Salient features of the "National Guidelines for Gene Therapy Product Development and Clinical Trials"

Inherited genetic diseases or "rare diseases" (RD) refer to medical conditions that affect a small percentage of the population but has vast, debilitating and often life threatening effects of the patients, many of whom are in the paediatric age group. Treatments for such diseases has long been neglected by the traditional pharma industry because of the notion that it will have uncertain or poor commercial outcomes given the smaller affected population size. Cumulatively, approximately 70 million Indians suffer from some form of RD. These include haemophilia, thalassemia, sickle-cell anaemia certain forms of muscular dystrophies, retinitis pigmentosa, primary immunodeficiency (PID) in children, lysosomal storage disorders such as Pompe disease, Gaucher's disease, haemangioma, cystic fibrosis etc. For a variety of debilitating diseases caused by genetic mutations, gene therapy offers a treatment modality that cannot be provided by conventional therapy including small molecule drugs or alternative medicine. However, the government agencies recognise this problem and have been working with many groups around the country to establish rare disease policies as has been done in many western nations, to encourage the development of products intended to diagnose, manage or treat RDs as well as spread awareness and education to prevent inherited conditions. The Central Drugs Standard Control Organization (CDSCO), the national regulatory body for Indian pharmaceuticals, in the New Drugs and Clinical Trials Rules, 2019 (NDCTR), has defined an rare disease drug or "orphan drug" as "a drug intended to treat a condition which affects not more than five lakh [5,00,000] persons in India".

Ever since the discovery of the human genome sequence, the pace of drug development has seen unprecedented pace and the knowledge of the genes and their mutations has led to the development of a variety of gene and cell based therapeutic approaches. Countries around the world have had to develop policies and guidelines to aid the development and monitor the applications of such drugs. In the past 3 years, several gene and cell therapy products have received approval for patient use from US and EU regulators, paving the way for development of therapies for a variety of previously untreatable disorders. Worldwide, the market for such treatments for rare diseases is predicted to grow at a compound annual growth rate (CAGR) of 11.3% from 2018 to 2024 and predicted to reach revenues of more than $250bn. In most countries, such policies for development of gene and cell therapy products is also accompanied by R & D support avenues, clinical trial pathways and education and awareness amongst the clinical community.

India did not have any guidelines for the development of gene and cell therapies, a lacuna that is being filled today with the hard work and inspiration of many stakeholders, including scientists from the field, leaders of the clinical community and many patient advocacy groups.

We recognise the huge burden of genetic diseases in India and therefore the need to accelerate the development of advanced therapeutic options for such conditions. This seminal document will also serve as an important resource and roadmap for

those in the field trying to develop gene and cell therapies. We hope this will spur innovation and accelerate research into RDs in our nation. There remain many hurdles that the scientific and clinical community working in the RD fields have yet to overcome, primarily the appropriate and timely diagnosis including genetic testing and genetic counselling, prohibitive costs of such gene therapies, adequate insurance coverage and management practices among treating physicians. Towards the goal of crossing these hurdles, the guidelines are being released to the nation.

To ensure that such therapies can be introduced in India and clinical trials for gene therapies can be performed in an ethical, scientific and safe manner, this national guideline document has been created. The salient features of this document are as follows:

1. Gene Therapy Products (GTP) are defined as any entity which includes a nucleic acid component being delivered by various means for therapeutic benefit to patients.
2. This term GTP is applicable to entities that are used for, but not limited to, gene augmentation, gene editing, gene silencing, synthetic or chimeric gene augmentation, etc.
3. These national guidelines provide the general principles for developing GTPs for any human ailment and provides the framework for human clinical trials which must follow the established general principles of biomedical research for any human applications.
4. The guidelines cover all areas of GTP production, pre-clinical testing and clinical administration as well as long term follow up.
5. All GTP research pertaining to human applications must be conducted within the principles of these guidelines in a scientific and ethical manner following all regulatory requirements as laid down for all forms of GTP.
6. Guidelines provide the Mechanism for Review & Oversight for all GTP development for human applications.
7. Responsibilities of investigators/institution/sponsors/Ethics committees are provided in the guidelines.
8. The guidelines cover all considerations for Chemistry, Manufacturing and Control, Quality Assurance, Product Attributes for GTP, including personnel training and infrastructure requirements.
9. Requirements for Preclinical evaluation of investigational strategies/products for gene therapy are also clearly outlined in the document.
10. All GTP development activities will be steered by Gene Therapy Advisory and Evaluation Committee (GTAEC) with the secretariat at ICMR, which shall be notified by DHR.
11. The guidelines detail all the requirements for enrolling patients in GTP human trials, their risk and safety assessments and trial designs which must be approved by the GTAEC, RCGM and CDSCO prior to patient administration.
12. These national guidelines apply to all stakeholders in the field of gene therapy including researchers, clinicians, oversight/regulatory committees, industry, patient support groups and any others involved in GTP development or their application in humans and their derivatives.