# Newsletter

# Clinical Development Services Agency

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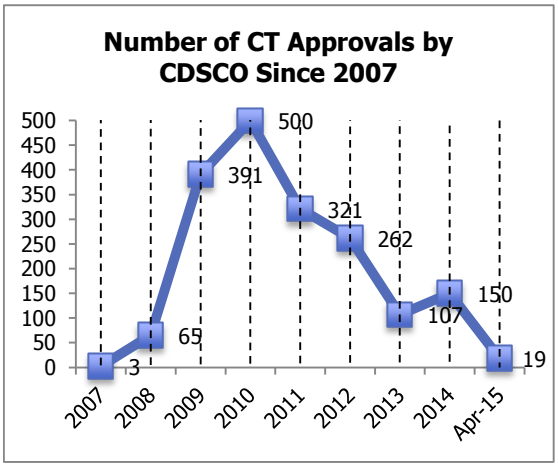
Combat against the disease is ever evolving frontline for mankind. To enable discovery of more effective and safer medication there is a sustained demand to develop new drugs and devices. Government has the responsibility to regulate every aspect of the drugs i.e., manufacture, sale, distribution, import and clinical research in humans.

With the number of clinical trial approvals declining between from 500 in the calendar year 2010 to 107 in 2013, it has been rough for the clinical research professionals including those in the industry, physicians, ECs, institutions, and associated vendors and suppliers. Small to large size Indian CROs have closed down their operations and rendered many jobless. With several amendments, gazette notifications and orders from CDSCO, we hope there has been some orderly conduct of clinical trials in India. The number of CT approvals has increased from 107 in the year 2013 to 150 in 2014. Though an increase over previous years, similar trend is not seen in this calendar year when compared with corresponding months. The number of CT approvals in January 2014 was 20 compared to 8 this year. Correspondingly, it was 16 in Feb 2014 vs. 8; 15 in March 2014 vs. 2 and 26 in April 2014 vs. 1. Is this fall in approvals due to unnecessary over-cautiousness or have the biopharmaceutical companies stopped thinking of bringing in new drugs to market? Are we denying those patients access to medicines available only through clinical trials only and reducing their chance to continued survival?

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Once, India was considered to be the major preferred destination for clinical trials due to favorable economic and intellectual property, environment and regulations. The plunge in approved clinical trials came after the Government of India enforced multiple amendments to Schedule Y of the Drugs & Cosmetics Rules, 1945 to strengthen the regulatory regime governing clinical trials. The scope of these amendments has covered wide range of areas, including, but not limited to constitution of subject expert committees; mandatory registration of ethics committees; audio-visual informed consenting; and compensation formula for Serious Adverse Events (SAE).

The Central Drugs Standard Control Organization (CDSCO) has issued a substantial number of Office Orders in last 2 years.[1]

