# A Brief Overview of Regulation of Biomedical Research in Human Participants with Special Reference of Compensatory Jurisprudence of Subjects

**Anuj Kumar Singh S/O Mr Yash Pal Singh**
*Ph.d Research Scholar Law DR Shakuntala Misra National Rehabilitation University Lucknow*

## *Abstract*

*There are GCP guidelines and provisions of Drug and Cosmetic Act 1940 including schedule Y are there .There is lack of biomedical legal awareness and bioethics especially in the field of biomedical research on human participants. However there are guidelines for biomedical research on human participants 2017 issued by Indian Council of Medical Research. The proposal of amendment Bill 2015 as adjunct of new separate chapter 1A relating to clinical trial is pending in parliament for expediting the subject of clinical trials with the enhanced penalty against the infringement of rules of clinical trials. Clinical Trial Inspection Programme 2010 has been held for evaluating the clinical trials. There is also 72th standing committee report 2013 on alleged irregularities in conduct of studies using Human Pappilona Virus (HPV) Vaccine by PATH (Programme for Appropriate Technology in Health) in India.*

## 1.0 Introduction

India always remained the place of biomedical research because of large poor patient population. Investigator are in India are well trained and they can be hired on significantly lower cost. Therefore Government of India owes the responsibility of right and safety of subjects & it must be ensured that quality of conducting clinical trials should be at par with international standard. The objective of this paper is to put forth the brief the legal scenario of bio medical research on human participants with compensatory right and other rights of vulnerable group in society so that stake holders may attain rights and comply duties more efficiently.

Clinical trials of drugs developed in India have to undergo four phases. In administration of clinical trial in India there is GCP guideline and different executive order are released by CDSCO. In administration of clinical trial the principle of bioethics i.e autonomy, beneficence, non-malfeasance and justice must be adopted. These principles remind and guide clinicians and researchers to respect and protect the rights of the participants. Good clinical practice (GCP) is an international ethical and scientific standard for conducting biomedical and behavioral research

involving human participants. This standard ensures that rights, safety, well being and confidentiality of trial participants are protected and data collected in clinical trials are credible and accurate.

In an affidavit, the centre had admitted that 2644 person died during clinical trial of 475 new drug between 2005 to 2012. Serious adverse events of deaths during the clinical trials during the said period were 2644 out of which 80 deaths were found to attributable to clinical trials. Around 11,972 serious adverse events (excluding death) were reported during the period from January1, 2005 to June 30, 2012 out of which 506 events were found to be related to clinical trial.[1]

## 2.0International Council for Harmonization

The international council for harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceuticals industry to discuss scientific and technical aspects of drug registration. Since its inception 1990, ICH has gradually evolved, to respond to the increasingly global face of development. ICH's mission is to achieve greater harmonization worldwide to ensure safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. On 23 October 2015, ICH announced organizational changes as it marks 25 years of successful harmonization.[2]ICH met in Charlotte, NC, USA on 10-15 November 2018. Three years on the reform of ICH, all organizational changes have been implemented, with the Charlotte meeting being illustrative of ICH's steady evolution to a more global initiative.[3]

## 3.0 Clinical Trial regulation in U.K

There are various laws in U.K relating to clinical trials. These below mentioned are some key regulations of clinical trials in entire European Union & list is not exhaustive. These include The European Union Clinical Trials Directive (Directive 2001/20/EC) (Clinical Trials Directive),The Good Clinical Practice Directive (Directive 2005/28/EC) GCP Directive, The UK Medicines for Human Use (Clinical Trials) Regulation 2004(SI2004/1031) as amended ,The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) were amended by The Medicines for Human Use (Clinical Trials) Amendment Regulation 2006 (SI 2006/1928),The Medicines for Human Use ( Clinical Trials) Amendment Regulations (no 2) 2006(SI 2006/2984),The Medicines For Human Use (Clinical Trials) and Blood Safety and Quality (amendment) Regulation 2008(S.I.2008/941),The Medicines for Human Use (Miscellaneous Amendments) Regulation 2009(SI No.1164) came into force on 8 May 2009.Clinical trials of medicinal products conducted in the U.K, whether funded by industry , charity or led by a single academic

