ACTIONS ON THE RECOMMENDATIONS OF PROF. RANJIT ROY CHAUDHURY EXPERT COMMITTEE TO FORMULATE POLICY AND GUIDELINES FOR APPROVAL OF NEW DRUGS, CLINICAL TRIALS AND BANNING OF DRUGS

Ministry of Health & Family Welfare had constituted an Expert Committee under the Chairmanship of Prof. Ranjit Roy Chaudhury to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs. The Committee was constituted in pursuance of the averments made in the Action Taken Report submitted to the Department Related Parliamentary Standing Committee on Health and Family Welfare in response to the recommendations contained in the 59th Report of the said Committee on the functioning of Central Drugs Standard Control Organisation (CDSCO). The Expert Committee has submitted its report to the Ministry of Health & Family Welfare. The recommendations of the Expert Committee were discussed in a meeting with its members. During the meeting, clarifications on certain recommendations were obtained from the Committee. The actions proposed to be taken on the recommendations of the Expert Committee, as finalised by the Ministry of Health & Family Welfare after discussion with the Committee members are given below:

1. **Clinical Evaluation of New Drugs**

(a) Accreditation of Ethics Committee, Investigators and the clinical trial sites.

In order to strengthen the Clinical Evaluation of New Drugs, the clinical trials should be conducted in accredited sites by accredited Investigator with the oversight of accredited Ethics Committees (ECs). This is a long term measure. In the meantime, Quality Council of India will be considered for creating a system for accreditation of Investigators, Ethics Committee and Clinical Trial Sites. Although, the Drugs & Cosmetics Rules, 1945 already provide for Registration of Ethics Committee, accreditation of such committees will be undertaken following a specific procedure. This requires amendments in the Drugs & Cosmetics Rules. Immediately, CDSCO would initiate steps relating to the process of accreditation by constituting an expert body of 20-25 experts. The names of Experts will be finalized by CDSCO in consultation with Dr. Ranjit Roy Chaudhury, Dr. Y. K. Gupta, Prof. & Head, Dept. of Pharmacology,

AIIMS, New Delhi & Dr. Arun Aggarwal, Prof. of ENT, Maulana Azad Medical College, New Delhi.

(b) Procedure for review of applications of clinical trials and new drugs.

New Drug Advisory Committees (NDACs) will be renamed as Subject Expert Committees. The members for their meetings will be drawn randomly from a large pool of experts. Applications of clinical trials and new drugs will initially be evaluated by the Subject Expert Committees and their recommendations will be reviewed by the Technical Review Committee (TRC). The TRC will be constituted under DGHS and consisting of experts from each areas i.e. clinical pharmacology, regulatory clinical toxicology / pathology, medicinal / pharmaceutical chemistry, pharmacy and immunology including clinicians, basic scientists involved in drug development and subjects specialists (drug indication wise). CDSCO will grant approval of Clinical Trial and New Drugs based on the recommendations of TRC.

- Technical Review Committee (TRC) shall 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.
- The feasibility of setting up regional review/assessment committees to review the applications of clinical trials and new drugs will be explored.
- Video conferencing and other facilities would be used wherever feasible to reduce the commitments on time and travel of experts.

(c) Computerized database and selection of experts

Computerized database of experts in different areas will be created. Some of the criteria for selection of experts will be:

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

Well-defined criteria will be used for selecting these experts. Geographical and gender considerations would be kept in mind while preparing the database.

A roster of experts will be created which will be updated every year and names added or deleted based on a set of well-defined criteria.

(d) Requirement of filing application to market New Chemical Entities (NCEs) if India participated in Global clinical trials of those NCEs

If India participates in global clinical trials of NCEs to be used for diseases that are prevalent in our population, after approval for marketing in the innovator country or in well-regulated developed country markets, approval should be sought from CDSCO for marketing these NCEs in India. After approval from CDSCO, these NCEs should be marketed in India speedily, preferably by production within the country. As per present practice, applicant is required to submit an undertaking from the Sponsor that they will file applications seeking approval for marketing of the drug in the country, once such NCE is approved for marketing in the innovator's country. The existing practice would continue.

(e) Specifying time line for processing of applications

CDSCO will fix a timeline of six months for disposal of applications for approval of clinical trials and new drugs. In case of delay beyond six months, the Licensing Authority will record the reason for such delay. Efforts would be made to bring down the timelines ultimately to one month.

