डॉ विश्व मोहन कटोच
एम डी, एफ एन ए एससी, एफ ए एम एस, एफ ए एससी, एफ एन ए
सचिव, भारत सरकार
(स्वास्थ्य अनुसंधान विभाग)
स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं
महानिदेशक, आई सी एम आर
Dr. Vishwa Mohan Katoch
MD, FNASc, FAMS, FASc, FNA
Secretary to the Government of India
(Department of Health Research)
Ministry of Health & Family Welfare &
Director-General, ICMR

भारतीय आयुर्विज्ञान अनुसंधान परिषद
(स्वास्थ्य अनुसंधान विभाग)
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
वी. रामलिंगस्वामी भवन, अंसारी नगर
नई दिल्ली - 110 029 (भारत)

Indian Council of Medical Research
(Department of Health Research)
Ministry of Health & Family Welfare
V. Ramalingaswami Bhawan, Ansari Nagar
New Delhi - 110 029 (INDIA)

No.Secy.DHR/DG ICMR/CDSCO/2012
20th November 2012

Subject : 59th Report of the department Related Parliamentary Standing Committee on Health & Family Welfare on the 'Functioning of the Central Drug Standard Control Organisation (CDSCO) – Regarding

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Dear Dr. Panda,

This has reference to Order No. X-11035/32/2012-DFQC dated 7th September 2012 constituting an Expert Committee to examine functioning of CDSCO and related issues.

Please find enclosed herewith the Report of Expert Committee for further necessary action at your end.

With kind regards,

Yours sincerely,

(V. M. Katoch)

Dr. Arun Kumar Panda,
Joint Secretary(Regulations)
Department of Health & Family Welfare,
Room No. 256- A Wing,
Nirman Bhavan, New Delhi

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Report of the Expert Committee appointed by the Government of India Ministry of Health and Family Welfare (Department of Health and Family Welfare)

To advise for appropriate action for
Improvement in the functioning of the CDSCO
(Central Drugs Standard Control Organization)
In pursuance of the 59th Report of the Parliamentary
Standing Committee for the MOHFW

November 2012

Report of the Expert Committee appointed by the Government of India Ministry of Health and Family Welfare (Department of Health and Family Welfare)

Vide notification no. X-11035/32/2012 - DFQC dated May 10, 2012

to advise for appropriate action for
Improvement in the functioning of the CDSCO
(Central Drugs Standard Control Organization) in pursuance of the
59th Report of the Parliamentary Standing Committee for the MOHFW

November 2012

Contents

1. Executive Summary

The 59th Report of the Parliamentary Standing Committee (PSC) for the Ministry of Health and Family Welfare was presented to the Parliament on 8.5.2012. The PSC has examined various aspects of functioning of CDSCO, such as approval of new drugs, banning of drugs, approval of fixed dose combinations, Pharmacovigilance, spurious/substandard drugs etc. during the course of its review of the CDSCO. On critical evaluation the PSC has identified several deficiencies, most particularly in the approval of new drugs without mandatory clinical trials in India. It has also observed nexus between the manufacturers, doctors and the regulatory agency in some instances and has made a large number of recommendations for drastic revamping of the CDSCO.

The Ministry of Health and Family Welfare, Government of India constituted an Expert Committee on 10th May 2012 to enable immediate appropriate action in the matter. The Committee comprised of Dr. V.M. Katoch, Secretary, DHR and DG, ICMR, Dr. P.N. Tandon, President, National Brain Research Center, Manesar and Dr. S.S. Agarwal, Former Director, Sanjay Gandhi Postgraduate Institute for Medical Sciences, Lucknow with the following **terms of reference:**

I. *To examine the validity of the scientific and statutory basis adopted for approval of new drugs without clinical trials as pointed out in the Report for further appropriate action in the matter.*

II. *To outline appropriate measures to bring about systemic improvements in the processing and grant of statutory approvals.*

III. *To suggest steps to institutionalize improvements in other procedural aspects of the functioning of CDSCO.*

The Committee deliberated on the issues referred to it and decided to proceed as follows:

- Asking the DCGI to provide : 1) statutory provisions under which approvals were provided without clinical trials in India, and 2) its explanation for each case where such approval was provided,
- Obtaining views of the medical profession at large in the country on scientific validity of the statutory provisions to provide approvals without clinical trials in India, for drugs already approved abroad, and
- Obtaining of detailed information from the DCGI about procedures followed by it for granting approval to new drugs and various other statutory obligations.

After obtaining required information from DCGI and eliciting views of the medical professionals across the country in the matter, **the Committee has come to the following conclusions and recommendations:-**

I. Regarding recommendations of the Parliamentary Standing Committee

The Parliamentary Standing Committee Report (Annexure (c)) is a comprehensive and well researched document which has critically analyzed various aspects of the functioning of the CDSCO that are of immense importance for National health. The Expert Committee is of the opinion that the recommendations of the PSC can be grouped into the following three categories:-

a) Items where the Parliamentary Standing Committee has found prima-facie evidence of wrong doing viz., Para 7.31-7.33, 7.39-7.41, 7.42-7.43, 7.48-7.49, 7.50-7.52, 9.1-9.3 of the Parliamentary Standing Committee's report, **the Central Govt. shall institute an enquiry and take appropriate action as deemed fit.**

b) Items which are proposed by the Parliamentary Standing Committee for improvement in the functioning of the CDSCO viz., Para 2.2, 2.19, 2.20, 2.22, 4.5-4.8, 5.11, 6.2, 7.13-7.14, 7.16,

7.27, 7.34, 7.37- 7.38, 7.45-7.47, 8.4, 9.4, 10.2, 11.2, 12.2-12.6, 15.6, 15.9, 15.11, 16.2 of the Parliamentary Standing Committee report, **the action should be initiated by the CDSCO and implementation made with the approval of the Central Government.**

c) Various Policy and Procedural matters viz., Para 2.21, 2.23-3.6-3.7-3.8, 7.15, 7.28-7.29, 7.35-7.36, 7.37, 8.5, 8.7-8.8, 8.10-8.11, 9.5-9.8, 11.2 (part), 13.3, 14.3, 15.4, 15.5 of the Parliamentary Standing Committee report, **require deliberation by a group of professionals/experts and preparation of concrete recommendations for taking appropriate action. The views of the Expert Committee on theses are summarized in Table 1 of this report. The Central Govt. may constitute required committees and working groups as recommended in the Table1 on pages 14-26 of this report.**

II Is there scientific validity of the statutory provision for allowing approval of drugs (already approved in countries abroad) without clinical trial in India?

In general the requirement for bridging study in India should not be by-passed. It is necessary and required to study the effect of genetic and ethnic differences, and differences in diet, environment, BMI etc., both on efficacy and toxicity of the drug, as well as on dosage to be employed. These trials must be carried out in the most effective manner to meet the objectives stated above. However, in special circumstances the requirement to carry out clinical trial in India before approval of import/manufacture of the drugs developed abroad may be justified provided a well defined policy, procedure and mechanism is laid down for implementation of this exception. **This provision shall be applied only in highly selected cases and in a transparent and accountable manner.**

The committee recommends that:

i) A select group of knowledgeable medical professionals should be constituted to:
   a. lay down the principles of determining the circumstances where exemption from clinical trial in India may be considered, and
   b. lay down the procedure that should be adopted while applying this provision

The views and recommendations of the Expert group are detailed on pages 43-51 of this report.

ii) The Committee also recommends that a group of medical professionals and legal experts should be constituted *to revise* the existing Rule 122A (2), Rule 122B (3) (1) and sub-clause (3) of Clause 1 of Schedule Y on the basis of guidelines and procedures evolved by the group constituted vide recommendation no. i) above to provide for approval/licensing of drugs (already approved abroad from recognized countries) without clinical trial in India under exceptional circumstances *only*.

iii) The CDSCO shall take appropriate steps to implement the revised statutory provisions and the guidelines and the procedures laid down by the expert group constituted under recommendation no. i) above. For this purpose the CDSCO shall issue appropriate guidance to the Industry; and the NDACs should lay down SOPs for implementation of the provision providing approval/licensing of drugs in India without clinical trial in India. All future approvals/licensing of drugs without clinical trial in India should be regularly monitored.

iv) All the 38 approvals granted under existing provisions, as identified by the Parliamentary Standing Committee (and CDSCO), *and others, if any*, shall be *re-reviewed* by the respective newly constituted New Drug Advisory Committees (NDAC) as per revised provisions finalized as per iii) above and the SOPs laid down by them. It would be prudent to take any action on already approved/licensed drugs, such as withdrawal of the approval etc., only after such a re-review. The NDACs may ask additional desired information from the manufacturers as deemed necessary. This should be carried out in a time bound fashion.

v) The Committee endorses the recommendations of the Parliamentary Standing Committee to be extra careful in approving the FDCs. The CDSCO should constitute a

Committee of experts to lay down the *principles and procedures* to be adopted for approval of Fixed Dose Combinations (FDCs). The committee shall also review the *existing statutory provisions* for the approval of FDCs by the CDSCO and State Drug Authorities and recommend appropriate changes, if necessary. It should be a thorough and systematic exercise carried out with due diligence.

vi) In India, to by-pass the price regulatory requirement, the use of FDCs is rampant. Once the rationale principles and procedures for approval/licensing of new FDCs are laid down as per v) above, all the existing FDCs may be re-reviewed in the interest of public health at large.

