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S&A PHARMA NEWSLETTER

EDITORIAL

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Founding Partner

The rapid growth and advancement in Health research is not only building the health practice standards globally, but also raising the social responsibility of healthcare personals towards health services. The latest edition of our Pharma newsletter addresses interesting chapters including research guidelines, research outcomes, drug approvals and public health reports.

The current issue covers the national guidelines released by Indian Council of Medical Research (ICMR): on stem cell research, which reiterates that any stem cell use in patients, other than that for hematopoietic stem cell reconstitution for approved indications, is investigational at present. Then there is report on ICMR's National guideline for biomedical research involving children; and National guideline for biomedical research on human participants, which address newer emerging ethical issues keeping in view the social, cultural, economic, legal and religious aspects of our country. Then we discuss Pharmacovigilance guidance for Pharmaceutical industries, introduced for the first time by Government of India in order to ensure smooth functioning of Pharmacovigilance activities by Marketing Authorization Holders of Pharmaceutical Products. Thereafter we have covered a news report on Phase I/II clinical research outcomes, where two vaccines from Hilleman Laboratories demonstrated impressive results against deadly Rotavirus disease and cholera. Furthermore, a report on Médecins Sans Frontières (MSF) which is an international medical humanitarian organization that has filed a petition before the Delhi High Court challenging unmerited patent grant for pneumonia vaccine to a US pharmaceutical giant by the Indian Patent Office.

We also discuss a news article on the United States Court ruling on Allergan's Restasis Patents, where the judge has also raised serious concerns about Allergan-Mohawk Tribe Agreement. This ruling could have serious implications on usage of sovereign immunity clause by corporate entities.

We wrap up this newsletter with news of US FDA's CAR-T cell therapy (Yescarta (axicabtagene ciloleucel)) approval for certain types of non-Hodgkin lymphoma (NHL), first approval of a gene therapy (Luxturna) to treat a disease caused by a genetic mutation (hereditary blindness) recommended by USFDA advisory committee. US FDA's grant of Breakthrough Therapy (BTD) designation to Osimertinib for certain patients suffering from a specific type of Lung Cancer.

We sincerely hope that you find the articles of this newsletter interesting & enriching.

Please feel free to send your valuable inputs / comments at newsletter@singhassociates.in

Thank you.

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Indian Council of Medical Research (ICMR) issues National Guidelines for Stem Cell Research - To Curb 'Rampant' Unethical Therapeutic Practices

In October 2017, the Indian Council of Medical Research (ICMR) released the National Guidelines for Stem Cell Research[1]. The National Guidelines for Stem Cell Research, 2017, is an outcome of concerted efforts of different stakeholders. It has been formulated taking into account several new scientific and technical advancements as well as the perceived challenges in the field. Efforts were made to bring together all concerned ministries/ agencies to chalk out strategies to curb rampant unethical practices in banking and therapeutic applications.

The guideline reiterates that any stem cell usage in patients, other than that for hematopoietic stem cell reconstitution for approved indications, is investigational at present. Accordingly, any stem cell use in patients must only be done within the purview of an approved and monitored clinical trial with the intent to advance science and medicine, and not for offering it as therapy. In accordance with this stringent definition, any use of stem cells in patients outside an approved clinical trial is unethical and shall be considered as malpractice.

Some major amendments in this guideline include: mandatory registration of Institutional Committee for Stem Cell Research (ICSCR) and Institutional Ethics Committee (IEC) with National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) and CDSCO respectively; undertaking clinical trials only at institutes with registered IC-SCR, IEC, and only at Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) certified facilities; research undertaken by medical professionals registered with the Medical Council Of India (MCI) having an MCI approved post graduate qualification in the domain area of the specific trial.

These guidelines are applicable to all stakeholders including individual researchers, organizations, sponsors, oversight/regulatory committees and all others associated with both basic and clinical research involving any kind of human stem cells and their derivatives.

ICMR's guidelines states that sponsors must gain approval from the Central Drugs Standard Control Organization (CDSCO) before starting clinical trials of stem cells. Trials can only take place at registered Institutional Committee for Stem Cell Research and under the oversight of medical professionals registered with the Medical Council of India. These rules apply to all stem cell trials. ICMR has also introduced tiered regulatory requirements tied to the level of manipulation performed on the stem cells. Cells that undergo genetic modifications are subject to different regulatory requirements than those that are used in a form close to their natural state.

ICMR has found no scientific evidence "to substantiate clinical benefits with the use of stem cells derived from cord tissue, placenta, tooth extract, adipose tissue, dental pulp, menstrual blood and olfactory ensheathing cells." Given Indian companies' offers to bank these materials, ICMR is concerned about the "exploitation and commoditization of the resources."

As of now, CDSCO only permits and licenses umbilical cord banking. A list of approved indications for Hematopoietic Stem Cell Transplantation (HSCT) has also been provided as an annexure in the guideline. The guideline lists 20 types of indications (diseases) for adults and another 13 categories of indications for children below 18 years, where stem cell treatment is approved.

1 http://icmr.nic.in/guidelines/Guidelines_for_stem_cell_research_2017.pdf

Accordingly, commercial banking of all other biological materials is not permitted until further notification. ICMR wants the regulator to enforce this rule.

Banking of Umbilical Cord Blood (UCB)

The guideline says that UCB is a rich source of CD34+ hematopoietic and mesenchymal (stromal) stem cells. Use of UCB derived Hematopoietic Stem Cells (HSCs) for treatment of various haematological and immunological disorders is currently well established, particularly where an HLA-matched sibling is not available. However, there is a paucity of public funded UCB banks in India. On the other hand several private banks have come-up, that engage themselves in promotional advertising offering storage of cord blood with the promise of future therapeutic use. Such advertisements are often misleading for the public and lack comprehensive and accurate information. So far there is no scientific basis for preservation of cord blood for future self-use and this practice therefore raises ethical and social concerns.

Publicity and Advertisements in Media

The guideline also states that the advertising and publicity through any mode is not permitted. It may be noted that actions can be taken against the erring clinicians/entities under existing rules and regulations of Medical Council of India, The Drugs and Magical Remedies (The Objectionable Advertisements) Act- 1954, Advertisement of treatment of several diseases as listed in Schedule J of Drugs and Cosmetics Act, 1940 and rules therein, and any advertisement that violates the code for self regulation in advertising, as adopted by the Advertising Standards Council of India (ASCI).

Conclusion:

The 2017 guidelines, reiterate that any stem cell use in patients, other than that for hematopoietic stem cell reconstitution for approved indications, is investigational at present. Accordingly, any stem cell use in patients must only be carried out within the purview of an approved and monitored clinical trial with the intent to advance science and medicine, and not as offering it as therapy.

Central Drugs Standard Control Organization (CDSCO)'s marketing approval of four medicines in September 2017

The Central Drugs Standard Control Organization (CDSCO), India, has approved four drugs in the month of September 2017[2]. Two of the approved drugs belong to Oncology & Haematology (Ribociclib and Treosulfan), one from Neurology and Psychiatry (Brivaracetam) and one from Reproductive & Urology (Dienogest) subject expert committee. The details of these four drugs are described –

1. Briveracetam film coated tablets: On September 07, 2017 CDSCO has approved Briveracetam film coated tablets in the strengths of 50 mg, 75 mg and 100 mg; indicated as an adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 16 years of age and older with epilepsy.

   The import and marketing approval of Brivaracetam 50mg, 75 mg &100mg film-coated tablets has been granted to UCB India Pvt. Ltd. based on the global clinical study report including data generated from various clinical studies conducted on 256 Indian patients on tablet formulations. The Subject Expert Committee (ESC) of CDSCO observed that the data from the Indian subset analysis is in line with the global data[3].

2. Treosulfan Bulk & injection 5g/vial: On September 26, 2017, CDSCO has approved Treosulfan Bulk & injection 5g/vial for the conditioning treatment prior to haematopoetic stem-cell transplantation.

   The manufacturing and marketing approval of Treosulfan Bulk & injection 5g/vial has been granted to Emcure Pharmaceutical Ltd. The approval is subject to the condition that the firm shall conduct phase IV clinical trial in 50 patients. Accordingly, the firm shall submit phase IV protocol within 3 months of grant of manufacture and marketing permission[4].

3. Ribociclib 200 mg film coated tablets: On September 27,2017 CDSCO has approved Ribociclib 200 mg film coated tablets in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of post menopausal women with the hormone receptor (HR)-Positive, human epidermal growth factor receptor 2 (HER2)-Negative advanced or metastatic breast cancer.