(f) All proposals need not be evaluated by Technical Review Committee (TRC)

The Department agrees with the Committee's recommendations that all proposals of clinical trials and new drugs need not be evaluated by the Technical Review Committee. Ways and criteria in this regard will be defined.

(g) Placebo-controlled trials

Placebo-controlled trials are fairly uncommon these days, although there

will always be a case for such trials in special circumstances. Since other remedies are usually available, the drug to be tested is compared to the existing therapy. There is thus no reason to deprive a patient of a drug in such placebo controlled trial. The pharmaceutical companies, the Investigators, the drugs regulator and the ECs all would have to ensure that the design used in a placebo controlled clinical trial is appropriate, efficient and ethical.

(h) Post trial access of investigational product

In case a New Chemical Entity (NCE) is found to be beneficial in clinical trial, the trial participants should have post-trial access to such NCE. Necessary provisions will be made in this regard.

(i) Informed Consent

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.

The draft rules have already been published for making mandatory audio / video recording of informed consent process. The rules will be finalized after due consultation. Audiovisual recording of the informed consent process as per rules would be undertaken and the documentation preserved, adhering to the principles of confidentiality.

(j) Action in case of violation of the informed consent processes

Any violation of the informed consent process will be dealt with as a serious lapse on the part of the Investigators, for which the Investigator can be debarred from clinical trials. The Drugs and Cosmetics Rules have provisions for debarment of Investigators, in case of violation of conditions of clinical trials.

(k) Number of clinical trials an Investigator can undertake at a time

Number of clinical trials an Investigator can undertake should be commensurate with the nature of the trial, facility available with the Investigator etc. However, under no circumstances the number of trials

should be more than three at a time. In all cases, the details of payment to the Investigator by the Sponsor for conducting the Study would be made available to the DCG(I).

(l) Use of Information Technology

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 filed, every step will be recorded and made available in the public domain.

(m) Monitoring of clinical trials

- The Drugs & Cosmetics Rules have already been amended on 01.02.2013 specifying provisions for conducting inspection of sites of Investigators and Sponsors by CDSCO officials who may be accompanied by the State Drug Regulatory officials. In order to have proper monitoring of clinical trials and information-sharing with States and UTs, Ministry of Health & Family Welfare had written a letter in May 2012 to Health Secretaries of States & Union Territories requesting to constitute a cell under a nodal officer by the State Drug Controllers. Some of the States have already created such cells. The matter was also discussed in the meeting taken by Secretary (Health & Family Welfare) with Chief Secretary/ Principal Secretary (Health) of State Governments. Further actions will be taken in the spirit of the discussion held in the said meeting to enhance association of states Regulatory bodies in monitoring of clinical trial.

- Training on continuous basis will be imparted to upgrade the skill and knowledge of State Drug Control officials in clinical trial monitoring.

(n)Parallel phase II and phase III clinical trials

All NCEs/NMEs undergoing clinical trials anywhere can undergo parallel Phase II and Phase III Clinical trials in India after carrying out safety assessment of Phase I Clinical Trial data generated abroad. This is the current practice followed under Drugs and Cosmetics Rules, which will be continued.

(o)Clinical Trial of Medical Device

Clinical Trial of Medical Device is different in nature as compared to that of Drugs or Vaccine. In case of Medical Device, there is no concept of conducting Phase I Clinical trial to assess safety, tolerability of the Medical Device. However, the procedures for the Clinical Trials approval, accreditations of Investigators, sites, Ethics Committee and such other conditions would be similar to the Clinical Trials of New Drugs/Vaccines

(p)Reporting of Serious Adverse Events (SAEs) by the Investigator

The present provision requires investigators to report SAEs within 24 hours of their occurrence. In light of the concerns raised and recommendations, it is proposed to amend the Rules to insert the following clause after the provision of requirement for the Investigator to report Serious Adverse Events within 24 hours of their occurrence:

"in case the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the DCG(I) along with the report of the serious adverse event".

(q) Compensation in case of injury or death due to failure of intended therapeutic effect of investigational product

Present provision in the Rules requires payment of compensation in cases of injury or death of a subject occurring in a clinical trial due to failure of the investigational product to provide the intended therapeutic effect. In light of the concerns raised and the recommendations, it is proposed to amend the Rules specifying that compensation should be paid in case of injury or death due to lack of intended therapeutic effect of Investigational Product when standard care, though available, was not to be provided to the patient as per the protocol.