III Measures to bring about systemic improvements in the processing and grant of statutory approvals

IV Steps to institutionalize improvements in other procedural aspects of the functioning of CDSCO.

i) The Expert Committee has found that the Mashelkar Committee in 2003 has already addressed these issues in depth. It found the Mashelkar Committee recommendations to be relevant even today and endorses them fully. Since many of the recommendations of the Mashelkar Committee are already in the process of implementation, a stock checking is required. The Committee has also reviewed the updated website of the CDSCO and finds that there has been a flurry of activity recently, much of which is spurred by the Parliamentary Standing Committee's investigations on the functioning of the CDSCO. Since many of these things are ongoing, **the Committee in its considered opinion feels that a consultant /consultancy shall be commissioned to carry out the following :-**

a) Review of implementation of the Mashelkar Committee report with a view to identify items implemented and those in the pipeline; the likely timeframe of their implementation and decisions on remainder recommendations.

b) Study of international role model/s in the field of drug regulation to identify qualitative changes that Indian regulatory system should adopt in its functioning.

c) Study of the self-assessment report of the CDSCO extracted under 4.3.5 on pages 33-42 of this report and make critical appraisal of it in context of i) and ii) above.

d) Carry out in-depth 'wet' study of the current structure and functioning of the CDSCO, including newly constituted NDACs, employing work-motion studies, individual and group interviews and other techniques of qualitative research

e) On the basis of the above studies the consultant/consultancy shall prepare a blueprint of structure and functioning of the CDSCO, with identification of inputs, implementation programme and outcome of revamping – with clear cut goals and timelines

f) The report so prepared should be critically appraised and accepted by the Government

After acceptance of the report by the Govt., a SFC should be prepared for timely implementation and the same shall be placed before the Parliamentary Standing Committee as a follow up action taken by the Govt.

ii) Simultaneously, in the immediate future the following actions are recommended to be taken:-

a) Implementation of various suggestions made in the last column of Table no.1 on pages 14-26 of this report. To reiterate:

C1) Laying down of the procedure for Fast Track approval where required

C2a) Laying down of qualifications, experience, selection process, powers etc. for the post of DCGI

C2b) Cadre review and harmonization of senior posts of CDSCO with that of DCGI

C3) Establishment of transparency in the decision making processes of CDSCO – posting of necessary information regarding drug approval deliberations/consultation on the website

C4) Guidance and SOPs for Industry and the Committees of the CDSCO for various statutory functions of the CDSCO like granting of license for import/manufacture of new drugs in India, conduct of clinical trials on 'new' drugs etc.

C5) Laying down of Code of conduct for experts and various Committee members etc., and implementation procedures there for

C6) Training of the members of the NDACs in regulatory affairs and streamlining of their functioning

C7) System for continuous monitoring of approved drugs; and their timely withdrawal/issuing of warning/modification of drug information sheet etc., as and where required

C8) Creation/enlargement of data base of experts and streamlining of the system of obtaining expert opinion – maintaining highest degree of objectivity and confidentiality as in review of manuscripts and allocation of benches in the judiciary

C9) Accountability of Experts

C10) Comprehensive review and laying down of policy and procedures for the approval of fixed Dose Combination Drugs (FDCs), both at the Central and State levels

C11) Tackling of the problem of Similar Brand Names

C12) Strengthening of Pharmacovigilance activity

C13) Strengthening of Drug Testing Laboratories both at Central and State levels

b) The committee observes that the function of Drug regulation in the country is split between the Center and the States. This needs to be properly coordinated. The Committee recommends in-depth study of this important aspect of Drug Regulation and taking of suitable steps to streamline the system.

c) Training of the selected professional staff of DCGI/CDSCO at FDA or its equivalent

d) Laying down of standards in terms of Personnel, Space and Equipment requirements for Drug Testing Laboratories to carry out their modernization

iii) In the long run the Committee recommends Creation of the Departments of Clinical Pharmacology in selected Medical Colleges and Schools of Pharmacy in various parts of the country for overall improvement in the climate of Drug regulation in the country as whole.

2. Terms of Reference

The Parliamentary Standing Committee for the Ministry of Health & Family Welfare presented its 59th Report on the functioning of the CDSCO to the Parliament on May 8th, 2012. In order to enable immediate appropriate action, the Government of India, Ministry of Health and Family Welfare, vide letter no X-11035/32/2012 – DFQC dated May 10, 2012 (Annexure (a)) has constituted a committee of following 3 experts:

1. Dr.V.M.Katoch, Secretary, Department of Health Research and DG, ICMR
2. Dr.P.N.Tandon, President, National Brain Research Center, Manesar, Gurgaon
3. Dr.S.S.Agarwal, former Director, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow

With the following terms of reference:

1. To examine the validity of the scientific and statutory basis adopted for approval of new drugs without clinical trials as pointed out in the Report for further appropriate action in the matter.
2. To outline appropriate measures to bring about systemic improvements in the processing and grant of statutory approvals.
3. To suggest steps to institutionalize improvements in other procedural aspects of the functioning of CDSCO.

3. Conduct of Expert committee deliberations

The committee met five times. The first meting was held on June 7, 2012; the second on June 23rd, 2012, third on August 30th, 2012, fourth on October 23rd, 2012 and the fifth on 6th November 2012. The minutes of the meetings are given in Annexure (b).

In the first meeting the committee was briefed about the purpose of constituting the committee and its terms of reference. A copy of the report of the Parliamentary Standing Committee was provided to the members for their information and review (Annexure (c)). The committee asked the DCGI to provide 1) statutory provisions under which approval was provided without clinical trial in India, and 2) its explanation for each case where such approval was provided. The desired information from the DCGI was provided at the second meeting of the committee (Annexure (d)).

On going through the Report of the Parliamentary standing Committee and the material provided by the DCGI the Committee decided to 1) obtain views of the medical profession at large in the country on scientific validity of the statutory provisions to provide approval without clinical trial in India, for drugs already approved abroad, and 2) detailed information from the DCGI about procedures followed by it for granting approval to the listed drugs without clinical trials in India, general procedure of licensing drugs and self appraisal about their deficiencies.

The observations and recommendations of the Parliamentary Standing Committee regarding functioning of the CDSCO were noted by the Expert Committee. It felt that the recommendations of the Parliamentary Standing Committee can be divided into 3 groups, viz., a) Negligent actions of 'CDSCO' requiring Departmental enquiry for fixing of responsibility and taking appropriate action by the Central Government, b) Deficiencies in the functioning of the CDSCO which require remedial steps to be taken by the Ministry so that mistakes and errors do not happen in future and c) Policy and procedural matters for improvement of the functioning of the CDSCO which require deliberation and debate by an appropriate group for further necessary action.

A short questionnaire to elicit the views of the Medical Professionals regarding scientific validity of the provisions in the present Rules about approval of drugs (already

approved and marketed abroad) without clinical trial in Indian subjects was sent to 104 Professors and Heads of the Departments of various Postgraduate Institutes and Medical Colleges across the country. Replies received from 63 medical professionals were reviewed at the third meeting of the Committee. A critical analysis of the responses is annexed with the minutes of the third meeting of the Committee. A digitized copy of all the responses is given the CD annexed (Annexure (e). The replies to the letter sent to the DCGI were received on August 30th (Annexure (f)) which was analyzed and discussed in the meeting on October 23rd, 2012.

The Expert Committee finally met on November 6th, 2012 to finalize the report for submission to Govt. of India. All the information has been critically analyzed by the Committee, deliberated upon and conclusions and recommendations drawn are provided in this report for further necessary action by the Government of India.

4. Observations

4.1. Analysis of the Report of the Parliamentary Standing Committee of Ministry of Health and Family Welfare

The Parliamentary Standing Committee Report (Annexure (c)) is a comprehensive and well researched document which has critically analyzed various aspects of the functioning of the CDSCO that are of immense importance for National health.

The Expert committee on going through the Parliamentary Standing Committee report observes that the recommendations of the Parliamentary Standing Committee can be grouped into the following three categories:

a) Items where the Parliamentary Standing Committee has found prima-facie evidence of wrong doing which require institution of an enquiry and appropriate action by the Central Government.

Para 7.31-7.33, 7.39-7.41, 7.42-7.43, 7.48-7.49, 7.50-7.52, 9.1-9.3

b) Items which are proposed by the Parliamentary Standing Committee for improvement in the functioning of the CDSCO. Actions on these recommendations can be initiated by the CDSCO and implemented with the approval of the Central Government.

Para 2.2, 2.19, 2.20, 2.22, 4.5-4.8, 5.11, 6.2, 7.13-7.14, 7.16, 7.27, 7.34, 7.37-7.38, 7.45-7.47, 8.4, 9.4, 10.2, 11.2, 12.2-12.6, 15.6, 15.9, 15.11, 16.2

c) Various Policy and Procedural matters which may require deliberation with a group of professionals/experts for taking appropriate action.

Para 2.21, 2.23-3.6-3.7-3.8, 7.15, 7.28-7.29, 7.35-7.36, 7.37, 8.5, 8.7-8.8, 8.10-8.11, 9.5-9.8, 11.2 (part), 13.3, 14.3, 15.4, 15.5

The views of the Expert Committee on the issues are summarized in Table No. I.

TABLE I

	OBSERVATIONS OF PARLIAMENTARY STANDING COMMITTEE	SUGGESTONS OF THE EXPERT COMMITTEE
C 1	The optimal utilization of the current staff in the best interest of public is the responsibility of those who run the CDSCO. In a resource-constrained country like India, it is extremely difficult to meet the demands, however, genuine, of all the State entities in full. Hence, prioritization is the key. For example, work relating to an application for Marketing Approval of a New Drug that will be used by millions and thus have an impact on the well being of public at large in India for years to come, is far_more important and urgent than giving permission to foreign company to conduct clinical trials on an untested new patented, monopoly (Para 2.21)	A national regulatory body should not follow the policy of pick & choose. Any criteria for prioritization can be debated. For transparency, the policy of first come –first serve would be more desirable. The decision process should be time bound. In case of emergency/acute need/ national interest, **a fast track mechanism** can be followed. But the manner in which the fast-track should be pursued should be properly prescribed in a Standard Operating Procedure (SOP).

