

**REPORT OF THE PROF. RANJIT ROY
CHAUDHURY EXPERT COMMITTEE**

TO

**FORMULATE POLICY AND
GUIDELINES FOR APPROVAL OF
NEW DRUGS, CLINICAL TRIALS AND
BANNING OF DRUGS**

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GUIDELINES FOR APPROVAL OF NEW
DRUGS, CLINICAL TRIALS AND
BANNING OF DRUGS

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Members of the Committee

1. Professor Ranjit Roy Chaudhury Chairman
National Professor of Pharmacology
Adviser - Department of Health and Family Welfare
Govt of NCT of Delhi
Former Member, Board of Governors
Medical Council of India
Y-85, Hauz Khas, New Delhi - 110016
2. Dr V.P.Kamboj Member
Former Director
Central Drug Research Institute. Lucknow - 226 001
C-III, Opposite Church, Indira Nagar, Lucknow - 226 016
3. Dr BTKaul Member
Professor of Law
Delhi University, Delhi Law Centre - II
Dhaura Kuan, New Delhi - 110 021
4. Dr Vasantha Muthuswamy Member
Former Senior Deputy Director General
Indian Council of Medical Research
A-IOI, Manchester Regent, Avinashi Road,
P N Palayam, Coimbatore - 641 037
5. Dr Mira Shiva Member
Coordinator, Initiative for Health, Equity and Society
A-60, Hauz Khas, New Delhi - 110 016
6. Dr Uma Tekur Member
Professor and Head
Department of Pharmacology
Maulana Azad Medical College, New Delhi - 110 002

Salient recommendations

1. Clinical trials can only be carried out at centres which have been accredited for such purpose. The principal investigator of the trial should be an accredited clinical investigator. The ethics committee of the institute must also have been accredited. Only those trials conducted at centres meeting these stipulations will be accepted by the Drugs Controller General of India (DCGI).
2. A Central Accreditation Council should be set up to oversee the accreditation of institutes, clinical investigators and institute ethics committees.
3. Selection of assessors for accreditation and of experts to review new drug applications and other purposes will be made by a blind randomized procedure from a Roster of Experts. This Roster will be prepared after a nationwide search of appropriate experts and approval by the Technical Review Committee. The selection will have built-in safeguards for gender sensitivity and geographical representation.
4. A roster will be maintained of accredited institutes and medical centres approved for carrying out clinical trials. Pharmaceutical houses will be permitted to identify centres from this roster where they wish a particular clinical trial to be carried out.
5. The 12 drug advisory committees which are functioning at present will be replaced by one broad expertise-based Technical Review Committee to ensure speedy clearance of applications without compromising on quality of data and rules and regulations. The Committee would be assisted as required by appropriate subject experts selected from the Roster of Experts.
6. An informed consent from each participant is a mandatory prerequisite for a clinical trial. In circumstances where informed consent has to be obtained from special groups of people who have diminished capacity to protect their interests or give consent for themselves, the consent given by the guardian should be witnessed by an independent person who also has to sign the informed consent document. Audiovisual recording of

the informed consent process should be undertaken and the documentation preserved, adhering to the principles of confidentiality.

7. If any adverse effect (AE) or serious adverse effect (SAE) occurs during a clinical trial, the sponsor investigator will be responsible for providing medical treatment and care to the patient at his/their cost till the resolution of the *AE/SAE*. This is to be given irrespective of whether the patient is in the control group, placebo group, standard drug treatment group or the test drug administered group.
- 8.a) Compensation need not be paid for injury or death due to totally proven unrelated causes. In all other cases of death or injury/disability, compensation should be paid to the participant or his legal heirs.
 - b) Compensation will be paid to the trial participant if any drug-related anomaly is discerned at a later stage and accepted to be drug related by a competent authority whether in India or abroad.
9. Any SAE arising in the group receiving the placebo in place of the standard treatment should also be compensable if the SAE is related to the use of placebo.
10. There must be strong provision for ancillary care to cater for patients suffering from any other illness during the trial.
11. No compensation needs to be paid for therapeutic inefficiency, since the very purpose of a clinical trial is to determine the efficacy and safety of a given drug/vaccine/device.
12. Academic research may be approved by the institute ethics committee (IEe).

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 needed.
13. The Government of India, state governments and institutions should create a fund in order to encourage academic and clinical research (non-pharmaceutical company

related) in institutions. The fund may be raised by imposing a cess if needed. This fund will be available to the institution for paying compensation.

14. In cases of clinical trials being carried out on patients suffering from terminal illnesses such as cancer, compensation may be payable if the IEE, after deliberation, is of the considered opinion that
- there is an increase in the number of SAEs occurring in such a patient as compared to a standard treatment, and which may be irreversible; or
 - life expectancy has been severely curtailed.

For such patients, compensation may not be given if the primary end-point is death, as per the clinical trial protocol.

15. The IEC, assisted if necessary by experts, will determine if the drug under trial is the cause of injury or death. The opinion of the investigator and the sponsor will be reviewed by the IEC. The IEC will forward its recommendation to the DCGI, who will ordinarily accept the recommendations of the IEE on the causality.
16. Phases I to IV clinical trials of all new entities developed in India to be marketed in India will need to be carried out in India.
17. All NCEs/NMEs undergoing clinical trials anywhere can also undergo parallel Phase II and Phase III trials in India after carrying out a safety assessment through Phase I trials.
- 18.(a) Drugs which have already been on the market in well-regulated countries with good post-marketing surveillance (PMS) for more than four years and which have a satisfactory report may be granted marketing licence, subject to strict PMS for four to six years. The period of four years may be reduced or waived off in cases where no therapy or only palliative therapy is available, or in national healthcare emergencies.

- (b) First-time generics manufactured in India will undergo bridging Phase III trials and bioequivalence (BE) studies in humans.
 - (c) BE studies in humans should be undertaken in subsequent generics along with strict PMS.
 - (d) Similar biologics (biosimilars) will undergo both pre-clinical development and bridging Phase III clinical trials as per Department of Biotechnology (DBT)- Central Drugs Standard Control Organization (CDS CO) guidelines.
- 19.(a) In cases where new chemical entities (NCEs)/ new biological entities (NBEs) or new drug substances or their generic drugs or similar biologics are to be introduced in India, bioavailability (BA)/BE studies in patients should be done preferably as a part of the clinical trial.
- b) BA and BE studies of new drug substances discovered abroad and not marketed in India should not be approved to be conducted in India.
 - c) BA and BE studies once conducted with a generic should not be repeated for export purposes only.
20. The CDSCO will provide a written assurance to the pharmaceutical house or investigator seeking approval for a clinical trial that if all the papers needed for the review are complete, then a decision, either interim or full, will be given within three months.
21. At any point of time, the representative of the pharmaceutical house or investigator shall have the right of dialogue with an officer of the CDSCO regarding the application on payment of a fee for such consideration.
22. Information technology will be used at all steps of a clinical trial to ensure total transparency in the system. From the first step when the application is placed at the

single window, till the final approval is received, every step will be recorded and made available in the public domain.

23. Three types of activities should be initiated at the state level to help in monitoring clinical trials carried out in state institutions. These are:

- Joint monitoring of clinical trials with personnel from CDSCO
- Coordination and information sharing
- Training of state drug regulatory personnel.

24. (a) A Special Expert Committee should be set up independent of the Drug Technical Advisory Board to review all drug formulations in the market and identify drugs which are potentially hazardous and/or of doubtful therapeutic efficacy.

(b) A mechanism should be put in place to remove these drugs from the market by the CDSCO at the earliest.

25. The CDSCO needs to be reorganized, upgraded and strengthened if it is to perform the various functions envisaged above.

Terms of reference

1. To formulate policy, guidelines and standard operating procedures (SOPs) for approval of new drugs including biologicals, with special emphasis on the following:
 - a) Planning a transparent and equitable system of clinical evaluation of new drugs
 - b) Requirements of a local clinical trial on the Indian population for drugs approved in other countries
 - c) Specific circumstances, if any, under which a local clinical trial can be abbreviated, relaxed or omitted
 - d) Types of local clinical trial, their design, sample size, sites and their distribution, inclusion of ethnic population, etc. in the local clinical trial
 - e) Requirements of post-marketing (Phase IV) trials to assess safety of new drugs in the post-marketing scenario.
2. To formulate policy, guidelines and SOPs for approval of clinical trials including global clinical trials of new drug substances discovered abroad and bioavailability and bioequivalence study for export, with special emphasis on the following:
 - a) Monitoring the functions of ethics committees
 - b) Accreditation of clinical trial sites and investigators
 - c) Clinical trial inspections
 - d) Participation of state authorities in monitoring of clinical trials.
3. To formulate policy, guidelines and procedures for examination of issues related to continued marketing of drugs, not only due to safety or other reasons, but also due to launch/availability of safer and more efficacious alternative drugs in the country
4. To formulate guidelines and SOPs on the functioning of new drug advisory committees (NDACs)
5. To formulate policy and procedures for identification of experts for advising Central Drugs Standard Control Organization (CDSCO) in various matters
6. To advise CDSCO in other matters referred to it for advice.

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Preface

The Expert Committee constituted by the Ministry of Health and Family Welfare to formulate policy, guidelines and standard operating procedures for approval of new drugs including biologicals, clinical trials and banning of drugs was announced on 6th February 2013. The members commenced their work on 14th February 2013 with their first meeting.

The vision of the Committee, based on the extensive mandate given to it, was to recommend changes and introduce measures which would result in a drug regulatory system for India which is robust, transparent and built on the foundations of science and ethics. This report contains the recommendations which the Committee feel will establish such a system.

It is not easy to institute changes in a country as large as India with complexities that are inherent due to varying levels of development in different states and different types of populations. The fact that 'Public Health' is a state subject in the Constitution also had to be kept in mind. The people of the country and their good health are our concern, and throughout our deliberations one guiding principle was paramount - to see that they were not exploited in any way. At the same time, we were also acutely aware that the people of the country are entitled to the most advanced therapy available.

In an endeavour to understand the present system better and to understand the perceptions of different segments of society involved in drug regulation and use, the Committee met a large number of people. These included (a) representatives of civil society; (b) representatives of the pharmaceutical industry- Organization of Pharmaceutical Producers of India (OPPI), Indian Drug Manufacturers Association (IDMA) and Indian Pharmaceutical Alliance (IPA); (c) representatives of contract research organizations- Association of Contract Research Organizations (ACRO) and Indian Society for Clinical Research (ISCR); and (d) representatives from industry-Confederation-of Indian Industry (CII), Federation of Indian Chambers of Commerce and Industry (FICCI) and Associated Chambers of Commerce and Industry of India (ASSOCHAM). The Committee also met clinical investigators and heads of institutes

carrying out clinical trials, regulators and government officials. In addition, the Committee met several experts and academicians at an individual level as well as heads of industry and leaders of non-governmental agencies.

What was remarkable was that even though there were markedly different perceptions about specific issues, there was total unanimity that a robust regulatory system was the need of the

hour and that this would be welcomed by all. Following these discussions, the Committee deliberated on the different issues intensively, went back to the different organizations and individuals where necessary, and prepared this Expert Committee Report which they are presenting to the Government for their consideration and implementation. This Report, we earnestly hope, addresses the concerns expressed by the Parliamentary Committee on Health and the Supreme Court of India.

The Committee is well aware that all the 25 recommendations listed in the Expert Committee Report cannot be implemented at the same time. There are, however, several important recommendations which can be implemented immediately. The basic rationale for the changes rests on the following principles: (a) Transparency by use of information technology, (b) Removal of bias and conflict of interest, (c) Accreditation, (d) Science-based decision making, (e) Efficient functioning of institute ethics committees, (f) Equitable compensation for volunteers who experience serious adverse events during the trials, and (g) Strengthening of infrastructure. While some decisions can be taken immediately, others may need changes in the Drugs and Cosmetics Act, 1940 and the rules framed thereunder. We hope that the Government will speedily accept these recommendations.

The Committee would like to thank the many persons and organizations who helped us by giving us their frank views and by participating in our discussions. Not a single person or society refused our invitation to them to meet us. Besides this, a large number of organizations and government agencies both in India and abroad and several foreign universities spontaneously offered to help us. We take this opportunity to thank them all for their suggestions. The Committee appreciates the courtesy extended to it by the CDSCO in organizing various meetings.

The Committee appreciates the trust placed in it by the Ministry of Health and Family Welfare, Government of India and has tried its utmost to discharge the mandate given to it.

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Prof Ra.(jit RJ; ChflUdhUr

(Chairman)

Dr VP Kamboj
Dr VP Kamboj

Prof BT Kaul
Prof BT Kaul

Dr Vasantha Muthuswamy
Dr Vasantha Muthuswamy

Dr Mir
Dr Mir

Prof U rna Tcku r
Prof U rna Tcku r

Abbreviations

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ACRO	Association of Contract Research Organizations
ADC	assistant drugs controller
AE	adverse event
ASSOCHAM	Associated Chambers of Commerce and Industry of India
BA	bioavailability
BE	bioequivalence
CAC	Central Accreditation Council
CDSCO	Central Drugs Standard Control Organization
CII	Confederation of Indian Industry
CIOMS	Council for International Organizations of Medical Sciences
CRO	contract research organization
CTRI	Clinical Trials Registry India
DBT	Department of Biotechnology
DCA	Drug control authority
DCC	Drugs Consultative Committee
DCGI	Drugs Controller General of India
DDC	Deputy Drugs Controller
DDCI	Deputy Drugs Controller (I) Drugs
DTAB	Technical Advisory Board
EC	ethics committee
EMA	European Medicines Agency
FICCI	Federation of Indian Chambers of Commerce and Industry
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
GOI	Government of India
GVHD	graft versus host disease

HPV	human papillomavirus
ICH	International Conference on Harmonization
ICMR	Indian Council of Medical Research
ISCR	Indian Society for Clinical Research
IDMA	Indian Drug Manufacturers Association
IEC	institute ethics committee
IPA	Indian Pharmaceutical Alliance
IT	information technology
MCI	Medical Council of India
MNC	multinational corporation
NBE	new biological entity
NCE	new chemical entity
NDA	National Drug Authority
NDAC	New Drug Advisory Committee non-
NGO	governmental organization National
NIHS	Institute of Health Sciences National
NIMS	Institute of Medical Statistics
NME	new medical entity
OPPI	Organization of Pharmaceutical Producers of India
PI	principal investigator
PIL	public-interest litigation
PMS	post-marketing surveillance
RCGM	Review Committee on Genetic Manipulation
SAE	serious adverse event
SDSCO	State Drugs Standard Control Organization
SOP	standard operating procedure
TRC	Technical Review Committee
USFDA	Food and Drug Administration

1. A transparent and equitable system of clinical evaluation of new drugs

The system of clinical evaluation of new drugs that is being proposed will be ethical, transparent and equitable. The proposed system will be based on recommendations and decisions taken solely on a scientific basis. Once modifications suggested in this report have been implemented, there will be little opportunity of introducing bias or of a nexus developing in the system.