   The import and market approval of Ribociclib 200 mg film coated tablets has been granted to Sandoz Pvt. Ltd. The approval is subject to the condition that the firm shall submit the report of ongoing global clinical trials where India is one of the participating countries[5].

4. Dienogest Bulk & 2mg Tablet: On September 28 2017, CDSCO has approved Dienogest Bulk & 2mg Tablet for the management of Pelvic pain associated with Endometriosis.

2 http://www.cdsco.nic.in/forms/list.aspx?lid=2034&ld=11

3 http://www.cdsco.nic.in/writereaddata/Recommendation17_3_2017.pdf

4 http://www.cdsco.nic.in/writereaddata/Recommendation%20Oncology_16_05_17.pdf

5 http://www.cdsco.nic.in/writereaddata/Recommendation%20Oncology_16_05_17.pdf

India releases Pharmacovigilance Guidance Document for Marketing Authorization Holders of Pharmaceutical Products

The Secretary, Ministry of Health and Family Welfare, Government of India has released Pharmacovigilance Guidance Document for Marketing Authorization Holders of Pharmaceutical Products.

Pharmacovigilance

According to the World Health Organization, Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. WHO established its Programme for International Drug Monitoring in response to the Thalidomide disaster detected in the year 1961. Together with the WHO Collaborating Centre for International Drug Monitoring, Uppsala, WHO promotes PV at the country level. By the end of 2010, 134 countries were part of the WHO PV Programme. The aims of PV are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines[6].

Pharmacovigilance Program of India

The Central Drugs Standard Control Organisation (CDSCO), New Delhi, under the aegis of Ministry of Health & Family Welfare, Government of India has initiated a nation-wide Pharmacovigilance programme in July 2010. The Pharmacovigilance Program of India (PvPI) was launched with a broad objective to safe guard the health of 1.27 billion people of India. Adverse Drug Reactions (ADRs) are reported from all over the country to National Coordination Centre (NCC)-PvPI, which also works in collaboration with the global ADR monitoring centre (WHO-UMC), Sweden, to contribute in the global ADRs data base. NCC-PvPI monitors the ADRs among Indian population and helps the regulatory authorities of India (CDSCO, Indian Pharmacopeia Commission (IPC)) in taking decision for safe use of medicines.

PvPI collects and evaluates spontaneous reports of Adverse Drug Reactions (ADRs) due to use of medicines, vaccines, medical devices and herbal products from all healthcare professionals and consumers/patients. To monitor ADRs and reporting the same to NCCPvPI, ADR Monitoring Centres (AMCs) have been set up all over India. At present 250 AMCs (medical colleges, district and corporate hospitals etc) are enrolled under PvPI across the country[7].

Pharmacovigilance Guidance Document for Marketing Authorization Holders (MAHs)

In order to ensure smooth functioning of Pharmacovigilance activities by Pharmaceutical industries, National Coordination Centre-Pharmacovigilance Programme of India (NCC-PvPI), in collaboration with Central Drugs Standard Control Organization (CDSCO), has developed Pharmacovigilance Guidance for Marketing Authorization Holders (MAHs) of Pharmaceutical Products.

This Pharmacovigilance guidance document is introduced for the first time by the Government of India for Pharmaceutical industries which aims to establish and ensure an effective Pharmacovigilance system at their site as per recent amendment in the Drugs & Cosmetics Rules, 1945, Schedule Y vide Gazette Notification G.S.R. 32 (E) published on March 08, 2016. This guidance document is prepared under the aegis of CDSCO by the NCC – Pharmacovigilance Programme of India (PvPI), The Indian Pharmacopoeia Commission (IPC), for guiding MAHs involved in the manufacture, sale, import, and distribution of pharmaceutical products in India.

6 http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

7 http://ipc.nic.in/showfile.asp?lid=833&EncHid=

The MAHs Pharmacovigilance Guidance Document comprises following modules:

- MODULE 1 – Pharmacovigilance System Master File
- MODULE 2 – Collection, Processing & Reporting of Individual Case Safety Reports
- MODULE 3 – Preparation & Submission of Periodic Safety Update Report
- MODULE 4 – Quality Management System at Marketing Authorization Holder organization
- MODULE 5 – Audits & Inspections of Pharmacovigilance System at Marketing Authorization Holder organization
- MODULE 6 – Submission of Risk Management Plan

The effective date for this guidance document has been set as January 2018[8].
The guidance document defines the roles of CDSCO, IPC, NCC-PvPI, States(s)/UT(s) Drug Regulatory Authority and the MAHs in Individual Case Safety Reports (ICSRs) processing; submission of Periodic Safety Update Reports (PSURs); Audits and Inspections, and Risk Management Plans (RMPs) wherever applicable. The guidance document also provides assistance to MAHs on establishing and ensuring an effective pharmacovigilance system at their site.

Conclusion:

This guidance document intends to be an aid to the Marketing Authorization Holders and other stakeholders in meeting the pharmacovigilance regulations and requirements of the Indian Drug Regulator (CDSCO). The main focus of the guidance document is to ensure identification of risks associated with pharmaceutical products and establishment of an ideal pharmacovigilance system to mitigate such risks.

8 www.ipc.gov.in/PvPI/pub/Guidance Document for Marketing Authorization Holders.pdf

Hilleman Laboratories announces successful outcome in Phase I/II Clinical Trials of two under development vaccines

The Hilleman Laboratories, which is a joint-venture between Merck Sharp & Dohme (MSD) and the Wellcome Trust. The Hilleman Laboratories has been named after renowned scientist and father of modern vaccines - Dr. Maurice Hilleman. His dedication to making a difference through the practical application of vaccine research and delivering vaccines to people in need, forms the core mission of Hilleman Laboratories.

On October 12, 2017, the Laboratories has announced the successful completion of Phase I/II clinical trial of its two vaccines: **Heat Stable Rotavirus Vaccine (HSRV)** oral vaccine against the deadly Rotavirus disease and its novel **Oral Cholera Vaccine Hillchol™**.

The clinical trials were conducted in partnership with the International Centre for Diarrhoeal Disease Research (ICDDR), Bangladesh. The results of these clinical trials were presented at the Vaccines for Enteric Disease Conference 2017, held in Albufeira, Portugal.

Oral Cholera Vaccine Hillchol:

Hillchol™ was tested on 840 subjects that included adults, adolescents as well as small children to assess safety and tolerability. The Hillchol™ vaccine consists of a novel Hikojima strain that expresses both the Ogawa and Inaba serotypes, and also replaces three virulent O1 strains inactivated by two different processes used in currently licensed vaccines.

According to the WHO, Cholera is endemic in over 50 countries with an estimated mortality of 100,000 - 120,000 deaths annually, and a morbidity of 3.8 - 4.4 million annual cases attributed to this disease. Cholera vaccine production is low, with demands currently exceeding supply. In 2014, the Hilleman Laboratories partnered with Gotovax AB of Sweden and Incepta Vaccines of Bangladesh for the development of an affordable Cholera vaccine[9]. Speaking on the results Dr. Tarun Sharma, Director R&D at Hilleman Labs said, "The Hillchol™ Phase I/II clinical trial results support the Hikojima vaccine design and mirrors the impressive results achieved in preclinical studies. This encourages conducting further clinical studies as well as undertaking further research in for additional innovations in next-generation Oral Cholera Vaccines"

Dr Davinder Gill, CEO Hilleman Laboratories said, "There is an urgent need for effective and affordable Cholera vaccines for use both during Cholera outbreaks and in mass vaccination campaigns. Currently, WHO recommends Oral Cholera Vaccines for humanitarian crises and in outbreaks. With the advancement of Hillchol™, we hope to make available to the global health community, an affordable vaccine for mass vaccination in hotspots against Cholera-endemic countries. This will greatly assist in the global initiative recently announced by WHO to reduce Cholera deaths by 90% by the year 2030".

Heat Stable Rotavirus Vaccine (HSRV):

HSRV study has demonstrated safety profile when administered and compared with placebo, did not result in an increased reporting of solicited AEs in the adult cohort. In infants, when administered as 3-dose primary series, HSRV had a safety profile similar to RotaTeq in terms of frequency, severity, and causality of solicited adverse effect. Immunogenicity assessment was found to be comparable between the HSRV and RotaTeq in infants.
The percentage of infants exhibiting a 3-fold rise in serum anti-rotavirus IgA at 1 month post-dose 3 administration from baseline in HSRV group was 88%. The percentage of infants who had a similar increase in the RotaTeq group

9 http://www.hillemanlabs.org/news-details.aspx?mpgid=31&pgid=32&nid=51

was 84%. In addition, HSRV elicited comparable Geometric Mean Titre relative to RotaTeq, 1 month after completion of 3-dose vaccination schedule.