C.2	QUALIFICATION AND POWERS OF DCGI In the absence of any reason for unwillingness on the part of medically qualified persons to join CDSCO, the Committee is of the opinion that emoluments and perquisites may not be the main or only reason. It is noticed that minimum prescribed academic qualifications for the post of DCGI is barely B. Pharm. On the other hand for Deputy Drugs Controller (DDC), the prescribed minimum qualification is post-graduation for medically qualified person. The stumbling block is the requirement that DCGI should have experience in the "manufacture or testing of drugs or enforcement of the provisions of the Drugs and Cosmetic Act for a minimum period of five years." This requirement virtually excludes even highly qualified medical doctors from occupying the post of DCGI. Moreover the rule stipulates that doctors with post-graduation should be either in pharmacology or microbiology only, thus excluding post-graduates, even doctorates (like DM) in a clinical subject. Besides, highly qualified medical doctors may be reluctant to work under and report to a higher officer with lesser qualifications in a technology driven regulatory authority set-up. Unless these concerns are addressed, it would be difficult to get the desperately required medically qualified professionals on the rolls of CDSCO. (Para 2.23) The Committee fails to understand as to how a graduate in pharmacy or	1. The Qualifications, Experience, Selection process as well as the terms/ conditions of service (salary, tenure etc.) of the DCGI are crucial for selection of an appropriate leader for such an important organization. An appropriate committee of experts should be constituted to lay down the qualifications / experience, **job description, powers & responsibilities** etc. for the post of DCGI. The incumbent shall be treated as Head of the Department. The present state is absolutely anomalous. The Selection should be carried out by a high powered Search-cum-Selection committee. It should be empowered to decide on equivalence & negotiate the terms/conditions of service in case of an otherwise appropriate candidate. 2. It may also be worthwhile to do a cadre review of the senior administrative positions in the organization to evolve a harmonious recruitment and promotion plan.

	pharmaceutical chemistry (B. Pharm) is being equated with a medical graduated with MD in Pharmacology or Microbiology. Apart from the obvious anomaly, with rapid progress in pharmaceutical and biopharmaceutical fields, there is urgent need to revise the qualifications and experience as minimum eligibility criteria for appointment as DCGI. The Committee is of the view that it is not very rational to give powers to a graduated in pharmacy, who does not have any clinical or research experience to decide the kinds of drugs that can be prescribed by super specialists in clinical medicine such as those holding DM and PhD qualifications and vast experience in the practice of medicine and even research. (Para 3.6) On a larger plane, the Committee is disillusioned with the qualifications provided in the age old Rules for the head of a crucial authority like CDSCO. The extant Indian system is nowhere in so far as sheer competence and professional qualifications are concerned when compared with countries like USA and UK. There is, therefore, an urgent need to review the qualifications, procedure of selection and appointment, tenure, emoluments, allowances and powers, both administrative and financial of the DCGI. While doing so, the Government may not only rely on the Mashelkar Committee Report which recommended augmented financial powers to DCGI but also take cue from similar mechanisms functioning in some of the developed	

	countries like USA, UK, Canada, etc in order to ensure that only the best professional occupies the onerous responsibility. The Committee should be kept informed of the steps taken to address this issue. (Para 3.7) In the considered opinion of the Committee, there can never be a more opportune time than now, to usher in these changes recommended by it. The post of DCGI is vacant as of now, with an official holding temporary charge. They, therefore, desire that the government should take immediate measures in terms of their instant recommendations to ensure that CDSCO is headed by an eminent and professionally qualified person. (Para 3.8)	
C.3	Unless there is some legal hitch, the Committee is of the view that there is no justification in withholding opinions of experts in matters that affect the safety of patients from public. Consideration should be given to upload all opinions on CDSCO website. (Para 7.15)	The Expert Committee agrees that all regulatory activities should be fully transparent. Internet is a very good medium for this purpose. All decision making steps & activities should be open for public scrutiny. Appropriate mechanisms & procedures for uploading of information (and obtaining of feedback / comments) needs to be put in place. However, to safeguard confidentiality of the experts, the names should not be disclosed.
C.4	The Committee recommends that while approving Phase III clinical trials, the DCGI should ensure that subject to availability of facilities, such trials are spread across the country so as to cover patients from major ethnic backgrounds	The entire process of 'New' drug approval needs to be streamlined. The constitution of INDC & NDACs is a step in the right direction. However, their functioning needs to be strengthened. The selection of the

	and ensure a truly representative sample. Besides, trials should be conducted in well equipped medical colleges and large hospitals with round the clock emergency services to handle unexpected serious side effects and with expertise in research and not in private clinics given the presence of well equipped medical colleges and hospitals in most parts of the country in present times. (Para 7.28) The Committee is of the view that taking into account the size of our population and the enormous diversity of ethnic groups there is an urgent need to increase the minimum number of subjects that ought to be included in Phase III pre-approval clinical trials to determine safety and efficacy of New Drugs before marketing permission is granted. In most western countries the required numbers run into thousands. However since the major objective in India is to determine the applicability or otherwise of the data generated overseas to Indian population, the requirement should be re-assessed and revised as per principles of medical statistics so that major ethnic groups are covered. A corresponding increase in the number of sites so as to ensure a truly representative sample spread should also be laid down in black and white. Furthermore, it should be ensured that sites selected for clinical trials are able to enroll diverse ethnic groups. For domestically discovered drugs, the number of subjects should be revised as well. This can be easily achieved by changes in the Good Clinical Practice	members of these committees, their orientation &training to drug regulation, laying down of SOPs, and monitoring of their activities, all need to be looked into. A panel of experts from various parts of the country should be prepared by the CDSCO with the help of NDACs and continuously updated. The selection of the experts should be well matched, objective and confidential to inspire confidence in the process of evaluation of drug applications. The processes followed by the Medical journals to choose the reviewers/Judiciary to allocate the bench may be consulted. Appropriate guidelines need to be evolved, for both the Industry & the INDC & NDACs. Particular attention needs to be paid to Biologicals (Vaccines, r-DNA products, monoclonals, cell therapy products, gene therapy etc.) and Fixed Dose Combinations where the committee's should be extra vigilant in ensuring Safety & efficacy of the approved therapeutic products. The most crucial role of these committees is to provide approval for the conduct of clinical trials, and evaluation of the results of the pre-clinical and clinical studies. **Appropriate guidelines & SOPs need to be evolved specifically for this purpose.** There is also a need for enhancing the quality of clinical trials. The CDSCO has started some activity in

	(GCP) guidelines. (Para 7.29)	this area, but it needs to be enhanced. While approving Clinical trial protocols and sites for clinical trials greater care is needed to evaluate the qualifications, research experience and past track record of the clinicians selected to conduct the trial. Selection of non-academic sites and investigators should be discouraged.
C.5	The Committee is of the view that many actions by experts listed above are clearly unethical and may be in violation of the Code of Ethics of the Medical Council of India applicable to doctors. Hence the matter should be referred to MCI for necessary follow up and action. In addition, in the case of government-employed doctors, the matter must also be taken up with medical colleges/hospital authorities for suitable action. (Para 7.35) There is sufficient evidence on record to conclude that there is collusive nexus between drug manufacturers, some functionaries of CDSCO and some medical experts. (Para 7.36)	1. As far as the examples cited in the Parliamentary Standing Committee report are concerned, it is a matter of serious concern. After due enquiry of the cases concerned appropriate disciplinary action against the guilty will be fully justified and example setting. 2. However, as a general recommendation disciplining of the professionals could be double edged. The professionals must have full freedom to express their frank & honest opinion (because on this depends the safety & well being of the society).They should not feel threatened in expressing their opinion. On the other hand, they must be accountable if they transgress in their duty. 3. A careful **code of conduct** shall be laid down for all professionals participating in the regulatory processes. They should be asked to sign the contract to ensure fulfilling of their obligations. This should also be required of the members who serve the Ethics Committees.
C.6	On a more fundamental issue the Committee has come to conclusion that when it comes to approving new drugs,	Setting up of the New Drug Advisory Committees brought out as result of the Parliamentary Standing

	too much is left to the absolute discretion of the CDSCO officials. There are no well laid down guidelines for determining whether consultation with experts is required. Thus the decision to seek or not to seek expert opinion on new drugs lies exclusively with the non-medical functionaries of CDSCO leaving the doors wide open to the risk of irrational and incorrect decisions with potential to harm public health apart from the possibility of abuse of arbitrary discretionary power (Para 7.37)	Committee's investigation is a step in the right direction. Their functioning needs to be streamlined as suggested under C4 above.
C.7	It is to be kept in mind that a drug becomes a candidate for withdrawal not only due to serious side effects but also when safer, more efficacious drugs are launched. Unfortunately, no attention is being paid to this issue. The principle should apply to all cases and all drugs need to be evaluated periodically. (Para 8.5) The documents submitted by the Ministry show that even in large developed countries with well developed drug regulation such as US the adverse reactions are not detected by spontaneous reports from doctors in practice. All major side effects were detected in large scale controlled, focused Post-Marketing Phase IV trials involving thousands of patients such as SCOUT on anti-obesity drug sibutramine (now banned) and the RECORD trial on rosiglitazone (now banned). Therefore to expect that any spontaneous reports from medical profession, either in private practice or even institutions (medical colleges, large hospitals) will	Just like approval of 'New' drugs, the process of continuous monitoring of approved drugs & their withdrawal (Pharmacovigilance), should be streamlined. It should be India centric. This may be made a condition for the award of license. A system for the same should be developed. The composite group of NDACs may deliberate and evolve the system. Where the manufacturer fails to carry out the required post-marketing evaluation on its own, the Govt. should have the right to direct the manufacturer to carry out the same. The CDSCO already has initiated Pharmacovigilance programme but its utility/effectiveness so far is questionable. It should examine the need for carrying out Phase IV studies as mandatory for requirement for special situations. There is a need to re-visit the scheme and take mid-course correction as necessary. There should be a system

	pick up hitherto unknown side effects in India is not realistic. There is hardly any alternative but to take immediate cognizance of serious adverse drug reactions reported from countries with well developed and efficient regulatory systems. The health and lives of patients in India cannot be put to risk in the hope of detecting ADRs within the country. (Para 8.7) The Committee feels that since the chances of picking up unknown serious adverse effects of drugs being marketed in the country are remote, therefore CDSCO should keep a close watch on regulatory developments that take place in countries with well developed regulatory systems in the West and take appropriate action in the best interest of the patients. (Para 8.8)	for withdrawal of drugs – with appropriate guidelines & SOPs, so that unsafe drugs are weeded out in a timely fashion. The requirement for generating Indian Specific Post Marketing Reports should be made a condition of license, and so does the reporting of Adverse events any where in the world on a fixed basis. It should be ensured that the manufacturer fulfils all the conditions of the license. There should be an adequate infrastructure and appropriate mechanism within the system to evaluate these reports and take timely action on them. Both the above could be a part of the Pharmacovigilance programme of the CDSCO. Use of the provision of Phase IV clinical trials should be made use of more liberally.
C.8	In most cases, most of these experts whether appointed by CDSCO or DTAB are from Delhi. The following facts reveal this pattern: 1).Rimonabant was referred to a committee of six experts, all from Delhi. 2).Levonorgestrel: Four out of five from Delhi. 3).Letrozole: Four out of five from Delhi. 4).Sibutramine: All five from Delhi. 5).Rosiglitazone: All five from Delhi. A review of membership shows that one	The CDSCO should prepare a broad based database of experts and regularly update it. It should also evolve a mechanism of identifying specific subject experts from the 'net' as is regularly done by the Editors of reputed journals. The assistance of IJMR/National Medical Journal / Pediatrics etc. may be tapped. The selection of experts, obtaining their opinion etc. shall be done in a confidential manner, so that drug firms are not able to influence their opinion.

	expert sat on 5 of the 6 committees. One wonders whether expertise on drugs in confines to Delhi. (Para 8.10)	
C.9	The Committee strongly recommends that with some 330 teaching medical colleges in the country, there are adequate number of knowledge able medical experts with experience who can be requested to give their opinion on the safety and efficacy of drugs. The need is to make such consultations very broad based so as to get diverse opinion. The opinions, once received, can be put in public domain inviting comments. Once the experts know that their opinions will be scrutinized by others, including peers, they would be extra cautious and give credible evidence in support of their recommendation. (Para 8.11)	As mentioned under C.5 above, the Expert committee is in favor of transparency. However, it feels that for opinions to be frank & fair, confidentiality of the source shall be maintained. As far as accountability is concerned, a code of conduct needs to be evolved with appropriate corrective measures.

