor stem cells (such as those found in umbilical cord blood) and manipulated somatic stem cells (induced pluripotent stem cells) into appropriate lineages to cure damaged organs. Each type of manipulated cell has unique properties and can regenerate into desired lineages. Many of the regenerative strategies being developed in his labs employ patient's own cells and reprogram them to induce unique characteristics to treat his or her specific disease. The potential of regenerative medicine for patient treatment for a wide variety of debilitating diseases is great. Realizing the promise of regenerative medicine, "early pre-clinical trials" are emerging in his labs, individually and collaboratively involving scientists in labs at University of Maryland, Johns Hopkins University and University of Miami, USA. However, there are no national regulations to regulate laboratory/ clinical work on stem cells for therapeutic purposes as was the case for the production of biopharmaceutical proteins (biosimilars) when his laboratory indigenously produced interferon, (the only therapeutic drug against hepatitis C at the time). This matter was agitated in the print and electronic media. The Honorable Supreme Court took notice of the news reports that CEMB and AIMC had developed stem cells and plan on using them for the repair of burnt skin injuries and that several labs were also developing stem cell technologies to produce cornea substitutes but could not take this research breakthrough to fruition because of lack of an appropriate regulatory mechanism. The Hon'ble Court entertained human right case no 69699-P of 2018 on this issue. The case was heard on 6-01-2019 in which the hon'ble court observed that all emerging economies had developed "national regulations" to regulate the uses and applications of new and emerging biotechnologies in general and stem cell technologies in particular, however, Pakistan still had none. The Hon'ble Court ordered on 15.01.19 that,

> *"Stem cells/ cell research and laboratory regulations should be developed by Clinical Studies Committee (CSC) with in a period of three months; the CSC to coopt Prof. Dr Sheikh Riazuddin as its member to avail benefits of his expertise immediately after notification of CSC".*

The Law and Justice Commission of Pakistan, Islamabad convened a meeting of all stakeholders on 15.01.19 in Islamabad to discuss the matter in detail and suggest a way-forward. The meeting, attended by all the stake holders, including Chairman HEC, Minister of Health, thoroughly debated all related issues and unanimously proposed to constitute a Sub Committee, mandated to develop national biosafety regulations to regulate all laboratory and clinical work on stem cell in Pakistan.

We are delighted that a group of eminent researchers, under the leadership of Prof. Riazuddin have developed national biosafety regulations which will have an important role in promoting the uses and applications of stem cells for basic research and therapeutic purposes. We are particularly pleased to note that all authority to accord approval for basic university research and pre-clinical trials is vested in the university in which this work is being carried out and Higher Education Commission and all authority to accord approval for "deregulation of regulated materials" for commercial purposes is vested in the National Biosafety Committee, being the supreme regulatory authority. Furthermore, all anticipated risks have been dealt with subsequent to categorization into minimal, moderate and high risks according to robust scientific knowledge. Accordingly, a 3-tier monitoring and evaluation system is devised such that responsibilities of various monitoring and evaluation authorities and committees have been brought in line with the requirements of their technical obligations so that optimum efficiency is achievable most expeditiously. The approval for work with known minimal risk is vested locally with Institutional Biosafety Committee whereas approval for high risk category or uncharacterized category is vested in National Biosafety Committee, being the supreme authority in such matters. In the day-to-day working, local IBC will have all decision making which will evidently ensure expedient functioning. In case of differences of opinion, the matter will be referred to NBC through MBC, i.e., the administrative ministry. It is clear that even on ordinary reader of these regulations that the frame work is designed in such a manner that it can function with least interference from the usual hierarchical drags and that the regulations will promote safe uses of scientifically based concepts and restrict applications of those concepts which are yet to be proven through sound scientific rigor. Nevertheless, scientific research is progressing very fast and new scientific discoveries are being made which may change presently designated "risk categories". We believe, therefore, that these regulations will require a regular periodic review in order to accommodate new concepts and discoveries. As we believe that Laboratory research will continue to improve existing concepts and the process of regular review of regulations will ensure update.

In the end, we commend the efforts of all those who contributed to the accomplishment of this **important national task** and wish all users of these regulations good luck and success in every endeavor.