Control mechanisms

The modified system will depend on the following mechanisms to make it efficient, transparent and equitable:

- *Accreditation* of all centres carrying out clinical trials, principal investigators and institute ethics committees
- *Standard operating procedures (SOPs)* to be followed for all steps
- *Randomization* of the system of allocations of experts for review of applications and assessment of centres for accreditation
- Use of *oi information technology* at every stage to ensure transparency of the system
- Use of a *single window system*
- A process of *dialogue* to be set up for communications
- Establishment of a *computerized database* of carefully selected experts, which will be updated every year. Experts will be selected only from this database keeping gender bias and geographical considerations in mind.

Evaluation procedures will be equitable for proposals seeking approval for a clinical trial to be conducted by any of the following - an individual scientist, a government institute, a national or foreign research organization, or a national or international pharmaceutical house.

In the proposed system, all information about the new drug or vaccine for which an application is being made will have to be sent to the single window at the Central Drugs Standard Control Organization (CDSCO). This will be followed by a series of sequential steps. These are delineated below.

Steps of the trial

Step 1

The pharmaceutical house or investigator will be given an acknowledgement and a reference number. This will enable the CDSCO to place the correct status of the progress on the Internet from time to time. The applicant should also be given a written assurance that if all the papers needed for the review are complete, then a decision, either interim or full, will be given within three months.

Step 2

The application will be reviewed by the Technical Review Committee (TRC). This Committee will be assisted, if needed, by carefully selected experts from the roster of experts. The Committee will decide as to whether a clinical trial with the new drug is justified keeping in mind the criteria of safety, effectiveness and need for such a drug, taking into consideration other similar drugs already in the market.

Step 3

Once the TRC approves the clinical trial proposal the sponsor is informed of the same.

Step 4

At this stage the proposal will be sent to the Randomization Unit (which may or may not be situated at the CDSCO). This unit will list at least six accredited centres that are considered suitable for carrying out trials with the drug.

Step 5

The sponsor/applicant will be required to select two or three centres, as recommended by the TRC. The Chief Investigator, the heads of the centres and the CDSCO will be informed of the centres selected.

Step 6

The proposal with the protocol will be submitted to the Institute Ethics Committee (IEC) for ethical review and approval.

Step 7

If any modification to the protocol is introduced by the Principal Investigator, the CDSCO will need to be informed. If the modification is a major one, it will need to be approved by the TRC.

Step 8

As soon as the IEC approves the clinical trial, this information will be entered into the central trial registry presently being maintained by the Indian Council of Medical Research (ICMR). Eventually, this registry will be maintained by the CDS CO, which will also be informed of the approval of the IEC.

Step 9

The clinical trial will be initiated.

Step 10

The progress of the clinical trial will be reported every six months to the IEC and the CDSCO.

Step 11

Serious adverse events (SAEs) during the trial, if any, will be reported to the IEC. This aspect has been covered in the chapter on compensation and legal matters. The issue of compensation, in addition to free medical management of the side effects, will be taken up by the IEC in accordance with the guidelines/rules pertaining to this.

Step 12

The final report of the clinical trial will be submitted to the CDSCO and the IEC.

Step 13

The final report will be reviewed by the TRC of the CDSCO, and if approved, the CDSCO will inform the sponsor/applicant of the outcome of the trial.

Step 14

The results of the clinical trial, the approval of the IEC and the final decision of the TRC will be placed on the website of the CDSCO.

Step 15

The CDSCO will take the subsequent steps regarding the drug based on the recommendations of the Technical Advisory Committee.

At any point of time, the sponsor can request for a discussion with a staff member of the Public Information Unit of the CDSCO. Such dialogue will be encouraged, although there will be a fee for this consultation.

2. Requirements for clinical trials in India

Introduction

It is important that all pharmaceutical products go through a standard quality, safety and efficacy study, both during the pre-marketing evaluation and also during the post-marketing review.

An application for marketing authorization in any country should include the following:

- a) Product information, such as any new chemical or biological active pharmaceutical ingredient, new routes of administration, new strengths and new indications
- b) New dosage form for drugs already existing in the country
- c) Variation in existing marketing authorization in terms of formulations, shelf life, new manufacturing sites, etc.

We will be primarily considering points (a) and (b).

Role of the Drugs Controller General of India

The objectives of the Drugs Controller General of India (DCGI) in relation to new drugs to be marketed in the country are as follows:

- a) To carry out pre-market evaluation of the new chemical entity (NCE)/new medical entity (NME) for its efficacy and safety
- b) To ensure quality of the NCE/NME.

Ideally, before giving sanction for new medicines, the DCGI should decide on the number of drugs and/or drug trials that should be conducted in the country. Should these be finite or unlimited? This decision will be based on several other factors including the requirement for the country, which in turn may be based on the morbidity and mortality pattern, the number of standardized and accredited facilities for conducting these trials, etc.

It is also important for the Technical Review Committee (TRC) to deliberate and decide whether the approval should be given to only such protocols for which there is a definitive

need in the country. This decision needs to be taken on a case-by-case basis. If a new drug is added, the Committee can consider if one of the existing drugs on the approved list can be deleted.

Requirement of clinical trials on Indian populations

The requirement for clinical trials on Indian populations will be governed by the following stipulations:

- For all new chemical entities developed in India to be marketed in India, all the trial phases (Phases I-IV) will be carried out in India.
- For all NMEs/NCEs developed outside India which are of relevance to our population, it is presently not always necessary to carry out Phase I trials in our country, provided Phase I trials have either been done or are being done in the country of origin.
- All NCEs/NMEs undergoing clinical trials anywhere can also undergo parallel Phase II and Phase III trials in India, after carrying out a safety assessment through Phase I trials. The Phase I trials should have been done in the country of origin if the disease is prevalent there.

If Indians have participated in these global trials in requisite numbers, i.e. in statistically significant numbers, and provided the safety data is satisfactory, direct marketing may be permissible thereafter without the need of Phase III trials or bridging studies. This is however subject to two conditions:

- Strict post-marketing surveillance (PMS) for four to six years, and
- The TRC should have scrutinized the data carefully.

Such permission for direct marketing will be granted on a case-by-case basis.

- Drugs which are already in the market in well-regulated countries with a good PMS for more than four years, and which have a satisfactory report, may also be permitted for direct marketing in India, subject to strict PMS for four to six years or after bridging studies, on a case-by-case basis.

- Generics and similar biologics (biosimilars) that have been marketed in well-regulated countries for more than four years and have a satisfactory report can be released for marketing in India after abbreviated trials.
- In all other cases, i.e. NCEs/NMEs undergoing clinical trials, drugs which have been in the regulated market for less than four years, and drugs marketed by countries with an inefficient or no regulatory system will have to go through Phase III clinical trials before permission is granted for marketing the drug in India.

The policy as enunciated above is in keeping with the current regulations. At the same time, these measures will lessen the burden of too many clinical trials with the attendant delays. The imperative is a strong PMS in the country.

Points for consideration

The following points are also required to be considered in deciding on the requirement of local clinical trials on Indian populations for drugs approved in other countries:

- The country of origin of the *NCE/NME* must have a reliable and dependable regulatory agency.
- The product in question must be identical to the one being marketed in its country of origin.
- The preclinical and clinical data packages must meet the regulatory requirements of our country. Also, the data thus submitted must be in the required format. In case any amendments are suggested, these should be acceptable to the Indian regulatory agency.
- Countries with efficient and good regulatory agencies such as the USA, UK, countries of the European Union, Japan, Australia, Canada, etc. should be marketing the drug under study.
- In the event of the *NCE/NME* being different from the original chemical/medical entity and these differences not being acceptable to the Indian system, it is mandatory that we generate our own data base. These studies could be anything from bioavailability (BA)/bioequivalence (BE) studies to Phase III/Phase IV clinical trials.

These trials must include pharmacokinetic studies. The decision has to be taken on a case-by-case basis.

- In the event of the drug having undergone global clinical trials, it must be confirmed that the product to be marketed in India is identical to the one approved in its country of origin. However, in the event that the drug is different from the one approved in its country of origin, these differences must conform to the Indian requirements.
- In the event of India being a part of the global multi-centric trial, then
 - the numbers of subjects included from India should be adequate, such that there is a reasonable likelihood of showing an effect;
 - the sub-analysis data of the Indian subjects should be available to India and be acceptable for drug approval in India;
 - If the answer is in the negative for either of the above, then Phase III clinical trial data along with the pharmacokinetic data should be generated for the Indian population.
- In all cases and under all circumstances, PMS has to be conducted in India over a period of four to six years.

Additional points

In addition, some of the other points that may have to be considered for approval of drug trials in India are:

- Approval of 'me too' drugs similar to drugs already in the Indian market
- The stability of the drug at high temperatures and humidity such as is present in our subcontinent
- Adequate clinical/toxicological studies in support of its use
- Its use in endemic diseases prevalent in India
- Outcome of studies conducted on different ethnic groups globally. Were any significant differences observed? If the drug has shown significant ethnic variations in studies conducted earlier, then it is imperative that the trial be done on the Indian

population and in different regions of India. This is important because of the vast ethnic variations in our country.

The patient populations for trials conducted in India should be representative of the ethnic population. It is important that at all stages pharmacokinetic data be collected on the Indian population.

Similar guidelines have to be laid down for the following situations:

- Clinical trials for the paediatric population (outside the purview of vulnerable populations)
- Trials for medical devices for which pre- and post-assessment have to be made. The assessment of these medical devices may be made depending on their use and safety profile.
- Clinical trials of vaccines which may be used for
 - Their preventive role
 - Therapeutic use.

It is important that post-marketing surveillance (PMS) be strengthened.

Abbreviated clinical trials

Classically, abbreviated trials are conducted for generic equivalents of the innovator drug where bioequivalent studies are advocated. The same may be applied to the biosimilar drug group. These drugs should have been marketed for at least four years in a country with an efficient and well regulated drug control agency (USA, UK, countries of the European Union, Japan, Australia, Canada, etc.). For these studies, the pre-clinical and clinical data for establishing the efficacy and safety profiles are not required. It is also imperative that at least the first hundred cases included in the study be monitored very closely.

Some of the products for which the process may be expedited/abbreviated or omitted in emergency situations could include:

- Drugs for treatment of HIV / AIDS
- Drugs for graft versus host disease (GVHD) crisis in organ transplantation
- The drug is the only choice of treatment for a severe or rare disease

- Diseases for which there is only palliative therapy available at present
- Drugs for life-threatening diseases including cancer therapy which have demonstrated efficacy
- Drugs for new and emerging diseases, e.g. H1N1.

Bridging studies

A bridging study is defined as a supplemental study performed in the new region, e.g. India, to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the population of the new region. A bridging study for efficacy could provide additional pharmacokinetic information on the population of the new region. When no bridging study is needed to provide clinical data for efficacy, a pharmacokinetic study in the new region may be considered as a bridging study.

A new indication or an indication for its use in a special population will necessitate a separate bridging study.

For a bridging study to be conducted, the drug under consideration must have been available in a country with a well-regulated market for more than four years.

Objectives of bridging studies

- To evaluate the efficacy and safety parameters in the Indian population
- Minimize duplication of clinical data
- Show relevance between completed studies and local (regional) factors.

Ethnic factors

Ethnic differences affect the efficacy, safety and dose regimen of a medicine. The following factors may be taken into consideration in deciding whether the available data could be ethnically sensitive or insensitive:

- Definition of the disease and diagnosis of the patient
- Choice of control group
- Method of assessment of safety

- Similarity of medical practice to the country of origin
- Duration of trial
- Regional medical practice of concomitant medication use
- Severity distribution of eligible subjects
- Similarity of dose and dosage regimen
- Clinical end-point has to be acceptable to the region in assessing efficacy.

The following properties of a compound make it more likely to be sensitive to ethnic factors:

- Non-linear pharmacokinetics
- A steep pharmacodynamic curve (a small change in dose results in a large change in effect) for both efficacy and safety in the range of the recommended dosage and dose regimen
- A narrow therapeutic dose range
- Highly metabolized, especially through a single pathway, thereby increasing the potential for drug-drug interaction
- Metabolism by enzymes known to show genetic polymorphism
- Administration as a prodrug, with the potential for ethnically variable enzymatic conversion
- High inter-subject variation in bioavailability
- Low bioavailability, thus more susceptible to dietary absorption effects
- High likelihood of use in a setting of multiple-co-medications
- High likelihood of inappropriate use, e.g. analgesics and tranquilizers.

Waiver of clinical trials

Provision of a waiver should be used only when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable and are in place. The waiver request has to be made to the Technical review Committee (TRC) and applied for

prospectively. This information should subsequently be intimated to the concerned institute ethics committee (IEC).

Waiver in emergency situations

Waiver of clinical trials may be considered

if the study is designed to evaluate or examine public health emergencies, e.g. 111 epidemic situations

when there is a need for emergency healthcare services to respond to a disaster, significant outbreak of an infectious disease, bioterrorist attack or any other significant or catastrophic event, and the health consequences have the potential to overwhelm routine community capabilities.

Even in such cases, it is important to ensure that the drug has been in the global market for a minimum period of four years. Strict post-marketing surveillance must be carried out. *Conditions for grant of waiver*

The waiver will not adversely affect the rights and welfare of the participants.

- The participants will be provided additional pertinent information whenever required.
- There is no known or likely reason for thinking that the participants would not have consented had they been asked.
- There is sufficient protection of their privacy.
- There is an adequate plan to protect the confidentiality of data.
- In case the results have significance for the participants' welfare, there is (where practicable) a plan for making information available to them.
- The possibility of commercial exploitation of derivatives of the data will not deprive the participants of any financial benefits to which they would be entitled.
- A waiver request should contain the following information:
 - The reason the sponsor believes that a waiver is justified
 - A description of the alternative mechanism/s for human subject protection that the sponsor intends to use in the community

Written information should be provided to the participants explaining the implications. This should be translated into the local language.

Summary

- Clinical trials for drugs developed in India will have to undergo all four phases of trials in India.

- Drugs discovered and approved in foreign countries will be governed by the following:
 - If clinical trials are going on for NCEs/NMEs, parallel Phase II and Phase III trials can be conducted after safety is established through Phase I trials. The trial should have been done in the country of origin if the disease is prevalent there.
 - If the drug has been marketed in well-regulated markets for more than four years without any SAEs, it can be released in India after appropriate bridging studies or with strict PMS for four to six years.
 - Generics and biosimilars that have been marketed for more than four years in well-regulated countries can be released for marketing in India after abbreviated trials.
 - All other drugs marketed in other countries have to undergo mandatory Phase III trials in India before release.
 - In global clinical trials with India as a participating country, if sufficient quantity and ethnic distribution satisfy the regulatory requirements, marketing permission may be granted with strict PMS for four to six years. -

Clinical trials may be abbreviated, relaxed or omitted only under special circumstances keeping in mind the risk-benefit ratio, public interest and welfare of patients, but strict PMS should be insisted upon.

PMS for four to six years should be mandatory for all drugs permitted to be marketed in India.

This includes vaccines, devices and biologicals.

Clinical trials for medical devices and vaccines should be carried out under similar conditions as suggested for a NCE.

- In global trials where India is one of the centres, it must be ensured that there are an adequate number (statistically significant number) of patients participating in the trial. The subgroup analysis of the Indian data should show that the NCE will be useful for Indian patients. In addition, the physicochemical properties of the NCE should be appropriate for Indian conditions. Any difference in the NCE compared to the innovator. product should be acceptable to the regulatory agency of India. In the absence of the above, it is imperative that the complete Phase III studies be conducted in India.
- There should be a good regulatory system to oversee all of the above. This system should be transparent (for which new technological innovations may be used), robust and accountable.