C.10	FIXED DOSE COMBINATIONS (FDCs) Unfortunately some State Drug Authorities have issued manufacturing licenses for a very large number of FDCs without prior clearance from CDSCO. This is in violation of rules though till May 2002, there was some ambiguity on powers of the State Drug Authorities in this respect. However the end result is that many FDCs in the market have not been tested for efficacy and safety. This can put patients at risk. (Para 9.2) The Committee is of the view the Section 26A is adequate to deal with the problem of irrational and/or FDCs not cleared by CDSCO. There is a need to make the process of approving and banning FDCs more transparent and fair. In general, if an FDC is not approved anywhere in the world, it may not be cleared for use in India unless there is a specific disease or disorder prevalent in India, or a very specific reason backed by scientific evidence and irrefutable data applicable specifically to India that justifies the approval of a particular FDC. The Committee strongly recommends that a clear, transparent policy may be framed for approving FDCs based on scientific principles. (Para 9.8)	Fixed Dose Combinations have become a malaise. They are often resorted to for branding, to beat the price control. The rationality of the combinations is not critically examined. Even where multiple drugs are required for treatment, the FDCs jeopardize dose adjustment of individual medicines. Convenience and profit seem to have overtaken service. There is also lack of clarity in the role of the Center and the States, particularly regarding FDCs. There is a need for comprehensive review of the Policy for FDC. In future, the requirements for clearance of FDCs should be more stringent – requiring empirical clinical trial to show advantage of FDC- before their approval. This job can also be done by the composite of NDACs. Also, see recommendations in the main body of this report.
C.11	SIMILAR BRAND NAMES The Committee strongly recommends that all such cases should be thoroughly reviewed in close coordination with State Drug Authorities. Specific procedures may be framed for approval of brand names. The procedure adopted by the Registrar of Newspapers to avoid	This recommendation may be accepted & implemented.

	duplication may be worth emulating. As a beginning, a data bank of all branded pharmaceutical products along with their ingredients should be uploaded on the CDSCO website and regularly updated. (Para 11.2)	
C.12	PHARMACOVIGILANCE The Committee feels that the conventional system of locating side effects through spontaneous reporting by doctors to either drug companies or drug regulators has been found to be unsatisfactory. The most effective system is by controlled post-marketing Phase IV studies on a very large number of patients. In the past decade, all the major adverse effects that led to banning of drugs were identified in large scale Phase IV trials. The Ministry may wish to consider the possibility of using this format in the country. (Para 13.3)	See the suggestions under C.7 above. This activity needs to be strengthened in a big way.
	UPDATION OF INFORMATION ON MARKETED DRUGS The Committee feels that unless information on marketed drugs is continuously updated, there is risk of irrational or inappropriate use of medicines putting patients at risk. The Committee, therefore, recommends that immediate steps need to be taken to address this issue. The CDSCO should be directed to continuously update monographs based on information from regulatory authorities the world over. (Para 14.3)	One of the recommendations of this Committee is to set up the Departments of Clinical Pharmacology in selected Medical colleges and Schools of Pharmacy. This responsibility may be entrusted to them.

C.13	SPURIOUS/SUB-STANDARD DRUGS A drug can be categorized 'Not of Standard Quality' for a variety of both major and minor technical reasons such as not stating the name of the pharmacopoeia correctly, problem with quality of bonding agent, coloring agent, dissolution time, etc. However, there are other more serious cases, where the active ingredient is significantly less in quantity that can harm patients. Therefore, this problem needs to be addressed with all the seriousness that it deserves both by more rigorous checks in procuring bulk drugs (particularly from developing countries with not so stringent quality checks and export controls) and by in-house quality control by manufacturers or solving the problem in transportation and/or storage at distribution/retail levels.(Para 15.4) By the time a sample is tested, a large number of packs get sold out with undeterminable injury to patients. There is no effective method of recalling unsold stocks lying in the distribution network. This cannot be allowed to go on. (Para 15.5)	The recommendations of the Chidambaram Committee's may be seen. A comprehensive Policy & Action Plan needs to be evolved for tackling the menace of Spurious /Sub-standard drugs. Besides public safety, it is even more important for generation of confidence in Generic drugs so that tomorrow's cost of medical care can be kept under control. This would require strengthening of Drug Testing Laboratories, both at the Center and State levels.
C.14	It is known that retail chemists also stock and sell items other than drugs including chocolates, cold drinks etc. During summer these items are stored in the refrigerator while due to paucity of space temperature-sensitive medicines may be lying outside. When samples are picked up, tested and found to be sub-standard the Stated Drug Authorities blame and prosecute	The suggestion is worth considering. However, it shall not eliminate the responsibility of the retail pharmacy. There should be closer scrutiny by Drug Inspectors.

	manufacturers. Theréfore the Committee recommends that specifically in the case of temperature sensitive products such as insulin, due consideration should be given to the reference samples of the same batch preserved by the manufacturers. (Para 15.7)	
C.15	CONSUMER INFORMATION The Committee is of the firm opinion that accurate information on drugs for patients is absolutely essential to prevent inappropriate use more particularly in children, elderly, during pregnancy and lactation. The Committee recommends that the matter may be looked in to ensure that consumers have the required information to use medicines safely. Given the widespread internet connectivity, it is advisable to devise a system where patients can get unbiased information on drugs at the click of the mouse in any language. (Para 17.3)	This is a good suggestion. An interactive and educative website may be created for consumers.

4.2 Survey of medical professionals of different medical disciplines across the country regarding scientific validity of the statutory provision of approval/licensing of drugs in India without clinical trial in India

A short questionnaire to elicit the views of the Medical Professionals regarding scientific validity of the provisions in the present Rules about approval of drugs (already approved and marketed abroad) without clinical trial in Indian subjects was sent to 104 Professors and Head of the Departments of various Postgraduate Institutes and Medical Colleges across the country. A reply was received from 63 of them. A summary of the responses is tabulated below:

Question/Reply	Yes	No	Don't know	No response
1. Is approval of new drug (approved abroad) without Clinical trial in India scientifically valid?	21 (33.3%) Conditional – in special circumstances only	37 (58.7%) Conditional – except in special circumstances	4 (6.3%)	1 (1.6%)
2. Shall the provisions and Practices continue?	35 (55.6%) Conditional – with specific provisions	23 (36.5%) Conditional – unless well regulated	2 (3.2%)	3 (4.8%)
3. Can expert's advice substitute for clinical trial?	18 (28.6%) Conditional – in special situations only	40 (63.5%) Conditional – expert opinion can not be a substitute for trial	3 (4.8%)	2 (3.2%)
4. Any other observations, Suggestions, recommendations	42 (66.7%) Details in full responses	6 (9.5%)	2 (3.2%)	13 (20.6%)
5. Would you like to be quoted/Stay anonymous?	39 (61.9%)	19 (30.2%)		5 (7.9%)

There are two extreme views about the need for trial in India for drugs already approved in other countries. One says that if the drug is approved by agencies like US- FDA, UK -MHRA (Medicine and Healthcare products Regulatory Agency), European Union's- EMA (European Medicine Agency), TAG (Therapeutic Goods Administration), Australia, PDMA (Pharmaceutical Medical Devices Agency), Japan; it is a waste of time and money to repeat the studies in India (experts do not recommend Russia or China or other countries for parity). According to this view there is hardly any drug which is not effective or unduly toxic in Indian population. Also, the quality of trials in India is not the same as of the above countries. And a bridging-trial in 100 subjects does not provide the desired information about geo-ethnic variation in true sense. Insisting on trial in India deprives Indian public the benefit of new medication as early as possible. Alternate regulatory mechanisms may be evolved to safeguard the health of the Indian people.

According to the other view no drug, under any circumstances, shall be permitted to be marketed in India unless it has undergone clinical trial in India, not a bridging one, but of full scale. This view believes that genetic, ethnic, dietary, environmental and cultural differences are too great to be ignored.

Majority of the responses were in favor of a conditional yes. In general the requirement for bridging study in India should not be by-passed. It is necessary and required to study the effect of genetic and ethnic differences, and differences in diet, environment, BMI etc., both on efficacy and toxicity of the drug, as well as on dosage to be employed. These trials must be carried out in the most effective manner to meet the objectives stated above. However, in special circumstances the requirement to carry out clinical trial in India before approval of import/manufacture of the drugs developed abroad may be relaxed provided a well defined policy, procedure and mechanism is laid down for implementation of this exception.

4.3 Investigation about the current functioning of the CDSCO

The CDSCO was asked to provide a written reply to the following questions:

1. Implementation procedures for legal provisions in the Rule 122A (2) and 122B (3) and Schedule Y clause (1), sub-clause (3)
2. Establishment and functioning of New Drug Advisory Committees (NDACs)
3. New drugs recommended by the NDAC for approval without clinical trial in India – after the submission of the Parliamentary Standing Committee's report
4. Current procedures followed for grant of various statutory approvals
5. Adequacy and inadequacy of current procedures and improvements required
6. How is the provision of clinical trial exemption applied?
    a. Does the manufacturer has to apply for exemption from clinical trial in India
    b. Is every request accepted? If not, how is it decided, and who decides it?
    c. Can clinical trial in India be exempted even without manufacturer asking for it? If yes, how it is decided, under what rule, and who decides it?
    d. In what percentage of exemptions prior expert opinion is obtained? How it is decided to obtain expert opinion or not?
    e. Who decides it?
    f. How many new drugs, under each therapeutic class, are approved every year (on an average)? What is the default mode? Is every application on Form 44 has to be accompanied with clinical trial data from India, or the clinical trial data is submitted only if asked for?
    g. How many requests on an average are received every year for conducting clinical trials in India?
    h. Has any IND cleared by the IND committee been approved for marketing in India so far? If yes, provide total numbers, names and therapeutic class.