After successful completion of the preclinical animal studies and obtaining regulatory clearance for human studies, Hilleman Laboratories had initiated a clinical study in April 2016, to establish proof-of-concept for its heat stable Rotavirus vaccine. The vaccine is aimed at allowing greater temperature stability and less reliance on exact storage timing and refrigeration.

Dr Davinder Gill, CEO Hilleman Laboratories said, "Worldwide, Rotavirus is the leading cause of severe diarrhoea and related deaths in children less than 5 years of age. First-generation Rotavirus vaccines possess thermostability profiles that may not meet storage requirements in developing countries, highlighting the need for heat stable vaccines. Considering the urgent need for effective and affordable Rotavirus vaccines, we would like to accelerate development of our simplified, easy-to-use, heat stable vaccine[10]."

10 http://www.hillemanlabs.org/news-details.aspx?mpgid=31&pgid=32&nid=52

Osimertinib granted breakthrough designation by FDA for 1st-line treatment of patients with EGFR (Epidermal Growth Factor Receptor) mutation-positive Non-Small Cell Lung Cancer (NSCLC)

AstraZeneca announced on 09-October-2017, that the United States Food and Drug Administration (US-FDA) has granted Breakthrough Therapy Designation (BTD) for Osimertinib for the 1st-line treatment of patients with metastatic epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC)[11].

The FDA granted the BTD based on data from the Phase III FLAURA trial of osimertinib versus standard-of-care EGFR tyrosine kinase inhibitor (TKI) therapy in previously-untreated patients with locally-advanced or metastatic EGFR mutation-positive NSCLC.

BTD is designed to expedite the development and regulatory review of new medicines that are intended to treat a serious condition and have shown encouraging early clinical results, which demonstrate substantial improvement on a clinically-significant endpoint over available medicines and when there is significant unmet medical need.

In the trial, median progression-free survival was 18.9 months for Osimertinib compared with 10.2 months for EGFR-TKIs (Erlotinib or Gefitinib). Improvements were seen in all pre-specified subgroups, including patients with and without brain metastases.

Approximately 10% to 15% of lung cancer patients in the US and Europe, and 30% to 40% of patients in Asia have epidermal growth factor receptor mutation-positive (EGFRm) NSCLC.

These patients are particularly sensitive to treatment with currently-available EGFR Tyrosine Kinase Inhibitors (TKIs), which block the cell signaling pathways that drive the growth of tumour cells.

However, tumours almost always develop resistance to EGFR-TKI treatment, leading to disease progression. Approximately half of patients develop resistance to approved EGFR-TKIs, such as Gefitinib and Erlotinib, due to the resistance mutation, EGFR T790M.

Osimertinib targets this secondary mutation that leads to disease progression.

The Breakthrough Therapy Designation acknowledges not only Osimertinib's potential as a 1st-line standard of care in advanced EGFR mutation-positive NSCLC, but also the significant need for improved clinical outcomes in this disease. The results of the FLAURA trial have the potential to redefine clinical expectations and offer new hope for patients who currently have a poor prognosis.

On September 28, 2017, the US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology were updated to include the use of Osimertinib in the 1st-line treatment of patients with locally-advanced or metastatic EGFR mutation-positive NSCLC. The use of Osimertinib for the 1st-line treatment of patients with locally-advanced or metastatic EGFR mutation-positive NSCLC is not yet FDA approved. However, Osimertinib is currently approved in more than 50 countries, including the US, EU, Japan and China, as 2nd-line treatment for

11 https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2017/tagrisso-granted-breakthrough-therapy-designation-by-us-fda-for-the-1st-line-treatment-of-patients-with-egfr-mutation-positive-non-small-cell-lung-cancer-09102017.html

patients with advanced NSCLC who progress following treatment with an EGFR TKI due to the EGFR T790M resistance mutation.

About NSCLC

Lung cancer is the leading cause of cancer death among both men and women, accounting for about one-quarter of all cancer deaths. Deaths due to lung cancer surpass deaths due to breast, prostate and colorectal cancers combined together. Approximately 10-15% of patients in the US and Europe, and 30-40% of patients in Asia have EGFR-mutated NSCLC. These patients are particularly sensitive to treatment with currently-available EGFR TKIs, which block the cell-signaling pathways that drive the growth of tumour cells. However, tumours almost always develop resistance to EGFR TKI treatment leading to disease progression. Approximately half of the patients develop resistance to approved EGFR TKIs such as Gefitinib and Erlotinib due to the resistance mutation, EGFR T790M. Tagrisso also targets this secondary mutation that leads to disease progression. There is also a need for medicines with improved CNS efficacy, since approximately 25% of patients with EGFR-mutated NSCLC have brain metastases at diagnosis, increasing to approximately 40% within two years of diagnosis.

About Osimertinib

Osimertinib is a third-generation, irreversible EGFR TKI (Tyrokinase Inhibitor) designed to inhibit both EGFR-sensitizing and EGFR T790M-resistance mutations, with clinical activity against Central Nervous System (CNS) metastases.

MSF approaches Delhi High Court to challenge unmerited patent grant for pneumonia vaccine

Médecins Sans Frontières (MSF)/Doctors without Borders India announced on October 13, 2017 that it has filed a petition before the High Court of Delhi to overturn the patent granted on the Pneumococcal Conjugate Vaccine (PCV) to the US pharmaceutical corporation Pfizer[12].

Earlier this year on August 13, the Indian Patent Office dashed hopes for improved access to an affordable PCV13 when it granted a patent to Pfizer for its PCV 13 product, marketed as Prevnar13, which will expire only in 2026. MSF had challenged Pfizer's unmerited patent claims on the vaccine in India last year, to enable and accelerate the availability of more affordable versions of PCV.

Globally, pneumonia causes more than a quarter of deaths in children under the age of five – that is nearly one million young lives lost per year. India carries the world's highest burden of pneumonia, accounting for nearly 20% of these global infant pneumonia deaths. The PCV13, which safeguards against 13 types of pneumococcal bacteria, also lowers the likelihood of antimicrobial resistance (AMR) by significantly reducing common childhood infections and decreasing the need for antibiotic use among infants and children.

In a petition filed at the Delhi High Court, MSF India has argued that in August 2017, the Delhi Patent Office erroneously granted a patent to Pfizer by disregarding the evidence, produced by MSF, which indicated that the pharmaceutical giant's claim to a patent was spurious. MSF argued that the mere addition of serotypes to the already established 7-valent vaccine did not involve a technical advancement – it was merely a tactic to preserve Pfizer's monopoly for many more years. The decision also has broader implications, as it indicates a weakening of India's strict patentability standards, which results in granting monopolies for minor and trivial improvements of existing medical products and restricts access to affordable medicines.

The Pneumococcal Conjugate Vaccine (PCV) is currently available from only two pharmaceutical corporations: Pfizer and GlaxoSmithKline (GSK). Unfortunately, this vaccine is priced out of reach of many parents, governments and treatment providers, due to a duopoly market and a lack of sufficient competition from Developing Country Vaccine Manufacturers (DCVM). Approximately one-third of the world's countries have not been able to introduce PCV, largely because of high prices. Those who have introduced the vaccine are struggling with its costs. South Africa spends more than 50% of its vaccination budget on purchasing PCV13 alone and this is set to continue for another decade unless patent barriers are removed to bring in more competition.

Yuanqiong Hu, Legal & Policy Advisor, MSF Access Campaign concluded saying that "While MSF has initiated the legal process to challenge the patent, the actual revocation of an unmerited patent takes years. Looking at the urgent need for this vaccine, we really hope that the Indian Health Ministry in the meantime considers issuing a government use license, to encourage manufacturers who have been developing more affordable PCV13 vaccines to continue with phase 3 clinical trials and deliver the life-saving vaccine for the immunization program, not just in India but across the world".

Conclusion:

Pneumococcal disease is the leading cause of vaccine-preventable deaths in children under five years of age both globally and in India. India accounts for nearly 20% of global pneumonia deaths in this age group. In 2010, pneumococcal pneumonia accounted for approximately 16% of all severe pneumonia cases and 30% of pneumonia related deaths in children under five years of age in India[13]. Médecins Sans Frontières which has earlier also objected to the grant of the patent for this vaccine has now filed a petition before the High Court of Delhi to overturn the patent granted to the US pharmaceutical corporation Pfizer.