- **Prohibition of import of cosmetics tested on animals*:*** No cosmetic that has been tested on animals after the commencement of Drugs and Cosmetics Rules shall be imported into the country
- **Prohibition of use of Polyethylene Terephthalate (PET) in liquid oral formulations for primary packaging of drug formulations:** No manufacturer shall use the PET or Plastic containers for liquid oral formulations for primary packaging of drug formulations for pediatric use, geriatric use and for use in case of pregnant women and women of reproductive age group
- **New drug delivery systems as new drug:** All vaccines, recombinant DNA (r-DNA) derived drugs and all New Drug Delivery Systems including modified release dosage forms of a drug formulation shall be deemed to be new drugs unless certified otherwise by the licensing authority
- **Free medical management:** In the case of an injury occurring to the subject during the clinical trial, he or she shall be given free medical management as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier. In case there is no permanent injury, the quantum of compensation shall commensurate e with the nature of the non-permanent injury, loss of wages and transportation. The compensation has to be paid within 150 days of occurrence of adverse event.
- **Responsibilities of Sponsor:** Any report of the SAE, after due analysis shall be forwarded by the sponsor to the Licensing Authority; Chairman of the Ethics Committee and the Head of the Institution where the trial has been conducted within 14 calendar days of the occurrence of the SAE
- **Responsibilities of the Investigator(s):**, After due analysis, the report of SAE shall be forwarded by the investigator to the Licensing Authority; Chairman of the Ethics Committee and the Head of the Institution where the trial has been conducted within 14 calendar days of the occurrence of the SAE
- **Responsibilities of the EC:** In case of SAE occurring to the clinical trial subjects, the Ethics Committee shall forward its report after due analysis, along with its opinion on the financial compensation (if any) to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, to the Licensing Authority within 30 calendar days of the occurrence of the SAE
- **Reporting SAEs:** The Licensing Authority shall forward the SAE reports of the Investigator, Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conducting clinical trial and the Ethics Committee to the Chairman of the Expert Committee
- **Audio-video recording of the informed consent process**: An entire process of audio-video recording of the informed consent of subject, including the procedure of providing information and his understanding on such consent, shall be maintained by the investigator for record
- **Therapeutic effect of investigational product*:*** 'There is a possibility of failure of investigational product to provide intended therapeutic effect' and 'in the case of placebo-controlled trial, the placebo administered to the subjects shall not have therapeutic effect'
- **Evaluation parameters for global CTs/NCEs:** All the Global Clinical Trials/ NCEs should be evaluated having regard to three parameters, namely and should include in their CT applications
  - Assessment of risk vs. benefit to the patients
  - Innovation vis-à-vis existing therapeutic option
  - Unmet medical need in the country
- **Renaming of New Drugs Advisory Committees (NDACs) to Subject Expert Committees (SECs):** Constitution of 12 SECs consisting of experts of various subjects. Applications of CTs and new drugs will be evaluated by the respective SECs and recommendations will be reviewed by the Technical Review Committee. CDSCO will grant approval of clinical trial based on these recommendations.

- **Limiting number of clinical trials an investigator can undertake at a time:** Under no circumstances the number of trials should be more than three at a time.
- **Clinical trial on medical devices:** The procedure for CT of Medical Device approvals would be similar to CT of Drugs/ Vaccines
- **Compensation in case of injury or death discerned at a later stage:** Compensation to be paid to the trial participant/ his/ her nominee as the case may be, if any drug related death/ anomaly is discerned at a later stage and accepted to be drug related.
- **Providing ancillary care to the clinical trial subjects:** Sponsor to provide ancillary care to the subject for brief illness in the same hospital/ trial site, wherever required
- **Approval of academic clinical trials:** Academic clinical research may be approved by the institutional ethics committee (IEC). However, if a new drug is being evaluated or a new use for an existing drug is being evaluated, then approval of the DCGI is required as per Drug & Cosmetic Rules.
- **Waiver of clinical trial in Indian population for approval of new drugs:** Waiver of clinical trial in Indian population for approval of new drugs, which have already been approved outside India, can presently be considered only in cases of national emergency, extreme urgency and epidemic and for orphan drugs for rare diseases and drugs indicated for conditions / diseases for which there is no therapy.
- **Requirements of local trial for a genetics or similar biologics (Bio-similars) in other country like USA for its approval in the country:** The drugs considered generics and similar biologics (bio-similars) in other countries like USA that have been marketed in such countries for more than four years and have satisfactory report would be approved for marketing in India after abbreviated trials.
- **Number of subjects in phase III global clinical trials:** If Indian population participated in global phase 3 CT, would be adequate for considering approval of the drug in India after marketing in innovator country
- **Placebo controlled trials:** Only appropriate, ethical and efficiently-designed placebo-controlled trials in special circumstances are considered and submitted for approval
- **Requirement for filling of application to market new chemical entities (NCEs):** Indian participants will participate in global clinical trials of NCEs to be used for diseases if that disease is prevalent in Indian population. After approval for marketing in the innovator or in well – regulated developed country markets, approval should be sought from CDSCO for marketing these NCEs in India speedily, preferably by production within the country.
- **Consideration of banning of a marketed drug:** If two or more countries remove a drug from their market on grounds of efficacy and safety, then the continued marketing of the drug in India will be considered for examination and appropriate action.
- **Creation of cell for co-ordination with institutes like ICMR for sponsoring various studies:** Unit instituted within CDSCO to coordinate with agencies such as ICMR to give regular update on post-marketing surveillance of drugs, rational use of medicines, drug utilization studies and adverse drug reaction monitoring etc.