The reply received from the CDSCO is placed at Annexure (f).

Salient observations of the Expert Committee are as follows:

4.3.1 Implementation procedures for legal provisions in the Rule 122A (2) and 122B (3) and Schedule Y clause (1), sub-clause (3)

i. Prior to introduction of Schedule Y in 1988 the new drugs were approved under Rule 30A. This did not require any clinical trial in India.

ii. Rules 122A and 122B and Schedule Y were introduced in 1988. CDSCO did not prepare any written guidelines/procedures, office order, SOP for implementation of the provision exempting conduct of clinical trial in India. DCGI applied the provision on case by case basis. Even the Expert opinion was not obtained in all the cases. Between years 2007 and 2010 a total of 47 drugs were approved without clinical trials in India. Out of these expert opinion was called in only 25 cases.

There were no written specific criteria for selection of experts. Nor was there any permanent panel (subject wise) of experts to advise the DCGI.

iii. In March 2011 the Ministry of Health constituted New Drug Advisory Committees. **These committees have also not laid down any criteria or procedures for implementation of the provision of exemption.**

Draft guidelines for approval of new drugs and clinical trials (and not for providing exemption) have now been prepared by the CDSCO. These have been posted on the website (www.csco.nic.in) but have not been finalized yet.

4.3.2 Establishment and functioning of New Drug Advisory Committees (NDACs)

i. While Parliamentary Standing Committee was reviewing the functioning of the CDSCO (Oct-Nov 2010), the Ministry of Health vide order no, X.19029/5/2011-DFQC dated 31.03.2011 appointed 12 "New Drug Advisory Committees" in different therapeutic categories, viz., 1) Oncology and Hematology, 2) Cardiovascular and Renal, 3) Metabolism and Endocrinology, 4) Antimicrobial, Antiparasitic and Antifungal, Antiviral, 5) Reproductive and Urology, 6) Gastroenterology and Hepatology, 7) Dermatology and

Allergy, Immunology, 8)Pulmonary, 9) Neurology and Psychiatry, 10) Analgesics, Anesthetics and Rheumatology, 11) Ophthalmology, and 12) Vaccines.

ii. All the committees have started functioning. A total of 26 meetings have been convened which have considered 305 proposals.

iii. **No specific mention has been made regarding the provision of exemption from clinical trials in India in the terms of reference of these committees.**

iv. **The functioning of the NDACs appears to be open ended and variable** from committee to committee. While it is a positive step in improving the decision making process of approval of new drugs, it leaves a lot to be desired. Besides laying down a transparent procedure, it would be useful to enhance the regulatory skills of the committee members by appropriate exposure to international standards. Also, the CDSCO shall build in an appropriate secretarial support system to assist these committees. The needs for expanding the number of committees to make them more focused and prepare them with the desired expertise, and also the provision of a professionally competent member of the CDSCO as the secretary of each committee deserves to be examined by a professional group.

4.3.3 <u>New drugs recommended by the NDAC for approval without clinical trial in India – after the submission of the Parliamentary Standing Committee's report</u>

i. So far NDACs have recommended 15 new drugs for approval without clinical trial data in Indian patients. Out of these 9 have been approved.

ii. **Although no SOP has been drawn for these recommendations and approvals, the minutes of the Committees have recorded the indication, reasons presented by the firms for waiver of local CT, Opinions of experts, and the Recommendations of the Committee regarding exemption. There is scope for further improvement and greater vigilance. The criteria of availability of the alternatives and pharmacoeconomic implications also need to be considered by the committees.**

iii. The drugs approved are Degarelix, Abiraterone acetate, Plerixafor, Eribulin mesylate, Mucotrol, Crizotinib, Etravirine, Nelarbine, Fingolimod, Tolvaptan, Rilpivirine, Vemurafenib, Lipiodol UF. Cabazitaxel and Panitumumab.

4.3.4 Current procedures followed for grant of various statutory approvals

The CDSCO is responsible for granting following statutory approvals:

i. Grant of approval to manufacture and / or import new drugs including vaccines and bio-therapeutic products after examining their safety and efficacy.

ii. Grant of permission to conduct clinical trials.

iii. Approval of the licenses to manufacture certain category of drugs as Central License Approving Authority (CLAA) i.e. blood Banks, Large Volume Parenterals, Vaccines/Sera, r-DNA derived products, in-vitro diagnostic kits for detection of HIV1&2, HCV and HBsAg and notified medical devices.

iv. Import of drugs in the country.

4.3.4.1 Registration of foreign manufacturers whose products are to be imported into the country, in respect f drug formulations / Bulk drugs, Medical Devices, Blood Products.

4.3.4.2 Grant of import licenses

v. Grant of test licenses for import of drugs for the purpose of examination, test and analysis

vi. Grant of licenses to import drugs by Government Hospitals or Medical Institutes for the use of their patients.

At present the procedures followed for grant of various statutory approvals revolve around the provisions of various clauses and sub-clauses of single Rule i.e. Rule 122. There are no prescribed Guidances and Procedures for implementation of the same. It is also not clear whether all these functions are included in the terms of reference of the NDACs or not. It would be advisable to hold brain-storming workshops for each of the functions of the CDSCO, including international participation, at the end of which working groups should be constituted to lay down all the details in black and white (SOPs) so that international standards are achieved.

4.3.5 Adequacy and inadequacy of current procedures

A self appraisal of the adequacy/inadequacy of the current procedures provided by the CDSCO is included on pages 61 to 74 of their reply placed at Annexure (f). Since this is one of the major terms of reference for this committee, the relevant portions of the felt needs from the reply of CDSCO are extracted below:

a. Inadequate or weak Drug Control infrastructure

The functions of CDSCO are derived from Drugs and Cosmetic Act 1940 and Drugs and Cosmetic Rules 1945 as amended from time to time. The objective of the Act is to regulate the import, manufacture, distribution and sale of drugs and cosmetics in the country. The definition of drugs under the Drugs & Cosmetics Act includes a variety of therapeutic products, medical devices and diagnostics. Therefore, multidisciplinary expertise should be available with CDSCO to discharge the functions assigned to it under the Drugs & Cosmetics Act in an efficient manner to safeguard and enhance public health by assuring the safety, efficacy and quality of drugs, medical devices and cosmetics.

The approval process for new drugs includes expertise of various scientific fields like Pharmaceutics, Pharmaceutical chemistry, Biochemistry, Pharmacology, toxicology and various medical specialties. From early days the CDSCO has been without medical specialists. Therefore, CDSCO was engaging consultation of outside experts for evaluation of safety & efficacy of drugs. However, it is considered necessary to ensure that such consultations are managed efficiently, within well-defined time frame manner. The present cumbersome system of providing TA/DA to the outside experts is a major constraint in getting external expertise. It further requires a well-supported secretarial assistance.

Resource in terms of manpower and other infrastructural facilities like working area, archiving, maintaining software based data bank etc. are grossly inadequate for effective functioning in various multi disciplinary activities of CDSCO.

Currently, CDSCO HQ is managed only with 6 Dy. Drugs Controller (I), 5 Asstt. Drugs Controller (I), who are assisted by 9Technical Officer, 30Drugs inspectors, 55 Technical Data Associates (Contractual) and 1 Legal Consultant. These officials have to handle each year the workload of approx. 15,000 applications for various statutory approvals, over 200 meetings, attending approx. 10,000 public / industry representatives, around 150 court cases, apart from handling of issues raised by the Parliamentary Standing Committee, Parliament Questions, Information under RTI, Interministerial correspondences etc.

There is a weak administrative infrastructure with respect to handling of administrative activities, like service matters, budgets, recruitment, procurement matters etc. In administrative matter DCG(I) is assisted by one Dy. Director, Administration who is also handling administrative matter of one more subordinate office of DGHS.

The administrative and financial power assigned to the head of the CDSCO, i.e. DCG(I) are not equivalent to the head of any of the comparable organizations like NICD, NIHFW etc. as well as similarly placed international bodies like US-FDA, MHRA,UK, TGA-Australia etc.

The Mashelkar Committee in year 2003 had recommended for providing financial power to the DCGI as is available with CSIR and ICMR. Since constitution of twelve NDACs, the applications of new drugs and clinical trials are evaluated by these committees.

It may also be mentioned that annually approximately 2000 applications of new drugs of various categories including new drug substance, new claims viz. indication, dosage form, route of administration etc., approved new drugs, fixed dose combinations, vaccine, recombinant products etc. are received and processed by the existing staff strength of the Division of New Drugs and Biologicals Division. Apart from such applications for regulatory approvals, issues like replying to queries under Right to information Act, parliament questions and parliamentary standing committees related matters, court cases, clinical trial inspections, amendments of rules and regulations, preparing guidelines and guidance documents etc. related to new drugs are also handled by the same division. It is pertinent to mention here that the manpower and infrastructure/ facility of CDSCO which deals with the various categories of new drugs including IND, New chemical entity etc. is substantially inadequate.

Earlier several committees like HATTI committee, Mashelkar Committee etc. have strongly recommended that CDSCO should have qualified and experienced scientists in different areas viz., Pharmaceutical, Pharmacology, Toxicology, Clinical as well as legal and administrative staff in order to have effective system of drug evaluation in the country.