12 https://www.msfindia.in/msf-approaches-delhi-high-court-challenge-unmerited-patent-grant-pneumonia-vaccine-0

13 http://pib.nic.in/newsite/PrintRelease.aspx?relid=161763

Department of Pharmaceuticals (DoP) has invoked the powers under paragraph 3 of Drugs Prices Control Order, 2013

National Pharmaceutical Pricing Authority (NPPA), a regulatory body under Department of Pharmaceuticals, Government of India, is authorized to fix/ revise the prices of controlled bulk drugs and formulations and to enforce prices and availability of the medicines in the country under Drug Price Control Order (DPCO), 2013.

Whereas the NPPA has fixed the prices of some medical devices such as coronary stents and knee implant system. Further in larger public interest, uninterrupted supply of these medical devices will also be ensured by the government. In this context, the Department of Pharmaceuticals (DoP), Indian government has invoked the powers under paragraph 3 of Drugs Prices Control Order (DPCO), 2013 to ensure the compliance of price capping of medical devises with maintaining its uninterrupted supply.

Paragraph 3 of DPCO, 2013 prescribes that "the government may (i) with a view to achieve adequate availability and to regulate the distribution of drugs, in case of emergency or in circumstances of urgency or in case of non-commercial use in public interest, direct any manufacturer of any active pharmaceutical ingredient or bulk drug or formulation to increase the production and to sell such active pharmaceutical ingredient or bulk drug to such other manufacturer(s) of formulations and to direct formulators to sell the formulations to institutions, hospitals or any agency as the case may be;

(ii) for the purpose of giving any direction under sub-paragraph (i), call for such information from manufacturers of active pharmaceutical ingredients or bulk drugs or formulations, as it may consider necessary and such manufacturer shall furnish the required information within such time the Government may fix."

On September 18, 2017, through its notification, Department of Pharmaceuticals (DoP), Indian Government has advised Knee Implant manufacturers and importers to ensure compliance to the price capping of the Primary Knee and Revision Knee along with maintaining uninterrupted supply.

The companies are also directed to:

1) Furnish the production figures for 2015-16, 2016-17, and 2017-18;
2) To maintain production/ import/ supply of the orthopedic knee implant systems at the same levels before August 2017, and
3) To submit a weekly report on orthopedic knee implant systems produced and distributed[14].

Similarly, on September 27, 2017, through its notification, Department of Pharmaceuticals (DoP), Indian Government has advised 62 coronary stent manufacturers to ensure compliance to the price capping of the coronary stent along with maintaining uninterrupted supply.

The Companies manufacturing coronary stent in India are also directed to:

1) Maintain production/ import/ supply of coronary stents
2) To submit a weekly report on coronary stents produced and distributed. They will also submit a weekly production plan for the next week to NPPA and DCGI.

14 http://pharmaceuticals.gov.in/sites/default/files/implants%20para%203%20order.pdf

This order will be valid for next three month from the date of notification (except for absorb classic BVS and Absorb GTI BVS stent of M/s Abbott Healthcare) and NPPA and DCGI will recommend withdrawal or extension as the case may be. NPPA and Drug Controller General of India (DCGI) are also empowered to extend these directions to any other producers of coronary stents in India during this three-month period[15].

15 http://pharmaceuticals.gov.in/sites/default/files/Para%203%20order%20dated%2027-09-2017.pdf

New World Health Organization (WHO) report signals urgent need for greater political commitment to end tuberculosis

Tuberculosis remains leading infectious killer

According to the new Global TB Report 2017[16] released by the World Health Organization (WHO) in October 2017, global efforts to combat Tuberculosis (TB) have saved an estimated 53 million lives since 2000 and reduced the TB mortality rate by 37%.

However, despite these achievements, the latest picture is grim. TB remained the top infectious killer in 2016. TB is also the main cause of deaths related to antimicrobial resistance and the leading killer of people with HIV. Progress in most countries is not fast enough to reach global targets or even close persistent gaps in TB care and prevention.

TB is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB). The disease spreads when people who are sick with pulmonary TB expel bacteria into the air, for example by coughing.

High global burden of disease and death in 2016

Overall, the latest picture emerges as one of a still high burden of disease, and progress that is not fast enough to reach neither targets nor making a major headway in closing persistent gaps. TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS.
In 2016, there were an estimated 10.4 million new TB cases worldwide; 10% of which were people living with HIV. Seven countries accounted for 64% of the total burden - with India bearing the brunt, followed by Indonesia, China, Philippines, Pakistan, Nigeria and South Africa. An estimated 1.7 million people died from TB, including nearly 400 000 people who were co-infected with HIV. There is a drop in numbers by 4% compared to 2015[17].
Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. WHO estimates that there were 600 000 new cases with resistance to Rifampicin – the most effective first-line drug, of which 490 000 had MDR-TB. Almost half (47%) of these cases were in India, China and the Russian Federation.

Persistent gaps in care and financing

Tackling the epidemic requires action to close gaps in care and financing. It also requires progress in a particular subset of high TB burden countries such as India, Indonesia, Nigeria, the Philippines, South Africa, Pakistan, Bangladesh, the Democratic Republic of the Congo, China and the United Republic of Tanzania.

Underreporting and under diagnosis of TB cases continues to be a challenge, especially in countries with large unregulated private sectors and weak health systems. Of the estimated 10.4 million new cases, only 6.3 million were detected and officially notified in 2016, leaving a gap of 4.1 million. India, Indonesia and Nigeria accounted for almost half of this global gap.

Only one in five MDR-TB cases was started on treatment. India and China accounted for 39% of the global gap. Treatment success remains low, at 54% globally.
Of the almost half a million reported cases of HIV-associated TB, 15% were not on antiretroviral therapy (ART) as recommended by WHO. Most of the gaps related to HIV-associated TB were in the WHO African Region.

16 http://www.who.int/mediacentre/news/releases/2017/political-commitment-tb/en/

17 http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf

Preventive treatment for TB is expanding in two priority risk groups - people living with HIV and children under 5 years. However, most people eligible for TB preventive treatment are not accessing it.

For TB care and prevention, investments in low- and middle-income countries fell almost US$ 2.3 billion short of the US$ 9.2 billion needed in 2017. In addition, at least an extra US$ 1.2 billion per year is required to accelerate the development of new vaccines, diagnostics, and medicines.

Shortfalls in TB funding are one of the main reasons why progress is not fast enough to be on track to reach the end TB targets. More domestic funding is needed in middle-income countries, and more international donor support is needed to support low-income countries.

Political commitment and multi-sectoral action

Ending the TB epidemic requires actions beyond the health sector so as to address the risk factors and determinants of the disease. For the first time, the Global TB Report presents results from a new multi-sectoral monitoring framework that identifies linkages with the TB epidemic across seven Sustainable Development Goals (SDGs). Analysis of the latest status of the indicators for the 30 high TB burden countries show that most will be challenged to reach SDG targets.

In order to increase multi-sectoral action, plans to galvanize all sectors and secure attention at the highest levels, the WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era is scheduled to be held in Moscow on 16 and 17 November 2017. This will be followed by the very first UN General Assembly High-Level Meeting on TB in 2018, which will seek commitment from heads of state.

Global Hunger Index (GHI) 2017: India's position is at the high end of serious category

Global Hunger Index (GHI) is designed to comprehensively measure and track hunger score globally and by country and region. Since 2006, GHI calculated each year by the International Food Policy Research Institute (IFPRI), highlights successes and failures in hunger reduction and provides insights into the drivers of hunger. GHI is released by the International Food Policy Research Institute (IFPRI). IFPRI provides research-based policy solutions to sustainably reduce poverty and end hunger and malnutrition in developing countries.

GHI score is calculated based on three dimensions and four indicator parameters therein. The three dimensions followed by four indicators are:

A) *Inadequate food supply:*

1) **Undernourished population** - The share of the population whose caloric intake is insufficient,

B) *Child undernutrition:*

2) **Child wasting** - The share of children under the age of five who have low weight for their height, reflecting acute under nutrition,

3) **Child stunting** - the share of children under the age of five who have low height for their age, reflecting chronic under nutrition, and

C) *Child mortality:*

4) **Infant mortality rate** - the mortality rate of children under the age of five is a reflection of the fatal mix of inadequate nutrition and unhealthy environments.