Office Orders and the amendment released by CDSCO have brought several significant changes as well as challenges in terms of EC registration, GCP Compliance and other related quality changes. The current regulation is leaning primarily to guard the safety of trial participants and to improve the much criticized clinical trials with a justifiable reason. The major challenge is that many of these amendments have not been done in consultation with the researchers at academic and industrial entity to avoid the anguish that the CT industry is undergoing currently.

However, further clarification in several of these amendments may be counterproductive to revitalizing the clinical trials industry in India. There is optimism amongst the clinical trial industry stakeholders, that the recent amendments to the regulations should be able to address the solutions to protect the integrity of clinical research in India.

**References**


- Gazette Notifications at Notification/Circulars/ Publications available at http://www.cdsco.nic.in/forms/list.aspx?lid=2057&Id=31

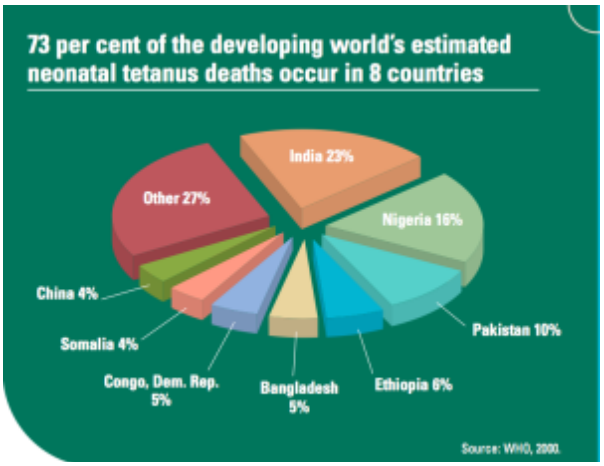
# Check It Out

## Yet another Public Health milestone for India: WHO declares India free of Maternal & Neonatal Tetanus (MNT)

**Jasmine Sharon Luke**


Two doses of tetanus toxoid vaccine were introduced to all pregnant women during each pregnancy in India for the first time in the year 1983. As per UNICEF, by 1990 neonatal tetanus still accounted for almost 80,000 deaths. In the year 2013; 15 states and union territories in India were validated to have eliminated MNT.

MNT elimination in a country is defined as neonatal tetanus rate of less than one case of neonatal tetanus per 1000 live births in every district of the country. WHO, Deputy Regional director for South East Asia, Poonam Khetrapal Singh mentioned that Nagaland in northeast India was the last state to achieve MNT elimination; thereafter on 15 May 2015 WHO declared India free of maternal and neonatal tetanus. Once the neonatal tetanus elimination is attained maternal tetanus elimination is also achieved.




Dr. Vinod Paul, professor of neonatology at AIIMS, New Delhi stated three main reasons as to why India is successful in achieving this milestone:

a) "First and foremost, maternal tetanus immunization rates have gone up," he said. "They are not universal, but they are very high.
b) "Secondly, we introduced cash incentives for institutional deliveries"
c) Lastly, "delivery kits that reduce contamination along with safe umbilical cord practices have been important. In the last seven years, facility births have increased, even in rural India. We've moved from homes where deliveries are unhygienic to facility births where we're dealing with nurses and doctors where there are greater chances of better care and practices."