In order to have an efficient drug regulatory system, CDSCO HQ should have following divisions each headed by an officer of the level of JDC(I) [Director, Govt. of India]:-

1. Regulatory Affairs & Enforcement
2. New Drugs
3. Clinical Trials
4. Biological & Biotechnology Products
5. Monitoring of Clinical Trials
6. Pharmacovigilance
7. Medical Devices and Diagnostics
8. Cosmetics
9. Organizational Services
10. Training and Empowerment
11. Imports
12. Quality Control Affairs
13. Legal Affairs

14. Consumer affairs and pre-screening of applications

Each of these divisions should have several sections as under as per the scope of the activities of the respective division:

1. Division for Regulatory Affairs & Enforcement
   - I. Drug Technical Advisory Board &Drug Consultative Committee issues
   - II. Legislation Amendments
   - III. Zonal / sub-Zonal and State Offices
   - IV. Inspections, investigations and prosecutions
   - V. Guidelines and directives
   - VI. Interstate issues , Spurious /substandard drugs
   - VII. Drug recalls
   - VIII. Regulation of promotion of medicines & product information
2. Division For New Drugs
   - I. Evaluation of new drug substances developed in other countries
   - II. Evaluation of INDs
   - III. Evaluation of new claims of already approved drugs
   - IV. Evaluation of FDCs
   - V. Evaluation of approved new drugs
   - VI. Non-clinical safety & efficacy evaluation
   - VII. Clinical safety & efficacy evaluation
   - VIII. Pharmaceutical & quality evaluation
   - IX. Package insert, promotional literature approvals
   - X. Veterinary new drugs
   - XI. Issues related to border-line products viz. neutraceuticals
   - XII. Screening of existent drug formulations
3. Division of Clinical Trials
   - I Global Clinical Trials approvals
   - II Bioequivalence study approvals for Export
   - III Biostatistics
4. Division for Biological & Biotechnology Products
   - I. Vaccines & Sera (human & veterinary)
   - II. Blood & blood products
   - III. Recombinant and other biotechnology products
5. Division for Monitoring of Clinical Trials
   - I. Regulatory inspections of clinical trial sites, sponsor sites and ethics committees

II. Regulation and registration of investigation sites, ethics committees & investigators

III. Review of reports of serious adverse events in clinical trials

IV. Issues related to compensation in trial related injury or death

6. Division for Pharmacovigilance

I. Evaluation of Periodic Safety Update Reports

II. Safety monitoring and banning / restriction on use of drugs and devices

III. Pharmacovigilance programme of India

7. Division for Medical Devices and Diagnostics

I. Devices' evaluation

II. Diagnostics' evaluation

III. Licensing & enforcement

IV. Imports

8. Division for Cosmetics

I. Registration of cosmetics

II. Quality monitoring of cosmetics

9. Division for Organizational Services

I. Administrative matters

II. Interministerial Correspondences

III. Vigilance

IV. Accounts

V. Planning & Finance

VI. Information technology

10. Division for Training and Empowerment

I. Planning & forecasting

II. Training

III. Evaluation and impact assessment

11. Division for Imports

I. Registration of overseas manufacturing premises for drugs

II. Overseas inspections

III. Managing Port offices

IV. Import Licenses

V. Quality monitoring of imported products

12. Division for Quality Control Affairs

I. Central Licensing

II. Managing Central drug laboratories

III. Monitoring of State and private laboratories

IV. Audits (including proficiency testing) and accreditations

V. Drug standards
VI. International cooperation
VII. Exports
13. Division for Legal Affairs
I. Legal Affairs &Court cases
II. Parliament affairs
III. Public complaints
IV. Implementation of Drugs and Magic Remedies (DMR) Act.
14. Division for Consumer affairs and Pre-screening of applications
I Consumer information (healthcare)
II Press, public relations & publications
III Website
IV Licensee's information
V Pre- screening of various applications for statutory approvals
VI Receiving and Dispatch

For every three to four sections (depending upon workload) there should be one Deputy Drugs Controller who shall be supported by two Assistant Drugs Controllers, four to six Technical Officers / Drugs Inspector along with supportive staff like Assistant Drug Inspector / Technical Data Associate, Data Entry Operators, Office Assistants etc.

Therefore, considering the present workload in CDSCO HQ, the DCG(I) should be assisted by 14 JDC(i), 22 DDC(I), 44ADC(I), 132Technical officers / Drugs Inspector, 132 Assistant Drug Inspector / Technical Data Associate and other supporting staff apart from well-equipped administrative infrastructure. In order to ensure a substantially enhanced evaluation capability in CDSCO, full time experts in various fields like Pharmacology, Toxicology, Medical specialties, Bio-statistics, Biotechnology, Biomedical engineering etc. are also needed to be provided urgently.

b. Inadequate training of the regulatory personnel

The abilities and commitment of regulatory personnel is most important which determine the regulatory authority's effectiveness and efficiency. The knowledge and scientific skills of regulatory officials must be continuously updated to keep pace with the current regulatory requirements in various multi-disciplinary activities including development and discovery of new medicines. Therefore it is essential to offer regular training and practical experience to the regulatory officials in their respective fields. It is common practice in well-defined regulatory agencies abroad to organize regular training and continuing education programs for their staff. There is an urgent need to put in place such system of providing training and ongoing professional updates regularly to the regulatory officials of CDSCO which is not there at present.

c. Inadequate access to sources of information

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CDSCO officers and other professionals should have access to the latest information related to the advancement in scientific as well as regulatory activities at global level through literature search facilities, Newsletter, Medical journals etc. Presently there is a need of such system which will help in efficient review of various applications for statutory approvals including New drugs, clinical trials etc. as well as updating of the knowledge and skills of regulatory officials.

d. Review of Regulatory provisions and guidelines for approval of New drugs

As regards to the current regulatory provisions, for approval of new drugs and clinical trials it may be mentioned that Schedule Y under Drugs and cosmetics rules is reasonably well drafted regulation specifying requirements and guidelines for approval of new drugs and clinical trials. However, further detailed provisions with respect to certain categories of new drugs approval viz. requirements for approval of New claims viz. new indication, new route of administration, new dosage form of approved drug and detailed requirements for approval of FDCs are required to be specified in the schedule in order to ensure a scientific and consistent review process for approval of such categories of new drugs. Although schedule Y and rule 122A, 122B of drugs and cosmetics rules specify certain conditions under which new drugs are approved without local clinical trials, a detailed guidelines need to be laid down in this regard. Various terminologies like public interest, serious life threatening diseases, disease of special relevance to the Indian health scenario etc. mentioned in regulatory provisions for relaxation of toxicological and clinical data requirements, need to be clearly defined and elaborated in the guidelines. Further guidelines are also required to be prepared specifying detailed requirements, procedures for various manufacturing and quality control related issues.

In order to strengthen the review process of new drug application, following measures have been taken:

1. Twelve New Drug Advisory Committees (NDAC) consisting of experts/specialists from various reputed government medical colleges and institutions across the country have been constituted with the approval of the Ministry of Health & Family Welfare. Applications for global clinical trial, new drugs and Fixed Dose Combinations (FDCs) going to be introduced for the first time in the country are now being evaluated by these committees.

2. A System of Pre-screening to determine the acceptability of different categories of new drug applications at the time of submission has been introduced.

3. Format of Common Technical Documents for submission of applications for marketing authorization of Biological products have already been introduced.

4. Draft guidelines for approval of new drugs and clinical trials have been prepared and posted in the CDSCO website. The guidelines, however, are yet to be finalized.

5. Draft guidelines for format of Common Technical Documents for submission of new drug applications (other than Biological) have been prepared and posted in CDSCO website. The guidelines, however, are yet to be finalized.

6. In April, 2008 there were only 64 persons in position in CDSCO HQ and zonal, sub-zonal and port offices to carry out various responsibilities of drug regulation under the Drugs and Cosmetics Rules. The Ministry of Health and Family Welfare therefore took initiatives to strengthen the manpower at CDSCO to cope up with the work load which has increased manifold during the last few years.216 new posts of different levels in the CDSCO were sanctioned in the year 2008 and 2009. These posts are being filled through the UPSC. At present 119 regular personnel are in position. The strength of CDSCO would rise to 327 after filling up these posts. The Government also sanctioned the appointment of 250 contractual staff to assist the organization in coping with the work load at the Head quarter as well as zonal offices.

7. It has been further proposed for the creation of 1045 additional posts in the CDSCO on regular basis to strengthen the Indian Drug Regulatory System. The proposal has been recommended by the Working Group on Drug and Food Regulation for the 12th Five Year Plan under the Chairmanship of Secretary, Ministry of Health and Family Welfare. It has been proposed to induct 64 specialists to handle various technical matters related to approval of new drugs, medical devices etc. These posts include persons from medical specialties like clinical pharmacologists, biochemist, immunologist, toxicologist, oncologist, cardiologist, gynecologist and specialists in other therapeutic categories.

e. Review of Regulatory provisions and guidelines for approval of Clinical trials

As regards the regulation of clinical trials, currently there are no requirements for registration of Ethics Committees, CROs / Sponsors and investigators / investigation sites. In order to ensure that clinical trials are conducted in the country in scientific and ethical manner, it is considered necessary to have regulatory provisions for registration of various stakeholders involved in clinical trials as mentioned above. Further, clear regulatory provisions mentioning authority of CDSCO for inspection of sites of investigator, sponsor, CRO, ethics committee should be incorporated in the Drugs & Cosmetics Rules. Similarly, detail regulatory provisions and guidelines is required to be prepared for handling of reports of serious adverse events including reports of deaths in clinical trials submitted to CDSCO by the sponsor / CROs.

In order to strengthen the regulation of clinical trials various measures have already been taken which are as under:

- 12 New Drug Advisory Committees (NDAC) consisting of experts from the government medical colleges, institutes from all over the country have been constituted to assist CDSCO in evaluation of clinical trial proposals.
- All IND applications are evaluated by the IND committees.
- Registration of clinical trial in ICMR registry has been made mandatory since 15.6.2009.
- Every approval / permission for conducting clinical trials now includes a condition that in case of study related injury or death, applicant will provide complete medical care as well as compensation for the injury or death and statement to this effect should be incorporated in the informed consent form.

Further in case of such injury or death the details of compensation provided should be intimated to the office of DCG (I).

➢ Guidelines for conducting Clinical Trial inspection of site and sponsor /CROs have been prepared and posted on CDSCO website.

Further, following amendments in Drugs & Cosmetics rules in respect of regulation of clinical trials are under various stages of processing. In order to ensure well protection of safety, rights and well being of trial subjects, these amendments are required to be finalized in a timely manner:

- Draft rules for incorporation / amendments of following proposals in Drugs and Cosmetics Rules related to clinical trials have been notified on 18.11.2011 vide G.S.R No. 821(E):
- To incorporate a new rule for provisions for payment of compensation in case of clinical trial related injury or death
- To incorporate New Appendix in Schedule-Y specifying the detail procedures and methods of providing compensation.
- To amend the informed consent format to capture the details of address, qualification and occupation, and annual income of the subject.
- To amend patient information sheet to mention that the applicant will provide compensation in case of trial related injury or death.
- To expand responsibilities of Ethics Committees to ensure that committees review and recommend for compensation in Clinical Trial related injury.
- To expand responsibilities of investigators to ensure that compensation is provided in case of in trial related injuries on death.
- To expand the responsibilities of Sponsor to ensure that they provide compensation in case of trial injury or death and details of compensation paid is submitted to CDSCO within 90 days.

A large no. of comments on the above draft rules were received from various stakeholders which had been examined for consideration for notification of final rules.