(r) Medical management in case of serious adverse events

Present provision in the Rules requires that in case of any injury, subjects should be provided with medical management as long as required. In light of the concerns raised, it is proposed to amend the rules specifying that medical management should be provided as long as required or till such time it is established that the SAE is not related to Clinical Trial, whichever is earlier.

(s) Compensation in case of injury or death due to use of placebo in place of standard therapy

With respect to the compensation in case of any SAE arising in the group receiving the placebo in place of the standard treatment, it is proposed to amend the Rules specifying that compensation should be paid in case of injury or death caused due to use of Placebo where the standard care, though available was not to be provided to the subject as per the protocol.

(t) Compensation in case of clinical trial related injury or death

Compensation need not be paid for injury or death due to totally proven unrelated causes. In all other related cases of death or injury/disability, compensation should be paid to the participant or his legal heirs; This provision is already available under the Rules. However, certain conditions considered as clinical trial related injury or death are under consideration for further amendment, as stated in paras above.

(u) Compensation for injury or death due to SAE caused by a procedure undertaken to deal with an SAE caused by the original drug being evaluated

It is covered under Rule 122DAB of Drugs & Cosmetics Rules. As per the Rule, in case of any injury or death of subject occurring during clinical trial due to adverse effect of the investigational product or any clinical trial procedures involved in the study, the subject is entitled for financial compensation.

(v) Compensation in case of injury or death discerned at a later stage

Compensation in case of injury or death discerned at a later stage should 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. As it requires necessary amendments in Rule 122DAB and Schedule XII, process will be initiated to amend the Rules after following due procedure.

(w) Ancillary care to the patients

There should be provision for providing ancillary care to patients suffering from any other illness during the trial. It requires amendment in the Rules. However, in the meanwhile, an executive order as advisory would be issued stating that ancillary care should be provided for brief illness in the same hospital/trial site. Separately steps will be taken to amend the Rules.

(x) Approval of academic clinical trials

Academic clinical research may be approved by the Institutional Ethics Committee (IEC). However, if a new drug is being evaluated or a new use for an existing drug is being evaluated, then approval of the DCGI is needed as per D&C Rules. Such requirement will continue.

(y) Compensation in case of injury or death in academic trial

Institutions involved in academic trials should create a fund for this purpose in order to encourage academic and clinical research (non-pharmaceutical company related) in institutions. This fund will be available to the institution for paying compensation. Ministry of Health and Family Welfare will advise the institutes to create such funds.

(z) Compensation in case there is an increase in the number of SAEs in clinical trials being carried out on patients suffering from terminal illnesses

In this regard, it may be mentioned that the formula prepared for determining the quantum of compensation in case of clinical trial related death takes into account the risk factor of the subject. Hence, there is no need to have separate regulatory provisions for compensation in case of trial on patients suffering from terminal illness.

(aa) Causality analysis of SAEs to determine the cause of injury or death

Since Ethics Committees oversee the conduct of clinical trials, provision of examinations of SAEs of deaths by an Independent Expert Committee to determine the cause of death is more appropriate. Ethics committees would give their opinion on the SAE to the Independent Expert Committee. This procedure has already been incorporated in the D&C Rules, which will continue.

2. Approval of New Drugs

(a) Restriction of number of clinical trials / new drugs to be approved

There should not be any fixed number of drugs / drug trials that should be approved in the country. Drugs / drug trials would be approved based on merit. Even in countries like USA, UK, and EU, no such provisions are there to restrict the number of drugs to be approved or drug trials that should be conducted in those countries.

(b) Deletion of existing drugs, if a new drug is approved

There should not be any such system of deleting existing drugs on the approved list if a new drug is approved. New drugs would be approved based on merit. Even in countries like USA, UK and EU, no such provision exists to delete existing drug in the approved list if a new drug is approved.

(c) Requirement for a new drug to have advantage over the existing drug for considering approval of the new drug

New drug should be considered for approval if it is found to be safe and efficacious. There should not always be specific requirement of some advantage of the new drug over the already existing drugs for considering its approval. New drug would be approved based on merit. Even in countries like USA, UK, EU no such provision exists.