3.Types of clinical trials

All clinical trials of new drugs need to be approved by the Drugs Controller General of India (DCGI) and the institute ethics committee (IEC) of the centre where the trial is to be carried out. The trial would need to be registered in the Clinical Trials Registry - India (CTRI) hosted at the National Institute of Medical Statistics (NIMS) of the Indian Council of Medical Research (ICMR). The trial can be carried out only at a centre that has been accredited for carrying out clinical trials, and by a principal investigator who has been accredited for the same.

Types of clinical trials

The trials which could be carried out would probably be one of the types listed below:

- Phase 0 clinical trials
- Phase I clinical trials
- Phase II clinical trials
- Phase III clinical trials
- Phase IV clinical trials (post-marketing clinical trials)
- Observational clinical trials
- Single case studies
- Adaptive clinical trials
- Add-on studies.

Phase 0 clinical trials

These are studies carried out using sub-therapeutic doses of candidate drugs to enable the investigator to select a particular compound/drug for further toxicological and clinical studies. These studies are carried out on 10-15 volunteers.

Phase I clinical trials

Phase I clinical trials, also referred to sometimes as first-in-man studies, are carried out in closely-monitored surroundings to see the effect of the drug the first time it is administered to humans. The study is usually carried out on human volunteers. The dose range can be established in these studies. Certain pharmacokinetic studies can also be conducted as part of Phase I studies.

Phase II clinical trials

These studies are conducted for the first time on a selected group of 100 to 200 patients to determine the safety of the drug, assess its effectiveness and also determine the dose to be administered.

Phase III clinical trials

These are an extension of Phase II trials. carried out on a larger number of patients (up to 3000) and at a larger number of centres. The centres should be in different geographical areas of the country so that patients of different ethnic origins can be exposed to the drug. The results of the study determine the efficacy and side effects of the drug being evaluated, and may also shed some light on compliance.

Phase IV clinical trials

After regulatory approval is obtained and the drug is released in the market, Phase IV studies need to be carried out on the first thousand patients treated with the drug. These studies are carried out when the drug is being used in an uncontrolled environment. Rare side-effects may be identified in these studies.

Post-marketing studies

These studies are observational studies and are non-experimental in nature. It is expected that the adverse side-effects of a drug would be detected in post-marketing studies since a large number of persons are exposed to the drug.

Design of clinical trials

There are a wide range of designs of clinical trials which could be undertaken during different phases of a trial depending on the question that is being sought to be answered in that particular trial.

The trial could be an *open uncontrolled trial* wherein there is no comparison with another drug. These trials are very rare and are only carried out when a controlled comparative trial is not possible. A *controlled comparative trial* is a trial when one group of patients is given the drug on trial and the other group is given another drug. This control group could also be given a placebo instead of any drug.

In *randomized controlled trials*, the drugs are allocated according to a process of randomization such as the use of random numbers, to reduce bias. In a *non-randomized trial*, the drugs are not given randomly.

The clinical trial could be an open trial, a single-blind trial or a double-blind trial. In an *open trial*, the patients know that they are receiving the drug that is being clinically evaluated. A *single-blind trial* is when either the patient or the doctor does not know which drug is being given to which patient. A *double-blind trial* is when neither the patient nor the doctor knows which patient is receiving which drug.

For the past few decades, the *controlled, comparative, randomized, multi-centre double blind clinical trial* has been held by regulatory authorities to be the gold standard. However, today other designs are being used. One such design is the *observational clinical trial* where the investigator observes the effect of a drug but does not intervene. The investigator has no role in the administration of the drug.

Single case study entails observation of the effect of a drug on a single person at one place, followed by another observation at another place. The protocol and recording of the data is the same. In this way, a large number of patients make up an adequate sample.

Adaptive clinical trial is a type of randomized clinical trial which allows modifications of the ongoing trial while aiming to preserve the statistical validity and integrity of the trial.

With so many possible designs, the regulator has to decide which design would be the most appropriate, scientific and ethical. The DCGI's office or the Technical Review Committee could change the design of the trial. The design may also need to be changed to obtain the approval of the IEC, who will have the final say. Centres for clinical trials are encouraged to set up a technical review group. It is suggested that this group could approve the trial on technical grounds and thereafter the drug could go for approval by the IEC.

Add-on studies

Another type of clinical trial is the add-on study. Here, both groups of patients receive the same treatment, but one group also receives another drug which may make a difference. The other group receives a placebo. There is no ethical problem in this design as both groups are receiving the standard treatment drug. The add-on study could be randomized and double blind.

Use of the placebo

Placebo-controlled trials are fairly uncommon these days, although there will always be a case for such trials in special circumstances. These days, since other remedies are usually available, the drug to be tested is compared to the existing therapy. There is thus no issue of depriving a patient of a drug as is the case for the placebo group.

The pharmaceutical houses, the principal investigators, the drugs regulatory agency and the IECs all need to ensure that the design used in a clinical trial is appropriate, efficient and ethical. .

4.Guidelines for post-marketing surveillance of drugs and biologicals

Introduction

Post-marketing surveillance (PMS) is an essential component of pharmacovigilance activities. These guidelines deal with safety specifications and a protocol for monitoring that is submitted by the pharmaceutical company at the time of requesting for market authorisation. It is aimed at confirming the safety and efficacy of the newly-marketed product and its use in various groups and large populations, as also recording and reporting of adverse drug effects. This is a part of the safety assurance system of the product to promote its use and marketing.

PMS pertains to observational studies during the early post-marketing of a new drug (chemical entity, biotechnology-derived product or vaccine). PMS also encompasses its new dosage forms, new routes of administration or a new manufacturing process. The main focus of these studies is to generate additional information on treatment risks, adverse effects (AEs), serious adverse effects (SAEs), benefits, the effect of the drug on various populations and any adverse events observed after its large-scale long-term use.

These guidelines do not cover the entire scope of pharmacovigilance. The objectives of the PMS do not encompass the use of pharmacoepidemiological studies as laid down in the WHO definition of pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems'.

Background

The drug/biological is approved for marketing after considering the risk-benefit ratio, based on the information available through clinical trials. In case of generic drugs, similar biologics or new chemical entities (NCEs)/new biological entities (NBEs), the background information available on the safety profile from the innovator's trials, marketing experience and the limited trials within the country under the conditions specified is given on the product label.

However, the safety profile may change due to changes in patient characteristics, larger patient population and ethnicity. Thus, a continuous monitoring of the drug safety profile in different patient populations is of utmost importance for identifying rare side effects.

In order to ensure uniformity in reporting data, a well-developed basic format will be provided by Central Drugs Standard Control Organization (CDSCO) which should be filled by the pharmaceutical company to highlight the profile of the drug/biological approved by the Drugs Controller General of India (DCGI). It is essential to capture AEs/SAEs, if any, as also to establish its efficacy by a wider use of the product.

Scope

These guidelines are intended to cover the following:

- NCEs and NBEs
- Established products, their new dosage forms, new routes of administration or a new manufacturing process including for a biotechnology derived product when introduced, or in new populations or for new indications.

Objective

The focus of a PMS study should be to monitor hitherto-identified risks, potential risks and missing information.

A detailed protocol should be developed to monitor and record the side-effects and efficacy of the drug. The protocol should contain background information, including efficacy and the type of population in which the study was carried out. It should include adverse events and side-effects observed during the pre-clinical and different clinical phases as also the envisaged potential risks. The identified and potential interactions such as food-drug and drug-drug should be mentioned. The protocol should also include observations on the nonclinical safety findings which had not been hitherto addressed and any unexpected potential risks anticipated based on clinical data.

The benefits of PMS are to identify low-frequency reactions, high-risk groups, long-term effects, any drug-food or drug-drug interactions, increased severity and/or reporting frequency of known reactions.

Prompt and continuous analysis of the data reports by the safety management division of the pharmaceuticals company and the DCGI, and remedial actions by the DCGI, are essential components of the objective.

Responsibilities

All AEs and SAEs occurring during the use of the product should be reported as per the details provided in Appendix XI of Schedule Y of the Drugs and Cosmetics Rules, 1945 (as amended). The applicable guideline is 14 days from the time of occurrence and 48 hours of knowledge thereof. The report should be sent to the CDSCO by the drug marketing pharmaceutical company, clinician treating the patient or his/her hospital, or even by a practicing clinician. The product's use for a year or two should be restricted to hospital treated patients to capture AEs/SAEs and efficacy of the product through better monitoring and proper recording.

PMS

PMS would include the following:

- Spontaneous/voluntary reporting including reporting from scientific literature, publications or meetings
- Voluntary or required reporting from observational studies and randomized clinical trials
 - Drug-induced injury
 - Detection of events not seen in clinical trials such as new, previously unknown adverse events or new drug interactions
 - Any observed increase either in quantity or severity of a known adverse event.

In the PMS guidelines, only spontaneous reports and observational studies have been included for recording and reporting.

Spontaneous reports

A spontaneous report gives useful information about the drug used. This report can be submitted by a clinician, health-care person or patient to the regulatory authority or the pharmaceutical company. This report may describe one or more SAEs not observed/reported earlier. Such reports may also give information about risk groups, risk factors and clinical features of known serious adverse drug reactions. Spontaneous reports are often incomplete but serve to identify safety signals.

It should be mandatory for pharmaceutical companies, hospitals and health professionals to report benefits and side-effects or SAEs published in scientific literature, meeting reports/discussions or newspapers.

Observational studies

Observations on AEs, SAEs and benefits seen by the clinician or health personnel during or after treatment with a new drug or biological after marketing of the drug and thereafter for a period of five or six years are carefully recorded as per protocol by the treating clinician. These observations can also be reported by the patient or community to the treating clinician, who would then record and report the same directly to the DCGI and pharmaceutical company in case of AEs and SAEs. The pharmaceutical company will be required to make detailed records of the patient and report to the DCGI as per the laid-down protocol. Special attention should be paid to recording of expected SAEs and occurrence of unexpected SAEs not listed on the package insert such as death, disability or any events or signs and symptoms which could possibly lead to death or disability or hospitalisation for treatment. Such events should be immediately reported to the ethics committee, DCGI and the pharmaceutical company. Thereafter, procedures laid down by the DCGI will be followed.

Phase IV trials

Phase IV trials in vulnerable and special groups, e.g. pregnant women, children, the elderly population (with reduced dose or the same dose or a new use of the drug) should be evaluated using a well-planned and designed protocol by a pharmaceutical company in consultation with the DCGI for approval of the Technical Review Committee (TRC). Any higher dose, i.e. beyond the prescribed dose range, should be within the dose permitted as per animal and

human safety studies. The dose outside this range should be first considered for animal toxicological studies. If found safe for human Phase I to Phase III clinical trials as per the advice of the TRC, Phase IV trials should also be conducted by the sponsor of the drug trial after approval by the DCGI and institute ethics committee (IEC).

Reporting of PMS to DCGI

PMS data should be sent by the pharmaceutical industry/sites/institutions/clinicians to the DCGI once every six months for the first two years and thereafter yearly for two years for new drugs and similar biologics. SAEs or life-threatening adverse effects should be reported by sites/institutions/clinicians (or even by patients immediately after occurrence of the SAE) within 48 hours of their knowledge to the DCGI, allowing the case to first be managed and then reported at the earliest to the DCGL. The TRC should fix the cut-off limit for SAEs to suspend use of the drug. In order to monitor the SAE's data speedily, the DCGI's office should be strengthened with sufficient numbers of staff/contractual consultants.

5. Changes recommended in Central Drugs Standard Control Organization guidelines for bioavailability and bioequivalence studies

Introduction

Bioavailability (BA) and bioequivalence (BE) studies of new drug substances discovered abroad and not marketed in India should not be approved to be conducted in India. If new chemical entities (NCEs), new drug substances or their generic drugs are to be introduced in India, BA/BE studies in patients should be done as a part of the clinical trials. Generic drugs produced in India for the first time should undergo BE studies in comparison with the innovator molecule. The subsequent generics of the same drug (i.e. same synthetic chemical compound) showing good absorption orally (i.e. high solubility and high permeability) and similar *in vitro* dissolution rate need not undergo *in vivo* BE studies. The molecules with low solubility and less permeability profile should be subjected to both BA and BE studies. The same pattern should be followed for exporting drugs. In case some countries insist on BA and BE studies in humans with each generic drug containing the same chemical compound, such countries should be convinced, based on scientific data, of the futility of such a study for every trade name.

India should participate in global clinical trials of NCEs to be used for diseases prevalent in our population. BA studies including pharmacokinetic and pharmacodynamic studies should also be conducted on the Indian population. After these NCEs have been approved for marketing in the innovator country or in well-regulated developed country markets, a request should also be submitted to the Drugs Controller General of India (DCGI) for approval for marketing in India. After approval by the DCGI, these NCEs should be marketed in India speedily, and preferably by production within the country. Ethnic and tribal population trials should be conducted before prescribing the NCE for such population groups.

Each similar biologic or biosimilar undergoes the following stages:

- (a) Recombinant molecule development

- (b) Production at laboratory scale and its physicochemical characterization, which should be comparable to the innovator molecule
- (c) Stability studies
- (d) Up-scaling and production of three consistent batches-each production batch should have physicochemical characteristics similar to the innovator molecule and be at a scale sufficient to complete pre-clinical toxicity studies with one batch.

The innovator product is to be used as the reference standard in pre-clinical toxicity studies. (See Department of Biotechnology (DBT) Central Drugs Standard Control Organization (CDSCO) *Guidelines on Similar Biologics*, 2012).

Current practice

The generic drugs produced in India and in all well-regulated markets (USA, UK, Europe, Japan, Australia and Canada) undergo BE studies in comparison with the innovator molecule. The Food and Drug Administration (USFDA) was the first to adopt *in vivo* biowaivers in 2000 and still is comparatively more stringent. This agency considers biowaivers for only those immediate-release oral-dose forms which are highly soluble, highly permeable and show rapid *in vitro* dissolution. The European Medicines Agency (EMA) adopted biowaivers in 2001 and is comparatively more lenient. It gives importance to high solubility and *in vitro* dissolution, but low consideration to permeability.

Biowaivers are permitted for subsequent generics of the same drug (i.e. the same synthetic chemical compound) in immediate-release solid oral-dose formulations showing good absorption orally (i.e. high solubility and high permeability) and rapid similar *in vitro* dissolution rates using methods recommended by various national and international agencies. The recommended methods for determining solubility, permeability and *in vitro* dissolution are given in the respective guidelines. A biowaiver can also be permitted if the immediate-release solid oral-dosage form is very rapidly dissolving-85% or more dissolution of the generic drug (active pharmaceutical ingredient) should be achieved within 15 minutes in standard media at pH 1.2, 4.5 and 6.8 using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm (i.e. high solubility and low permeability) using methods recommended in the guidelines. Further, in both methods, drugs must use excipients that are qualitatively the same and quantitatively very similar to those of the innovator product and must not

excipients that are known to have an impact on bioavailability. WHO and Japan have further relaxed their norms and permitted biowaivers even for those immediate-release solid oral dosage forms which show low solubility and high permeability, i.e. weak acids given in the WHO document *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

Rationale of recommendations

EMA-Europe, National Institute of Health Sciences (NIHS)-Japan and WHO have permitted biowaivers for *in vivo* BA and BE studies in cases of high solubility and low permeability immediate-release solid oral-dosage forms, in addition to high solubility and high permeability solid oral-dosage forms given by USFDA. Adoption of guidelines followed by EMA-Europe, NIBS-Japan and WHO will reduce the unnecessary use of humans in BA and BE studies with subsequent generics and will also save on cost. India currently follows the USFDA practice for biowaivers.