[1] Swasthaya Adhikar Manch Vs UOI 2012 PIL W.P (c ) No.33 Courtesy www.supremecourtcases.com retrieved on October 5,2018

[2] http://www.ich.org/home.html retrieved on February 20, 2019

[3] ICH37 Charlotte PressRelease 2018 1123 Final available at http://www.ich.org/fileadmin/Public_Web_Site/News_room/B-Press_Releases retrieved on February 20,2019

investigator, are subject to the European Union Clinical . These collectively ensure that clinical research is undertaken to the highest ethical, scientific and financial standards and protect the rights welfare and dignity of the research participants.[4]

### 3.1 Trial Monitoring and ethics approval-

Before researcher can begin to enroll participants in a trial, the protocol must be reviewed by an independent panel composed of medical experts and laypersons. These individuals determine whether the trial's risks are acceptable with regard to the participant's medical condition. Ethics board are also responsible for reviewing the consent form to make sure that the study plan and risks are adequately explained to all participants. Throughout the conduct of clinical trials, side effects are closely monitored, and changes in the study design are introduced through protocol amendments as necessary. In addition, Phase 3 trials are required to have an independent data-safety-monitoring committee that reviews study outcomes and side effects during the course of the trial to assure participants that the study remains appropriate for their medical condition.[5]

## 4.0 Clinical Trial Regulation in USA

In United States, a clinical trial is commonly defined as a scientific investigation involving the use of an experimental drug, medical device or clinical intervention on a human being. The conduct of clinical trials in United States is regulated by two federal agencies – the Food and Drug Administration (FDA) and the Office of Human Research Protection (OHRP)- Both of which are within the US Department of Health and Human Services. Clinical trials conducted for the purpose of seeking approval to market and sell a new drug, medical device or clinical intervention are regulated by FDA under the authority of the Federal Food, Drug and Cosmetic Act and its associated regulations.[6]

For both FDA and OHRP –regulated trials, the clinical trial must be conducted under the immediate oversight of a non-governmental human subject protection committee called an institutional review board. The regulation set forth the requirements for the composition and the charge of the institutional review board to ensure that the clinical trial is conducted in a manner that protects the rights of the human subjects, including the right to know that participation in the clinical trial is voluntary and subject to the participants' informed consent.[7]

## 5.0 Good Clinical Practice Guideline issued by WHO

The purpose of these WHO Guidelines for Good Clinical Practice for Pharmaceutical products is to set globally applicable standards for conduct of such biomedical research on human subjects.

[4] http://intranet.birmingham.ac.uk/finance/documents/public/Clinical Trials.pdf retrieved on November 1,2018
[5] http://www.britannica.com/science/clinical-trial retrieved on October20,2018
[6] Coei Perkins LLP on file:///c:/users/admin/desktop/clinical trials in the USA-Lexology.html retrieved on October 21,2018
[7] ibid

These guideline inevitably vary somewhat in content and emphasis, but all are consonant with regards to the prerequisites to be satisfied and the principles to be applied as a basis for assuring the ethical and scientific integrity of clinical trials. The guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufactures and other sponsors of research and drug regulatory authorities. Guidelines includes the protection of trial subject, responsibilities of the investigator, responsibilities of the sponsor, responsibilities of monitor, monitoring of safety, record-keeping and handling of data, statistics and calculations, handling of and accountability for pharmaceutical products, role of drug regulatory authority, quality assurance for the conduct of a clinical trial and consideration for multicentre trials.

## 6.0 Regime of clinical trials in India

There are following laws, regulation and guidelines regarding clinical trials in India-

Rule 122DA, 122DAA, 122DAB, 122DAC, 122DB, 122DC, 122E of Drug and Cosmetic Act 1940

Schedule Y and its appendices of Drug and Cosmetic Act 1940

GCP guidelines issued by CDSCO

Guidelines issued by ICMR

GCP guideline declared by WHO

72nd parliament standing committee report

**6.1 Definition of Clinical Trial-** Definition of clinical trial is provided in section 122DA of Drug &Cosmetic Act 1940 which states that clinical trial means a systematic study of new drug (s) in human subjects to generate data for discovering and/or verifying the clinical pharmacological (including pharmacodynamics[8] and pharmacokinetic[9]) and /or adverse effects with the objective of determining safety and/or efficacy of new drug.

