REPORT
OF
COMMITTEE CONSTITUTED TO REVIEW THE PROCEDURES & PRACTICES FOLLOWED BY CDSCO FOR GRANTING APPROVAL AND CLINCICAL TRIALS ON CERTAIN DRUGS

Ref: Order no: DCG(I)Misc/2013-(18) dated 26/03/2013 of the Drugs Controller General of India

1. Preamble: By the order under reference the Drugs Controller General of India constituted a Committee of experts for investigating certain cases mentioned in the Report of the Honourable Standing Committee of the Parliament. The enquiry as per the terms of reference, was to enable the DCGI/ the Government to fix responsibilities and to take appropriate actions against the guilty in respect of the irregularities observed by the Hon' Parliamentary Committee. Though the order did not specify the modalities and time limit for the Committee to function and to furnish its report, it was imperative that the matter should be investigated at the earliest. The DCGI convening the first meeting of the Committee on the 4th of May 2013 at FDA Bhavan, Kotla Road New Delhi. Accordingly the Committee met on the date and time fixed. The Committee was chaired by its notified Chairman Dr.T.M.Mahapatra.

The DCGI had referred four cases of approval of New Drugs without observing the statutory provisions by his office as observed by the Hon' Parliamentary Committee. Accordingly, the Committee examined the files relating to the four cases during its sittings. The DCGI had extended the services of Shri.A.K.Pradhan, Dy.DC(I) and Assistant Drugs Controllers detailed in this report for providing logistic support to the Committee.

Approval of New Drugs is a statutory process under the Drugs and Cosmetics Act, 1940 and the Rules, 1945. Carrying out statutory regulatory functions require proper procedures. If the law itself does not prescribe the procedures, executive orders are to be issued and adopted to secure compliance of the statutory requirements by all at the organization level. Orders specifying the duties, responsibilities and powers of officers at different levels are also essential.

As the Hon' Parliamentary Committee had already examined the cases referred to this Committee in detail and had concluded that there were irregularities of non-compliance of the statutory provisions with the intention of helping the manufacturers unduly, the prime duty of this committee was to find out the commissions and omissions on the part of the officials that led to the irregularities found by the Hon' Parliamentary Committee.

The Committee noted that the following actions were needed in the matter:

1. Detailed perusals of the files relating to the four cases referred together with office orders specifying the duties and responsibilities of officers at various levels.

2. The order(s) specifying the procedures for taking actions on matters relating to approval of New Drugs.

3. Verifications as to whether the office orders and procedures had been duly complied with at all levels and if so the situations that caused the irregularities and if not, the nature and extent of deviations from the orders and procedures and officers responsible for the same.

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The Committee held its meetings at the Conference room of the CDSCO at the FDA Bhavan and verifications of files were done. The Committee's findings are detailed in this report. The details of the Committee, the nature, scope and extent of the enquiries, details of the findings in the individual cases and the summary of the findings together with recommendations are furnished.

2. Constitution of the Committee: The Committee was constituted by the Drugs Controller General of India vide Order no: DCG(I)Misc/2013-(18) dated 26/03/2013 of the Drugs Controller General of India. The Constitution of the Committee was as under:

1. Prof.T.M.Mahapatra,OSD & Former Director, Institute of Medical Sciences, Banaras Hindu University, Varanasi. - Chairman
2. Prof. Satyawan Singh, Former Scientist, CDRI, Lucknow - Member
3. The Representative of the Chief Vigilance Officer(CVO), Ministry of Health & FW, Govt of India, Nirman Bhawan, New Delhi. - Member
4. S.S.Venkatakrishnan, Former Drugs Controller, Kerala State - Member

As the CVO could not be represented, he was replaced by Dr. Shailendra Kumar, Director, Ministry of Health & Family Welfare as the Member as per the directions of the Government.

The order of the DCGI mentioned above is appended to this report as **Annexure I.**

3. Terms of reference: The Order of the DCGI detailed the terms of reference to the Committee. The Order reads as under:

"To review the procedure and practices followed by the CDSCO for granting marketing approval and clinical trials on new drugs including FDC and to see that the scientific requirements and the regulatory compliance have been adhered with respect to the following four cases, as recommended by the department related Parliamentary Standing Committee on Health & family Welfare in its 59th report:-

1. The Fixed Dose Combination of Aceclofenac with Drotaverine is not permitted in any developed country of North America, Europe or Australia. In this case, vide this office letter number 12-298/06-DC dated 12-2-2007, an official of CDSCO advised the manufacturer, Themis Medicare Ltd. not only to select experts but get their opinions and deliver them to the office of the DCGI. Many experts gave letters of recommendation in identical language apparently drafted by the interested manufacturer and finally the drug was approved.

   In this case the Hon'ble Parliamentary Standing Committee recommended that the Ministry should direct DCGI to conduct an enquiry and take appropriate action against the official(s) who gave authority to the interested party to select and obtain expert opinion and finally approved the drug. **(Para 7.32, 7.33 of the 59th Department related Parliamentary Standing Committee on Health & Family Welfare report).**

2. Buclizine (applicant:UCB, Belgium) was approved on 28-06-2006 for appetite stimulation without clinical trials and without consulting experts for use in children. Under the law of the land if an old drug approved for a disorder (such as allergy) is to be used for another indication (such as appetite stimulation), then it is deemed to be a New Drug and must undergo the entire procedure applicable to New Drugs and meet all regulatory requirements. The Company's own Core Data Sheet issued from its headquarters in Belgium says: 'Because of lack of approved clinical studies and scientific data, the benefit/risk is negative for the indication of Buclizine for appetite stimulation.' Buclizine is just one of the many drugs that have been approved in violation of the Indian laws.