GHI ranks countries on a 0-100 point scale, wherein 0 indicates no hunger and 100 stands for worst position of hunger. The GHI severity scale applied to 119 countries in the GHI 2017 report shows varied result.

GHI Severity Scale	
0 - 9.9	Low
10.0 – 19.9	Moderate
20.0 – 37.9	Serious
35.0 – 49.9	Alarming
50 ≤	Extremely Alarming

GHI 2017 shows that India has serious hunger problem, as the country has slipped 3 ranks from 97th position in 2016 to 100th position in 2017 among 119 countries listed in the report. Moreover, GHI 2017 also reports that three-quarters of South Asia's population resides in India, therefore, the situation in this country strongly influences South Asia's regional score. At 31.4, India's 2017 GHI score is at the high end of the serious category. According to the 2015–2016 survey data, more than a fifth (21 percent) of children in India suffer from wasting. Further, India's child wasting rate has not improved substantially over the past 25 years. But country has made progress in child stunting rate from its GHI 1992 score.

India ranks behind its neighbor countries except Pakistan and Afghanistan. It has third highest global hunger score in whole Asia. The South Asian countries' GHI index score over the years including GHI 2017 rank details are:

Rank (2017)	Country	1992	2000	2008	2017
29	China	25.9	15.8	11.2	7.5
72	Nepal	42.5	36.8	28.9	22.0
77	Myanmar	55.6	43.6	30.1	22.6
84	Sri Lanka	31.6	26.8	24.2	25.5
88	Bangladesh	53.6	37.6	32.2	26.5
100	India	46.2	38.2	35.6	31.4
106	Pakistan	42.7	38.2	34.7	32.6
107	Afghanistan	50.7	52.7	37.9	33.3
-	Bhutan*	-	-	-	-

* *Ranks detail could not be included because of unavailability of data from the country*

The two major National programs that addresses nutrition and primary healthcare in India - Integrated Child Development Service and National Health Mission have not achieved their adequate milestones.

The GHI 2017 also reports the extremely alarming position of Central African Republic, which has the highest GHI score followed by Chad, Sierra Leone, Madagascar and Zambia.

Apart from these, there are fourteen countries, including China, Peru, Brazil, Panama and Azerbaijan that have made significant improvements since 2000.

United States Court Rules Restasis Patents Invalid, Raises Concerns about Allergan-Mohawk Tribe Agreement

The United States District Court for the Eastern District of Texas, on October 16, 2017, ruled four of the Allergan's patents as invalid concerning its blockbuster eye drug Restasis. Allergan has said that it will appeal the decision, but what might have a wider ripple effect was another order that raised questions about Allergan's decision to transfer the patents to a Native American tribe to prolong the launch of Restasis generics.

Background

Restasis, one of the blockbuster products for Allergan, used for treatment of dry eyes, is an ophthalmic formulation of cyclosporine. It's a valuable part of their portfolio (net revenues of more than a billion dollars per year), but has been under threat from a patent challenge. Mylan and Teva are both trying to force the drug off patent before its appointed time (which is about 2024). Last December, the US Patent Office granted an inter partes review of the relevant patents, a decision that did not go down well with Allergan or its investors.

About a month ago, Allergan agreed to transfer the patents on its blockbuster Restasis to the Saint Regis Mohawk Tribe, which has sovereign immunity and can protect them from challenges from generic competitors. As part of the agreement, the Tribe received a one-time payment of $13.75 million and possible annual royalties of about $15 million for as long as the patents remain valid. After the transfer, lawyers representing Allergan and the Tribe moved to dismiss an IPR against their patents on the grounds that the patents now enjoyed "sovereign immunity."

Allergan had made this unorthodox agreement to protect Restasis patents from challenges made through the U.S. Patent and Trade Office's inter partes review process, which is separate from any court decisions.

Generics company Mylan essentially called the move by Allergan a sham and said that it was merely an attempt to evade generic competition for a longer period of time.

Order

The United States District Court for the Eastern District of Texas issued a 135-page decision finding all asserted claims of the patents relating to Restasis® invalid based on obviousness. The Court, recognizing that Allergan's patent protection for Restasis ended in 2014, concluded that "Allergan is not entitled to renewed patent rights for Restasis in the form of a second wave of patent protection." The invalidated patents are United States Patent Numbers 8,629,111; 8,648,048; 8,685,930 and 9,248,191[18].

In another 11-page order, separate from the one invalidating the Restasis patents for obviousness, US Circuit Judge William Bryson wrote that the court "has serious concerns about the legitimacy of the tactic that Allergan and the Tribe have employed. The essence of the matter is this: Allergan purports to have sold the patents to the Tribe, but in reality it has paid the Tribe to allow Allergan to purchase—or perhaps more precisely, to rent—the Tribe's sovereign immunity in order to defeat the pending IPR proceedings in the PTO. This is not a situation in which the patentee was entitled to sovereign immunity in the first instance. Rather, Allergan, which does not enjoy sovereign immunity, has invoked the benefits of the patent system and has obtained valuable patent protection for its product, Restasis[19].
"What Allergan seeks is the right to continue to enjoy the considerable benefits of the U.S. patent system without accepting the limits that Congress has placed on those benefits through the administrative mechanism for canceling invalid patents," Bryson added.

18 http://www.ipwatchdog.com/wp-content/uploads/2017/10/523-Allergan-Opinion.pdf

19 http://www.ipwatchdog.com/wp-content/uploads/2017/10/522-Allergan-Joinder.pdf

Bryson also concluded that "Sovereign immunity should not be treated as a monetizable commodity that can be purchased by private entities as part of a scheme to evade their legal responsibility".

Case Reference:

Case 2:15-cv-01455-WCB, ALLERGAN, INC., and THE SAINT REGIS MOHAWK TRIBE, (Plaintiffs) v. TEVA PHARMACEUTICALS USA, INC., et al., (Defendants)

National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017: ICMR

The Indian Council of Medical Research (ICMR) has issued the latest version of "*National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017*" which is a subsequent amendment of its "Ethical Guidelines for Biomedical Research on Human Participants" released in 2006. The ICMR had introduced its first statement policy on "*Ethical Considerations Involved in Research on Human Subjects***"** in 1980. Further, due to rapid advances in Biomedical Science and Technology, the "*Ethical Guidelines for Biomedical Research on Human Subjects*" was released in 2000, followed by the revised "*Ethical Guidelines for Biomedical Research on Human Participants*" in 2006.

The latest "*National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017*" has adopted some important guidance points from the international guidelines, and addresses the newer emerging ethical issues keeping in view the social, cultural, economic, legal and religious aspects of our country.

The new expanded guideline has included separate sections on–

1. **Responsible Conduct of Research,**
2. **Informed Consent Process,**
3. **Vulnerability,**
4. **Public Health Research,**
5. **Social and Behavioural Sciences Research for Health,**
6. **Biological Materials, Biobanking and Datasets,**
7. **International Collaboration, and**
8. **Research during Humanitarian Emergencies and Disasters**.

Responsible Conduct of Research (RCR)

This new section describes that the value and benefits of research are dependent on the integrity of the researchers. Responsible researchers abide by the standards prescribed by their professions, disciplines and institutions and also by relevant laws. Therefore, the institutions conducting research must establish a research office within their institution to facilitate research, manage grants, and oversee all aspects of RCR. Standard operating procedures should be in place to address all the major components of RCR as outlined in the following table.

The RCR involves the following major components:

- Values of research
- Policies of research
- Planning and conducting research – Specific Issues
- Reviewing and reporting research

- Responsible authorship and publication
- Research misconduct and policies for handling misconduct

Informed consent process

This section broadly addresses the informed consent process with the headings of essential information for prospective research participants, documentation of consent, waiver of consent and also explains the special consent processes such as –

- Electronic consent,
- Re-consent or fresh consent in case of new information availability, changes in treatment protocol, extension of research or follow up etc.
- Consent in special situations like - gatekeeper consent, community consent and consent from vulnerable groups
- Consent for studies using deception (Some types of research studies require deception due to nature of research design).

Vulnerability

Vulnerable persons are those individuals who are relatively or absolutely incapable of protecting their own interests due to lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so.