- Dr. K.R. Bharath Kumar Reddy : Pie Chart Retrieved from http://thedoctorschronicles.com/who-declares-india-free-of-neonatal-tetanus-a-milestone-in-vaccination/
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- WHO MNT Elimination initiatives : Retrieved from http://www.who.int/immunization/diseases/MNTE_initiative/en/index1.html

# Check it Out

Compiled by Pawandeep Kaur Dhawan

## New class of cancer drugs developed

The Saint Louis University, MO, USA has for the first time, found a way to stop cancer cell growth by targeting the Warburg Effect, a trait of cancer cell metabolism that scientists have been eager to exploit. The new compound, SR9243 affect a receptor that regulates fat synthesis. The study, which was conducted in animal models and in human tumor cells in the lab, showed that a drug developed by Burris and colleagues at Scripps Research Institute can stop cancer cells without causing damage to healthy cells or leading to other severe side effects.

http://www.slu.edu/rel-cancer-drugs-626 (accessed on June 30, 2015)

## 'Single-dose' anti-malaria drug developed at Dundee University

The Dundee University and Medicines for Malaria Venture has developed DDD107498, a compound with a potent and novel spectrum of antimalarial activity against multiple life-cycle stages of the Plasmodium parasite, with good pharmacokinetic properties and an acceptable safety profile. It demonstrates potential to address a variety of clinical needs, including single-dose treatment, transmission blocking and chemoprotection. DDD107498 was developed from a screening programme against blood-stage malaria parasites; its molecular target has been identified as translation elongation factor 2 (eEF2), which is responsible for the GTP-dependent translocation of the ribosome along messenger RNA, and is essential for protein synthesis.

http://www.nature.com/nature/journal/v522/n7556/full/nature14451.html (accessed on June 17, 2015)

## WHO researching yoga's role for healthier world

The WHO is researching how to integrate yoga with universal health care needs, according to Nata Menabde, WHO's Executive Director. Calling yoga the "ancient Vedic gift to the world", she stressed its ability to bring together body, soul and mind for a holistic approach to health. She told reporters that WHO was working with centres in India and elsewhere to find ways to standardise yoga for use around the world as part of health care systems.

http://economictimes.indiatimes.com/news/politics-and-nation/who-researching-yogas-role-for-healthier-world/articleshow/47743157.cms (accessed on June 20, 2015)

## India's Step towards Medical devices Regulation

India is the world's third-largest pharmaceutical market, however its share of the medical devices market is way behind. More than 70 percent of medical equipment sold in the country is imported, mostly from the United States. The National Pharmaceutical Pricing Authority (NPPA) Department of Pharmaceuticals, which currently oversees medical device regulation in India, has issued the Draft National Medical Device Policy recommending formation of an autonomous National Medical Device Authority (NDMA). The NDMA would be tasked with promoting the local device sector, enforcing stricter safety standards, and installing price controls for devices, including surgical instruments, implants, and diagnostic equipment.

http://www.reuters.com/article/2015/06/12/india-healthcare-regulations-idUSL3N0YW4QK20150612 (accessed on June 15, 2015)

## Is polio back? UP samples ring alarm bells

A mere year after the country was declared polio free, there was a recent scare of its re-occurrence with positive polio-like symptoms. The children, between the ages of 5 and 15 years, had complained of paralysis and loss of muscular strength in hands and legs. However, the Ministry of Health and Family Welfare (MoHFW) has cleared that the 208 cases reported are of acute flaccid paralysis (AFP) and all the cases received from the laboratories in 2015 are negative for polio-virus.

http://www.financialexpress.com/article/healthcare/happening-now/cases-reported-from-up-in-media-are-of-afp-not-polio-mohfw/88486/ (accessed on June 22, 2015)

## Artificial neuron that mimics human cells created

Scientists at Sweden's Karolinska Institutet have managed to build a fully functional neuron by using organic bioelectronics. This artificial neuron contain no 'living' parts, but is capable of mimicking the function of a human nerve cell and communicate in the same way as our own neurons do.

http://www.sciencebusiness.net/news/77096/Karolinska-Institutet-Artificial-neuron-mimics-function-of-human-cells (accessed on June 26, 2015)

# CDSA Training Programs

In 2015-16, CDSA has planned to pursue its continual effort towards nationwide awareness program on strengthening and empowerment of Institutional Ethics Committee Members and Investigators on Current Regulatory Requirements.