   The Hon'ble Parliamentary Standing Committee is of the view that responsibility needs to be fixed for unlawfully approving Buclizine, a drug of hardly any consequence to public health in India, more so since it is being administered to babies/children. At the same time approval granted should be reviewed in the light of latest scientific evidence, regulatory status in developed countries, particularly Belgium, the country of its origin. **(Para 7.39 to 7.41 of the Department related Parliamentary Standing Committee on Health & Family Welfare report)**.

3. Letrozole, is an anti-cancer drug for use only in post menopausal women and is contraindicated to be used in women of reproductive age. On 10-04-2007, DCGI approved the use of letrozole for improving female fertility. The Drugs and Cosmetics Act require that while approving a drug for use in females of reproductive age, animal studies are to be done in this specific group. No such studies were done in India. The innovator also did not conduct such studies abroad because there was no plan to use letrozole in women of reproductive age. Under Indian Rules, Phase II studies should have been conducted before Phase III since such studies were not conducted anywhere. Permission to conduct Phase III studies was given without prior Phase II studies. After approval, the sponsor, Sun Pharmaceuticals did not submit periodic PSURs due every six months as required by law. No action was taken against the company in such a sensitive case since India is the only country where the drug is permitted to be used for female infertility. Post-marketing data is crucial and critical in detecting adverse effects both in women and babies born to them if they use letrozole before onset of pregnancy. Clearly there was a serious lapse on the part of CDSCO. In the wake of the media outcry, in a diversionary move, the DCGI instead of investigating the allegations of regulatory lapse and taking corrective measures, referred the matter to clinical experts, DTAB etc. on the restricted issue of safety and efficacy.

   The Hon'ble Parliamentary Standing Committee recommended that the DCGI is expected to take action against those CDSCO functionaries who colluded with private interests and got the drug approved in violation of laws. **(Para 7.42 to 7.43 of the Department related Parliamentary Standing Committee on Health & Family Welfare report)**.

4. Placenta Extract: As per Drugs and Cosmetics Rules, whenever there is either an additional formulation or proposal to use in additional indications, the drug is deemed to be a New Drug. In violation of this clear rule, vide its letter number 4-97/89-DC dated 11th February 2000, an

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official of the office of the Drugs Controller General (India) wrote a letter to the manufacturer that Placenta Extract was "not a New Drug" and gave permission to promote placenta extract gel in additional indications (Burns and Wounds, Non-Healing Indolent Ulcers, Bed Sores, Mucositis etc.) By including the term "etc", loopholes were left wide open to add other indications. Thus CDSCO went out of the way to unlawfully and wrongly certify, in black and white, that the drug was "not a New Drug" thus helping the manufacturer to market an additional formulation for additional indications.

The Hon'ble Parliamentary Standing Committee recommended for an enquiry into the said letter. The responsibility should be fixed and appropriate action taken against the guilty. **(Para 7.48 to 7.49 of the Department related Parliamentary Standing Committee on Health & Family Welfare report).**"

4. Meetings of the Committee:

The Committee's meetings took place on the following dates:

04.05.2013: Preliminary discussions on the terms of reference, the approach to the issue, possible time schedule within which the task could be accomplished etc.

06.06.2013: Study of the case of Aceclofenac and Drotaverine tablets.

07.06.2013: Study of the case of Buclizine.

08.06.2013: Study of the case Placenta Extract.

15.07.2013: Study of the case of Letrozole.

16.07.2013: Consideration of all evidences available in the cases referred. Preparation of the draft of the report to be submitted together with the annexures to be appended to the report and recommendations to be made.

17.07.2013: Confirmation of the Minutes of the meetings of the Committee Finalization of the report to be presented.

The venue of the meetings was the Conference room in the first floor of the FDA Bhavan.

The Proceedings of the meetings are attached to this report as **Annexure II** series.

5. Findings:

5.1. Case of Fixed dose Combination Aceclofenac & Drotaverine:

The case referred to the Committee as stated in the Order No.DCG(I)/Misc./2013-(18) dated 26.03.2013 has been detailed in paragraph 3.1 above.

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File No. 4-298/06-DC related to the matter was perused by the Committee. The Note file of the file contained 17 pages. The current file did not bear numbers for the pages.

The file commenced with a note on the application for new drugs made by M/s. Themis Medicare Ltd. The note in a printed format detailed the contents of the application. The application was one seeking New Drug approval for manufacture of the fixed dose combination of Aceclofenac 100mg and Drotaverine 80mg in tablets dosage form. The note dated 02.01.2007 was made by Senior Scientific Assistant Shri.Rishi and submitted to Shri.Pradhan, Technical officer and further to the Joint Drugs Controller, Shri.Ramteke and finally to the DCGI. The last note in the file was on 13.09.2008 approving the combination. The DCGI at the time of deciding to require manufacturers to obtain and furnish reports of experts was Dr.M.Venkateswaralu and the DCGI at the time of the approval was Dr. Surinder Singh.

Page 2 of the notes file detailing the contents of the application mentioned that Animal toxicology report, Clinical trials data in respect of Ph I to Ph III trials, regulatory status in other countries were not stated. The file did not specify anything adverse about the non furnishing of the data and it was explained that both the molecules were those already approved individually and hence there was no need for the same.