Rule122DA of Drug and Cosmetic Act 1940 inter alia states that no clinical trial for a new drug, whether for clinical investigation, or any clinical experiment by any Institution, shall be conducted except under , and in accordance with the permission ,in writing, of the licensing authority defined in clause(b) of rule 21. Permission to conduct clinical trial is given for different phases separately after giving prescribed fee.

Rule 122DAB of Drug & Cosmetic Act 1940 inter alia states that in case of injury occurring to the clinical trial subject, he or she shall be given free medical management as long as required

[8] Pharmacodynamics is the branch of pharmacology concerned with action of drugs on the body or on microorganism within or on the body.

[9] Pharmacokinetic is described as what the body does to a drug, refers to a movement of drug into, though, and out of the body- the time course of its absorption, bioavailability , distribution,metabolism and excretion.

and such subject or his/her nominee in case of death shall also be entitled for financial compensation as per order of the licensing authority defined under clause (b) of rule 21 and financial compensation will be additional of expenses incurred on medical management of the subject and it shall be borne by sponsor of clinical trial.

Rule DAC of Drug & Cosmetic Act 1940 inter alia states Licensing Authority as defined in clause (b) of rule 21 on being satisfied that the data submitted along with the application in support of proposed clinical trial is adequate in all respects, issue permission for conduct of clinical trial if the conditions of schedule Y, GMP guidelines for clinical trials in India, approval of ethics committee, registry of clinical trial ,reporting of any serious event according schedule Y, sponsor's premises infrastructure according schedule Y and Good clinical Practices , access of any officer CDSCO and state Drug Control Authority to inspect, search and seize any record, data, document, books, investigational drugs etc must be complied with.

Licensing Authority may cancel or suspend the permission or approval if importer or manufacturer fails to comply with any of the conditions of permission or approval after giving an opportunity to show because why such an order should not be passed, by an order in writing stating the reasons.[10]

There is the provision within the sixty days of the order of licensing authority aggrieved can appeal to central government .[11]

Under Rule 122 E of Drug & Cosmetic Act 1940 means and include a new drug for the purpose of clinical trial which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labeling thereof and has not been recognized as effective and safe by the licensing authority mentioned under rule 21 for proposed claims, any drug which is now claimed with modification like indication, dosage, dosage form and route of administration, a fix dose combination of two or more drug which has now proposed to combined for first time for new claims viz., indication, dosage etc.

**6.2Schedule Y of Drug & Cosmetic Act 1940-**

Schedule Y may be summarized as following-In clause (1) of schedule Y procedure of application of clinical trial is given. Clause (2) (i) of schedule Y states the approval for clinical trial. The Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under Rule 21(b), and the approval obtained from the respective ethics committee(s). In Clause (2) of Schedule Y Responsibilities of Sponsors are provided. The clinical trial sponsor is responsible for implementation and maintaining quality assurance system to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice (GCP). In Clause (3) (i) responsibilities

[10] Section 122DB of D & C Act 1940
[11] Section 122DC of D & C Act 1940

of investigator are provided. The Investigator(s) shall be responsible for conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per undertaking given in Appendix vii. The investigator shall provide information to the clinical trial subject through informed consent process as provided in Appendix V about the essential elements of clinical trial and subject's right to claim compensation in case of trial related injury or death. In clause (5) of schedule Y responsibilities of Ethics committee are provided. It is responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and wellbeing of all trial subjects. The ethics committee should exercise particular care to protect the right, safety and well being of all vulnerable subjects participating the study e.g., members of group with hierarchical structure (e.g. prisoners, armed force personnel, staff and students of medical, nursing and pharmacy academic institutions),patients with incurable disease, unemployed or impoverished persons, patients with emergency situation, ethnic minority groups, homeless persons, nomads, refugee, minors or others incapable of personally giving consent.