(d) Requirement of conduct of all phases from Phase I to Phase IV trial in the country for a new entities developed in India

For new entities developed in India and to be marketed in India, all phases from Phase I to Phase IV may not be mandatorily required to be conducted in India. Phase III (Therapeutic Confirmatory trials) which

have primary objective of demonstration or confirmation of therapeutic benefit of the drug, should be conducted in India before the drug is considered for approval in the country. Similarly Phase IV trials are also required to be conducted in India to assess the safety of such drug in post market scenario. Phase I is conducted to estimate the safety and tolerability of investigational new drug. Phase II which is therapeutic exploratory trial is conducted to evaluate the efficacy of the drug and the common short-term side effects and risk associated with the drug. An important goal for the phase II trials is to determine the dose and regimen for the Phase III trials. Therefore, Phase I and Phase II trial may be conducted in India or outside India. Based on Phase I and Phase II data generated, Phase III trials should be conducted in India to confirm the safety and efficacy of the drug. Even for new entities developed and approved outside India, all phases of clinical trial in Indian patients are not mandatory for the purpose of their approval for marketing in India. For marketing of such drug in India, Phase III trial is required to be conducted in the country. Hence, the existing provisions will continue.

(e) Waiver of Clinical Trial in Indian population for approval of new drugs, which have already been approved outside

Waiver of Clinical Trial in Indian population for approval of new drugs, which have already been approved outside India, can be considered only in cases of national emergency, extreme urgency, epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy.

Presently, there are provisions under rule 122A (2) and rule 122B (3) for waiver of local clinical trial in public interest.

Schedule Y further provides that requirements of clinical trial may be abbreviated, deferred or omitted for drugs indicated in life threatening / serious diseases or diseases of relevance to Indian Health scenario.

Therefore, the Rules will be amended to restrict the waiver in case of only national emergency, extreme urgency, epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy.

(f) Consideration of ethnicity for approval of new drugs

The Department agrees with the recommendations in this regard. Various factors, as recommended would be taken into consideration.

(g)Approval of new drugs already approved in other countries, based on clinical trial conducted in Indian patients as part of global clinical trial

If Indians have participated in phase III global trials, the number of Indians participated in phase III global clinical trial in India would have to be adequate for considering approval of drug in India. This is already in practice, which will continue.

(h)Requirement of clinical trial for a drug which is considered generic drug in other country like USA but not approved in India

Approval for a drug which is considered generic drug in other countries like USA but not approved in India and to be manufactured in India would require bridging Phase III trials and bioequivalence (BE) studies in India, as recommended by the Committee.

(i) Requirements of local trial for a generics or similar biologics (Bio-similars) in other country like USA for its approval in the country

Drugs considered generics and similar biologics (biosimilars) in other countries like USA that have been marketed in such countries for more than four years and have a satisfactory report would be approved for marketing in India after abbreviated trials, as recommended by the Committee.

(j) Requirement of Bioequivalence (BE)study for subsequent approval of new drugs already approved in the country

Presently, BE study for oral dosage form of only new drugs is required till four years of approvals of these drugs. In order to make it mandatory for all drugs other than new drugs, it would require amendment in Rules. Such a provision will have an impact on cost, time required for grant of license, infrastructure etc. Hence, this Ministry will seek wider consultation with the stakeholders on this recommendation.

(k) Guidelines to be followed for approval of Similar biologics (Biosimilars)

Similar biologics (Biosimilars) would require both pre-clinical development and bridging Phase III clinical trials as per Department of Biotechnology (DBT)- Central Drugs Standard Control Organization (CDSCO) guidelines for its approval in India.

3. Post Marketing Surveillance

- **Post Marketing Surveillance for six years**

As per Schedule Y, PMS is mandatory for four years of approval of new drugs in the country. It should be made mandatory for six years for all drugs permitted to be marketed in India. It is proposed to amend the Drugs & Cosmetics Rules in this regard.

- **Reporting of Adverse Drug Reactions (ADR) of marketed drugs**

All ADRs 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. It is proposed to amend the Rules to make provisions that the pharmaceutical company, clinician treating the patient or his/her hospital, or even a practicing clinician would also report the ADR to CDSCO.