Copy of the note files is appended as **Annexure III.**

The note of 16.01.2007 detailed the status of the two individual drugs involved in the combination applied for and the details were as under:

Aceclofenac had a dosage regimen of 100mg twice daily and Drotaverine had the dosage regimen of 40 to 80mg 3 to 4 times a day. It was also noted that such situation existed in the case of combinations like Ibuprofen and Paracetamol and Diacerin and Paracetamol also. The note suggested to seek published reports of clinical trials of the combination together with data of pharmacodynamic, pharmacokinetic interactions. The opinions of nine experts were also sought from the manufacturer.

In response to the Committee's request for furnishing the Office Order or Policy document in accordance with which such reports were sought, it was informed to the Committee by Sri.A.K.Pradhan, Dy. Drugs Controller (I) that the note was one in accordance with the policy that existed at that time. There, however, was no policy document and such policy decisions were said to be in vogue as per the directions of the DCGI. It was informed that manufacturers were to furnish expert opinions of which there should be at least one from the AIIMS, the JIPMER, the PGI, Chandigarh. The note had been approved by the JDC and the DCGI. Communication was also sent to the manufacturer in accordance with the above note. The reply received from the manufacturer furnished opinions of 9 Medical experts from different places. While 8 experts agreed to the combination, the expert at JIPMER, Pondicherry observed that the combination was irrational and should not be approved.

The Points to be considered at this stage were: i). The issue to be decided was not the therapeutic efficacy of the drug but the rationality of the combination. (ii) the advantage of the combination over administration of individual drugs. (iii) The note of 15.06.2007 raised question about the rationality of

the drug. (iv) the opinion of the expert of JIPMER, which was also against approval. (v) Though the manufacturer had made some claims about the advantages of the combination, there was no case made out projecting the advantage of the combination and the note file is also silent of this aspect (vi) No such report was sought from the manufacturer by the CDSCO also. The manufacturer while furnishing the opinions of the experts had not furnished the other data sought namely the pharmacodynamics, pharmacokinetics and drug interactions vii) Published Clinical trials were also not furnished. the company had stated that no similar combination had been approved in any other country.

Based on the reports of the experts, the manufacturer was required to furnish reports of Bio-equivalence and clinical trials in 220 persons. The manufacturer furnished these reports on 11.07.2008. Clinical trials were reported to had been conducted in three centres and it was reported that no adverse reports of serious concern were received. Bio-equivalence tests had been conducted in male population only while the drug is one indicated to all. This deficiency in the bio-equivalence studies had not been noticed by the administration. The claims of clinical trials were accepted just on their face value without any verification. However, approval was granted for manufacture and marketing of the combination applied for.

The findings of the committee in this case were as under:

- The approval of combination was irregular as the reports of the medical experts furnished by the company were evidently those prepared by the company itself and signed by the experts as observed by the Hon'ble Parliamentary Committee. There was no laid down norms for processing such matters. Approval was the sole discretion of the DCGI.

- There was no laid down SOPs to process applications for approval of New Drugs as no such document was available. There was apparently verbal direction by the then DCGI to require the manufacturers to furnish reports of experts for the reason that communications sent directly by the CDSCO to identified experts had poor response and applications remained unduly delayed.

- The file does not contain any note stating the reasons by which the DCGI concluded that the fixed - combination was rational and had advantages over use of individual drugs. Relying upon the views of a few experts identified by the applicant was not the proper procedure as viewed by the Hon' Parliamentary Committee also.

- There were no system and proper mechanism in place to handle such matters and to advise the DCGI in deciding the rationale of a fixed dose combination applied for and evidently the organization was not equipped with the staff or support of identified expert committee for the purpose. Taking decisions in such matters was only the discretory power of the DCGI rather than the result of a proper assessment by experts.

- Schedule Y of the rules made it mandatory to furnish animal study reports for approval of clinical trials. In this case no clinical trial of the combination had been conducted. The legal

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status of the combination in other countries was that a similar combination had not been approved in anywhere else.

- There was error of judgment on the part of the DCGI in deciding that the combination was a rational one. On the contrary, the notes in the file show that the dosage regimen of the two individual molecules were different and hence was irrational. Existence of similar combinations could not be a sound reason as the organization was striving to eliminate irrational combinations and to limit such drugs to combinations that were inevitable and advantageous to the patients for the treatment regime as in the case of anti-tubercular, anti-malarial and anti HIV drugs. There was also no system for verification of the bioequivalence test reports and the reports of clinical trials.

- *The Committee is of the view that when discretory powers were exercised, there should be sufficient justification for the same, which should be recorded and in this case the Committee did not find any such justification recorded.*

The Committee finds that the DCGI was solely responsible for the irregularity noted by the Hon' Parliamentary Committee.

5.2. Case of Buclizine:

The case presented to the Committee in the Order No.DCG(I)/Misc./2013-(18) dated 26.03.2013 of the DCGI has been detailed paragraph 3.2 of this report.

The Committee verified the file -No: 4-179/05 DC relating to the approval of Buclizine tablets and syrup for indications other than the one for which licence had been granted earlier. As per the application made by the manufacturer, Buclizine had been in use globally since 1953 and was in India since 1982 and that the safety of the drug had been well established as there had been no report of adverse reactions. Though the document relating to the first approval is not available, it is reported that it had been approved as an antihistaminic for allergies in general. The application made was for approval of the drug as New Drug for the additional indication of stimulant of appetite to gain weight.

As in all applications relating to approval of New Drugs the Senior Technical assistant who handled the file made the first notes stating the purpose of the application and suggesting that the applicant be required to furnish published (from therapeutic journals) clinical trial reports of Buclizine as appetite stimulant, the details of the countries where the product was marketed for the indication claimed and also the package insert for the product.