Human Clinical Trial comprises four phases. In Clause 6 of schedule Y Phase 1 i.e Human Pharmacology is provided. The objective of this study is the estimation of safety and tolerability with initial administration of investigational new drug into human. Studies in this phase of development usually have non-therapeutic objectives and may be conducted on healthy volunteer subjects or certain type of patients.

Studies in phase 1 trial includes-[12]

- ✓ Maximum Tolerated Dose
- ✓ Pharmacokinetic
- ✓ Pharmacodynamics
- ✓ Early Measurement of Drug Activity

Phase II trial is said to be Therapeutic Exploratory Trial. The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the conditions under study and to determine the common side effects and risks associated with the drug. Studies of Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population.[13]

Phase III clinical trial is called Therapeutic Confirmatory Trial. Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits. Studies in Phase III are designed to confirm the preliminary evidence accumulated in phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be

[12] Clause(6)(ii) of schedule Y of D& C Act 1940
[13] Clause (7) of schedule Y of D&C Act 1940

intended to provide an adequate basis for marketing approval. Intended administration of drug for long period is looked under this Phase III.[14]

Phase IV clinical trial is said to be Post Marketing Trials. Post Marketing Trials are studied (other than the routine surveillance) performed after drug approval and related to the approved indications. These trials go beyond the prior demonstration of drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug use. They may be of any type but should have some scientific objective. Phase IV trials include additional drug-drug interaction, dose responses or safety studies and trials designed to support use under the approved indication(s),dose responses, or safety studies and trials designed to support use under the approved indication(s) ,e.g. morality/morbidity studies, epidemiological studies etc.

## 7.0 Ethical Guidelines for Biomedical Research on Human Participants 2017 issued by Indian Council of Medical Research [15] -

This guideline has been published by ICMR for the standard adopted by the ethics committee which supervises research carried out on the human participants in the medical institutions which took place of guidelines 2006. For the first time, guidelines have addressed concerns in subject areas where there is scanty guidance available such as public health research, socio behavioral research, conducting research during disaster or emergencies, dealing with vulnerable population or conducting collaborative research. Elaborate procedure for ethical standard for biomedical research has been given which shall be inter alia based on following general principles- (1) Principle of essentiality whereby after due consideration of all alternatives in the light of existing knowledge, use of human participants is considered to be essential for the proposed research.[16] (2) The Principles of voluntariness whereby informed consent & respect for the right of the participant to agree or not to agree to participate in research, or to withdraw from research[17] . (3) Principle of non- exploitation whereby research participants are equitably selected so that the benefits and burdens of research are distributed fairly and without arbitrariness or discrimination. [18](4) Principle of social responsibility whereby the research is planed and conducted so as to avoid creation or deepening of social and historic division or in any way disturb social harmony.[19](5)Principle of privacy and confidentiality whereby the identity and records of the human participants of the research or experiment are as far as possible is kept confidential and access is limited who are authorized. [20](6) Principles of precaution and risk minimization whereby due care is taken by all stakeholders at all stages and compensation is given if any harm

[14] Clause (8) of schedule Y of D & C Act 1940
[15] http://www.iitm.ac.in/downloads/ICMR_Ethical_Guidelines_2017.pdf January 25,2019
[16] Section 1 para 1.1.1
[17] ibid at para 1.1.2
[18] Ibid at para 1.1.3
[19] Ibid at para 1.1.4
[20] Ibid at para 1.1.5

occurs. [21] (7) Principles of professional competence whereby the research is planned, conducted, evaluated and monitored throughout by persons who are competent and qualified, experienced & trained. [22](8) Principle of maximization of benefit whereby due care is taken to design and conduct the research in such a way as to directly or indirectly maximize the benefits of research participants and/or to the society.[23](9) Principle of institutional arrangements whereby institutions where the research is being conducted, have policies for appropriate research governance and take the responsibility to facilitate research by providing required infrastructure , manpower , funds and training opportunities.[24] (10)Principle of transparency and accountability whereby the research plan and outcomes emanating from the research are brought into the public domain through registries, reports and scientific and other publications while safeguarding the right to privacy of stakeholders. Stakeholder involved in the research should disclose any existing conflict of interest and manage it properly. The research should be conducted in a fair, honest, impartial and transparent manner to guarantee accountability. Related records, data and notes should be retained for the required period for possible external scrutiny/audit.[25] (11)Principles of totality of responsibility whereby all stakeholders involved in research are responsible for their actions. The professional, social and moral responsibilities compliant with ethical guidelines and related regulations are binding on all stakeholders directly or indirectly.[26] (12) Principles of environmental protection whereby researchers are accountable for ensuring protection of the protection of the environment and resources at all stages of the research, in compliance with existing guidelines and regulations.[27]

GCP Guidelines in India have been adopted by CDSCO in the line of WHO GCP Guideline and ICMR Guidelines.