Recommendations

The Committee has made these recommendations after also considering the guidelines laid down by CDSCO-India, FDA-USA, EMA-Europe, NIBS-Japan and WHO.

- a) BA and BE studies of new drug substances discovered abroad and not marketed in India should not be approved to be conducted in India.
- b) If NCEs, new drug substances or their generic drugs are to be introduced in India, *BA/BE* studies in patients should be done as a part of the clinical trial.
- c) A generic drug produced in India for the first time should undergo BE studies in comparison with the innovator molecule. The subsequent generics of the same drug (i.e. the same active pharmaceutical ingredient) showing good absorption orally (i.e. high solubility and high permeability) and similar *in vitro* release rate need not undergo BA and BE studies. They should be cleared based on data from recommended methods for determining solubility, permeability and *in vitro* dissolution using the innovator molecule for comparison.

- d) Biowaiver should also be permitted if the immediate-release solid oral-dosage form is very rapidly dissolving-85% or more dissolution of the generic drug (active pharmaceutical ingredient) should be achieved within 15 minutes in standard media at pH 1.2, 4.5 and 6.8 using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm using recommended methods in their guidelines. This means that biowaivers will be permitted for *in vivo* BA and BE studies in cases of high solubility and low permeability immediate-release solid oral-dosage forms.
- e) India should participate in global clinical trials of NCEs to be used for diseases that are prevalent in our population. BA studies including pharmacokinetic and pharmacodynamic studies should also be conducted on the Indian population. After approval for marketing in the innovator country or in well-regulated developed country markets, approval should be sought from the DCGI for marketing these NCEs in India. After approval by the DCGI, these NCEs should be marketed in India speedily, preferably by production within the country. Ethnic and tribal population trials should be conducted before prescribing the NCE for such population groups.
- f) These recommendations should also be followed for exporting drugs. In case some countries insist on BE and BA studies with each subsequent generic drug containing the same active pharmaceutical ingredient in humans, they should be convinced, based on scientific data, of the futility of such a study for every trade name.

5. Accreditation

Any clinical trial of a new or existing drug or medical device needs to be carried out at a centre where facilities for carrying out such trials exist, and the investigators carrying out the trial are competent and have experience in the successful conduct of such trials. In addition, the institute ethics committee (IEC) of the institute where the trial is to be carried out should understand the ethics involved in clinical trials and should consist of persons from different walks of life.

When a clinical trial is carried out under such conditions, it gives confidence to the volunteer and patients participating in the trial that they will not be subjected to any unjustified or hazardous trial. It also gives confidence to the drugs regulator and the government that the trial is going to be well-run, and a sense of confidence to the public and the civil society that the clinical trials being carried out are justifiable, both on ethical and scientific grounds.

To ensure implementation of these concepts, it is proposed to introduce a system of accreditation for the following:

- a) Institute ethics committees (IECs)
- b) Principal investigators (PIs) of clinical trials
- c) Centres desirous of carrying out clinical trials.

Clinical trials will only be allowed to be conducted at those centres which have been accredited in all three areas as above. These centres could be in the public or the private sector. Conducting clinical trials at centres that have not been accredited would be illegal and will not be recognized by the Drugs Controller General of India (DCGI).

The accreditation process will be supervised by a Central Accreditation Council (CAC). Details of the composition and functioning of the CAC are given subsequently. The criteria to be followed for accreditation of IECs, PIs and the centres where clinical trials are to be carried out are given below.

Institute ethics committees

IECs are presently being registered by the Indian Council of Medical Research (ICMR). The process of accreditation of IECs will be a further step to ensure that these committees are effective and independent in the performance of their duties. There is a separate chapter in this report on IECs. In this chapter, the emphasis is on accreditation.

These recommendations will cover all IECs, to include

- all institution-based IECs in universities, colleges, research organizations and non-governmental organizations (NGOs) of repute;
- hospital-based committees; and
- central IECs.

Any organization conducting research studies on human subjects and having a registered IEC should apply for accreditation to the CAe. On successful accreditation, the CAC will issue a certificate of accreditation. The CAC will forward the list of accredited IECs to the DCGI and keep the DCGI updated on the certification process, including any complaints received, cancellation or non-renewal of certification every three years.

The criteria for accreditation of IECs will include:

- Adequacy of structure and membership
- Appropriateness of the standard operating procedures (SOPs) and consistency in their implementation
- Completeness of the review process
- Adequacy of the after-review procedures
- Adequacy of administrative support for IEC activities
- Efficiency of the systemic recording and archiving process.

Principal investigators of clinical trials

The principal investigator (PI) could perhaps be called the key stakeholder in the conduct of clinical trials, because it is he/she who decides, after study of the background information, whether a clinical trial is justified or not: and subsequently, whether a trial is to continue or be stopped. He/she plays a key role in determining whether a side-effect has been induced by

the drug on trial or not, and plays a part in determining the compensation, if justified, in case of injury or death of a trial participant.

Criteria for accreditation

It is therefore very important that even though we need more clinicians versed in the ethical practice of clinical research, the criteria for assessing whether a clinician is fit to be an accredited PI must be rigidly enforced. These are elaborated below.

Minimum qualifications

- The PI or co-PI should either be a physician registered with the Medical Council of India (MCI)/State Medical Council, or a dental surgeon registered with the Dental council of India.
- The investigator should have a recognized qualification in the concerned specialty before participating in a particular clinical trial.
Should have had training in Good Clinical Practice (GCP) and national/international guidelines before being part of clinical trials
- Be well-versed in the regulatory requirements for clinical trials
- Be well-versed in obtaining informed consent and should be able to resolve all queries of participating subjects
- Have a clear understanding of ethical issues involved in human representation, patient rights and risks
- Have an understanding of the regulatory environment
- Have knowledge in the area being studied in a particular trial
- Possess leadership qualities to be able to lead the whole clinical trial team.

Experience

- Practical experience of at least three years in handling similar groups of patients or study cohorts under supervision and mentoring before being allowed to be a PI
- Been a co-investigator in at least two successfully-completed studies in the relevant field in the past.

Training and certification

The investigator should have had the requisite training on clinical research ethics, rights and responsibilities to be able to run clinical trials competently. In order to have an adequate pool of such trained principal/co-investigators, a course should be initiated for investigators to become certified clinical investigators, who will be registered at a central registry and reaccredited every three years.

Number of clinical trials a PI could undertake

It is recommended that this decision be taken by the PI and the IEC. Leaders in the field may be able to manage several trials simultaneously whereas the same may not be true of PIs who are not so proficient.

Accreditation of centres carrying out clinical trials

Regulatory authorities need to rely on the clinical trial sites to protect the rights and wellbeing of patients and volunteers in a clinical trial. A National Accreditation Council will help set and enforce basic standards for clinical trial sites, thus assuring regulators and other stakeholders that sites participating in clinical trials possess the basic infrastructure, personnel, processes and systems required for protection of patients, generation of reliable data and compliance with all applicable regulatory requirements. It is strongly recommended that only accredited sites be permitted to conduct clinical trials for new drugs as defined in Rule 122 E of the Drugs and Cosmetics Act, 1940.

The criteria to be used for assessing a centre for accreditation to be a clinical trials centre are given below.

(a) Site standard operating procedures (SOPs)

Well-defined SOPs should be in place for the areas discussed below.

Informed consent

Outline of process of administration and documentation of informed consent, including provisions and procedures for illiterate and vulnerable subjects.

Safety reporting and management

Responsibilities and measures for ensuring patient safety, including review of investigation reports and reporting of serious adverse events (SAEs) as required by applicable regulations.

Delegation of responsibilities and training

Appointment of site staff for specific clinical trial responsibilities, documentation of qualifications and their maintenance, delegation of responsibilities, training of site staff and handing/taking over of responsibilities in case of change in personnel, including PIs.

Protocol compliance and protocol deviations

Should address measures to ensure protocol compliance and outline the process for recording and reporting deviations.

Clinical trial documentation

Process for ensuring adequate clinical documentation for trial patients at source, its review by the PI and the management and upkeep of other essential documents as per GCP guidelines.

Records retention, archival and destruction

Responsibilities and time frame for retention and archival of all source and study-related documents, storage conditions, process for access/retrieval, process for transitions and handing/taking over and process for destruction at the end of the archival period.

*(b) Documentation systems**Patient registration and clinical documentation*

The evaluators should confirm the existence of a patient unique identification system. its linkage with all patient-related clinical records and documentation practices that would allow accurate and sufficiently detailed chronological build-up of clinical events.

Personnel-related documentation

The site should maintain a file for each member of the staff assigned to clinical trials that should include copies of curriculum vitae, professional registration certificate (if applicable), qualification certificates and all relevant training certificates.

(c) Personnel

Research credentials of PIs

The site should have at least one PI meeting the criteria for investigator accreditation. A list of all accredited PIs should be available with the site. All PIs should have medical or dental qualifications and be assigned to projects based on the appropriate qualification/specialty. All PIs must be familiar with GCP guidelines, ICMR guidelines, applicable regulations and site SOPs.

Qualifications, experience and research credentials of other site staff

For each PI at the site, there should be at least one co-investigator with medical/dental qualifications in the team. Other team members should have qualifications and experience appropriate to their role in clinical trial activities. All staff with responsibilities for clinical trials should be familiar with aspects of GCP guidelines, applicable regulations and site SOPs relevant to their role in clinical trials.

All responsibilities related to clinical trials should be covered among the available qualified staff at the site.

(d) Clinical trials material storage

Storage facility for investigational products and biological samples

The site should have an access-controlled location for storage of investigational products, with access restricted only to delegated trial staff. The location should be protected from extremes of temperature and humidity as well as from pests and seepage. The site should be provided with a refrigerator, a -20°C freezer, power backup, and thermo-hygrometric monitoring.

Clinical trial document storage

This site should have a dedicated, access-controlled cupboard or cabinet for storage of current trial documents with document inventory and separate sections for each trial. Fire-control equipment should be readily available, and the location should not be vulnerable to water hazard.

Long-term document archival facility

This site should have adequate in-house or outsourced facilities for long-term archival of clinical trial documents that meet all the criteria as above, as well as documented periodic pest control and a system of document tracking and retrieval. A valid contract should be available in case of outsourcing.

*(e) Ethics committee**Proof of registration*

The site should have access to an ethics committee (EC) with a valid proof of registration with the CDSCO. (This has been dealt with separately.)

Compliance with EC accreditation criteria

The site EC should be able to demonstrate compliance with applicable EC accreditation criteria. (This has been dealt with separately.)

*(j) Facilities and equipment**General facilities and equipment*

Availability of the following general facilities and equipment is considered essential for clinical research sites: at least one computer with contemporary software, broadband internet access, e-mail facility and individual password-protected access to clinical research personnel only; photocopier, telephone and telefax with STD facility; power back-up.

Basic equipment and facilities for patient evaluation and emergencies

The following basic equipment for patient evaluation and medical emergencies should be available: calibrated weighing scale; stadiometer, thermometer; sphygmomanometer; 12-lead ECG; centrifuge; crash-cart with emergency drugs and emergency-care facilities/equipment.

(f) Statutory licenses

The evaluators should check the following statutory licenses as applicable: hospital/clinic registration, valid professional indemnity insurance, fire safety certification, biomedical

waste-management license, narcotics license, radiology facility certification and other applicable certificates and licenses.

(g) Third-party contracts and agreements

If applicable, the site should have valid signed contracts with all the consultants working at the site, as well as with all the associated vendors such as laboratories, waste management agency, emergency services, pest control, equipment maintenance, etc.

(h) Past inspection experience

The site should not be under debarment or current enforcement action following regulatory authority inspection. There should be no conviction or ongoing prosecution of members of the hospital administration.

(j) Proof of practice of SOPs and conditions of accreditation

The assessment team should satisfy itself that the SOPs provided by the site and all other conditions of accreditation are being satisfactorily practiced by the site/institution.

These criteria have been drawn up with respect to clinical trials of pharmaceutical products, which is the main thrust area of this report. Centres carrying out non-drug-related clinical research at academic institutes could draw up their own criteria from this list.

Accreditation process

A pre-assessment questionnaire will be forwarded to the centre being assessed. The responses received will be discussed as necessary during the on-site assessment visit. On-site assessment will be followed by an outcome letter sent to the CAC. Accreditation will be valid for three years. Accreditation may be temporarily suspended if the Council is convinced of violation of the criteria by the centre. If a centre does not get accredited in the first instance, it can request for re-assessment after three months of the original assessment. The CAC will publish a running list of accredited sites/institutions on the first working day of every month. Names of sites and institutions which have been suspended or revoked shall be deleted from this list.

Central Accreditation Council (CAC)

This will be a semi-autonomous council consisting of three full-time members including the chairperson. They will be senior clinicians selected' on the basis of their competence, good track record, integrity and competence from different parts of the country, keeping gender sensitivity in mind. The Council will have full-time employees and its own secretarial staff. The Council will supervise the accreditation of all three areas, viz. IECs, PIs and centres carrying out clinical trials. The Council may ask agencies to carry out accreditation, or may do so themselves. The CAC needs to have an independent status and not be a subsidiary of the Central Drugs Standard Control Organization (CDSCO). The decisions of the CAC will be final.

Specific recommendations

- Accreditation will require to be done of centres carrying out clinical trials, PIs and IECs. Only centres with all three accreditations would be allowed to carry out clinical trials by the Drugs Controller General of India (DCGI).
- A Central Accreditation Council (CAC) should be set up which will oversee the accreditation of these three based on the criteria adopted and keep the three registers listing the accredited entities/persons updated.
- Selection of assessors should be carried out by a blind randomization procedure.
- A course for becoming a certified clinical investigator should be set up so that the much-needed pool of clinicians eligible to become PIs can be created.

6. Institute ethics committees

An institute ethics committee (IEC) is formed by an institution or a hospital for the purpose of reviewing research conducted at the institution. The committee is formed of a group of people who go through the research protocol/proposal and state whether or not it is ethically acceptable.

There are two types of IECs-local and central. Local IECs are functions of the academic institutions/hospital that conduct research and review only their trials, while central IECs provide review services for multiple entities.

Central IEC

For multicentre studies, the central IEC is the IEC that conducts reviews on behalf of all study sites that agree to participate in the centralized review process. The central IEC should reach agreement with the individual institutions participating in the centralized review.

Investigators and sponsors typically rely on the review and oversight of a central IEC. In this situation, the central IEC should document, in minutes of meetings or other records, how it considered relevant local factors for the various communities from which research subjects were to be drawn. The central IEC must also document its action in agreeing to conduct an IEC review for the sites, and must have written standard operating procedures (SOPs) in place that describe how it will perform its initial and continuing review responsibilities at remote sites.