The applicant company furnished the data sought but the data were incomplete in the matter of regulatory status in other countries. Proof of approval for appetite stimulation in the countries where it was marketed for the purpose claimed were not furnished. Cases of withdrawal/ cancellation etc of approval were not stated also.

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The Joint Drugs Controller made a note on 27.06.2007 pointing out that the drug had been withdrawn in USA for use as appetite stimulant and suggested approval for use in adults only. However, the DCGI ignored the above note without stating any reason and approved the drug for the new indication for use in adults and in children of age 6yrs and above. The copy of the notes file is appended as **Annexure IV**.

The order of the DCGI ignoring the statutory requirements under Schedule Y and the valid note of the JDC, the committee finds, was arbitrary, whimsical and inconsistent with the provisions of law that required consideration of legal status in other countries (clause 9 of Appendix 1 of the Schedule Y.)

The Committee also finds from the file that at a later stage when the company furnished a statement detailing the regulatory status in other countries, there were cases where the drug had been withdrawn from use. In such cases the company merely stated as 'not due to safety reasons' where ever the approval had been withdrawn or cancelled. This can never be considered as proper statement of the legal status. The reasons for the withdrawal/ cancellation of approval ought to have been stated and the CDSCO ought to have investigated the matter in further. Here the issue was approval for use as appetite stimulant and the reason for withdrawal could be lack of evidence in support of the claim or other relevant regulatory reasons. Instead of ascertaining the cases of such withdrawals in full and the reasons thereof, the decision of the DCGI was to approve the drug without assigning any reason to ignore even the note of the JDC that the drug had been withdrawn from USA market.

A few other situations noted are that the first note in the file states furnishing of the bulk drug specification and its method of testing only. As the drug had been in the market from 1982 onwards as per the claims made, it is not known why the report of the formulations were not sought.

The published trial reports focus more on body weight gain and not on appetite stimulation leading to better intake of food and the resultant gain of body weight.

The observation of the Hon' Parliament Committee was that the situation that the drug had not been approved as appetite stimulant in Belgium, the country of origin throws light on the fact that there was no verification of the claims of an applicant and lack of proof of the claims. The applicant claimed approvals in about forty countries including Belgium. No document showing approval of the drug for the use claimed was produced in support of the claim nor were sought. Most of the countries stated were undeveloped or under developed countries barring Brazil and Belgium, where existence of a proper regulatory mechanism was not known. Significantly the names of the countries like USA, UK, Canada, Australia etc where proper regulatory mechanisms existed did not figure in the list and the evidence available was that in USA the approval had been withdrawn.

The Committee also found that the mere situation that the drug had been in use for several years could not be the ground for deciding the safety of the drug as the use of the drug would be limited to a few doses only for treatment of allergy whereas the use for appetite stimulation in order to gain body weight could be for long periods. The package inserts very often do not serve the intended purpose as the insert will be available in the carton containing the specified number of strips in the case of tablets or in the unit carton of the bottle (if there is a carton) and the physician would not usually have access to the package insert. The consumer also will not have access to the package insert in the case of tablets or

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if there is no unit carton for the bottle. There is no evidence from the notes of the file that these situations had been considered.

- **From the facts available in the file, the Committee finds that the DCGI was solely responsible for the irregular approval of the drug.**

5.3. Case of Letrozole:

The case is one of approval of a drug already in use for a specific indication for an altogether new indication. The drug had been approved as anti-cancer drug with specific direction 'not to be used in women of reproductive age'. The points advanced in support of the approval are that the question of safety does not arise as the drug had been in use for a long time and for long durations while the use as a drug for treating female infertility involved use only for a few days and that too during the phase of the menstrual cycle when it did not pose any risk or produce any adverse effects.

The DCGI evidently relied upon the evidences that the drug had been used in other countries for treating female infertility and the opinions of experts that the drug could be approved for treating female infertility. There was no evidence of approval of the drug in other countries for treatment of female infertility and whatever evidence was available showed off-label use. The experts in India were in no position to give opinion in the matter

The Committee finds that there was still no evidence that legal approval had been given in any country for treating female infertility. It is a legal question to be considered whether clinical trials were required to prove the therapeutic efficacy claimed. Treatment of female infertility is not a situation to be tackled on an emergent basis without going through regular procedures, especially animal studies. There is no explanation as to why post marketing studies were not conducted by the manufacturer and why the CDSCO did not insist upon the same. It is seen that this part of the statutory requirement stipulating post marketing studies is ignored by the organization as actions were not taken to implement this provision of the law in any case of new drug approval. Once the new drug is approved, licence is granted by the State licensing authority and there is no procedure or system seeking reports from the manufacturer and verifications by the zonal offices and State regulatory bodies.

File No: 04-122/03-DC pertained to the case. The case as well as the file have three parts. The first part relates to the approval of conducting clinical trials in human beings for treatment of female infertility. The second part relates to 'New Drug' approval of the drug for treatment of infertility in women based on the results of the clinical trials. The third part relates to seeking post marketing surveillance reports from the manufacturer in pursuance of the enquiries conducted by the Hon'ble Parliamantary Committee.

Our committee is concerned mostly with the first two parts to fix accountability of the officers responsible for the irregularities observed by the Hon'ble Parliamentary Committee, namely approval of

human clinical trials bye-passing animal studies and approval of the drug subsequently for the indication proposed.