## 8.0 Data protection of Clinical Trial

TRIPS agreement mandates protection for the test data submitted by pharmaceutical and agro-chemical industries for market approval. According TRIPS agreement, "members when requiring as a condition of approving the marketing of pharmaceutical or of agricultural chemicals entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect against unfair commercial use. In addition, members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use."[28]

[21] Ibid at para 1.1.6
[22] Ibid at para 1.1.7
[23] Ibid at para 1.1.8
[24] Ibid at para 1.1.9
[25] Ibid at para 1.1.10
[26] Ibid at para 1.1.11
[27] Idid at para 1.1.12
[28] Article 39.3 TRIPS AGREEMENT

There is no legislation of data protection of clinical trial. However there is glimpse in Drug & Cosmetic Rules 1945 under Rule 53. This Rule provides that an inspector of Drug regulator shall not without the sanction in writing of his official superior , disclose to any person any information acquired by him in the course of his official duties. But there is no clear cut law which may prevent the competitor to use data regarding clinical trial.

## 9.0 Quantum of compensation in case of death-[29]

The apex committee and Technical committee appointed by CDSCO in their 7th meeting held on 30.08.2013 and 23.08.2013 respectively , after detailed discussion agreed to the above formula for determining the quantum of compensation in cases of clinical trial related to deaths.

The independent expert committee constituted for examining of SAE of deaths has already devised a formula being followed for determining the quantum of compensation in case of clinical trial related death which is as under-

Compensation= (B x F x R)/99.37

Where,

B= Base amount (i.e 8 lacs)

F= Factor depending on the age of the subject as per Annexure 1 (Based on the Workmen Compensation Act)

R= Risk Factor depending on the seriousness and severity of disease, presence of co-morbidity and duration of disease of the subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

0.50 terminally ill patient

1.0 Patient with high risk
2.0 Patient with moderate risk
3.0 Patient with mild risk
4.0 Healthy Volunteer or subject of no risk

However, in case of patients whose expected mortality is 90% or more within 30 days, a fixed amount of Rs 2 Lacs should be given.

[29] http://www.cdsco.nic.in- formula2013SAE retrieved 1, October 2018

**9.1Formula to determine the quantum of Compensation in cases of clinical trial related serious adverse events of injury other than deaths occurring during Clinical Trials-[30]**

In view of above, a committee was constituted under chairmanship of Shri R.K.Jain. AS & DG recommended the under mentioned formula for determination of quantum of compensation in case of Clinical Trial related SAE other than death-

**(i) SAE causing permanent disability-**

Accordingly, the following formula is recommended

Compensation = (CxDx90)/(100x100)

Where,

D=percentage disability the subject has suffered

C= Quantum of compensation which would have been due for payment to the subject's nominee(s) in case of death of the subject.

**(ii) SAE causing congenital anomaly or birth defect-**

The compensation in such cases which may be the case of (a) still birth

(b) Early death due to anomaly

(c) No death but deformity which can be fully corrected through appropriate intervention

(d) Permanent disability (mental or Physical).

The compensation in such cases would be a lumpsum amount such that if that amount is kept by of fixed deposit or alike ,it should bring a monthly interest amount which is approximately equivalent to half of minimum wage of the unskilled worker(in Delhi). This aspect was duly considered while fixing Rs 8 Lacs as base amount for determining the amount of compensation in case of SAE resulting into death. Hence, the quantum of compensation in such cases of SAE would be half of the base amount as per formula for determining the compensation for SAE resulting into death.

In case of birth defect leading to (c) & (d) above to any child, the medical management as long as required would be proved by the sponsor or his representative which will be over and above the financial compensation.