(a) Restriction of use of new drug for a year or two only in hospitals

The recommendation of the Committee that the product's use for a year or two should be restricted to hospital only was made in light of the recommendation of the Committee to consider waiver of local clinical trial for a new drug approved for marketing for four years in countries with well-developed Regulatory Authorities. This

recommendation is not applicable as the waiver of Clinical Trial in Indian population for approval of new drugs, which have already been approved outside India can be considered only in cases of national emergency, extreme urgency, epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy. Hence there is no need to proceed further on this recommendation.

(b) Continued permitting of Bioavailability / Bioequivalence (BA/BE) studies for export purpose

The recommendation regarding Bioavailability / Bioequivalence (BA/BE) studies of drugs of foreign manufacturer or by Indian manufacturer for generating data for submission to foreign Regulatory Authority for export purpose requires wider consultation with the stake holders and also with the Ministry of Commerce and Industry, and Department of Pharmaceuticals.

4. Banning of drug

(a) Weeding out of hazardous / irrational drugs from the market

A Special Expert Committee would be set up to review all drug formulations in the market and identify drugs which are potentially hazardous and/or of doubtful therapeutic efficacy.

A mechanism would be put in place to remove these drugs from the market by the CDSCO at the earliest.

(b) Consideration of banning of a marketed drug if two or more countries remove the drug from their market due to issues related to safety and efficacy of the drug

If two or more countries remove a drug from their market on grounds of efficacy and safety, then the continued marketing of the drug in the country will be considered for examination and appropriate action.

(c) Continued evaluation of drugs marketed in the country

CDSCO would be supported by experts who would recommend, from

time to time, removal of drugs from the market due to safety and efficacy issues.

5. Strengthening of CDSCO

(a) Overall strengthening of CDSCO

Strengthening and upgradation of CDSCO is under consideration in the 12th Five Year Plan. There is an outlay of Rs. 1800 crore in the 12th Plan for such purpose.

(b) Creation of Research Unit

It has been agreed in principle to create a research unit within the Central Drugs Standard Control Organization (CDSCO). This unit would initiate and sponsor studies to be able to get the needed information to help in decision-making for removal of hazardous and irrational drugs from the market.

(c) Interaction with the applicants

At any point of time, the representative of the pharmaceutical companies 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. It requires amendment of Rules. In any case, office of the DCGI is open for interaction with the stake holders.

(d) Qualification and experience of the DCGI

The Department agrees with the recommendation that the rank and status of DCG(I) should be upgraded. However, the level and the emolument would be considered separately.

(e) Strengthening of CDSCO in terms of manpower

The additional posts required in various categories for effective functioning of the CDSCO 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 would be identified and created as soon as possible. The steps are already under way. The Central Drugs Standard Control

Organization (CDSCO) is continuously being expanded so as to improve its functioning. From a total sanctioned strength of 111 posts in 2008 with 32 Drugs Inspectors, CDSCO has increased its sanctioned strength to 475 posts with 279 Drug Inspectors in 2013. It is proposed to increase the strength of the organisation substantially to 1102 posts at different levels during the Twelfth Five Year Plan.

(f) Updating skill and knowledge of regulators and experts

The Department agrees with the recommendation that in-house staff as well as experts need constant updating of their skills. Till in-house expertise is developed, expertise of subject specialists would be utilized on a contractual basis with appropriate confidentiality and conflict of interest agreements.

(g) Effective communication system of CDSCO

The recommendations for an effective communication system for facilitating the functions of the CDSCO, is already under consideration in the proposed e-governance system under 12th Five Year Plan.

(h) Licensing of manufacture of drugs by State Licensing Authority / Central Licensing Authority

As per Drugs and Cosmetics Act, and Rules made thereunder, licence to manufacture of drugs is granted by the State Licensing Authorities appointed by State Governments. In the Drugs and Cosmetics (Amendment) Bill, 2013, it has been proposed to have Central Licensing for 17 critical categories of drugs. The Bill is under the consideration of the Parliament.

(i) Strengthening of Pharmacovigilance programme

The Department agrees with the recommendation that the current Pharmacovigilance programme needs expansion and strengthening to cover the whole country. It would be reviewed and reorganized to detect unsafe drugs at the earliest. In addition, a participative system would be put in place involving the medical community, pharmacists, industry and patients. The strengthening of the Pharmacovigilance programme of India is also under consideration in 12th Five Year Plan.

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