Clause 1 of Schedule Y of the Drugs and Cosmetics Rules read as under:

"1. Application for permission

(1) Application for permission to import or manufacture new drugs for sale or undertake clinical trials shall be made in Form 44 accompanied with the following data in accordance with the appendices, namely: -
(i) chemical and pharmaceutical information as prescribed in Item 2 of Appendix I;

(ii) animal pharmacology data as prescribed in Item 3 of Appendix I and Appendix IV;"

The rule thus makes it mandatory to furnish the chemical profile and animal study data while making application in Form 44 for conducting clinical trials.

M/s. Sun Pharmaceutical Industries ltd had made application in Form 44 for conducting clinical trials in human beings for treatment of female infertility. The company while seeking permission for conducting clinical trials submitted the chemical profile of the drug but the application was silent on animal study data and there was no statement as to why the same was not submitted. Note file is also silent in the matter. The JDC who is the officer to evaluate the application before submission to the DCGI had noted as under in page 4 of the note file:

"Before approval of C/T protocol of Letrozole in infertility, we may request the firm to furnish "International Status" of Letrozole in said indication. Recently the firm also warn regarding off-label claim of Letrozole in the country. (Pre-clinical - animal study report for said indication is not provided by the firm)"

The above note of the JDC did point out and stress the need for animal study data prior to clinical trials in human beings and also the legal status of the drug for proposed use in other countries. The above note also pointed out that the applicant manufacturer had already been promoting use of the drug for treating female infertility and had been warned by the CDSCO.

However, the Drugs Controller ordered for referring the protocol submitted by the Company to a few experts considering the published literature furnished by the company and the view expressed by Dr.Sunita Mittal. The note dated 29/11 of the DCGI read as under:

"We may refer the protocol to few experts in view of published literature furnished by firms. and the view expressed by Dr.Sunita Mittal."

The copy of the Note file is appended as **Annexure V**.

The above order of the DCGI did not state any reason for overruling the observations and suggestions of the JDC(I). It also shows that actions in such sensitive and vital matters were more out of discrete decisions taken by the DCGI rather than any laid down norms and even the statutory norm was overlooked for reasons not stated. This is a case where experts could have no say as the drug had not been approved for sale in the country for the intended use and whatever off-label use that might have existed did not have any legal sanctity under these rules and could be no substitute or guiding factor for doing away with the statutory requirement of animal studies. This Committee finds that the then DCGI was solely responsible for the irregularity observed by the Hon'ble Parliamentary Committee. The case was a total misuse of the statutory and discretory power by the DCGI and disregard for the statutory provisions and the observations and suggestions of the immediate senior most officer of the system. Shri. Aswini Kumar was the DCGI at that time.

The second part of the case is non-furnishing of PMS data by the company and inaction on the part of the CDSCO in the matter. The approval of Letrozole as a New Drug for treatment of female infertility in human beings was given on 10/04/2007. The letter dated 10/04/2007 signed by the then DCGI Dr.M.Venkateswaralu himself stipulates conducting PMS studies within a period of two years after getting the protocol etc approved by the CDSCO. The file does not show any follow up action in the matter and the Committee finds that the CDSCO in general had not given any thrust to the PMS data. This Committee is of the firm view that PMS studies are more important than any of the other three phases of trials for drug approval as the entire population of the country is exposed to the drug. Inaction in the matter was the failure of the organization in total and the Committee cannot but hold the office of the DCGI only as responsible for the state of affairs.

- **This Committee is therefore of the opinion that the DCGI and the was primarily accountable for the irregularity in the matter. Shri.Aswini Kumar was the DCGi at the time of approval of the clinical trials and Dr.M.Venkateswaralu was the DCGI when the approval was granted.**

5.4. Case of Placenta Extract:

The case presented to the Committee in the Order No.DCG(I)/Misc./2013-(18) dated 26.03.2013 of the DCGI is as under:

"4. Placenta Extract: As per Drugs and Cosmetics Rules, whenever there is either an additional formulation or proposal to use in additional indications, the drug is deemed to be a 'New Drug'. In violation of this clear rule, vide its letter number 4-97/89-DC dated 11th February 2000, an official of the office of the Drugs Controller General (India) wrote a letter to the manufacturer that Placenta Extract was 'not a New Drug' and gave permission to promote placenta extract gel in additional indications (Burns and Wounds, Non-Healing Indolent Ulcers, Bed Sores, Mucositis etc.) By including the term "etc", loopholes were left wide open to add other indications. Thus CDSCO went out of the way to unlawfully and wrongly certify, in black and white, that the drug was 'not a New Drug, thus helping the manufacturer to market an additional formulation for additional indications.

The Hon'ble Parliamentary Standing Committee recommended for an enquiry into the said letter. The responsibility should be fixed and appropriate action taken against the guilty. **(Para 7.48 to 7.49 of the Department related Parliamentary Standing Committee on Health & Family Welfare report)."**

The Hon'ble Parliamentary Committee noted two irregularities in the case namely approval of a drug in a new dosage form without complying with the requirements of the law and secondly leaving additional indications open to the manufacturer, which is against the stated provision and the object of the law.

This Committee was informed that the file relating to the issue of the letter was not traceable and the position had been informed to the Hon' Parliamentary Committee also when the file was sought. Only a copy of the letter obtained from the manufacturer during the course of the Hon' Parliamentary Committee enquiries was available. This letter was one signed by Sri.A.B.Ramteke, Dy. Drugs Controller. This Committee found that without examining the file relating to the issue, responsibilities could not be fixed to any person other than the signatory of the letter, Sri.Ramteke and the DCGI. The letter had been signed as 'for Drugs Controller General(I)' and hence the letter had been issued with the concurrence of the DCG(I) only. The Copy of the letter is appended as **Annexure VI**.