**(iii) SAE causing life-threatening disease And Reversible SAE -**

In case of clinical trial related SAE causing life- threatening disease & reversible SAE it is resolved, the quantum of compensation would be linked to the number of day's hospitalization of the subject. The compensation per day would be calculated based upon the minimum wage of the unskilled worker (in Delhi).

Since, in case of hospitalization of any patient not only the patient loses his/her wage, there will be direct or indirect losses of various kind including inconvenience, wage loss of attendant. The compensation per day of hospitalization in such cases would be double the minimum wage.

Accordingly, the following formula is recommended.

[30] File No: CT/SAE-ND-COMPENSATION FORMULA/2014 ON http:// www.cdsco.nic.in visited on october 15, 2018

Compensation= 2xWxN

Where,

W= minimum wage per day of the unskilled worker (in Delhi)

N=Number of days of hospitalization

## 10.0 Guidance on Clinical Trial Inspection 2010[31]-

The aim of the clinical trial inspection programme 2010 are to verify GCP compliance to protect the rights, safety and well being of the subjects involved in clinical trial , to verify the credibility and integrity of clinical trial data generated and to verify the compliance with the various regulatory provisions as per Drugs & Cosmetic Rules.

Inspection can be conducted before, during or after a clinical trial is completed. Inspection can be carried out as a routine surveillance or for any specific cause(s) . Study may be selected for inspection based but not restricted to following criteria-

(i) Nature of study
(ii) For regulatory decision based on clinical trial data
(iii) Data irregularities
(iv) Complaints
(v) Vulnerability of subjects
(vi) Number of CT including number of subject enrolled at a particular site

## 11.0 Proposed Drug & Cosmetic Amendment Bill 2015

A Draft of Drug & Cosmetic (Amendment) Bill 2015 is proposed in Parliament. In 2015 bill a separate new chapter IA relating to clinical trial is being proposed.

In proposed bill section 4A is relating to permission of clinical trial and no person, sponsor, clinical research organization or any other organization or investigator shall conduct any clinical trial without the permission of Central Licensing Authority and ethics committee. Section 4C of proposed bill states where a participant is injured or disabled in a clinical trial, the person or body permitted under section 4A and sponsor shall provide such medical treatment and compensation in such manner as may be prescribed and where death of participant is caused due to clinical trial, the person or a body permitted under section 4A and sponsor shall provide to his legal heir, such compensation, in such manner as may be prescribed. Section 4D is regarding deferment or waive off the pre clinical and clinical data in public interest. There is provision of registration of ethics committee in section 4(E). Section 4(I) is regarding

[31] Clinical Trial Inspection programme 2010 on http//: www.cdsco.nic.in retrieved on December 25, 2018

disclosure of name, address etc of person involved in clinical trials if required by Drug Control Officer or other officer authorized by Central Licensing Authority.

(vii) Section 4K of proposed bill 2015 is regarding the penalty for conducting clinical trial. There is provision of imprisonment which may extend to three years or fine which may extend to five lakh rupees or both if there is a contravention of section 4A. Any notified category of new medical device, in contravention of section 4A and rules made there under, shall be punishable with imprisonment which may extend to two years or fine of three lakh rupees or both. In case of repeat offence, imprisonment shall not be less than three years which may extend to five years and liable to fine which shall not be less than 15 lakh rupees.

## 12.0 Draft New Drug & Clinical Trial Rule 2018

The ministry of Health & Family welfare of Government of India has released draft clinical trial Rules 2018, which will come into force after its final publication in official gazette. The new rules have been drafted after consultation with the Drugs Technical Advisory Board (DTAB) and under part XA and schedule y of the Drug & Cosmetic Act 1940. The new rules contains 12 chapters 8 schedule and will apply on new drugs, investigational new drug for human use, clinical trial, and bioequivalence study and ethics committee.[32]

The new regulation clearly define feature of an academic study, the role of central licensing authority, trial protocol, biomedical and health research. According to new rules, the clinical trial in relation to new drug in humans has to generate data for discovering or verifying its pharmacological interactions including pharcodynamics, pharmacokinetic and adverse effects in order to determine the safety, efficacy or tolerance of new drug. Proposed Draft of Clinical Trial Rules covers full spectrum from ethics committees and manufacturing permission to inspection and injury compensation.[33]