CDSA has completed four trainings in the current financial year 2015-16 till date. Two Awareness Programs on "Current Regulatory Requirements for members of Institutional Ethics Committees" were conducted at Faridabad and Mangalore. Other programs were on "Good Laboratory Practice" and "Human Research Protection and Good Clinical Practice" were held at Faridabad.

**EC Program at Father Muller Medical College, Mangalore**

**Human Research Protection & GCP Program with RCB Team at NCR Biotech Cluster, Faridabad**

## Adjunct Faculty

CDSA is proud to announce the joining of Dr. Nandini K Kumar, Former Deputy Director General (Senior Grade), ICMR and Dr. TMA Pai Endowment Chair, Manipal University as our first Adjunct Faculty. She is the recipient of ISCR Lifetime Achievement Award (2015).

*"Nice to note the hectic activities you are organizing. Such a small group and so many activities. My all appreciation to you".*

**Prof. Y K Gupta,**
**Professor & Head of Pharmacology, AIIMS, New Delhi**

*"Thanks for the invitation to the Mangalore Program on 19th May 2015 for EC training. I am too happy to be part of the energetic team".*

**Ms. Shanthy Gunasekaran,**
**Deputy Drugs Controller (I), CDSCO, Bangalore**

*"The workshop was grand success, being secretary of ethics committee since 8 years, first time I have seen such a clock precised workshop organised for the ethics committee members in Maharashtra with the correct selection of plenary speakers and the lectures covered a broad spectrum of topics".*

**Participant, Pune (February, 2015)**

*"I must say Thank you & appreciate you all for organizing such a wonderful event. It was the best awareness programme I have participated in recent times. The speakers were very good, discussions happened were also good. The hospitality, food and the way you all managed this event was more than GOOD, it was excellent".*

**Participant, Pune (February, 2015)**

*"Let me thank you for conducting a workshop that was very useful for me both as a researcher and a member of the IEC. The presentations were really good and of good quality and clarity. Other arrangements including food, stationery etc. were also good."*

**Participant, Thiruvananthapuram (January, 2015)**


CDSA is planning a 3 days hands-on, residential training program jointly with National Institute of Biologicals on Laboratory Quality Management System (LQMS) in various testing areas like biologicals, vaccines and diagnostic kits. A series of 3 programs are envisaged this year.

**Upcoming Training Programs (July - September 2015)**

| Sr. No. | Dates | Training Title | Venue |
|---|---|---|---|
| **1** | July 14-15, 2015 | Current Regulatory Requirements for members of Institutional Ethics Committees (Awareness Program) | Bangalore Medical College & Research Institute, Bangalore |
| **2** | July 16, 2015 | Regulatory and Med-Tech workshop | C-CAMP, NCBS, Bangalore |
| **3** | Aug 18 , 2015 | Good Clinical Practice (An Awareness Program) | Govt. Kilpauk Medical College, Chennai |
| **4** | Aug 19-20 , 2015 | Current Regulatory Requirements for members of Institutional Ethics Committees (Awareness Program | Govt. Kilpauk Medical College, Chennai |
| **5** | Aug 29 , 2015 | Good Clinical Practice (An Awareness Program) | Tata Medical Center, Kolkata |
| **6** | Sept 15-16, 2015 | Current Regulatory Requirements for members of Institutional Ethics Committees (Awareness Program) | BBD University, Lucknow |

Route Map to CDSA