The current guideline broadly categorizes the vulnerable population and addresses the key principles, additional safeguard mechanism and responsibility of stakeholders to be followed when research is planned on these persons so that others will be responsible for protecting their interests because the participants cannot do so. These are the examples of vulnerable populations as per the guideline:

- Economically and socially disadvantaged (unemployed individuals, orphans, abandoned individuals etc.)
- Unduly influenced either by the expectation of benefits or fear of retaliation in case of refusal to participate which may lead them to give consent;
- Children (up to 18 years);
- Women in special situations (pregnant or lactating women, or those who have poor decision-making powers/poor access to healthcare);
- Tribals and marginalized communities;
- Refugees, migrants, homeless, persons or populations in conflict zones, riot areas or disaster situations;
- Afflicted with mental illness and cognitively impaired individuals, differently abled – mentally and physically disabled;
- Terminally ill or are in search of new interventions having exhausted all therapies;
- Suffering from stigmatizing or rare diseases; or

- Have diminished autonomy due to dependency or being under a hierarchical system (students, employees, subordinates, defense services personnel, healthcare workers, institutionalized individuals, under trials and prisoners).

Public Health Research:

Public health practice involves data collection through surveillance, vital statistics, disease reporting and registries; investigation of outbreaks including contact tracing etc. By using epidemiological designs, sampling techniques and analysis, some of these activities could create generalizable knowledge, which is the primary intent of research. The new section of national ethical guideline highlights the principles, ethical issues and informed consent process under the following public health research designs:

- Epidemiological and public health research studies
- Surveillance, programme monitoring data and programme evaluations
- Demographic surveillance sites and registries
- Implementation research
- Demonstration projects
- Community trials

Social and Behavioral Sciences Research for health

Social and Behavioural Sciences include, but are not limited to, anthropology, sociology, psychology, philosophy, political science, economics, history, communications and education. Many of the research initiatives in these areas are relevant in the mid to long-term for knowledge production, science and society. In the Indian context, this is evident due to multi-religious, caste, class, endogamic, gender and geo-ethnic variations which are important characteristics of society that need to be considered in socio-behavioural research proposals.

In view of the above, the guideline elaborates some key features like ethical issues, appropriate designing of studies, ethical review, risk assessment, community engagement, informed consent etc which should be considered while performing Social and Behavioral sciences research for health.

Biological materials, Biobanking and Datasets

Biological materials or *biospecimens* or samples include biological fluids, tissues, organs etc., whereas a *biobank* is an organized collection of resources that can be accessed to retrieve human biological material and data for research purposes. A *dataset* is an organized collection of data and information maintained in physical and/or electronic/digital form that can be used for biomedical and health research.

As the fields of biobanking and dataset are concerned with storage of data and material and research at a later time, the ethical issues pertaining to consent requirements for the collection and banking of samples and further uses of tissue and DNA samples and/or data are the same but with greater responsibilities relating to their ownership, access and benefit sharing to the individual or community. Therefore, the guideline to prevent any exploitation and protect the rights of donors, the main requirements are individual informed consent, clarity on custodianship, approval of the EC and the repository governance committee and post-research benefit sharing, wherever applicable.

Research during humanitarian emergencies and disasters

A humanitarian emergency or disaster is an event or series of events that represents a critical threat to the health, safety, security or well-being of a community or other large group of people, usually spanning a wide land area. The humanitarian emergencies and disasters can be either natural or man-made such as earthquake, flood, mass migration, conflict or outbreak of disease, leading to substantial material damage affecting persons, communities, society and state(s).

Research is necessary in such circumstances to enable provision of efficient and appropriate health and humanitarian response during an ongoing emergency and to be able to plan for future emergency situations. Also there may be a need to undertake research quickly within a disrupted physical-socio-cultural environment, with a number of unique scientific and ethical challenges. The guideline suggests some ethical requirements to be followed in such situations like - pre-emptive research preparation, informed consent, ethics review special consideration etc.

NOTE- These guidelines are applicable to all biomedical, social and behavioural science research for health conducted in India involving human participants, their biological material and data[20].

20 http://icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf

US FDA advisory committee backs gene therapy for rare form of blindness

On October 12, 2017, the U.S. Food and Drug Administration's (FDA) Cellular, Tissue and Gene Therapies Advisory Committee has paved the way for the agency's first approval of a gene therapy to treat a disease caused by a genetic mutation.

A panel of external experts from this committee unanimously voted that the benefits of the therapy, which treats a form of hereditary blindness, outweigh its risks. The FDA is not required to follow the guidance of its advisory committee(s), but it often does. A final decision on the fate of the drug being developed, called Voretigene Neparvovec (Luxturna), is expected by January 12, 2018[21].

Voretigene Neparvovec (Luxturna) is being developed by Spark Therapeutics, and is designed to treat an individual who has two mutated copies of a gene called RPE65. The mutation impairs the eye's ability to respond to light, and ultimately lead to the destruction of photoreceptors in the retina.

The treatment consists of a virus loaded with a normal copy of the RPE65 gene. The virus is injected into the eye, where the gene is expressed and supplies a normal copy of the RPE65 protein.

The advisory committee's recommendation is based on Luxturna's clinical development program, which includes the first completed randomized, controlled Phase 3 gene therapy clinical trial ever conducted for a genetic disease. In the original Phase 3 intervention group, participants aged four to 44 years on an average maintained the functional vision and visual function improvements were demonstrated 30 days after Luxturna administration through their last annual follow-up visit, as measured by bilateral Multi-luminance Mobility Test (MLMT) score change and full-field light sensitivity threshold (FST) testing. Data from a cohort of the Phase 1 clinical trial, in which investigational Luxturna was administered to the contralateral, or second previously uninjected eye, showed similarly maintained mean improvements. As part of the Biologics License Application (BLA) to FDA, Spark also submitted the results of two Phase 1 clinical trials, a natural history study and a MLMT validation study.

There are currently no pharmacological treatment options for people living with RPE65-mediated IRD, who in most cases progress to complete blindness.

Luxturna is under Priority Review with FDA, with an assigned Prescription Drug User Fee Act (PDUFA) dated January. 12, 2018. LUXTURNA has received orphan drug, breakthrough therapy and rare pediatric disease designations from FDA. In August 2017, Spark Therapeutics' Marketing Authorization Application (MAA) for LUXTURNA was validated by European Medicines Agency (EMA). LUXTURNA also has received orphan product designations from EMA.

Conclusion

If Luxturna gets approved by the US regulator, it will be the first gene therapy for an inherited condition. And will probably open the door for other gene-therapy treatments for genetic disorders.

21 http://ir.sparktx.com/phoenix.zhtml?c=253900&p=irol-newsArticle&cat=news&id=2306441

19th Annual International Meeting of Institute of Human Virology (IHV): Two Indian origin Epidemiologists receive Lifetime Achievement Awards

The 19th Annual International Meeting of the Institute of Human Virology (IHV) was organized from October 23-26, 2017 at Baltimore, Maryland. IHV's Annual International Meeting attracted hundreds of elite scientists who descended upon Baltimore to share ideas and inspire medical virus research collaborations. Additionally, a set of junior investigators also participated and submitted their research abstracts in this meeting for oral and poster presentations.

The Annual Meeting 2017 has featured the presentations and intense discussion on the below therapeutic research domains:

- HIV "Cure" Research
- Preventative and Therapeutic Vaccines
- Immunology and Viral Pathogenesis
- Viral Diagnostics
- Emerging Concepts in Cancer Therapy
- Cancer and Stem Cells
- Infectious Agents and Cancer
- Public Health Science and Responses - From Local to Global
- Clinical Virology - Cardiovascular and Liver Complications of Viral Infections

The 2017 IHV Lifetime Achievement Award for Public Service was awarded to an Indian origin researcher couple:

Quarraisha Abdool Karim, PhD, Associate Scientific Director, Centre for the AIDS Programme of Research in South Africa (CAPRISA), Adjunct Professor in Public Health, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, South Africa, and

Salim Abdool Karim, MBChB, PhD, DSc, Director & Professor for Global Health Department of Epidemiology, Centre for the AIDS Programme of Research in South Africa (CAPRISA), Pro Vice-Chancellor (Research), University of KwaZulu-Natal, South Africa[22].

They are the first researchers to report that antiretroviral could prevent sexual transmission of HIV by their CAPRISA 004 Clinical Trial. The trial results recommended that Tenofovir (Antiretroviral) gel used before and after sex reduces HIV infection by 39 percent, and women who used the gel more often were up to 54 percent less likely to contract HIV. The trial also suggests that Tenofovir gel usage before and after sex reduces genital herpes infections by 51 percent[23].