## 13.0 Recent initiatives and priorities by CDSCO for Ethical and Quality Clinical

## Research [34]–

Since 2008-09 CDSCO has taken up from number of World Health Organization**,** **USA** FDA, Health Canada ANVISA Brazil and South Africa to develop methodical approach for clinical

[32] http://www.cdsco.nic.in/writerreaddata/GSR%20104(E)%20dated%2001_02=2018_New%20Drug%20&20CLinical%2020Trial%20Rules%202 retrieved on February 1,2019

[33] Not Secure www.mondaq.com/india/x/682904/food+drug+law/Health+Ministry+Release+Draft+New+Drug+Clinical+Trial+Rule+2018 retrieved on February 20, 2019

[34] https://www.omicsonline.org/open-acess/clinical trial-regulations-in-india-2167-7689.1000e118.php?aid=14913 retrieved on December 27,2018

trial regulatory systems. Since then many changes, amendments were drafted and finalized and a roadmap was developed to strength the regulatory process.

- Building of regulatory framework to allow phase 0 (micro dosing) and phase-1 studies in the country in a phase wise manner.
- Mandatory registration of clinical trial on clinical trial registry since June 2009.
- 12 New Drug Advisory Committee (NDAC) were constituted to examine the applications for permissions for clinical trials and approval of new drugs.
- Draft notification for registration of clinical research organization issued on January 2011
- Guidance of Clinical Trial Inspection-November 2010.
- Registration of Ethics Committee will be mandatory.
- Drafter guidelines for enhancement of the responsibilities of Ethics Committee, Investigator , Sponsor to ensure that financial compensation as well as medical care is provided to the trial subjects who suffer trial injury or deaths.
- Scheme M III guidelines for devices have been posted on website which are inline with GHTF.
- Rules to be amended and medical devices would be separated definition of drug. Provision for overseas inspections under Rules 24-A (5). The overseas inspections from 2011 were regularly conducted in different countries from where imports of drugs are taking place.
- Good Laboratories Practices were notified under notification GSR 780(E) dated 10.11.2008 and became operative since 1.11.2010.

## 14.0 72th Standing Committee report 2013 on alleged irregulatories in conduct of studies using Human Pappilona Virus (HPV) Vaccine by PATH( Programme for Appropriate Technology in Health) in India [35]–

In this report it is established that PATH by carrying out the clinical trials for HPV vaccines in Andhra Pradesh and Gujarat under the pretext of observation/demonstration project has violated all laws and regulation laid down for clinical trials by the Government. While doing so , its sole aim has been to promote the commercial interest of HPV vaccine manufacturers who would have been reaped windfall profits had the PATH been successful in getting the HPV vaccine included the Universal Immunization Programme (UIP ) of the country. This is a serious breach of trust by any entity as the project involved life and safety of girl children and adolescents who were mostly unaware of implication of vaccinations. The violation is also a serious breach of medical ethics. The act of PATH is a clear cut violation of human rights of these girl children and adolescents. It also deems it an established case of child abuse. The committee, therefore, recommends action by the Government against PATH.

[35] http://www.rajyasabha.nic.in retrieved on January 10,2019

In *Swasthya Adhikar Manch Vs UOI 2012* [36] the supreme court in an order states that large scale clinical drug trials across the country by pharmaceutical firms using Indian citizens as guinea pigs in those tests, a supreme court bench of justice R.M. Lodha and S.K.Singh has said that no trial of new drug be allowed till consent of people subjected to trial is recorded in audio/visual medium. The petition also alleged the clinical trials by several pharmaceutical companies are going indiscriminately in various states. Observing that the clinical trial India and not for the benefit of multinational companies, it allowed the trial for five entities but refused to pass order of 157 drugs which were allowed by the centre in the year 2013. The fate of 157 government approved global clinical trials seemed uncertain as the apex committees set up by the centre for the purpose must clear the clinical trials for 157 drugs with recent amendment to Drugs & Cosmetic Act after earlier direction of Supreme Court.