1. Draft rules for incorporation / amendments of following proposals have been notified on 17.07.2012 vide G.S.R No. 572(E) to incorporate Rule to have authority for clinical trial inspection by CDSCO assisted by concerned state authority and to take administrative actions like restriction of investigator, sponsor/CRO to conduct future clinical trial, in case of non-compliance.

2. Draft rules for incorporation of following proposals have been notified on 17.07.2012 vide G.S.R No. 573(E) to incorporate Rules and Schedule Y-1 specifying requirements and guidelines for registration of Ethics Committee.

3. Following proposals to amend the provisions of Drugs and Cosmetics Rules related to clinical trials have been considered and approved by DTAB in its 60th meeting held on 10.10.11 and are under consideration for notification of draft Rules:

- To incorporate amendment in Schedule-Y specifying that clinical trials are required to be conducted at sites which have their own Ethics Committee.
- To amend the toxicity study data requirements for further submission of approval of clinical trial / new drugs to make it harmonized with the international guidelines.

In addition to above amendments in regulatory provisions for Clinical trials, there is a need for putting a system of Registration of investigation sites and GCP certification for Investigators to ensure GCP compliance by the Investigators and the trials are conducted in sites which have adequate medical and other facilities required for clinical trials.

f. Inadequate Working space:

Adequate working space with suitable support system for officials is required to discharge duties assigned to them efficiently. Currently, CDSCO HQ is under severe shortage of working space for its officials. Immediate attention is required to be put to find solution to this problem.

g. Non- existence of data bank:

Drug being in the concurrent list of constitution, it is regulated by both State and Central Governments. While control on manufacture is primarily is the responsibility of State Licensing Authority, import of drug is regulated by CDSCO. Presently there are 35 Drug Control authorities of State / UT. There are more than 10,000 manufacturers and more than 6.0 lac sale outlets (whole sale as well as retail). It is estimated that the number of brands available in India is around 80,000.However, there is no central data bank of number of licensed premises and products / drug formulations available in the country. In order to address, various issues related to quality of drugs, it is very much essential to have a databank (software based) of manufacturing licenses, sale licenses, brands available etc. at central level which should be linked to various States / stakeholders to enable continuous updating of the data.

So far as data bank of various statutory approvals / licenses by CDSCO is concerned, it may be mentioned that presently the infrastructure and manpower available is grossly inadequate to maintain such databank. Continuously, CDSCO faces difficulties in retrieval of various data to address the issues raised by various stake holders including parliamentary standing committee, parliament, RTI, media etc. There is an urgent need to develop software based facility to maintain databank with adequate manpower.

h. Inadequate archiving facility:

In order to address the issues raised technically, legally and politically related to functioning of CDSCO access to earlier documents is essential. Annually, CDSCO grants various statutory approvals / licenses which amounts to around 20000 approvals. The dossiers of new drugs including recombinant products,

biological etc are submitted along with the applications which are voluminous. Currently, archiving facility for CDSCO is grossly inadequate. The files and documents are stored in different locations like Sadiq Nagar, IPC Ghaziabad etc. In order to store properly such bulky documents and files, professionally managed archiving facility is very much required. Therefore, there is an urgent need to develop such archiving facility for CDSCO. The facility should be electronic as well as physical archiving facilities. This would also help the CDSCO to qualify the needs of up-keeping the data for purpose of ensuring the confidentiality."

(Extracted from the reply of CDSCO given at Annexure (f))

The Expert Committee feels that overall the need for structural and functional reorganization of the CDSCO is fully justified. However, instead of making another set of recommendations the committee strongly feels that the job of preparing a detailed blueprint shall be entrusted to a professional consultancy well versed in the field of drug regulation as suggested on page 51 of this report.

4.3.6 How is the provision of clinical trial exemption applied?

The CDSCO does not have a laid down procedure for the purpose. In the past it used to be executive decision as per provisions of the Rules 122A (2), Rule 122B (3) (1) and sub-clause (3) of Clause 1 of Schedule Y. At present, the NDAC's examine the cases and decide whether to grant exemption from clinical trial to be given or not. In the past one year, the NDAC's also have recommended exemption in 15 cases. But there is no laid down procedure or guidelines for it.

5. Conclusions and Recommendations

I Is there scientific validity of the statutory provision for allowing approval of drugs (already approved in countries abroad) without clinical trial in India?

Overwhelming response of the selected medical professional community to this question was "conditional Yes". The committee agrees with the same. However, this provision shall be applied only in highly selected cases and in a transparent and accountable manner. The committee recommends:

i) A select group should be constituted of knowledgeable medical professionals to:

a. lay down the principles of determining the circumstances where such provision may apply, and

b. lay down the procedure that should be adopted while applying this provision

A list of names that can be considered for constituting this group is given in Annexure (g). The issues and considerations in the view of this Expert Committee, that the above group should consider, are as follows:

- *In general the requirement for bridging study in India should not be by-passed. It is necessary and required to study the effect of genetic and ethnic differences, and differences in diet, environment, BMI etc., both on efficacy and toxicity of the drug, as well as on dosage to be employed. However, the clinical trial should be well conducted. Just a ritual serves no purpose. A group should look into defining the requirements for such a trial. The group may also look into the utility of generating Pharmacokinetic (PK) data in different geo-ethnic groups in India and strict Pharmacovigilance for the newly introduced drugs for 3-5 years, either in addition to the clinical trial or in lieu of it.*
- *In special situations (both disease and indication) this requirement may be waived. A provision for it is scientifically justified but it should be used with utmost caution and in a transparent way (recording the reasons for the decision). Some examples are:*

- *Anticancer drugs – where all other treatment has been exhausted–for terminally ill patients, where conducting a trial could be time consuming and difficult.*
- *Drugs for infections – resistant bacterial (NDM1), viral (H1N1), AIDS, MDR/XDR tuberculosis etc. where no other drug is available*
- *Orphan diseases such as genetic disorders which are rare and not enough patients may be available to carry out a meaningful trial. This may include uncommon autoimmune (Multiple sclerosis) and other disorders as well.*
- *Vaccines for impending epidemics where the vaccine is urgently required – JE, Polio, H1N1*

- *This list should be well defined, rational and periodically updated. It should not be at the subjective discretion of the licensing authority. While the requirement for trial in India in such special situations may be waived but there should be no abridgment of data required to evaluate the safety and efficacy of the drug.*
- *There should be a well defined procedure for such approvals – with provision of fast tracking. Initial approval may be given for 1-2 years of marketing, with specific requirement of prescription by qualified specialists, ban on OTC (over-the-counter) sale, submission of post-marketing surveillance data/conduct of Phase IV study and others as deemed fit.*
- *The Pharma Company should specifically apply for waiver on a prescribed Performa with all the necessary information as laid down for the purpose. The NDAC if satisfied shall constitute a specific expert group to evaluate the information and make recommendation. All decisions taken should be periodically reviewed.*
- *The provision of exemption may be restricted to drugs approved by selected agencies like US FDA, UK MHRA (Medicine and Healthcare products Regulatory Agency), European Union's EMA (European Medicine Agency), TGA (Therapeutic Goods Administration), Australia, and PDMA*

(Pharmaceutical . Medical Devices Agency), Japan. A provision for reciprocity may be explored.

- *Availability of alternatives, or their lack may be point for consideration*
- *Alternate regulatory mechanisms may be evolved to safeguard health protection.*

For the purposes of review by experts following procedure may be adopted:-

- A database of experts shall be created from all over India from which the most appropriate experts for the particular drug application may be identified – as is customarily done by the Editors of most reputed Journals. Expertise of the Indian J Medical Research editorial staff may be sought for the purpose. Alternately the process followed by the judiciary to allocate bench for hearing he petitions may be consulted. The process should be as objective as possible to inspire confidence in the system.
- The entire process of obtaining expert opinion shall be kept strictly confidential. The procedures adopted by the UPSC may be considered.
- A code of conduct for the Experts shall be laid down, which should be strictly observed by the Experts.

ii) **A group of medical professionals and legal experts shall be constituted to <u>revise</u> the existing Rule 122A (2), Rule 122B (3) (1) and sub-clause (3) of Clause 1 of Schedule Y on the basis of guidelines and procedures evolved by the group constituted vide recommendation no. 1 above to provide for approval/licensing of drugs (already approved abroad from recognized countries) in India without clinical trial in India under exceptional circumstances <u>only</u>.**

iii) **The CDSCO shall take appropriate steps to implement the revised statutory provisions and the guidelines and the procedures laid down by the expert group constituted under** recommendation no. 1 above. For this purpose the CDSCO shall issue appropriate guidance to the Industry and the NDACs should lay down SOPs for implementation of the provision of providing approval/licensing of drugs in India without clinical trial in

India. All future approvals/licensing of drugs without clinical trial in India should be regularly monitored.

iv) All the 38 approvals granted under existing provisions, as identified by the Parliamentary Standing Committee (and CDSCO), *and also others, if any*, shall be re-reviewed by the respective newly constituted New Drug Advisory Committees as per revised provisions and the SOPs laid down by them. It would be prudent to take any action on already approved/licensed drugs, such as withdrawal of the approval etc., only after such a re-review. The NDACs may ask additional desired information from the manufacturers as deemed necessary. This should be carried out in a time bound fashion.

The NDAC while re-reviewing the above drugs may consider the following:

- *Whether the drug under consideration fulfills the requirements of exemption from clinical trial in India - at the time of approval and now.*
- *Adequacy of clinical data from the country of origin/other countries with recognized regulatory drug authority regarding the safety and efficacy of the drug, including the reports of post-marketing surveillance, published or otherwise.*
- *Approved alternatives available, if any.*
- *Evidence of any ethnic variability or genetically determined variation in effects from published reports – The Pharma Company may be asked to provide the required information.*
- *Experience with the use of drug in India since approval. The manufacturer shall provide the data regarding sales in India and any information known to it/or reported to it about Adverse Drug Reactions to the drug from India or globally.*
- *Need for generating any additional data at this stage*
- *Any other*

On the basis of the review the NDAC should recommend whether:-

i) approval granted earlier shall be withdrawn following due process

ii) additional information regarding safety and efficacy be generated in the Indian subjects, and the procedure to be adopted for the purpose

iii) the approval of the drug shall continue, with or without additional conditions.

with reasons to be recorded in either case.

The final decision taken with respect to all the 38 drugs shall be brought to the kind knowledge of the Parliamentary Standing committee.