➢ **This Committee is therefore of the opinion that the DCGI and the Dy.D.D(I) Sri.Ramteke were primarily accountable for the irregularity in the matter.**

6. Summary of findings:

The Committee after perusal of the four files involved observed that:
(i) There was no proper system in place to deal with matters pertaining to approval of New Drugs and this situation contributed to most of the irregularities observed by the Hon'ble Parliamentary Committee.

(ii) Irregularities are there in the maintenance of files and in various matters such as seeking the opinion of experts, taking decisions etc.

(iii) It is not possible to make out when the system of referring matters to experts started or the logics of the same.

(iv) Approval of New drugs on whatever basis is a matter to be decided on sound scientific reasoning based on evidences of clinical trials. Schedule Y does not provide for any general exemption for any new drug application from the requirement of furnishing data of animal studies and exemptions are available only in certain situations. The four cases considered by the Committee do not enjoy the exemptions available.

(v) In the four cases considered by this Committee, the first one was approval of a fixed dose combination for which animal studies are not mandatory now under the law. As the pharmacodynamic and pharmacokinetic actions of combinations could vary from those of the individual cases, pharmacodynamic/ kinetic data would be desirable in such cases.

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(vi) In the case of Buclizine, again the fact that the drug was already in use has no merits as the approved use earlier was Anti-histaminic where the use was as per the need, may be limited to a couple of doses. When it is used as an appetite stimulant the dosage regimen was different and could be longer.

(vii) The CDSCO had relied upon the logic that a drug used for a long period could be approved for a different indication for a shorter period without animal studies in the case of Letrozole but failed to apply the reverse logic in the case of Buclizine where the drug had been approved for a shorter therapy earlier while the new approval was for a longer period of therapy. There were strong evidences that the use of the drug for the indication proposed had been cancelled or withdrawn in several countries.

(viii)In the case of Letrozole, the approved earlier indication was as anti-cancer drug in women of post-menopause stage. There was no evidence that the safety of the drug had been evaluated in other cases.

(ix) In the case of Placenta Extract, the entire statutory requirements applicable to New Drugs had been waived. Had there been a proper system in place, such situations could have been avoided.

(x) The Committee finds that the exercise of the discretory power by the DCGI without stating any reason is totally irregular and undesirable. In the first place the Committee finds that the law does not provide for such decisions as Schedule Y prescribes several requirements for approval of new drugs and there is no provision for waiving the same on merits or case to case basis. To ignore even the note of the JDC without stating any reason was a serious misuse/ abuse of power on the part of the DCGI.

(xi) The process of grant of licences or approval of New Drugs is a matter of application science in law. Where expertise is not available, availing expertise may be the proper course of action. However, it is not impossible for corporate houses to influence experts, a situation which the Hon'ble Parliamentary Committee has observed in the case of approval of the Fixed dose combination of Aceclofenac and Dotraverine. A proper system is to be in place to address such situations.

(xii) Evaluation of the expert opinions and recommendations is essential as also proper application of mind while taking decisions based on such opinions and recommendations and these should be recorded in the file also. The CDSCO should have the services of a legal wing to seek legal opinion before issue of final orders to ensure proper compliance of the statutory norms.

(xiii) The Drugs Regulatory mechanisms of the country have not been subjected to any technical audit to check proper compliances and eliminate aberrations/ deviations etc and to take remedial measures. May be the Enquiry by the Hon' Parliamentary Committee is the first one in the matter of technical audit. It has thrown a lot of light in the inadequacies in the system and it stresses the need for regular audits - both self audit as well as external audit. The sub-offices of the CDSCO as well as the State Regulatory also are to be subjected to technical audit. It is a sad state of affairs that the law requires the industry to observe GMP, GLP etc and prescribes SOPs while the administrators of the law are not

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subjected to such disciplines and controls. GRP should be in place for the purpose. Regulatory bodies are to function as regulators as the names suggest and not as mere licensing agencies. Strict disciplines in licensing and real control of the quality and safety of the drugs are the needs. There is need to control the controllers of drugs. When the Governments take measures to improve the drug regulatory system in the country, the money spent will go to drains if there is no discipline in the administration of law. Fat regulatory bodies are not the need of the country and the need is sound and robust bodies.

(xiv) There is need for better and stronger coordination between the CDSCO and the State regulatory bodies and within the CDSCO. Once a new drug is approved, the licensing is done by the State bodies. The State bodies are not informed of the terms and conditions of such approvals and of the controls to be exercised. PMS and evaluation of the PMS data are totally ignored areas where the zonal and State bodies are to play vital roles. While approving new drugs, the manufacturers are required to supply drugs with package inserts. There is no mechanism in place to ensure in the first place availability of such package inserts and secondly, availability of the insert approved by the DGCI as these are not communicated to the State and zonal bodies. Approval of package insert shall also be subjected to expert and legal scrutiny.

(xv) Approval of New Drugs should be provisional and subject to confirmation or withdrawal/ cancellation after the prescribed period based on PMS and PvPI data and evaluation. The Rules may be amended for the purpose.

(xvi) While PMS and PvPI could ensure safety of the new drugs approved there is need to ensure the quality of the drugs approved also in different parts of the country. Quality control is exercised by a system of random sampling and the zonal and State bodies are to be sensitized of the issue and periodical testing shall be insisted. For testing such new drugs, the laboratories of the CDSCO and the State would need the validated method of test approved at the time of new drug approval. Master formula specifying the additives and processes involved shall also be scrutinized and approved while approving new drugs and the approved version of the master formulae shall be communicated to the zonal and State bodies for effective control of the manufacturing and quality assurance processes at their levels. It shall be onus of the licensee who secures New Drug approval to provide the reference substances required. The IPC and its laboratory are also to play vital roles in the processes of quality control and assurance to develope and provide the expertise needed.