22 http://news.medschool.umaryland.edu/?a=3664&z=51

23 https://academiccommons.columbia.edu/catalog/ac:181777

US FDA Approves Yescarta™ (Axicabtagene Ciloleucel): Becomes First CAR T Therapy Approved for the Treatment of Adult Patients with certain types of large B-cell lymphoma

Yescarta becomes the second gene therapy product to be approved in the United States

On October 18, 2017, the United States Food and Drug Administration (US FDA) approved Yescarta (Axicabtagene Ciloleucel), a cell-based gene therapy, to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatments. Yescarta, a chimeric antigen receptor (CAR) T cell therapy, is the second gene therapy approved by the FDA and the first for certain types of non-Hodgkin Lymphoma (NHL)[24].

CAR T therapy is a breakthrough in hematologic cancer treatment in which a patient's own T cells are engineered to seek and destroy cancer cells. CAR T therapy is produced uniquely for each individual patient.

Each dose of Yescarta is a customized treatment created by using a patient's own immune system to help fight the lymphoma. The patient's T-cells, a type of white blood cell, are collected and genetically modified to include a new gene that targets and kills the lymphoma cells. Once the cells are modified, they are infused back into the patient.

Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL in adults. NHLs are cancers that begin in certain cells of the immune system and can be either fast-growing (aggressive) or slow-growing. Approximately 72,000 new cases of NHL are diagnosed in the U.S. each year, and DLBCL represents approximately one in three newly diagnosed cases. Yescarta is approved for use in adult patients with large B-cell lymphoma in whom at least two other kinds of treatments have failed, including DLBCL, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

Commenting on this approval Peter Marks, M.D., Ph.D., Director of the FDA's Center for Biologics Evaluation and Research (CBER) said, "The approval of Yescarta brings this innovative class of CAR-T cell therapies to an additional group of cancer patients with few other options – those adults with certain types of lymphoma that have not responded to previous treatments."

Treatment with Yescarta has the potential to cause severe side effects. It carries a boxed warning for cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms, and for neurologic toxicities. Both CRS and neurologic toxicities can be fatal or life-threatening. Other side effects include serious infections, low blood cell counts and a weakened immune system. Side effects from treatment with Yescarta usually appear within the first one to two weeks, but some side effects may occur later.

Because of the risk of CRS and neurologic toxicities, Yescarta is being approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). The FDA is requiring that hospitals and their associated clinics that dispense Yescarta be specially certified. As part of that certification, staff involved in the prescribing, dispensing or administering of Yescarta are required to be trained to recognize and manage CRS and nervous system toxicities. Also, patients must be informed of the potential serious side effects and of the importance of promptly returning to the treatment site if side effects develop.

24 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm

The FDA granted approval of Yescarta to Kite Pharma, Inc. In August 2017, Gilead Sciences acquired Kite Pharma for 11.9 Billion US dollars.

Yescarta will be manufactured in Kite's state-of-the-art commercial manufacturing facility in El Segundo, California. Kite has demonstrated a 99 percent manufacturing success rate with a median manufacturing turnaround time of 17 days, which is important to patients given the potential for rapid disease progression in this population[25].

What is CAR-T therapy?

Chimeric Antigen Receptor T-cell (CAR-T) therapy represents a completely new kind of immunotherapy medicine. CAR-Ts are living cellular biologics—genetically reengineered versions of a patient's own immune cells that have been programmed to recognize and kill cancer cells.

The validation of this novel approach first came at the FDA-hosted Oncologic Drugs Advisory Committee (ODAC) meeting, held in July 2017, to review Novartis's application for the first CAR-T cell therapy. The US Food and Drug Administration's (FDA) Oncologic Drugs Advisory Committee voted unanimously, 10 to 0, in favor of the benefit-risk profile for the first of this new kind of cancer therapy, Chimeric Antigen Receptor T-cell (CAR-T) therapy[26]. Timothy Cripe, a panel member of Nationwide Children's Hospital in Columbus, Ohio, said that CAR-T is the "most exciting thing I've seen in my lifetime."

Principle of CAR-T cell therapy process

Individualized CAR-T therapy uses a patient's own immune system to fight certain types of cancers. A patient's T cells are extracted and reprogrammed outside of the body to recognize and fight cancer cells and other cells expressing a particular antigen.

How CAR-T therapy works is presented below[27,28]:

1. **Leukapheresis:** The process starts with Leukapheresis where a patient's white blood cells, including T cells, are extracted through a specialized blood filtration process (leukapheresis). The T cells are then cryopreserved and sent to manufacturing facility/ laboratory for reprogramming.

2. **Reprogramming:** Using an inactive virus (viral vector), T cells are genetically encoded to recognize cancer cells and other cells expressing a specific antigen.

3. **Expansion of the T-Cells**: Newly created CAR-T cells undergo expansion followed by product formulation.

4. **Lymphodepleting chemotherapy:** Lymphodepleting chemotherapy is given to the patient to reduce the level of white blood cells and help the body accept the reprogrammed CAR-T cells. This process is also called as pre-conditioning.
5. **Cell Infusion:** The reprogrammed CAR-T cells are infused back into the patient's blood.

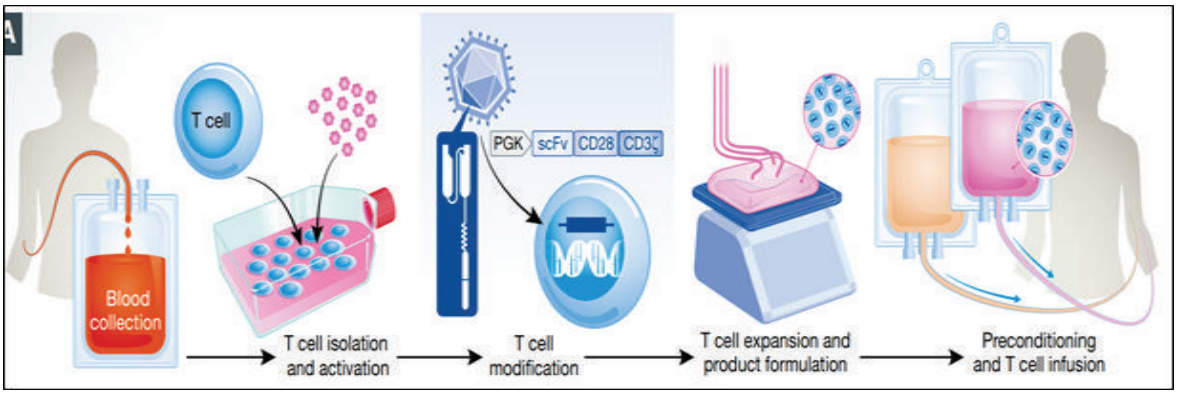
25 http://www.gilead.com/news/press-releases/2017/10/kites-yescarta-axicabtagene-ciloleucel-becomes-first-car-t-therapy-approved-by-the-fda-for-the-treatment-of-adult-patients-with-relapsed-or-refractory-large-bcell-lymphoma-after-two-or-more-lines-of-systemic-therapy

26 https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566166.pdf

27 https://novartis.gcs-web.com/static-files/d49ca1ae-3ec9-42bb-bd1a-37441a93e982

28 http://embomolmed.embopress.org/content/embomm/early/2017/07/31/emmm.201607485.full.pdf

6. **Cell Death:** Within the patient's body, the CAR-T cells have the potential to recognize the patient's cancer cells and other cells expressing a specific antigen and attach to them, which initiates direct cell death thereby killing the cancer cells.



Conclusion

CAR T therapy is a breakthrough in cancer treatment in which a patient's own T cells are engineered to seek and destroy cancer cells. Engineered cell therapies like Yescarta represent the potential for a changing treatment paradigm for cancer patients who have run out of options of conventional anti-cancer therapies.

WIPO and the Research-Based Pharmaceutical Industry Team up to Facilitate Access to Key Medicine Patent Information

On October 03, 2017, The World Intellectual Property Organization (WIPO) and the research-based pharmaceutical industry announced launch of a new partnership to promote the accessibility of patent information for health agencies tasked with procurement of medicines[29].

WIPO Director General Francis Gurry and Thomas Cueni, Director General of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), signed an agreement establishing the Patent Information Initiative for Medicines, or "Pat-INFORMED".

WIPO and IFPMA, the global trade association representing the research-based pharmaceutical industry, are co-sponsors of the initiative. The idea of the initiative originated in the industry's efforts to add clarity to the patent information around medicines. It couples with the industry's work in this area with WIPO's well-established expertise in organizing patent data from across the globe.