Requirements for IEC membership

The members of an IEC must have sufficient experience, expertise and diversity among themselves to promote respect for its advice and counsel in safeguarding the rights and welfare of human trial subjects. IEC members must be 'men and women of diverse backgrounds and sufficient maturity, experience and competence to assure that the IEC will be able to discharge its responsibilities and that its determinations will be accorded respect by investigators and the community served by the institution'. In addition, IEC members must 'be able to ascertain the acceptability of the proposed research/trial in terms of institutional commitments and regulations, applicable laws and standards or professional conduct and

practice'. Thus an IEC review, through its members, is intended to provide meaningful consideration of various local factors in assessing research activities, including the cultural backgrounds, e.g. ethnicity, educational level and religious affiliations of the population from which research subjects will be drawn, and the community attitudes.

Selection of IEC members

Members may be selected and appointed by the head of the institution/hospital concerned. The members should collectively have sufficient expertise to evaluate the quality of the science, medical aspects of the proposed research and the ethics of conducting a study. At least one member of the committee should be a physician, who is required to evaluate the medical aspects of a study.

Composition

The IEC must consist of at least seven members (as given in Schedule Y of the Drugs and Cosmetics Rules, 1945, Ministry of Health and Family Welfare, Government of India reflecting diversity of scientific and non-scientific backgrounds, professional specialties and cultural interests, must include both sexes and have at least one member who is not affiliated to the institution directly or through a family member (usually referred to as the community member). The chairperson should be an eminent person and should not have any affiliations to the concerned institute. This is to avoid any conflict of interest. The member secretary should belong to the institute hospital.

The IEC should comprise members with the following representations:

- a) Basic medical scientist
- b) Clinical pharmacologist
- c) Clinician
- d) Legal expert
- e) Social scientist/representative of a non-governmental voluntary agency, of a philosopher/ethicist/theologian or a similar person
- f) A lay person from the community.

The IEC may invite external consultants, if necessary, to provide insight into scientific or ethical issues that are beyond the expertise or the convened committee. While consultants can

assist in the review of a protocol, they should not be allowed to participate in the voting for the purpose of approval of the research.

Responsibilities of the ethics committee

- Safeguard the rights, safety and well-being of all trial subjects and vulnerable populations
- Have a documented SOPs manual and maintain a record of all its proceedings
- Review of trials
 - Carry out periodic study of progress reports submitted by the principal investigator (PI)
 - Carry out periodic monitoring of internal audit by the sponsor
 - Visit the site of study
- In case it revokes its approval of a trial, send reasons to the PI and licensing authority.

The IEC must ensure that the International Conference on Harmonization/Good Clinical Practice (ICH /GCP) guidelines are followed by all who are undertaking research.

7. Monitoring of institute ethics committees

Guidelines for institute ethics committees

The Council for International Organizations of Medical Sciences (CIOMS) states that 'all proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees'. Similar obligations have been mentioned in the guidelines issued by the International Conference on Harmonization (ICH), UNESCO and several other councils across the world. These guidelines require ethics committees to ensure that:

- the risks of the proposed studies are reasonable in relation to the anticipated benefits;
- the investigators have adequate plans for obtaining the participants' informed consent; and
- ethical issues such as confidentiality and equitable participant selection have been adequately addressed.

It is expected that institute ethics committee (IEC) reviews of the protocols of clinical trials will result in research that better complies with applicable ethical principles.

With an increase in the scope of the reviews of protocols submitted to the IECs, the possibility of having more than one IEC in an institution should be considered and permitted. Independent ethics committees should not be allowed to function, as these have not been recognized or accredited by any national agency and their past functioning has been found to be erratic and controversial.

IECs should be encouraged to co-opt members from different super-specialties from time to time to help review protocols requiring such expertise. Also, IECs should ensure inclusion of patients from special categories such as pregnant women, the geriatric population, the paediatric population, etc.

The guidelines mentioned above are not legally binding. However, the IEC review of clinical trial protocols will need to conform to the national policy as given in Schedule Y of the

Drugs and Cosmetics Rules, 1945, Ministry of Health and Family Welfare, Government of India (hereinafter referred to as Schedule Y). The International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guidelines must also be complied with.

Clinical trials in India

Of the 1,000,000 trials carried out globally, USA accounts for about 52,000 while India conducted only 15,000 studies during the same period. There has been a lot of hype that India is the hub of clinical trials and that Indian patients are guinea pigs for drug assessment. However, in recent times the number of clinical trials being conducted in India has shown a steady decline. While India was a preferred destination for foreign multinational companies sometime back, China is now fast taking over. The falling credibility of clinical trials in India has led to drug regulatory centres not accepting results from India.

Strengthening of IECs

One of the ways to stem this decline in the number of clinical trials coming into India could be to strengthen our IECs. It is expected that auditing and accreditation of IECs can improve the quality of IEC reviews, as this helps in

- developing standardized policies and procedures,
- promoting a common knowledge base,
- enhancing the status of research in the country,
- promoting consistent application of ethical practices, and
- creating more transparency in their functioning.

It is also important that the IEC members be qualified and/or trained in the functions and responsibilities of an IEC. IEC members should be encouraged to pass certification tests which are available on the Internet. These help to evaluate and validate the individual's knowledge of ethic principles, historical events, regulatory requirements and operational and functional issues relating to an IEC. Auditing and accreditation of IECs is expected to contribute to enhancing the quality of the research review system. At the same time, the

impact of these reviews on research practices in the research/clinical trial sites needs to be looked into.

Audit

In order to improve the quality of the working of IECs, it is proposed that the IECs undergo internal audit, audit procedures commissioned by the sponsors of clinical trials and inspections by regulatory authorities.

These audits may consider the compliance of the IEC based on the guidelines laid down in Schedule Y, which includes the stipulation that representation in an IEC must keep in mind gender issues and representation of lay persons. Details of composition and responsibilities of IECs are discussed in a separate chapter.

Elements of an audit

An audit should include the following objective parameters:

- Frequency of IEC meetings for reviewing of protocols
- Number of protocols reviewed in a year
- Serious adverse events (SAEs) and amendments discussed at each meeting
- Maintenance of the minutes of the meetings and their timely circulation to all IEC members
- Quorum maintained in each meeting of the IEC
- Maintenance of an office including staff, equipment (computers, stationery, telephone, photocopying machine) and adequacy of storage area
- Maintenance of financial records
- Number of clinical trial site visits by the IEC members. These could either be random visits or visits following the receipt of complaints.

- Registration of the IEC with the Drugs Controller General of India (DCGI). This may be confirmed on the DCGI website.
Submission of the annual report to the office of the DCGI.

Accreditation

Objectives of accreditation

The objectives of accreditation are to

- uphold the standard of ethics review in the country,
- develop public confidence and trust in the national research system,
- facilitate equitable access to research, and
- standardize the constitution and operation of IECs.

Points for consideration

Points that may be considered for accreditation include:

- Self assessment - external reviews focussing on issues such as membership of the committee,
operating procedures and documentation of meetings
- Composition of the IEC should be in conformity with the regulatory guidelines and appropriate to the amount and nature of research being conducted and managed.
- The availability of appropriate management and operational procedures
- Review of protocols in a timely fashion following established procedures
- Adequate and effective communication of all decisions to the principal investigators.

Additional points for consideration

Whether the ethics committee (EC) activities are co-ordinated with national regulatory authorities'?

The availability of adequate resources for members of the staff to fulfil their assigned functions, including office space and equipment (computers, stationery, telephone, photocopying machine) to conduct administrative business, adequate space for storage of all files, and security of the files

- Availability of adequate financial resources to carry out all the functions of the IEC
- Are members compensated for their time and effort?

A mechanism for research participants and other interested parties to lodge complaints against *IEC/EC* members. The provisions for such complaints to be reviewed by responsible persons other than members of the IEC itself. Also, means to check that appropriate follow-up action has been taken.

- The mode by which the decision following the review of clinical trial protocols are taken - whether by consensus or by voting
- Information and follow-up action on the SAEs reported
- End of trial report - status of volunteers at the end of the trial.

The duration of accreditation will be for three years. Applications for renewal of accreditation are required to be submitted six months before the expiry of the current accreditation period. Failure to renew the accreditation may lead to cessation of the IEC's functioning. The accreditation may be terminated if the IEC fails to maintain the required standards. The list of all accredited IECs will be displayed on the website of the DCGI.

Accreditation has been covered in detail in a separate chapter.

Conclusion

Auditing and accreditation of *IECs/ECs* should not follow a culture of red tape. Their culture must be driven by ethics.

The number of IECs in the country may be restricted by having one EC affiliated to more than one institution in the same city, i.e. joint and/or regional ECs. The roles and responsibilities of these joint and regional ECs should be similar to the central ECs. This is

important because a large number of IECs/ECs may not automatically guarantee better protection of rights, safety and welfare of the subjects enrolled in clinical trials.

To ensure that the above are implemented, it is important that a separate cell be created in the office of the DCGI with the sole responsibility of according registration, auditing and accreditation of the IECs in the country.

9. Role of the states in monitoring of clinical trials

Clinical trials are being undertaken in different parts of the country. The diversity of languages that are spoken by participants/subjects of clinical trials in different states suggests that state authorities need to play a significant role in monitoring of clinical trials. Since clinical trials are concerned with public health, and since 'Public Health and Sanitation; Hospitals and Dispensaries' is a subject falling in the State List (Entry 6 of list II), the state drug regulatory authorities have the responsibility of playing a significant role in monitoring of clinical trials in their states, besides fulfilling their other responsibilities. Also, 'Drugs' is a subject matter falling within Entry 19 of the Concurrent List (List III); and hence the Union as well as the states have the power to regulate clinical trials of drugs, etc. There should therefore be no difficulty in having a coordinated effort by the Central Drugs Standard Control Organization (CDSCO), through its zonal and sub-zonal offices, and the state drug regulatory authorities to jointly monitor clinical trials being held in various states. In addition to its central office in Delhi, the CDSCO has six zonal and three sub-zonal offices in different parts of our country. Notwithstanding this, it is not possible for the functionaries of CDSCO alone to monitor the increasing numbers of clinical trials. As of now, the states have little or no role in the conduct and monitoring of clinical trials approved by the CDSCO. State infrastructure and governance could well be utilized more for monitoring of clinical trials, with requisite training as necessary.

Functions of state drug regulatory authorities

State governments are responsible for the following:

- Licensing of manufacturing establishments and sales premises. Manufacturing licenses are to be issued only after approval of the central drug authority.
- Carrying out inspections of licensed premises for ensuring compliance with conditions for grant of license.
- Monitoring drug manufacturing standards for good manufacturing practice (GMP) and good laboratory practice (GLP), and inspecting pharmacies and retail outlets for date-expired drugs, etc

- Drawing test samples for monitoring the quality of drugs and cosmetics sold or produced in the state, and taking appropriate actions such as suspension/cancellation of licenses where necessary
- Surveillance over sale of spurious/adulterated (banned) drugs. Initiating legal action as provided for in the rules in the event of violations of the Drugs and Cosmetics Act, 1940 and the Drugs and Magic Remedies (Objectionable Advertisements) Act, 1955. Monitoring objectionable advertisements pertaining to drugs.

Points for consideration

- The effectiveness of drug regulation depends on the priority accorded to this activity, investment made in terms of infrastructure, offices and laboratories with the capacity to do testing of chemicals and biologicals, and an optimum number of qualified and experienced drug regulators, inspectors, etc. available at the Centre and in the states. Drug regulators have to function with clear mandates of transparency and accountability.
- Since 'Health' is a state subject, the state regulatory authorities report to the state government. Decisions related to issuing manufacturing licenses are expected to address the safety and health concerns of consumers of medicines in the state, while at the same time supporting rational functioning of the manufacturing units and retail outlets.
- In performing their laid-down functions, state regulatory authorities are required to keep track of the existing structure, the number of manufacturing units and retail outlets in the state. formulations in the market and the number of clinical trials being undertaken in the state at anyone time.
- States with a large number, medium number and very small number of manufacturing units need to be categorized and treated differently. States in which a large number of clinical trials are taking place, and states from where larger numbers of adverse drug

reports have been reported, should be given greater attention in terms of monitoring of clinical trials.

Parameters of functioning

Human resources

The Parliamentary Committee Report has highlighted the need for adequate numbers of drug inspectors and other appropriately-qualified and trained personnel. Keeping in mind their various functions related to monitoring of manufacturing units and retail outlets, collection of product samples related to medicines, medical devices and diagnostics and monitoring of clinical trials, the existing scaling needs to be substantially increased at the earliest. Since every state has medical colleges, hospitals and institutions, names of experts could be suggested by the state drug control authorities and the state government for inclusion in the pool for consideration as principal investigators.

Training

There is a need to have a reasonable ratio of trained human resources for monitoring of clinical trials and for monitoring the functioning of institute ethics committees. Training should also impart legal and investigative skills, understanding of protocols, and knowledge of Schedule 'Y' amendments, Indian Good Clinical Practice Guidelines and the Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Subjects. The state drug regulatory authority also has to assess whether the recommendations of the Drugs Controller General of India (DCGI) and the institute ethics committees (IECs) are being followed at the ground level in letter and spirit. This will require special skills and training.

The Committee therefore recommends training courses to be held at the zonal and sub-zonal centres of the CDSCO for the inspectors who will be involved in monitoring of clinical trials

Information

The state authorities need to know which clinical trials are being carried out in their state, on which drugs, diagnostics, medical devices or biologicals, the clinical trial sites, and who the investigators are. Although this information is available on the ICMR National Clinical Trial

Registry website, it is not adequate for effective monitoring. There needs to be continuous and effective flow of information between the state drug regulatory authorities, state health authorities and the CDSCO.

Ethics

The ethical dimensions of clinical trials are important. Representatives of the state government and experts in medical colleges and institutes engaged with ethical dimensions of clinical trials can help in explaining these concepts to the participants and others engaged in the trials. State authorities should also be explained the nuances of ethics in the conduct of various clinical trials.

Recommendations

The Committee recommends the following:

Joint monitoring

Monitoring of clinical trials should initially be undertaken jointly by the state regulatory personnel with personnel of the CDSCO Headquarters and zonal offices. Once the state regulatory personnel attain the desired competence, monitoring of trials can be independently undertaken by the states using their personnel picked up by random selection from the roster of trained and accredited personnel. Initially, only those states should be involved which have trained manpower and infrastructure and where trials are being conducted.

Coordination and information sharing

There should be a clear mechanism for coordination and information sharing between the CDSCO and the State Drugs Standard Control Organization (SDSCO) units on clinical trials approved in the state, nature of clinical trials, clinical trial sites and investigators. Such information sharing should be done on a continuous and real-time basis for guidance and quick and appropriate action in the process of monitoring of clinical trials.

Training of state drug regulatory personnel

Regulatory personnel should be speedily trained in different facets of clinical trial monitoring including understanding the requirements of clinical trials, trial protocols, role of ethics

committees, role of principal investigators (PIs), contract research organizations (CROs), sponsors and violations of protocol.