KHAWAJA ZAHEER AHMED
Federal Secretary
Ministry of Science and Technology
(2004 to 2005)

YASMEEN REHMAN
Chairperson
Public Accounts Sub-Committee-III
(2009 to 2013)

ACKNOWLEDGEMENT:

On a directive of the Honorable Supreme Court, all stakeholders working in the field of stem cells and cell based products, joined by national administrators and financers of Molecular and Cell biology research and members of judiciary met in the committee room of Law and Justice Commission of Pakistan, Islamabad on 15.01.19 at 4:00 PM under the Chairmanship of Honorable Chief Justice at the time, Mia Saqib Nisar. During discussion on various bottlenecks in the commercialization of basic laboratory research in biotechnology in general and stem cells in particular, the meeting participants expressed the need for national regulatory regulations for development and translation of stem cell research into public usable products and process. Accordingly, the Drug Regulatory Authority of Pakistan (DRAP), constituted a committee of experts, notified on 23.10.19. Prof. S. Riazuddin, a pioneer in Molecular Biology. Cell Biology and Stem Cell Research in Pakistan, who had earlier authored National Biosafety Regulations for work in plant biotechnology and its applications in agriculture, was given the main responsibility to prepare National Regulations for Stem Cell research.

Dr. Shaheen N. Khan, Professor CEMB (Retd) and Dr Asma Ali Khan, Assistant Professor, CEMB, provided extensive assistance in the survey of literature on regulations of several developed and developing countries. Guidance was sought from many experts at home and abroad involved in regulatory measures. Final draft of the national regulations was critically reviewed by people engaged in overseeing regulatory enforcement in three US universities. Subsequently, the document was discussed thread-bare in several "full committee" meetings and all its contents were unanimously agreed upon in the form of this comprehensive document. The final version was shared with collaborators at Johns Hopkins University (JHU), University of Maryland (UoM), University of Miami and all of them thoroughly and critically perused the document and made very constructive criticism and useful suggestions. All comments/ suggestions of the reviewers have been duly incorporated into the final version which seems considerably improved.

We are profoundly thankful to Dr. Asim Rauf Finalization of the document would not have been possible without the untiring efforts and relentless contribution. Special thanks are due to all the DRAP officers for the coordination and logistic support.

Finally, compelling patronage of the Minister and the Secretary is greatly acknowledged.

Last but not least, we gratefully acknowledge those who worked behind the scenes but without whose input, the document would not have been finalized. Most notable of them is Mr. Mahmood Ahmad, Senior Administrative Officer, Centre of Excellence in Molecular Biology who formatted the final version. The cover page was prepared jointly by Ph.D. students at CEMB. We believe that this compendium of information will help to reap a harvest of the new revolutionary stem cell therapy and also effectively restrict its misuses in Pakistan. We wish all users of these regulations a big success in all endeavours.

Prof. Dr. Javed Akram
Vice-Chancellor
University of Health Sciences
Lahore

Prof. Dr. S. Riazuddin
HEC Distinguished National Professor
CEMB, University of the Punjab
Lahore

Prof. Dr. Moazzam N. Tarar
Executive Director
JB&RSC, Jinnah Hospital
Lahore

ABBREVIATIONS

AE	- Adverse Event
ASC	- Adult Stem cells
AIMC	- Allama Iqbal Medical College
BM	- Bone Marrow
BSO	- Bio-Safety Officer
CBS	- Cord blood stem cells
CEO	- Chief Executive Officer
COI	- Conflict of Interest
CDWP	- Central Development Working Party
CEMB	- Centre of Excellence in Molecular Biology
CRISPR	- Clustered Regularly Interspaced Short Palindromic Repeats
DNA	- Deoxy-ribonucleic Acid
DRAP	- Drug Regulatory Authority of Pakistan
ELISA	- Enzyme-Linked Immunosorbent Assay
ESC	- Embryonic Stem Cells
EGC	- Embryonic Germ Cells
EMA	- European Medicine Agency
FACS	- Fluorescence Activated Cell Sorting
GCP	- Good Clinical Practice
GLP	- Good Laboratory Practice
GMP	- Good Manufacturing Practice
GOP	- Government of Pakistan
GTP	- Good Tissue Practices
Hb	- Hemoglobin
hESC	- Human Embryonic Stem Cells
HSC	- Hematopoietic Stem Cell
HSCT	- Hematopoietic Stem Cell Transplantation
HEC	- Higher Education Commission
IBC	- Institutional Biosafety Committee
ICM	- Inner Cell Mass
ICF	- Informed Consent Form
IPR	- Intellectual Property Rights
iPSC	- Induced Pluripotent Stem Cells
IVF	- *In vitro* Fertilization