Pat-INFORMED will clearly link public patent information to registered medicines in a new online global gateway, helping health professionals to navigate the medicine-procurement process for the benefit of their citizens. Pat-INFORMED will make it easier for procurement experts to assess the patent status of medicines, underlining how a well-designed and implemented patent system incentivizes innovation while making available and accessible, key information about patented inventions.

Pat-INFORMED will act as a global gateway to medicine patent information. It will offer new tools and resources to determine the existence of patents relevant to products sought by procurement bodies' disease-management strategies or other works addressing public health needs.

Twenty leading global research-based biopharmaceutical companies have already committed to make information available via a database to be established by Pat-INFORMED. More organizations are expected to join.

The Pat-INFORMED initiative launched by IFPMA and WIPO is an important step to reduce uncertainty and improve transparency in medicines procurement. By adding the information on the global patent status from patent-holding companies to that from national patent offices, the process for procurement agencies and others to determine the scope of patent protection for medicines will be markedly improved. The pharmaceutical industry has taken ana important step.

While patent information is publicly available around the world, resources that directly link granted patents to marketed medicines are currently available publicly only in certain countries (e.g. the USA's 'Orange Book') or through private third-party databases.

Pat-INFORMED aims to close these gaps, and make the management of patent issues in procurement less time and resource-intensive. Pat-INFORMED also offers qualified procurement agencies, a communication channel for follow-on inquiries, through which participating companies have agreed to provide more detailed information about granted patents on specific products.

29 https://www.ifpma.org/resource-centre/wipo-and-the-research-based-pharmaceutical-industry-team-up-to-facilitate-access-to-key-medicine-patent-information/

This online initiative is expected to be operational by mid-2018 and will provide patent information for small molecule products within oncology; hepatitis C, cardiovascular, HIV, diabetes, and respiratory therapy areas; and any products on the WHO Essential Medicines List that are not within these therapy areas. In the second phase, the initiative will expand to all therapeutic areas and explore the inclusion of complex therapeutics.

National Ethical Guidelines for Biomedical Research Involving Children: ICMR

In October 2017, the first National Ethical Guidelines for Biomedical Research Involving Children has been published by the division of publication and information on behalf of the Secretary, Department of Health Research (DHR) & Director General (DG), Indian Council of Medical Research (ICMR), New Delhi.

Moreover, the latest version of "National Ethical Guidelines for Biomedical Research involving Human Participants, 2017" also has a section pertaining to research involving children. However, a need was felt to develop more comprehensive guidelines which pertain to the specifics of ethics in biomedical research involving children. Therefore, this endeavor was undertaken under the aegis of ICMR Advance Center for Newborn Health Research at All India Institute of Medical Sciences, New Delhi for the development of this guideline.

This Guideline will lead to advances in medical care which can potentially improve the health and quality of life of children and also counter the below listed queries and concerns-

Why biomedical research is necessary for children?

Here are some of the reasons, which support necessities of biomedical research in children:

- There are some diseases which only affect children, and have no adult counterparts. Therefore, it is necessary to carry out research in children to advance the knowledge of these diseases. For example, hyaline membrane disease, birth asphyxia, neonatal hyperbilirubinemia, extrahepatic biliary atresia, infantile spasms, infantile tremor syndrome, Kawasaki disease, etc.
- The physiology of children is different from that of adults, and the pharmacokinetics of many drugs is age-dependent based on the maturation of the drug metabolism pathways. For example, children metabolize many drugs much more rapidly as compared to adults.
- The adverse effects of many drugs may also be different in children as compared to adults. For instance, Tetracycline causes teeth discoloration in young children and Aspirin use is associated with Reye's syndrome in children.
- Age appropriate delivery vehicles and formulations (such as syrups) are needed for accurate, safe and palatable administration of medicines to infants and children.
- The pathophysiology of many disorders is dependent on a child's growth, development and adaptive plasticity.
- Research in children is also one of the ways to understand some adult diseases that are thought to have their origins in early life.

What are the challenges of biomedical research involving children?

Some challenges of biomedical research involving children:

- Diseases in children may be rare, and there may not be sufficient numbers of affected patients to answer the research questions.

- Difficult to find funding for research in children as the market for pediatric drugs and treatments is quite small compared to the adult ones.
- The ethical concerns and obtaining informed consent of research involving children.
- The familial and socio-cultural concerns are higher than individual patients while planning the research in children.
- Research procedures and settings need to consider children's physical, cognitive, and emotional development.

What are the general guidelines for research involving children?

The following guidelines should be followed when conducting research in children:

- Research proposals should be scientifically sound.
- The equation between the potential benefit and the risk or potential harm should be at least as favorable for the proposed research procedure as for the alternatives available to the children.
- There should be benefit to children in general and, in most cases, to the individual child subject.
- The need for the study should be justified by a thorough review of literature.
- The research should be conducted by a team of investigators who have the requisite expertise. One or more members of the team should be a paediatrician and/or have prior experience of conducting research involving children.
- Research involving children should take into consideration the unique physiology, anatomy, psychology, pharmacology, social situation and special needs of children and their families.
- Research involving children must be conducted in a child-friendly environment, as far as possible.
- In general, drugs should be tested for safety, pharmacokinetics, and at least initial indications of efficacy in adults should be established before they are tested in children. It may often be appropriate to defer paediatric testing until adult testing has reached Phase III or beyond, when substantial data is available on the safety and efficacy of a drug in adults. However, there may be situations where studies involving children would be needed without prior adult studies, for example, Surfactant use in premature babies with respiratory distress syndrome.

How the consent or assent is obtained in research involving children?

The parental/ Legally Acceptable/ Authorized Representative (LARs) permission for the child's participation in the research is termed as '**consent'**, whereas the child's agreement to participate is termed as '**assent'**. The consent or assent obtained by and/or behalf of children are -

- Informed consent by parents/LAR: In research involving children, the traditional method of informed consent where decisions about research participation are made by those with the legal and intellectual capacity to make such choices for themselves, as children usually lack this capacity.
- Informed consent by illiterate parents/LAR: When a participant is willing to participate but not willing to sign or give thumb impression or cannot do so, then verbal/oral consent may be taken on approval of the EC, in the presence of an impartial witness who should sign and date the document. This can be

documented through audio or video recording of the participant, the PI and the impartial witness, all of whom should be captured in the frame.

Children assents:

- For children less than 7 years of age, parental consent is sufficient.
- For children between 7 (84 months and above) and 11 years of age, oral assent must be obtained in the presence of parent/LAR.
- For children between 12 and 18 years of age, written assent must be obtained. If a child becomes 13 years old during the course of the study, then written assent must be obtained in addition to parent/LAR consent.
- **The process of re-consent/re-assent**: In some cases, fresh or re-consent may need to be taken in case of new information becomes available which necessitates amendments in protocol, long term or study follow up extension, participants attain 18 year of age, treatment or protocol modalities etc.

What is Compensation in research involving children?

Compensation is two types:

- Compensation for participation: The compensation is reimbursement of reasonable expenses incurred by child or caregivers to participate in research (for example, travel, wage loss). Children involved in research may also receive free medical services. The Ethics Committees have to ensure that payments do not act as inducements. Protocols should clearly mention the details about the type, level, and timing of payments to participants. The details should also be included in the informed consent form.
- Compensation for Accidental Injury: Children are entitled to financial compensation and/or other assistance for any temporary or permanent impairment or disability resulting from participation in research. In the case of death, their parents are entitled to compensation.

What are special situations in research involving children?

There are various situations in research involving children where designing a research protocol needs consideration of ethics committee and subject expert committees such as -

- Research in neonates
- Research in HIV-positive children
- Vaccine studies in children
- Ethical issues in genetic research
- Research involving children in an emergency situation
- School-based research
- Internet /Telephone-based research in children
- Community-based Research in Children

- Research involving adolescents (12-18 years)[30].

NOTE- This document covers the ethical and legal issues that researchers need to consider when carrying out biomedical research in neonates and children. The aim is to set out general principles that can be applied in most situations rather than to cover every possible situation. These guidelines need to be used in conjunction with the current National Ethical Guidelines for Biomedical Research involving Human Participants, Indian Council of Medical Research (ICMR) Government of India and are meant for use by researchers, ethics committees and other involved stakeholders.

30 http://www.icmr.nic.in/guidelines/National_Ethical_Guidelines_for_BioMedical_Research_Involving_Children.pdf

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