Upgradation of capabilities

The Committee feels strongly that effective monitoring of clinical trials is feasible only after (a) training of available manpower, (b) recruitment of skilled manpower, and (c) upgradation of infrastructure both at the CDSCO and the state drug regulatory units. Appropriate centres for training may be considered at zonal, sub-zonal and at any other level.

Accountability

Once the state regulatory mechanism is fully functional, any illegal omission or commission resulting in violation of the human rights of the trial participants by the accredited investigators/institutions must be investigated thoroughly. Those responsible for such lapses must be held accountable, whether it be investigators or regulatory personnel.

10. Discontinuation of drugs when safer and more effective drugs are available - banning of drugs

11.

Introduction

Citizens of this country have a right to expect that drugs available in the country are safe and effective, and that all drugs that are available are indeed needed. They would also not be asking for too much if they expect the drugs to be of good quality. Unfortunately, the situation on ground is very different. We have an unacceptably large number of formulations in the market - somewhere between 60,000 and 85,000. Many of these medicines should not have been allowed to reach the market in the first place.

This Committee is not mandated to find out how such a situation has come to pass. If, however, the Committee has to recommend measures to remedy this situation, it has to know what drugs are in the market today and then make recommendations accordingly. In spite of existing governmental rules, regulations and Acts meant to protect the citizens that are listed at the end of this section, things are in a deplorable state at the moment.

Problem areas

The problem areas are as follows:

- Drugs which should never have been allowed to reach the market are being marketed.
Many of these drugs are inherently unsafe and potentially hazardous. They do not appear in any textbook of medicine or pharmacology; nor do they find a place in the market of any country which has a well-regulated market for drugs. Such drugs must be removed from the market.
- New drugs should be allowed to be marketed in the country only if the experts feel that the drug will have some advantages over the already existing drugs in terms of therapeutic efficacy and safety.
- Another consideration is whether the drug is being marketed in the country of origin.
If not, then questions arise as to why this is so, and this becomes a factor in approving its release in India.

- Again, if the drug is already in the market but two or more countries remove the drug from their market on grounds of efficacy and safety, then the national drug regulatory agency should consider the possibility of removing the drug from the Indian market as well.

Drug regulatory agency

What is needed is an alert drug regulatory agency supported by experts who would recommend, from time to time, removal of drugs from the market. This authority should be able to take rapid decisions which would be implemented immediately. To be able to do so, however, the regulatory agency will need information continuously on

- post-marketing surveillance of drugs,
- rational use of medicines,
- drug utilization studies, and
- adverse drug reaction monitoring.

It will be useful if a research unit is created within the Central Drugs Standard Control Organization (CDSCO). This unit would initiate and sponsor studies in these areas to be able to get the needed information to help in decision-making.

Recommended measures

The Committee deliberated at length regarding the active measures which need to be taken now to remove drugs which should not be on the market. These measures are:

- Setting up a committee outside of the Drugs Technical Advisory Board which will review all the drug formulations and vaccines now in the market and prepare a list of drugs which should be removed. The criteria for a drug to be on the market would be that it is therapeutically effective and acceptably safe: It should also be a drug which fulfils a real medical need.
- A list should be prepared of drugs not approved in the country of origin and those which have been banned or withdrawn in several countries. These should again be reviewed for withdrawal.

- The names of drugs which have been withdrawn should be regularly placed on the CDSCO website.

The Committee recommends that the programme of withdrawal of drugs should be undertaken in phases, as follows:

- a) Drugs to be weeded out immediately
- b) Drugs to be phased out in 3-6 months
- c) A few drugs could be listed for restricted use. These drugs would be those whose misuse would either lead to resistance to the drug, or those which may cause serious side-effects, but are still needed.

Existing regulations

Drug regulations already in existence are:

- Section 26-A and 33-P of the Drugs and Cosmetics Act, 1940
- Rule 122-B (2A) and Rule I 22-D (2) of the Drugs and Cosmetics Rules, 1945.

11. Technical Review Committee

Background

Interaction with the pharmaceutical industry leadership and their associations, namely the Organization of Pharmaceutical Producers of India (OPPI), Indian Drug Manufacturers Association (IDMA), Indian Pharmaceutical Alliance (IPA) and Associated Chambers of Commerce and Industry (ASSOCHAM), contract research organizations (CROs) conducting clinical trials in India on behalf of the sponsors (i.e. the pharmaceutical industry) and representatives of civil society and non-governmental organizations (NGOs) highlighted that there are a plethora of new drug advisory committees (NDACs) - 12 in all, advising the Drugs Controller General of India (DCGI) on new chemical entities (*NCEs*)/new biological entities (NBEs), new generic drugs and similar biologic approvals. Each committee consists of 10 to 15 subject-specialty experts having little experience of regulatory data review; some committees have even not met for over a year. Further, a committee sometimes does not take a decision if just one or two members do not attend the meeting.

On the other hand, sometimes decisions are taken when only two members are present. There is therefore a significant slowdown in consideration of applications and grant of approval for different phases of clinical trials or marketing and manufacture of new generic drugs, similar biologics or NCEs/NBEs. This concern of the entire pharmaceutical industry appears genuine. Delay in approvals was also highlighted by the Parliamentary Committee and hence needs immediate redressal. This committee feels that it is essential to clear pharmaceuticals applications speedily to maintain vibrancy and the global impact of this Rs 1200 billion industry. It is therefore proposed to constitute one broad expertise-based Technical Review Committee instead of the existing 12 NDACs to ensure speedy clearance of applications without compromising on quality of data and rules and regulations.

Composition and functions of the proposed Technical Review Committee

The proposed Technical Review Committee will consist of two clinical pharmacologists, two regulatory clinical toxicologists/pathologists, two medicinal/pharmaceutical chemists, two pharmacists, two clinicians, an immunologist, two basic scientists involved in drug development and two subject specialists (to be invited drug-indication wise and selected

randomly from the roster), with the joint/deputy DCGI as the Member-secretary and two more officers from the DCGI's office to assist the committee. Two members have been included from each specialty to ensure that at least one is present at each meeting.

The committee will review the following:

- Chemistry of NCEs and generic drugs
- Molecular biology including recombinant DNA technology of NBEs and similar biologics. Pre-clinical development data of NBEs or similar biologics, i.e. biosimilars, would in fact have been reviewed by the Review Committee on Genetic Manipulation (RCGM).
- Efficacy
- Mode of action
- Pharmacology
- Toxicology
- Clinical trials data.

Thereafter, the Committee will approve the protocol, investigators and centres for the conduct of clinical trials. The Committee will function in a time-bound manner and no application should await scrutiny and clearance for more than three months, to be ultimately reduced to one month. The reasons for delay, if any, should be clearly stated within the above-indicated time, failing which the proposal will be deemed to have been approved. The Chairman of the Committee will be authorized to co-opt one or two disease-wise experts in addition, if needed (through the DCGI). The expert's job will be to evaluate the clinical trial data generated through clinical trials of generic drugs and similar biologics or subsequent phase(s) of clinical trials for *NCEs/NBEs*, and give appropriate recommendations.

The tenure of the Committee will be for three years, and 33% of the experts will be replaced by rotation each year. The rotation of experts will start three years after constitution of the first Technical Review Committee. The decision of the Committee will be placed on the DCGI website immediately after the meeting (or within 24 hours after approval of minutes by the Chairman via e-mail) and the letter will be issued by the DCGI's office to the party within 15 working days.

The DCGI's office will maintain a roster of core committee specialty experts and disease-specialist experts. The experts will be picked up randomly for induction into committees. If any expert does not attend three consecutive meetings or 50% of the meetings during a year, he/she will be replaced.

Applications

Applications received from the industry will be serially numbered, entered in a register and an acknowledgement will be issued. They will be checked by the Member-secretary to ensure that the applications are in order and contain the requisite information. Incomplete applications will be returned to the applicant indicating the shortcomings and will lose their serial number. Complete applications will be put up to the Technical Review Committee in serial order. Applications concerning national emergencies or drugs/biologicals for tropical diseases will receive priority for expedited review.

12. Unbiased selection of experts

Background

Experts are needed for providing advice on approval of clinical trials and for assessment of accreditation. Selection of experts for advising the national drug regulatory authority is a very important aspect of an organization which regulates a Rs.1200 billion industry. Regardless of the number of experts that are selected and appointed in the drug regulatory system itself, there will always be a need for more experts in different specialized areas. Fortunately, the country has over 350 medical colleges, 1162 pharmacy colleges and dozens of centres of excellence in medical care, which collectively throws up a large number of qualified professionals. From among them, it should not be difficult to identify people of integrity and probity who can well be used as experts.

In the present system, the selection of experts has been left to the discretion of the staff of the drug regulatory system. While this gives the staff the authority to select the experts, it also makes them vulnerable to criticism of bias and nepotism. The present system has been widely criticized as not being fair to the officers of the drug regulatory agency, the experts selected (or not selected) and the centres where clinical trials are carried out.

A system needs to be put in place whereby the nexus referred to in the Parliamentary Committee would not be possible. This can only be achieved if the system is based on an unbiased and random selection of experts for each activity where such experts are needed.

Shortfalls in the present system

Lacunae in the present system in various areas are discussed below.

Experts

- Competent, busy clinicians are often not able to provide time and travel large distances to help the drug regulatory agency.
- Even when they agree to attend meetings at New Delhi at the headquarters of the Central Drugs Standard Control Organization (CDSCO), they are plagued by lack of time. Thus, they may have perhaps not read the background papers before the

meeting, or may be more concerned with being able to catch the flight back home than with the ongoing proceedings.

Video conferencing/teleconferencing are not being used

- The payment for the travel is not always immediate
- The honorarium for carrying out this responsible work is a pittance.

It is therefore not surprising that the CDSCO has fallen into the unhealthy practice of repeatedly inviting the same experts who are based in and around New Delhi. This leads to an unhealthy relationship between these experts and the authorities that is neither desirable nor acceptable. There is the possibility of an office of a drugs controller general sending a specific assessor to a centre for accreditation, or of a particular expert being identified and sent to review a particular request.

Selection process

- There is no computerised database of experts. The names of experts in a particular subject or from a particular geographical region are not readily available. Identification and selection of experts for any requirement is disorganized and subjective.

There is a lack of transparency, in that the bio data of the panel of experts is not available on the CDSCO website.

Proposed solution

Experts

An unbiased system of selection of experts can only work if all experts are willing and desirous of helping the drug regulatory agency in this task. Measures to achieve this are given in succeeding paras.

Reduction in the number of proposals coming to the committees/or approval of clinical trials

It is not necessary for every proposal to be assessed by a full technical review committee (TRC). There are ways in which the numbers being assessed by a full TRC can be reduced. This would enable a more detailed review of each case.

Reduction in the number of proposals which need to be seen by experts also has to be considered.

Regional reviews

In a country as large as India, given the geographical spread of institutes carrying out clinical trials, it is not feasible for all reviews to be carried out at New Delhi. There is a need for setting up regional committees. A sub-committee of the Government of India should look into the feasibility of setting up regional review/assessment committees.

Videoconferencing and teleconferencing

These facilities should be used wherever feasible to reduce the commitments on time and travel of experts. A large number of decisions can be taken by videoconferencing/teleconferencing if the papers are well-prepared and sent to the members in advance.

Sitting and evaluation fees

The honorarium being paid to the experts and assessors and members of the institute ethics committees need to be greatly enhanced. This could be charged to the pharmaceutical concerns. The visit of the assessors should be treated as 'on duty'. Considering the amount of background work to be done in review of proposals or in an on-site assessment, and the importance of these activities as the only protection available to the public and volunteers against misuse and exploitation, the amounts paid today are pathetically inadequate.

Selection process

Improvements are needed urgently as enumerated in succeeding paragraphs.

Creation of a database of experts in different areas

It is essential to create a computerized database of experts of potential assessors from all over the country for accreditation and for review of proposals. This database would comprise of experts who have been carefully selected by the Technical Advisory Committee. Some of the criteria for selection will be:

- Technical knowledge
- Experience
- Integrity
- National and international recognition
- Ability to devote time
- Knowledge of the regulatory system.

Clear-cut criteria will be used for selecting these experts. All methods should be pursued to identify persons who can be included in this roster. Geographical considerations and gender sensitivity should be kept in mind while preparing the database. Some of the options are:

- Open advertisement for obtaining suitable names for consideration
- Asking individuals and institution for names
 - Identifying persons by their publications, their known integrity and national/international recognition.

The Committee feels that all the above methods should be explored and used.

Transparency

Before a person's name is included in this list, the brief bio data of the person concerned should be placed on the website of the CDSCO to enable any member of the public or of the medical fraternity to raise any specific objection to a person being included in the roster of experts. The roster should include the names of the following:

- Experts from every field and all types of organizations including the private sector Experts listed according to their expertise and geographical location. This will enable identification of experts of any particular specialization.

The roster should be updated every year and names added or deleted based on a set of strict criteria. The deciding factors will be the experience, merit and integrity of the person concerned. It is suggested that this creation of the roster of experts be outsourced to an information technology (IT) organization.

Selection by randomization

Only experts on the roster should be called for meetings and carrying out assessments at the sites. The selection as to which expert is to be used to assess which proposal and which assessor will go to assess a particular site will be made by a process of randomization. Only one person will work on the randomization procedure and provide this information to the CDSCO. Developing the randomization software and thereafter drawing out names as per each specific requirement should be outsourced to a trusted IT firm or a national institute for IT. Staff members of the CDSCO or the officers of the Department of Health will not have any say in the nomination of experts required for a specific assessment, or for a specific proposal for a clinical trial. This random selection will be programmed keeping in mind gender sensitivity and geographical location of the person. The programme will also ensure that an assessor is not nominated from the same city as the centre being assessed and that two assessors are not nominated from the same institute.

It is proposed that this system of random selection of assessors and random selection of experts for specific proposals be introduced as soon as possible. Given the will and commitment, this system is very workable.

Deployment of the proposed system

The principles and system now being proposed will also apply to selection of experts for visiting centres of medical care for accreditation of the following:

- Institute ethics committees (IECs) at these centres
- Principal investigators (PIs) of clinical trials at these centres
- National Accreditation Council

Other members to the highest scientific and technical bodies of the CDSCO.

Such a system will offer confidence to the public and the Government that decisions are taken on the basis of merit, since assessors will be selected on sound principles and by randomization. The Committee believes that such a system will be widely welcomed by all stakeholders and different segments of the Government and the public.

Recommendations

Various recommendations made above will need to be implemented in a phased manner as long-term measures and immediate measures, depending on the urgency of the proposed measure and time-frame needed for country-wide deployment.

Long-term measures

- Reduction in the number of proposals which need to be seen by the full committee
- Establishment of regional committees.

Immediate measures

- Selection of experts as per the defined criteria, keeping geographical considerations and gender sensitivities in mind
- Ensuring transparency before finalizing the composition of the panel of experts by placing the biodata of likely panelists on the website of the CDSCO
- Creation of a finalized computerized database of experts in different subjects after selection
- Use of experts only from this database
 - Use of randomization procedures to determine which experts will go to review accreditation requests/review meetings at different centres
- Use of videoconferencing/teleconferencing facilities where feasible Suitable enhancement of the sitting and evaluation fees for experts.