JHU	- Johns Hopkins University
MNCs	- Mono Nuclear Cells
MNHSRC	- Ministry of National Health Services, Regulation and Coordination
MOE	- Ministry of Education
MoST	- Ministry of Science and Technology
MSC	- Mesenchymal Stem Cells
MBC	- Ministerial Biosafety Committee
MTA	- Material Transfer Agreement
NBC	- National Biosafety Committee
PAC	- Public Accounts Committee
PBSCs	- Peripheral Blood Stem Cells
PHRC	- Pakistan Health Research Council, formerly known as the Pakistan Medical Research Council
P.I	- Principal Investigator
pMBC	- provincial Ministerial Biosafety Committee
PMC	- Pakistan Medical Council
PMRC	- Pakistan Medical Research Council
PRP	- Protein rich plasma
PSC	- Pluripotent Stem Cell
QA	- Quality Assurance
QC	- Quality Control
R&D	- Research and Development
SAE	- Severe Adverse Event
SOP	- Standard Operating Procedures
SSCs	- Somatic Stem Cells
SVF	- Stromal Vascular Fraction
TOP	- Termination of pregnancy
UCB	- Umbilical Cord Blood
UoM	- University of Maryland
USFDA	- United States Food and Drug Administration
WHO	- World Health Organization

PREAMBLE:

During the last two decades, basic laboratory research in stem cells has generated great excitement surrounding this emerging field. Consequently, stem cell research has emerged as the most exciting of all biological sciences and applications of stem cell laboratory research is expected to give birth to revolutionary clinical practice that will prove to be a game changer in health and medicine. Nevertheless, there are still innumerable problems in translating laboratory "Bench research" into hospital "Bedside", application. Scientists across the globe are working to solve the unresolved problems which are solvable in theory and are being gradually solved in practice. Like all previous scientific revolutions, the conduct of basic laboratory research and its translation into products and processes of public benefits are challenged with religious and legal consideration.

Furthermore, the new therapy has been misused by irresponsible clinicians that has caused serious concerns in the public mind. The Higher Education Commission of Pakistan (HEC) has generously financed establishment of excellent infrastructure for stem cell research in different universities but none is cGMP compliant and the fear is that it may become a fertile ground for clinical malpractices. Lastly, like all previous revolutionary discoveries, stem cell research and technologies has given birth to legal, religious and societal issues which demands serious attentions of the government and regulatory agencies. To cope with these emerging needs, to eliminate the chances of ill-uses and to promote the rightful uses and applications of stem cells and to give birth to indigenous technologies, the Honorable Supreme Court of Pakistan directed (case No.69699-P-2018 dated 15.01.19) CSC to develop national biosafety regulations for Stem Cell research in order to regulate the new technology as well as to prevent its misuses in order to reap a harvest of all new biotechnologies. Accordingly, a set of guide lines have been developed by a team of eminent experts, laboratory researchers and clinicians. We are particularly pleased to know that a clear distinction has been made between **laboratory research/ preclinical studies by the academia** and **commercial work by the industry** in terms of evaluation, monitoring and approval authority. Furthermore, the regulations are designed to ensure safety of vulnerable in the society (orphaned children and poor women), protection of human rights and due respect to Islamic principles of human dignity, social values and legal concerns. We are confident that there will be no undue hierarchal drag nor unnecessary delays and legitimate stem cell work will move smoothly and unrestricted. We thank all those who contributed to this endeavor and wish all a big success.

SECRETARY
Ministry of National Health Services,
Regulations and Coordination
Islamabad

MINISTER
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