(xvii) Till such time proper controls in the form of SOPs are in place, the zonal offices and sub-ordinate officers may not be delegated with the power to grant New Drug approvals.

(xviii)The four case examined also presents the situation that commercial needs of the industry bear more focus than the regulatory norms. While commercial needs are essential for the industry to survive, regulatory controls are needed for safe and rational use of the drugs. It is pertinent to note that the promoter of Letrozole had resorted to promote off-label uses even before the application was considered. Off label uses may have legal sanctity on countries where there are better ethical practices of medicine and sale of drugs. Ours is a country where most drugs could be procured without any valid

prescription. Letrozole as an anti-cancer drug for treatment of breast cancer in post-menopause stage women and the chances of misuse/ abuse were less. However, when it is approved for treating infertility in women in reproductive age group, the picture changes and there ought be was more diligent approach on the part of the DCGI in the matter. Such situations could develope in future also and unless the regulatory perspectives of such issues get due or better focus than the commercial side to ensure proper decisions by the authority.

(xix)It is an undesirable situation that the file pertaining to approval of Placenta Extract is missing. Whatever be the reason, the inference is that there is poor record keeping system in CDSCO. The matter is to get immediate attention and efforts are required to preserve files as per the Government norms. Files pertaining to New Drug approvals may have to be preserved for indefinite period of time and appropriate measures are required in the matter. This Committee is to record its helplessness in making a proper evaluation of the case and fixing accountability for the irregularity observed by the Hon'ble Parliamentary Committee and the recommendation made in this case is based on the only document made available, namely the copy of the approval letter obtained from the manufacturer by the organization. The offices of the CDSCO shall have proper archiving systems and facilities for preservation and retrieving of files after actions in file are over.

7. Summary of recommendations:

Recommendations:

The findings of the Committee shows that the irregularities observed by the Hon'ble Parliamentary Committee was the result of the combination of several factors right from lack of proper control over maintenance of files, lack of laid down norms for carrying out critical activities such as approval of New Drugs, lack of adequate man power in the CDSCO, absence of identified expert committees to guide the CDSCO in taking appropriate actions, failure of the organization to ensure follow up actions by the zonal offices after approval of New Drugs, lack of coordination between the CDSCO and the State regulatory bodies, possible collusion/ nexus between the officials, experts and the industry as observed by the Hon'ble parliamentary Committee etc. While the lack of adequate manpower and absence of expert committees could be due to reasons beyond the control of the CDSCO, the other failures are the result of proper managerial control by the organization only. The Committee presents the following recommendations based on the summary of findings detailed in paragraph 6, starting from maintenance of files.

1. Verifications of the files pertaining to four of the three cases (file of one case not available) show that filing system was poor as the Notes file were not page numbered and the paragraphs of the notes were also not serial numbered. The name(s) and designations of the officers making the notes were also not recorded and as a result, the identity of the persons recording the notes could be ascertained only through discussions with officials. In the case of the current file also, the pages were not numbered and the documents were also not filed in order making the process of verifications difficult. If such situation still exists, it is to be rectified.

2. The serious case of missing file points out the need for robust methods of archiving of records and files..

3. It was reported that no office order assigning duties and responsibilities to officers or laying down procedures in the matter of dealing with files relating to Approval of New Drugs. If such situation still exists, the same is to be set right. It is not known whether stock files containing such orders and circulars are maintained. If not, such a system is to be adopted to locate office orders and circulars.

4. The process of grant of licences or approval of New Drugs is a matter of application science in law. A proper system is to be in place to address the needs. Evaluation of the expert opinions and recommendations is essential as also proper application of mind while taking decisions based on such opinions and recommendations and these should be recorded in the file also. The CDSCO has the services of a Law Officer and it is desirable to seek legal opinion of the Legal wing of the organization before issue of final orders to ensure proper compliance of the statutory norms.

5. The Drugs Regulatory mechanisms of the country have not been subjected to any technical audit to check proper compliances and eliminate aberrations/ deviations etc and to take remedial measures. May be the Enquiry by the Hon' Parliamentary Committee is the first one in the matter of technical audit. It has thrown a lot of light in the inadequacies in the system and it stresses the need for regular audits - both self audit as well as external audit. The sub-offices of the CDSCO as well as the State Regulatory also are to be subjected to technical audit. It is a sad state of affairs that the law requires the industry to observe GMP, GLP etc and prescribes SOPs while the administrators of the law are not subjected to such disciplines and controls. Regulatory bodies are to function as regulators as the names suggest and not as mere licensing agencies. Strict disciplines in licensing and real control of the quality and safety of the drugs are the needs. There is need to control the controllers of drugs. When the Governments take measures to improve the drug regulatory system in the country, the money spent will go to drains if there is no discipline in the administration of law. Fat regulatory bodies are not the need of the country and the need is sound and robust bodies.

6. There is need for better and stronger coordination between the CDSCO and the State regulatory bodies and within the CDSCO. Once a new drug is approved, the licensing is done by the State bodies. The State bodies are not informed of the terms and conditions of such approvals and of the controls to be exercised. PMS and evaluation of the PMS data by competent authority is to be in place. While approving new drugs, the manufacturers are required to supply drugs with package inserts. Approved package inserts shall be communicated to the State Licensing authorities and the zonal offices to ensure that the approved version of the package insert only is used by manufacturers. Approval of package insert shall also be subjected to expert and legal scrutiny.