13. Informed consent in clinical trials

The central issue of human (clinical) research is the principle of respect for the individual's autonomy. This is achieved by obtaining an 'informed consent' from autonomous adults who are capable of giving a valid and voluntary informed consent after receiving complete information on all aspects of participation. International guidelines specify that 'respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them'. Informed consent provides an opportunity to the participant to decide if he/she wants to contribute to a cause, as research is generally not custom-made to suit the requirements of the individual participant but is targeted to creating generalizable knowledge.

Informed consent process

Obtaining an informed consent does not mean merely obtaining verbal consent, or a signature/thumb impression. The consent process has three components-information, comprehension and voluntariness, through a process of information exchange that includes subject recruitment material, verbal instructions, written material, question-answer sessions and finally, agreement to participate, documented by a signature/thumb impression. It is not a one-time event, but a process that begins much before the study is initiated and continues throughout the study tenure and often also after the study is completed. The process requires that there be a good exchange of dialogue between the participant and the researcher in a simple, understandable language without any technical jargon. There must be sharing of relevant information by the researcher with the subject so as to enable the individual to make an informed choice or decision about his/her participation in research, and provide a written informed consent. It is the responsibility of the principal investigator (PI) to obtain this consent from the participant.

The participant/patient information sheet with all relevant details filled in the local language should be approved by the concerned institute ethics committee (IEC) along with the trial protocol. The essential elements of information to be provided in the information sheet should as per the checklist provided under Schedule Y of the Drugs and Cosmetics Rules,

1945. A copy of the patient/volunteer information sheet and the signed consent form should be provided to the participants for retaining with themselves.

Waiver of consent

For some specific types of research, a waiver of consent or waiver of written consent may be given by the IEC, e.g. in an emergency situation where obtaining consent is not possible, for research on stored tissue or data, retrospective studies, or behavioural research where knowledge about the research study may lead to bias in the research result. Such research needs to be carefully evaluated by the ethics committee before a waiver is granted, and a waiver should only be granted provided that the research poses minimal risk and consent is impracticable. However, in the case of clinical trials, a waiver should not be agreed to by the IEC unless there is a valid justification, such as in emergency situations. In such cases, consent should be obtained at a later date from appropriate individuals or a debriefing should be done. When participants are willing to participate, but do not agree to provide written consent, the informed consent process should be well documented by audiovisual methods. Such documents should be well preserved, adhering to principles of confidentiality. These should be made available for any subsequent scrutiny by relevant authorities.

Research on vulnerable populations

Research on special groups of people who have diminished capacity to protect their interests or to give consent for themselves requires great care. It is important to obtain consent, assent or permission from vulnerable participants in addition to obtaining permission from their legally-authorized representatives. Proxy consent should be obtained from guardians who are legally authorized for those who cannot provide valid informed consent, viz. children, the mentally differently abled, prisoners, institutionalized individuals, terminally ill patients, students, subordinate staff, in the presence of an independent witness who has to also sign the informed consent document. Audiovisual recording of the informed consent process should be undertaken and the documentation should be well preserved.

Obtaining subsequent consent

Obtaining consent is a continuous process and not a one-time affair. Obtaining initial consent for screening and recruitment to the trial is always followed by having to obtain subsequent

consent as the trial progresses. Any change in the protocol or any new information related to the trial, etc. requires a . subsequent consent to be obtained from the participants with the approval of the IEC. These documents should also be well preserved.

Responsibilities of the IEC

Approval of the trial protocol, patient information sheet and consent form is the primary responsibility of the IEC. Any advertisement in this regard should also be examined and approved before undertaking recruitment. Subsequent consent from participants should be insisted upon wherever needed. In case of sensitive trials, or whenever there is a doubt or complaint, the IEC can monitor the informed consent process by appropriate methods, e.g. examining the written or audiovisual documents, conducting site visits (either surprise or announced), interacting with participants, etc. as deemed fit for the trial.

Violation of informed consent

Any violation of the informed consent process will be dealt with as a serious lapse on the part of the investigators, for which the PI can be blacklisted or debarred from clinical trials for a period of up to five years.

14. Management of serious adverse events and compensation in clinical trials

15.

Introduction

In today's era of globalization, the availability of India's able and skilled medical fraternity, the many world-class medical institutions and the large treatment-naive population have put this country in the enviable position of being a potential global hub for clinical research. Also, cost competitiveness and technological infrastructure have given Indian industries and research institutions a definite advantage over other countries in contributing to global drug development in a significant way. In this new environment, many multinational corporations (MNCs) have been attracted to participate in clinical trials in this country.

The Mashelkar Committee (1999) in its report on Pharmaceutical R&D had identified clinical research as an area with immense potential for growth in this country. The Committee had called for basic changes in the legislation allowing import of animals, contract research and a legal status for institute ethics committees (IECs) if clinical research had to grow in India. Furthermore, it had recommended establishment and operationalization of a good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP) monitoring authority.

In an effort to ensure that clinical trials are conducted in consonance with established, globally-accepted ethical principles, the Central Drugs Standard Control Organization (CDSCO) planned a strategic intervention to improve the situation by releasing the Indian GCP guidelines. These guidelines, together with the Indian Council of Medical Research (ICMR)'s revised *Ethical guidelines for biomedical research on human subjects* were important steps in this direction. However, the basic legal framework for appropriate regulatory intervention in clinical research was only put in place in 2005 when Schedule 'Y' of the Drugs and Cosmetics Act, 1940 was overhauled to bring Indian clinical research regulations at par with contemporary global levels.

Good, bad and ugly clinical trials - Government response

. A large number of clinical trials have taken place in India in the recent past. Many of them were held in consonance with the required norms. However, some trials were reported where the norms and ethical issues were either not followed in letter and spirit or paid scant regard. Such cases have given rise to questions of accountability and laxity in implementation of the prescribed norms.

The fallout of these reports has been that some public interest litigations (PILs) have been filed in various courts including the Supreme Court of India by public-spirited bodies. It has been alleged therein that clinical trials in India are being conducted with bias by inexperienced investigators with some vested interests, and that the Indian public is being subjected to clinical trials without getting their genuine informed consent. A number of deaths have been documented before the courts. It has been contended that in many of the cases, serious adverse effects (SAEs) have not been medically managed, and that in many of the cases compensation has not been paid to the legal heirs/participants in cases of death/injuries connected with such clinical trials. In a PIL filed by an Indore-based NGO, the Supreme Court has expressed its deep anguish and has been constrained to pass orders bringing clinical trials directly under the supervision of the Secretary, Ministry of Health and not under the CDSCO.

The department-related Parliamentary Standing Committee on Health and Family Welfare in its 59th Report of May 2012 on the functioning of the CDSCO has observed that due to the sensitive nature of clinical trials in which foreign companies are involved in a big way, a wide spectrum of ethical issues and legal aspects are involved; therefore, different aspects of clinical trials needed a thorough and in-depth review.

In view of the aforesaid criticisms by the Parliamentary Standing Committee, some important measures have been announced by the Government, including appointment of this Committee. The aim is to ensure that a transparent and robust system based on a scientific foundation be put in place to regulate, *infer alia*, clinical trials so that the interests of all the stakeholders are safeguarded, transparent clinical trials are encouraged, human rights of the trial participants and the society at large are safeguarded and such clinical trials result in the public good.

At the same time, the Ministry of Health and Family Welfare, Government of India, has taken some immediate remedial measures and amended the Drugs and Cosmetic Rules, 1945. Under the amended rules, registration of IECs has been made mandatory. Further, provision for medical management of SAEs of participants in clinical trials has been made the exclusive responsibility of the sponsors/their representatives till the SAEs are resolved. Also, provisions for payment of compensation for injuries to participants that are relatable to such trials, and compensation to the heirs of the participants who die because of SAEs relatable to clinical trials, have been envisaged. The amended rules also make it the duty of the investigators/sponsors to report SAEs within a specified period of time from the date of occurrence.

One of the criticisms to these amended rules is that the notice of SAEs/deaths to the authorities/IECs should be relatable to the knowledge of the occurrence and not to the date of the occurrence. This seems to be a valid criticism and needs consideration by the concerned authorities. Also, injury or death of a subject occurring in a clinical trial due to some of the reasons specified in sub-rule (5) of rule 120-DAB of the Drugs and Cosmetics Rules, 1945, more particularly failure of the investigational product to provide the intended therapeutic effect, has come under criticism. It has been argued by the pharmaceutical industry and the investigators who were heard at length by the Committee that there is need for a relook at such provisions in the rules.

Importance of clinical trials

The purpose of clinical trials is advancement of science and technology in the field of healthcare, better treatment and progress of healthcare. Good clinical trials are possible only if the stakeholders observe the rules, regulations and best practices fairly, and work for the public good. The main stakeholder is the person who voluntarily agrees to participate in a clinical trial after he is explained the risks involved, and gives his informed consent to participate in the clinical trial. His human rights need to be protected and ensured at every stage of the trial.

The Committee believes that it is but fair, just and reasonable that the interests of the subject who participates in a clinical trial need to be safeguarded and the best ethical practices

followed while subjecting him to the clinical trial. In case there is an adverse event, he must be looked after all through and be provided best medical care till the SAE is resolved. In the event of his death taking place during the trial, or if he suffers any permanent or partial disability due to injury, he or his dependents must be given compensation that is just, fair and reasonable.

Issues relating to causality

The core issues to be considered are: (a) Medical management of SAEs during clinical trials, and (b) in the event that these remain unresolved and result in death, or injury resulting in permanent or partial disablement of the participant, when and what should be the compensation payable to the participant or his heirs. The issue of whether medical management and/or compensation should be relatable to the clinical trial has been debated at length before the Committee by various interest groups during discussions.

A further question for consideration of the Committee is-if the compensation issue is to be confined to causes which are related directly to the clinical trial, which forum should decide the causal factor or otherwise? The body which decides this issue must have no conflict of interest and should not only be neutral but also appear to be so. Also, can this responsibility be left to the IEC which has many non-technical and non-medical people in it?

Would the issue of causality or non-causality not be relegated to a non-issue if it were recommended that all SAEs during a clinical trial which result in death or partial or permanent disability need to be compensated, and that for this purpose the government should impose a cess on the pharmaceutical industry and create a fund from which the compensation can be paid? At the same time, it needs to be ensured that this recommendation does not ultimately result in any inducement or enticement for participation in clinical trials by persons who are without a job, illiterate or semi-literate or in dire need of money.

After resolving the above issues and making necessary recommendations, the most important issue is to decide on the formula for determining the compensation payable to those who suffer permanent or partial disablement, or to the heirs of those who die during clinical trials. There is a formula provided in the rules recently framed by the Drugs Controller General of India (DCGI) in regard to payment of compensation, which has come under grave criticism. Almost all groups feel that the said formula is neither scientifically based nor equitable or reasonable.

Recommendations of the committee on causality and compensation

After hearing the various stakeholders, namely the pharmaceutical industry, clinicians, civil society and research organizations, and after threadbare discussions among the members of the Committee on the aforesaid issues, recommendations of the Committee are enunciated below.

- a) The Committee is of the considered opinion that if any SAE occurs during a clinical trial, it should be the legal duty of the sponsor/investigator to take all steps necessary for providing medical treatment to the patient in the hospital at their cost, exercising due care and caution till the SAE is resolved. This should be done without getting into the technicalities of whether the SAE is related or unrelated to the clinical trial. The cost of treatment till resolution of the SAE should be exclusively borne by the sponsor/investigator. It is possible that a SAE or an adverse event (AE) could be caused by a procedure undertaken to deal with an SAE caused by the original drug being evaluated. Compensation needs to be provided for such *SAEs/AEs* as well. *SAEs/AEs* induced by drugs administered to the control group of patients also need to be compensated. The issue of causality may be relevant for payment of compensation in the event of an SAE remaining unresolved, but can have no bearing on the immediate treatment of the participant in the clinical trial for resolution of the SAE.
- b) In totally proven unrelated cases, e.g. building collapse, drowning, road accident, etc. occurring to the patient undergoing a clinical trial, compensation may not be payable. In all other cases of death or injury/disability, compensation should be paid to the participant or his legal heirs, as the case may be. Further, for the purposes of simplifying the procedure for award of compensation to the legal heirs, it will be proper and just that the participants in the clinical trial be required to nominate their legal heirs at the time of giving their informed consent, and also specify who will be entitled to receive compensation on behalf of all the legal heirs, to be distributed among themselves.

- c) Compensation should be paid to the trial participants if any drug-related anomaly is discerned at a later stage and accepted to be drug-related by a competent authority, whether in India or abroad.
- d) The opinion of the investigators/sponsors on the causality issue should be subject to review by the SAE committee of the institution for its considered opinion. The opinion of the SAE committee will be considered by the IEC, which will be entitled to either accept the opinion of the SAE committee, or come to its own conclusion based on a reasoned decision within the mandatory prescribed period. The IEC will in turn forward its recommendation to the DCGI who shall ordinarily accept the recommendations of the IEC on the causality, unless he takes his own considered decision on the causality for reasons to be recorded.
- e) Where there is no SAE committee, the opinion of the investigator/sponsor shall be considered directly by the IEC. Further processing of the matter will follow the same steps as above.
- f) Before forming its considered opinion on the causality as above, the IEC shall be within its powers to seek the opinion of experts in the field on the causality, which shall be given due consideration before taking a final decision to be forwarded to the DCGI.
- g) If the sponsor or his representative/investigator is aggrieved by the decision of the IEC on the causality, he will have the right to seek a review of the decision within 14 days of the receipt of the recommendation of the IEC by the sponsor/investigator. The said review petition will be decided by the IEC at the earliest possible, either by rejecting the review petition or by modifying its earlier decision after due consideration.
- h) In cases where the causality of death or injury is proved to be relatable to the clinical trial, it shall be the duty of the IEC to examine as to whether the compensation determined by the sponsor/his representatives/investigator has been calculated in

accordance with the norms in vogue or the rules prescribed in this behalf by the appropriate authority. The IEC will also ensure that the compensation is paid within the prescribed time limit; and in the event of delay in payment of compensation, it will decide on the rate of interest payable in addition to the compensation to the participant/heirs.

- i) In the event that the new norms which are expected to be framed by the competent authority on the basis of sound principles have not been framed, the IEC shall be within its powers to consider whether the compensation determined by the sponsor/his representative/investigator under the existing norms in vogue is a just, reasonable and fair compensation to the participant/heirs of the participant. In case the IEC comes to the conclusion, guided by principles of justness, fairness and reasonableness that the compensation needs to be revised, it shall be competent to do so and will ensure the payment of the compensation so determined.
- j) In the event of an SAE remaining unresolved and leading to the death or disablement/other serious consequences, the legal heirs/nominee or the participant, as the case may be, should be entitled to an interim compensation. This will be payable immediately, preferably within 15 days of the information of the SAE having been submitted to the office of the DCGI by the sponsors, with immediate intimation to the IEC concerned. The amount of interim compensation may be subsequently offset against the final compensation payable to the participant/his legal heirs.
- k) The sponsor, whether it be a pharmaceutical company or an institution, shall undertake before the clinical trial begins to provide interim as well as final compensation in case of injury or death for which the subjects are so entitled.
- l) In case the sponsor fails to provide compensation to the trial subject for clinical trial related injuries or compensation to the legal heirs in case of death, the DGCI may, after giving an opportunity to show cause why such an order should not be passed, by an order in 'writing stating the reason thereof, take any of the following actions: (i) Suspend and cancel the clinical trial; (ii) restrict the sponsor/contract research organization/local representative in the case of a foreign sponsor from conducting any

further clinical trials in the country; (iii) blacklist the sponsor from conducting clinical trials for a period of five years; or (iv) take any other action as deemed fit under the rules.