Approval of Fixed dose combinations without clinical trial data

The Parliamentary Standing Committee has rightly pointed out the malady of indiscriminate approval of Fixed Dose combinations by the CDSCO and even State Drug Authorities approval of various FDCs without prior clearance from CDSCO. The case in point is the example of acelofenac with drotaverine. These combinations without rationale and necessary empirical data do imperil the health of the people.

v) **The Committee endorses the recommendations of the Parliamentary Standing Committee to be extra careful in approving the FDCs. The CDSCO should constitute a Committee of experts to lay down the *principles and procedures* to be adopted for approval of FDCs. The committee shall also review the *existing statutory provisions* for the approval of FDCs by the CDSCO and State Drug Authorities and recommend appropriate changes, if necessary. It should be a thorough and systematic exercise carried out with due diligence.**

vi) **In India, to by-pass the price regulatory requirement, the use of FDCs is rampant. Once the rationale principles and procedures for approval/licensing of new FDCs are laid down, all the existing FDCs may be re-reviewed in the interest of public health at large.**

II *Measures to bring about systemic improvements in the processing and grant of statutory approvals*

III *Steps to institutionalize improvements in other procedural aspects of the functioning of CDSCO.*

1. **The Expert Committee has found that the Mashelkar Committee in 2003 has already addressed these issues in depth.** It found the Mashelkar Committee recommendations to be relevant even today and endorses them fully. Since many of the recommendations of the Mashelkar Committee are already in the process of implementation, a stock checking is required. The Committee has also reviewed the updated website of the CDSCO and finds that there has been a flurry of activity recently, much of which is spurred by the Parliamentary Standing Committee's investigations on the functioning of the CDSCO. Since many of these things are ongoing, the Committee in its considered opinion feels that a consultant /consultancy shall be commissioned to carry out the following:-

a) Review of implementation of the Mashelkar Committee report with a view to identify items implemented and those in the pipeline; the likely timeframe of their implementation and decisions on remainder recommendations.

b) Study of international role model/s in the field of drug regulation to identify qualitative changes that Indian regulatory system should adopt in its functioning.

c) Study of the self-assessment report of the CDSCO extracted under 4.3.5 on pages 34-43 of this report and make critical appraisal of it in context of i) and ii) above.

d) Carry out in-depth 'wet' study of the current structure and functioning of the CDSCO, including newly constituted NDACs, employing work-motion studies, individual and group interviews and other techniques of qualitative research

e) On the basis of the above studies the consultant/consultancy shall prepare a blueprint of structure and functioning of the CDSCO, with identification of inputs, implementation programme and outcome of revamping – with clear cut goals and timelines

f) The report so prepared should be critically appraised and accepted by the Government

After acceptance of the report by the Govt., a SFC should be prepared for timely implementation and the same shall be placed before the Parliamentary Standing Committee as a follow up action taken by the Govt.

2. **Simultaneously, in the immediate future the following actions are required to be taken:-**

Implementation of the recommendations under 4.1 a), b) and c) on page 13 of this report. This includes the execution of various suggestions made in the last column of Table no.1.

To reiterate:

a) The Central Govt. should set up enquiry committee/s to investigate the wrongdoings identified by the Parliamentary Standing Committee and take appropriate action for the following:-

Para 7.31-7.33, 7.39-7.41, 7.42-7.43, 7.48-7.49, 7.50-7.52, 9.1-9.3

b) The CDSCO should initiate action to improve the structure/function of its organization with the approval and financial sanction from the Central Govt. for the following:-

Para 2.2, 2.19, 2.20, 2.22, 4.5-4.8, 5.11, 6.2, 7.13-7.14, 7.16, 7.27, 7.34, 7.37-7.38, 7.45-7.47, 8.4, 9.4, 10.2, 11.2, 12.2-12.6, 15.6, 15.9, 15.11, 16.2

c) The Central Govt. shall Constitute Committees/Working groups for obtaining detailed recommendations and their implementation for the following issues:-

C1) Laying down of the procedure for Fast Track approval where required

C2a) Laying down of qualifications, experience, selection process, powers etc. for the post of DCGI

C2b) Cadre review and harmonization of senior posts of CDSCO with that of DCGI

C3) Establishment of transparency in the decision making processes of CDSCO – posting of necessary information regarding drug approval deliberations/consultation on the website

C4) Guidance and SOPs for Industry and the Committees of the CDSCO for various statutory functions of the CDSCO like granting of license for import/manufacture of new drugs in India, conduct of clinical trials on 'new' drugs etc.

C5) Laying down of Code of conduct for experts and various Committee members etc., and implementation procedures there for

C6) Training of the members of the NDACs in regulatory affairs and streamlining of their functioning

C7) System for continuous monitoring of approved drugs; and their timely withdrawal/issuing of warning/modification of drug information sheet etc., as and where required

C8) Creation/enlargement of data base of experts and streamlining of the system of obtaining expert opinion – maintaining highest degree of objectivity and confidentiality as in review of manuscripts and allocation of benches in the judiciary

C9) Accountability of Experts

C10) Comprehensive review and laying down of policy and procedures for the approval of fixed Dose Combination Drugs (FDCs), both at the Central and State levels

C11) Tackling of the problem of Similar Brand Names

C12) Strengthening of Pharmacovigilance activity

C13) Strengthening of Drug Testing Laboratories both at Central and State levels

3. The committee observes that the function of Drug regulation in the country is split between the Center and the States. This needs to be properly coordinated. The Committee recommends in-depth study of this important aspect of Drug Regulation and taking of suitable steps to streamline the system.

4. Training of the selected professional staff of DCGI/CDSCO at FDA or its equivalent

5. Laying down of standards in terms of Personnel, Space and Equipment requirements for Drug Testing Laboratories to carry out their modernization

6. Creation of the Departments of Clinical Pharmacology in selected Medical Colleges and Schools of Pharmacy

The root cause of our poor drug regulation is lack of professional expertise in the field of Clinical Pharmacology. This discipline is crucial both for the expertise of Clinical trials as well as regulatory aspects of Pharma industry. Since the training of the professionals flourishes sin academic departments, we need to create academic department of Clinical Pharmacology across the country.

The Pharmacy and pharmacology are parallel disciplines. It is important that Pharma students are also exposed to the concept of Clinical Pharmacology. That is why the recommendation to establish Clinical Pharmacology in Schools of Pharmacy as well.

6. List of Annexure

a) Copy of the Government Order (2 pages)

b) Minutes of the meetings of the Expert group (47 pages)

c) Report of the Parliamentary Standing Committee of MOHFW (118 pages)

d) Reply of the CDSCO (i) (98 pages)

e) Replies to the questionnaire from medical professionals of different specialties(223 pages)

f) Reply of the CDSCO (II) (80 pages)

g) List of names recommended for constituting expert groups (3 pages)

7. Brief Bio-data of the Experts

a) Prof. P.N.Tandon M.S., FRCS (England), FAMS, FNASc, FNA, FASc, FRSM, F.T.W.A.S., D.Sc. (h.c.) is Emeritus Professor at AIIMS, Emeritus Professor National Academy of Medical Sciences, Founder President National Brain Research Centre and Chairman, Central (National) Ethics Committee. Professor Tandon, after obtaining the M.S. Degree in 1952, was awarded FRCS England in 1956. In 1965, he was appointed Professor and founded the Department of Neurosurgery at the All India Institute of Medical Sciences, New Delhi. Under his leadership, this department grew to be the country's premier Neurosciences Centre. He catalyzed the establishment of the National Brain Research Centre (NBRC) at Manesar under the aegis of Department of Biotechnology, GOI. He has published more than 250 scientific papers, over a dozen monographs and a number of chapters in National and International text books. Prof. Tandon has been the President of Neurology Society of India, National Academy of Sciences, India, Indian National Science Academy, Indian Academy of Neurosciences. He has served as a member of the Governing Body of the Council of Scientific and Industrial Research (CSIR), Indian Council of Medical Research (ICMR), Indian Council of Social Science Research (ICSSR) and nominated Member of the University Grants Commission. Prof. Tandon has been decorated with Padma Sri (1973); Hon. Surgeon to the President of India (1977-80); and Padma Vibhusan (2006).

b) Dr.V.M.Katoch is Secretary to the Govt. of India (Department of Health Research), Ministry of Health & Family Welfare & Director General, Indian Council of Medical Research, New Delhi. Dr. Katoch obtained M.D. in Microbiology from AIIMS, New Delhi. He joined the Indian Council of Medical Research (ICMR) as Talent Search Scholar (TSS) and rose to become the Director of the JALMA in December 2001. He was selected as the First Secretary to the Govt. of India, Department of Health Research, Ministry of Health & Family Welfare & Director-General, Indian Council of Medical Research in Nov 2008. Dr. Katoch is credited with the development of molecular methods of rapid diagnosis of TB, leprosy, DNA chips and DNA fingerprinting methods besides viability determination using ATP bioluminescence. He has contributed more than 250 National/International research papers. These studies have resulted in identification of new genotypes and new diagnostic techniques / molecules for

better understanding of molecular basis of drug resistance and mechanisms of pathogenesis of TB, leprosy and other mycobacterial infections. Dr. Katoch has been the recipient of various awards. Dr. Katoch is the Fellow of all the prestigious academies of country, viz., National Academy of Sciences (FNASc); National Academy of Medical Sciences (FAMS); Academy of Sciences, Bangalore (FASc); and Fellow of Indian National Science Academy, New Delhi (FNA).

c) Prof. S.S.Agarwal, M.D. (Hons.), FRCPC, FAMS, FNA is a Physician-Scientist, presently working as Honorary Director (Research and Academics) and Senior Medical Consultant at the Vivekananda Polyclinic and Institute of Medical Sciences, Lucknow. He set up the Genetics Unit at King George Medical College, Lucknow in 1970, followed by the Department of Medical Genetics at the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow in 1986. At SGPGI he was instrumental in starting the first D.M. programme in Medical Genetics in the country. Prof. Agarwal is known for his basic research on DNA replication and DNA repair in human lymphocytes, genetic studies on population exposed to the MIC gas at Bhopal, establishment of prenatal diagnostic facilities at the SGPGI and defining of the Handigodu Syndrome, an autosomal dominant skeletal dysplasia in an endogamous group in Sagar, Karnataka. He has extensive experience in conducting clinical trials and translational clinical research. Presently he is closely connected with development of bioethics guidelines for research in Medical Genetics and Stem Cells in India, besides steering several ICMR multi-centric task force projects in field of Medical Genetics. He is a member of the Central Ethics Committee of the ICMR and Drafting Committee of the proposed bill on Biomedical and Health research regulation.

Annexure
In Separate CD
(Attached)