*Roche Products (India) Pvt. Ltd Vs Drug Controller General of India 2016*[37]

This was the question before Delhi high court whether recommendation was based on clinical trials purportedly conducted by defendant No.2 in relation to two additional indication of bio-similar[38]? It was held by Delhi high court that as per Rule 122E (b) of Drug Rules, a drug already approved by DCGI was proposed to be marketed for a new indication; was a new drug for the purpose of Drug Rules. There is no provision under Drug Act and Drug Rules permitting exemption from conducting such tests for approval of bio similar drug for new indications. As per clause D of form 44 of Drug Rules, which form was required to be filed, inter alia along with the application for approval for manufacture of new drug, Applicant should provide therapeutic justification for new claim and data generated on safety or quality parameters. It was evident that extrapolation of clinical data relating to one therapeutic indication to another different indication was not automatic or unqualified and must be therapeutically justified with safety and quality data. Moreover it could not be disputed that appropriate clinical trial end points for a drug targeting HER2+ early cancer was disease free survival ,which measured length of time after primary treatment for a cancer ends that patient survived without any sign or symptoms of that cancer. Admittedly, recommendation was not based on clinical trials purportedly conducted by defendant no. 2 in relation to two additional indications. Whatever studies and trials conducted by defendant no. 2 on patients were only in relation to with HER2+ metastic breast cancer. Approval of two additional additional indications was granted by without passing speaking orders and discussion. When approval of first indication itself was not granted strictly as per rules and guidelines. A party was entitled to the benefit of approval of extrapolation of clinical trial relating to one therapeutic indication to different if due compliance and protocol were satisfied .Drug Authority was supposed to examine application for same very carefully because it

[36] Pil W.P(c ) no.33 courtesy http://www.live.law.in retrieved january 200,2019
[37] MANU/DE/172/2016
[38] A bio similar is a biologic medical product which is almost an identical copy of an original product that is manufactured by different company.

was to be granted without clinical trial. Approval could not be granted in mechanical manner or on demand. Authority had to assign reason.

## 15.0 Conclusion and suggestion

CDSCO has recently launched a new tool (SUGAM) for online application as a part of efforts to increase accountability, transparency and efficiency of processing applications with speed. Recently, three workshops have been conducted by CDSCO involving industry members to provide hands on training and gather suggestion. This approach by CDSCO has been welcome by industry and research organizations. Infact, effective early October 2016, this tool is functional for online clinical trial applications.[39]Approval time must be reduced so that it could enable more clinical research in India.

International Conference on Harmonization (ICH) GCP E6 (R1) 1996 guideline has revised to keep pace with scale and complexity of clinical trials. The ICH GCPE6 (R2) 2016 guidelines takes this evolution of technology into consideration and encourages sponsors to pursue innovative approaches for conducting and monitoring clinical trials. It also emphasizes on establishing a risk based quality management system and conducting and reporting centralized monitoring in lieu of traditional monitoring processes. Quality -by –design and risk –based quality management are now recommended as approvals of choice to sponsor of clinical trials. It is worthwhile to watch how Indian clinical research stakeholders adopt these guidelines.[40]

There is a lack of regulatory framework in case of stem cell, phase 0-micro dosing, medical devices etc. Indian regulator must address the issue of stem cell clinical trial research. Strict guidelines and measures must be taken if subjects of clinical trials are pediatrics

There must be a single window clearance system for approval of clinical trials. There must be continuous training programme for investigators and other staff. There must be fix time line (maximum two months) for disposal of each application. Status of new drug application must be on website fortnightly. All infrastructure and staff relating to clinical trial should be available at one place. There must be exhaustive list of subject experts in the office of clinical trial to understand the intricacy in specialized area of clinical trial.

[39] Notice by CDSCO : 5 OCTOBER 2016 (CDSCO/IT) 2015-(48) Available on http:// www.cdsco.nic.in/writerreaddata/notice%20-dated 05-10-2016-pdf

[40] http:// www.picronline.org/article.asp?issn=2229-3485;year=2017;volume=8;issue=1;spage=11;epage=16;aulast=bhave retrieved on October 10,2018