7. While PMS and PvPI could ensure safety of the new drugs approved there is need to ensure the quality of the drugs approved also in different parts of the country. Quality control is exercised by a system of random sampling and the zonal and State bodies are to be sensitized of the issue and periodical testing shall be insisted. For testing such new drugs, the laboratories of the CDSCO and the State would need the validated method of test approved at the time of new drug approval. Master formula specifying the additives and processes involved shall also be scrutinized and approved while approving new drugs and the approved version of the master formulae shall be communicated to the zonal and State bodies for effective control of the manufacturing and quality assurance processes at their levels. It shall be onus of the licensee who secures New Drug approval to provide the reference substances required. The IPC and its laboratory are also to play vital roles in the processes of quality control and assurance to develope and provide the expertise needed.

8. Till such time proper controls in the form of SOPs are in place, the zonal offices and sub-ordinate officers may not be delegated with the power to grant New Drug approvals.

9. The four cases examined also presents the situation that commercial needs of the industry gain more focus than the regulatory norms. While commercial needs are essential for the industry to survive, regulatory controls are needed for safe and rational use of the drugs. It is pertinent to note that the promoter of Letrozole had resorted to promote off-label uses even before the application was considered. Off label uses may have legal sanctity on countries where there are better ethical practices of medicine and sale of drugs. Ours is a country where most drugs could be procured without any valid prescription. Letrozole as an anti-cancer drug for treatment of breast cancer in post-menopause stage women and the chances of misuse/ abuse were less. However, when it is approved for treating infertility in women in reproductive age group, the picture changes and there ought be was more diligent approach on the part of the DCGI in the matter. Such situations could develope in future also and unless the regulatory perspectives of such issues get due or better focus than the commercial side to ensure proper decisions by the authority.

10. It was noted that there was no system of marking copies to the zonal offices in the matter of approval of New Drugs. There was no system of requiring the zonal offices and the State regulatory bodies to carry out verifications in respect of Phase IV studies. It is essential that norms are prescribed for performing the Phase IV studies and the zonal offices and the State regulatory bodies are also involved in the verification processes so that proper studies are conducted by manufacturers and facts are not suppressed.

11. It is not known whether there is any regulation of permitting approved New Drugs manufactured under loan licence or on contract basis. While there is no provision in the law currently permitting contract manufacture of drugs, the practice has been in vogue for several years now. As New Drug is approved to a particular manufacturer, it cannot be manufactured by

any other manufacturer and hence the question of contract manufacture does not arise. However, in the absence of specific norms and verifications, such practices could exist or come into existence, which would be undesirable.

12. There has been no practice of validating master formulae at the time of New Drug approval. It is desirable that the applicant discloses the manufacturing process and also the quality control and assurance parameters so that deviations could be checked. The copies of the approved master formulae could be sent to the State Regulatory bodies who issue the licence, and the zonal offices.

13. This Committee is of the view that there is need for proper auditing systems in place for auditing of the Regulatory bodies of the States and of the subordinate offices of the CDSCO to make the implementation of the law proper and purposeful. Both self-auditing and external auditing systems are required. Self-auditing is required for the office of the DCGI also. External audits should be conducted involving outside experts also i.e., experts who are not part of the regulatory bodies. A panel of experts should nominated for the purpose by the CDSCO. In matters relating to New Drug approvals, compliance of the terms conditions of approval, such as package inserts, labeling requirements etc of New Drugs are to be implemented at the level of the manufacturer and the State Regulatory bodies and the subordinate offices are to play vital roles. Laxity or non-implementation will defeat the purposes of the regulatory measures, which in turn could place human life at risk.

14. This Committee is of the view that Post Marketing Surveillance is equally or even more important than the other phases of clinical trials as the entire population is exposed. CDSCO should draft protocols for the PMS studies for uniform adoption and implementation by all. To make the PMS mandatory and effective, the first approval should be provisional and for a limited period of two/ three years within which the manufacturer should submit the PMS data which shall be evaluated and confirmation or withdrawal of approval should be done based on the outcome of the evaluation. The rules should be amended for the purpose.

15. The benefits of e-administration could be adopted in regulatory matters also. While the present focus may be in the matters of licensing as for as e-administration is concerned, e-administration or regulation should be possible in matters of follow-up actions on New drug approvals especially in the matter of PMS just as in the case of PvPI where ADRs are monitored.

16. The CDSCO offices should be equipped with E- Library system for updating scientific knowledge of the technical staff.

8. Acknowledment: The Committee desires to place in record the excellent logistic supports provided by the DCGI in the enquiry processes and without the support, the Committee might have needed longer time for completing the work entrusted to it.

9. List of Annexures:

1. Copy of order of the DCGI constituting the Committee and containing the terms of reference.

2. Copies of the minutes of the meetings of the Committee.

3. Copy of the Note file of the case pertaining to approval of the FDC Aceclofenac and Dotraverine

4. Copy of the Note file of the case pertaining to approval of the Buclizine for new indication.

5. Copy of the Note file of the case pertaining to approval of the Letrozole for new indication.

6. Copy of the letter sent to M/s.Albert David in the matter of Placenta Extract.

1. S.S.Venkatakrishnan
Member

2. Prof.Satyavan Singh,
Member

3. Dr.Shailendra Kumar,
Member

4.Prof T.M.Mahapatra,
Chairman

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