- m) The Committee deliberated on the very important issue as to whether patients suffering from terminal illness/cancer should be entitled to compensation in the event of any SAE related to the clinical trial. The Committee is of the opinion that in cases of clinical trials being carried out on patients suffering from terminal illness such as cancer, compensation may not be given if the primary end-point is death, but may be payable if the IEC after deliberation is of the considered opinion that
- there is increase in the SAEs occurring in such a patient compared to a standard treatment and which may be irreversible, or
 - life expectancy has been severely curtailed.
- n) The Committee considered the question of creating a fund by imposing a cess on the pharmaceutical industry or sponsors which could be used to pay compensation to the participants who sustain injury or death related to the clinical trial. The Committee discussed the matter with various stakeholders and decided to leave this decision for the Central Government to take, after considering the matter further threadbare.
- o) No compensation should be payable for therapeutic inefficiency.
- p) No placebo treatment should be given if a standard treatment is available. Further, any SAE arising in the event of a placebo being used during the trial should also be compensable if the SAE is related to the use of the placebo.
- q) Any SAE arising in the group receiving a placebo in place of the standard treatment should be compensated if the SAE is related to the use of placebo.
- r) Compensation should be payable for any injury to a foetus *in utero* because of the participation of the parent in a clinical trial.

- s) There must be strong provision for ancillary care when the patient suffers from any other illness during the trial.
- t) If an international drug is found to be effective, the possibility of post-trial access to the drug should be included at the time of approval as an *a priori* agreement.

Compensation in investigator-initiated clinical trials in academic and research centres

The Committee considered the representation from academic institutions that medical colleges and research institutes would not be able to pay the compensation which may have been recommended in favour of patients and volunteers in non-pharmaceutical clinical trials. It was further represented that most of these studies are part of the theses of postgraduate students, and academic research will suffer if the same yardstick is applied to the academics in these studies as for pharmaceutical companies. It was further suggested that these studies could be approved by the IECs and need not be approved by the DCGI, except in cases of trials for new indications of already-approved drugs.

The Committee deliberated on these issues and makes the following recommendations:

- Academic research may be approved by the IEC and needs to go for approval to the DCGI only if a new drug is being evaluated or a new use for an existing drug is being tried out.
- Injury or death needs to be compensated, irrespective of whether the volunteer is participating in a pharmaceutical drug clinical trial or an academic research trial. The same yardstick applies to volunteers of both types of trials and the same procedures will have to be followed.
- In order to encourage academic and clinical research (non pharmaceutical-company related) in academic institutions, the Government of India and state governments should create a fund by imposing a cess. The fund so created should be made available to the academic institution for paying compensation.

Sponsor of the trial/clinical research

Since compensation is to be paid to the participant by the sponsor, the question as to who is the sponsor of a clinical trial or a clinical research project was put to the Committee.

It is very clear that for pharmaceutical-initiated clinical trials, the pharmaceutical company or the contract research organization (CRO) conducting the research on behalf of the company is the sponsor and has to pay the compensation by itself, or through insurance.

In academic non-pharmaceutical research, the sponsor could be either the funder of the research or the investigator and the institute where the research is being carried out.

If the investigator or institute has applied for a grant and has received the grant, then the investigator and the institute are the sponsors for the research, irrespective of whether a national or international organization is funding the research.

On the other hand, if an organization, for example, is funding a multi-centred clinical research project and has identified a specific institute or researcher and asks them to join the research programme, then it stands to reason that the concerned organization is the sponsor whether national or international is immaterial.

Formula for compensation

There is a formula provided in the rules recently framed by the DCGI in regard to payment of compensation which has come under grave criticism. It is alleged that the said formula is neither scientifically based nor equitable or reasonable.

This Committee understands that the Government is seized of the matter and may be in the process of coming out with a more rational formula. The Committee recommends that the appropriate authorities may take into account the formula evolved by the Supreme Court under the Motor Vehicles Act, 1988 with special care and concern for marginalized groups, who it appears are at a disadvantage under the said formula. If the concerns regarding marginalized groups, including children who are treated as having no capacity to earn under the said formula, are taken into account, and due attention is given to their interest during

clinical trial injury or death, the said formula, modified appropriately, can be a good basis for determining compensation.

16.Reorganization of the Central Drugs Standard Control Organization

The Central Drugs Standard Control Organization (CDSCO), headed by the Drugs Controller General of India (DCGI) in the Directorate General of Health Services under the Ministry of Health and Family Welfare, is a statutory body responsible for performing regulatory functions under the Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945. The stated mission of the CDSCO over the past many years had been 'to meet the aspiration ... demands and requirements of the pharmaceutical industry' which it had been trying to accomplish in the last two decades through various amendments to the Drugs and Cosmetics Act, 1940 (in 1988, 2003, 2005 and 2013). This was quoted and commented unfavourably upon in the 59th Report of the Parliamentary Standing Committee in May 2012. This has resulted in the CDSCO revisiting its mission, and what now appears on the website of CDSCO (cdsco.nic.in) as the stated vision is 'To protect and promote public health in India'. The mission states 'To safeguard and enhance the public health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices'.

The primary mandate of the drug regulatory authority in the USA, a developed country, (as given in the 59th Report of the Parliamentary Standing Committee on Health and Family Welfare submitted in May 2(12) is 'protecting the public health by assuring the safety, efficacy and security of the human and veterinary drugs'. In consonance with such mandates of developed countries, CDSCO has done well to revise its mission statement to convey in unambiguous terms that the responsibility of this organisation is to protect the safety and welfare of the population it serves. The regulatory functions are intended to achieve this goal by ensuring availability of safe and effective quality drugs at all times to the public at large.

Indian pharmaceutical industry

The responsibility entrusted to the CDSCO is enormous, considering the fact that the Indian pharmaceutical industry is currently worth over Rs.1200 billion with a growth rate of 12% for new drugs and 20% for biologicals over the last five years, which is the highest in the world. It is also the third-largest producer of generic drugs in terms of volume and 14th in terms of

value. India is the second-largest producer of certain generic drugs such as ciprofloxacin, ranitidine, simvastatin, I-ephedrine and chloroquine.

Functions of the CDSCO

All functions of the CDSCO are carried out through its Headquarters at New Delhi and six zonal and three sub-zonal offices situated in different parts of the country. Regulation of import and export of drugs and cosmetics is monitored by II offices at different seaports/airports. In addition, there are six testing laboratories which assist the CDSCO in quality checking and maintaining reference standards. The CDSCO Headquarters takes up the brunt of the responsibilities entrusted to it for drug regulation in the country by way of according approvals for manufacturing and import of new drugs, vaccines and bio-therapeutic products, granting permissions for conduct of clinical trials for new drugs, issue of licenses for import and export of drugs, convening the Drug Technical Advisory Board (DT AB) and Drugs Consultative Committee (DCC) meetings, co-ordinating with state drug authorities. monitoring pharrnacovigilance programmes, inspection of clinical trial sites, issues related to banning of harmful and sub-effective drugs and conducting of training programmes for maintaining quality control of drugs. The zonal and sub-zonal offices are only involved in inspection of manufacturing premises, private testing laboratories and sites on receiving complaints, launching prosecution in cases that are detected by zonal offices and coordination with state drug authorities on the quality of drugs manufactured in their respective states.

Workload and resources

The CDSCO currently handles nearly 20,000 applications each year for various statutory approvals of which over 2000 applications are for new drugs of various categories specified under the Drugs and Cosmetics Act, 1940. More than 200 meetings are organised every year and approximately 10,000 individuals come to meet the CDSCO officials. The current manpower of 6 Deputy Drugs Controllers (DCs) and 18 Assistant Drugs Controllers (ADCs), assisted by 75 drug inspectors and 55 technical data associates on contractual basis is far short of the actual manpower requirement proposed by the Hathi Committee in 1975 and the Mashelkar Committee in 2003.

The Drug Policy, 1994 clearly states that the National Drug Authority (NDA) has the mandate and responsibility to enforce quality standards of medicines and good manufacturing practices with conviction and intent, so that matters related to the rational use of drugs, registration of new formulations and rationalisation of existing formulations will be based on acceptably safe and therapeutically effective pharmaceutical products which meet the real medical needs of the people of this country. It also clearly states that the NDA should monitor standard practices in drug promotion to identify drugs which are acceptable and prohibit those which are unethical and unsafe for consumer interest. Although the subsequent draft policies in 2002, 2003 and 2006 were not passed, the problems with the current drug regulatory system in the country have been well-identified and remedial measures suggested. Unfortunately, these have never been seriously looked into. No infrastructural improvement whatsoever in respect of personnel has occurred in CDSCO over all these years.

Considering the enormous task envisaged to be performed by the CDSCO and the poor infrastructure and manpower available for its implementation, it is obvious that there is an urgent need of reorganising the CDSCO with enhanced facilities to have a strong, efficient and effective drug control authority (DCA) in the country which can match any similar organisation in developed countries and be able to effectively safeguard the public health of this country. With this aim in mind, the Committee's recommendations are given below.

Recommendations

- a) The CDSCO should be upgraded to a separate organization /authority, with the DCGI at par with heads of similar organisations of the Government of India (GOI). This will overcome the current malady of lack of functional and financial autonomy. This is the biggest bottleneck for decision-making and is causing enormous delays in day-to-day functioning.
- b)
- b) The qualification and experience of the DCGI should be similar to that of a secretary or director general of other councils under the Gal. This will overcome the current discrepancy that a Deputy Drugs Controller (1) (DDCJ) is expected to be more qualified and experienced than the DCGI.

- c) The knowledge and experience required for such high-level posts requires that these posts be given matching emoluments to attract better-qualified candidates while filling the post. The present problem of highly qualified medical and other professionals not willing to take up these responsibilities can then be obviated.
- d) The additional posts required in various categories for effective functioning of the CDS CO were recommended by the Mashelkar Committee in 2003. The need today is for even more positions in different disciplines which have become more important in drug regulation. These posts should be identified and created as soon as possible.
- e) The minimum additional requirement should be sanctioned and implemented immediately. Regular periodic reviews should be undertaken to assess the needs of further expansion to keep pace with the developments in science and regulatory aspects.
- f) Regulatory science is not well developed in various curricula for medicine, pharmaceutical science or other biological and related sciences. As such, there is a severe lacuna in expertise related to regulatory issues. In-house staff as well as experts need constant updating of their skills. Till in-house expertise is developed as in other regulatory agencies such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), expertise of subject specialists may be utilized on a contractual basis with appropriate confidentiality and conflict of interest agreements.
- g) A good regulatory agency is recognized by the accurate timeline it keeps for different activities. The current difficulties faced by the manufacturers and sponsors of clinical trials due to the inordinate delays in decision-making should be overcome by a transparent, time-bound decision-making process with clear-cut timelines.
- h) An effective communication system is required for facilitating the functions of the CDSCO. This envisages the following:
 - i. A transparent website containing up-to-date information

- ii. Regular updating of information
 - III. Clear-cut timelines for different activities
 - IV. A system of pre-submission dialogue with the applicants to clear all doubts and reduce the delays due to failure of communication channels
 - v. Display of the lists of members of all committees and subject experts
 - VI. Application forms, standard operating procedures (SOPs), model agreements for confidentiality and conflict of interest, samples of informed consent forms, checklist for participant information sheet, serious adverse effect (SAE) reporting form, etc. should be made available on the website.
 - VII. F AQs and answers
 - VIII. Relevant regulatory laws, guidelines and their amendments.
- i) The duty of ensuring safety of the drugs and cosmetics provided to the population lies with both the Central and state drug regulatory authorities, as public health is a shared responsibility. While all drug approvals, whether new or existing or generic, should lie only with the CDSCO, some of the functions related to inspections, monitoring clinical trials and pharmacovigilance can be shared with the state authorities. Reporting of adverse events (AEs) and SAEs can be made to both agencies for better coordination and early intervention for weeding out unsafe, ineffective or sub effective drugs. There should be a regular dialogue in this regard between the Central and state regulatory agencies.
- j) Strengthening and capacity building of zonal and sub-zonal offices and state DCAs are part of the revamping of the system to safeguard the public health of the country
- k) The current pharmacovigilance programme needs expansion and strengthening to cover the whole country. It should be reviewed and reorganized to detect unsafe drugs at the earliest. In addition, a participative system should be put in place involving the medical community, pharmacists, industry and patients.
- l) A continuing education programme for all officers and technical staff in the CDSCO and state DCAs to upgrade their knowledge by suitable in-service training

programmes within and outside the country should be put in place, so that the domestic knowledge base is at par with international standards.

Conclusion

A drug regulatory system/authority in any country is responsible for protecting the public health of that country by ensuring the safety, efficacy and quality of human and veterinary drugs, biological products, medical devices, diagnostics and cosmetics based on scientific excellence and best-possible regulatory practices. There is a strong trend towards global harmonization of scientific and regulatory requirements pertaining to safety, efficacy and quality of pharmaceutical products. India undoubtedly needs a strong, transparent, equitable, efficient and professionally-managed drug regulatory system/authority urgently to meet global standards and ensure the confidence of the politicians, industry and the public at large that the health of the nation is well-taken care of.

17. Information technology and transparency

Information technology (IT) needs to be used at all steps of a clinical trial to bring transparency to the system being introduced and implemented. There should be no scope for the pharmaceutical houses, hospitals, clinical investigators (CIs) and non-government organizations (NGOs) being able to say that they do not know what is happening regarding their application for carrying out a clinical trial. It is envisaged that from the first step, i.e. submitting the application at the single window, till the final approval is received, every step will be recorded and made available in the public domain. Inordinate delays in anyone sector will be immediately identified, the cause of the delay removed, and the reason for the delay made known to the public.

Some of the activities which will be placed in the public domain are:

- Correctness and adequacy of the information provided
- Names of members of the technical committee that will review the proposals
- Names of outside experts, if any
- Decision whether the proposal is going forward to the Randomization Unit
- Names of accredited sites where the clinical trial can be carried out
- Names of two or three accredited sites chosen by the sponsor

Date on which the proposal is sent to the institute ethics committee (IEC) Names of members of the IEC

- Decision of the IEC
- Issues raised by members of the IEC
- Modifications suggested to the protocol, if any

Entry of information in the Indian Council of Medical Research (ICMR) registry, with date of such entry

- Date of initiation of the trial
- Documentation of every serious adverse event (SAE) of a drug
- Final report of the trial, as also comments from peers on the SAEs and the outcome of the trial

- Decision of the Central Drugs Standard Control Organization (CDSCO) on the trial.

Introduction of such transparency will add strength to the drug regulatory system, reduce bias in the decisions being made, and give a sense of satisfaction and comfort to all stakeholders that the clinical trials carried out in this country are fair and no exploitation of the volunteers and participants is possible.