MINUTES OF 25th MEETING OF THE TECHNICAL COMMITTEE HELD ON 28.05.2015 UNDER THE CHAIRMANSHIP OF DGHS FOR SUPERVISING CLINICAL TRIALS ON NEW CHEMICAL ENTITIES IN THE LIGHT OF DIRECTIONS OF THE HON'BLE SUPREME COURT OF INDIA ON 03.01.2013.

Present:

1.	Dr. Jagdish Prasad, Director General of Health Services, Nirman Bhawan, New Delhi	Chairman
2.	Dr. Nandini Kumar, Former Dy. Dire. Gen. Sr. Grade, Adjunct Professor, KMC, Manipal, 5/1 (New) Padmalaye Apt. Chennai.	Member
3.	Dr.Rajutitus Chacko, Prof. & Head, Dept. of Medical Oncology, CMC, Vellore	Member

From CDSCO:

1. Dr. V. G. Somani,
   Joint Drugs Controller (I)
2. Mrs. Annam Visala
   Deputy Drugs Controller (I)
3. Mrs. Rubina Bose
   Deputy Drugs Controller (I)

Dr. V. G. Somani, JDC (I) welcomed the members of the meeting and initiated the proceedings of the Committee.

Thereafter the Committee discussed the clinical trial proposals one by one as under:

1. <u>Proposals of Clinical Trials recommended by SEC / IND.</u>

The Committee deliberated 13 cases related to approval of clinical trials. Out of these 13 cases, 01 case was related to clinical trials of NCEs. Remaining 12 cases were related to clinical trials for approval of New Drugs, medical devices and biologicals.

The Committee evaluated the 01 case related to clinical trial of NCEs and made recommendations considering all aspects of safety, efficacy especially in terms of the three parameters viz. risk versus benefit to the patients, innovation *vis-a-vis* existing therapeutic option and unmet medical need in the country. After detailed deliberation the Committee did not

recommend the proposal. The recommendation of the Committee in respect of that case related to clinical trial of NCEs is enclosed as **Annexure-I.**

The Committee also evaluated the remaining 12 cases of other than GCT/clinical trial of NCEs. After detailed deliberation, the Committee recommended for approval of 07 cases out of 12 cases. Out of 07 recommended cases, the Committee recommended 01 case (S. No. 06 of Annexure-II) subject to certain condition. The Committee did not recommend the 05 (S. No. 05, 07, 08, 09 and 12 of Annexure-II) cases and deferred the proposals for seeking clarification. The recommendations of the Committee in respect of these 12 cases are enclosed as **Annexure-II.**

Thus, the Committee recommended for approval of 08 cases, out of total 13 cases of clinical trial proposals.

2. <u>Waiver of Clinical Trial in Indian population for approval of new drugs, which have already been approved outside India</u>

Following 01 proposal (from Subsequent New Drugs) has been recommended by the SECs for approval for manufacture and marketing in the country with the condition to submit Phase IV protocol within 6 months. The firm requested to consider waiver to conduct Phase IV trial. The details of the same along with recommendations of SEC were placed before the Committee. The recommendations of the Technical Committee and SEC are at **Annexure-III**.

3. Others.

i) Request to reconsider the application from M/s George Institute for Global Health to conduct clinical study titled "TRIUMPH - Triple Pill vs. Usual care Management for Patients with mild-to-moderate Hypertension."

An application from M/s George Institute for Global Health, regarding conduct of clinical study titled "TRIUMPH - Triple Pill vs. Usual care Management for Patients with mild-to-moderate Hypertension" was received on 05-06-2013 by CDSCO.

The proposal of M/s. George Institute for Global Health, regarding permission to conduct Phase-III clinical study for Telmisartan, Amlodipine and Hydrochlorothiazide was deliberated in NDAC/SEC, details of deliberation are as below;

A. Details of SEC/NDAC deliberation:

1. 1st SEC/ NDAC Deliberation on 24-01-2014:

Recommendations: The committee opined that at present there is no scientific justification for use of these drugs combination pill as starting therapy in stage 1 hypertension. Therefore the NDAC does not recommend approval of study

2. 2nd SEC/NDAC Deliberation on 21-08-2014:

Recommendation: After detailed deliberation the committee opined that at present there is no scientific justification for the use three drugs combination pill as starting /first line therapy in stage 1 hypertension/mild hypertension. The investigators suggested submitting the published documents on this specific issue of triple drug

therapy, as first line approach in mild hypertension. The committee opined that the submitted documents should be forwarded to cardiologist for their opinion.

3. 3rd SEC Deliberation on 25-11-2014: (In presence of Cardiology experts)

Recommendation: After detailed deliberation the committee did not recommend the conduct of the trial

B. Appeal by M/s George Institute for Global Health to DGHS on 02-02-2015 for consideration in Technical Committee based upon following justification;

1. There is strong rational to anticipate that initial or early use of a low dose fixed dose combination pill of three blood pressure lowering drugs will result in reaching BP targets more quickly, with fewer side effects and more affordably. This approach has the potential to address therapeutic inertia, which is a major cause of inadequate treatment of hypertension worldwide. This is an untested hypothesis and the reason to design TRIUMPH is to test this hypothesis.

2. In TRIUMPH, initiation of treatment with Triple pill (in subjects randomized to triple pill treatment arm) will happen with low dose version of triple pill (Telmisartan 20 mg, amlodepine 2.5 mg, hydrochlorothiazide 6.25 mg) and subsequently up titrated, only if necessary, to high dose version pill (Telmisartan 24 mg, amlodipine 5 mg, hydrochlorothiazide 12.5 mg). The dose of BP lowering agents in low dose version of Triple pill is lower, which is assuring in terms of safety.

3. The key inclusion criteria for TRIUMPH is "Persistent (≥6 weeks) SBP >140 mmHg/or DBP> 90 mmHg (or SBP >130 mmHg and/or DBP>80 mmHg in patients with diabetes mellitus or chronic kidney disease) despite diet and lifestyle advice and/or the use of single BP-lowering drug therapy". Results from a number of trials in India have indicated that the use of FDC of three BP lowering drugs in patients with uncontrolled BP on monotherapy is likely to be safe and efficacious.

C. Consideration of proposal by 23rd Technical Committee:

The proposal was placed before the Technical Committee along with the recommendations of the SEC and justification furnished by firm.

After detailed deliberation on the appeal, the Committee recommended that the applicant shall make detail presentation in the forthcoming Technical Committee meeting.

D. Recommendation of the 25th Technical Committee:

The applicant made the presentation of their proposal before the committee. After detailed deliberation the committee did not recommend the conduct of the trial as per the recommendation of the SEC.

ii) Request to deliberate the application of M/s George Institute for Global Health, to conduct clinical study titled "To evaluate the long- term efficacy and safety of oral Methylprednisolone compared to matching placebo, on a background RAS Inhibitor therapy, in preventing kidney events in patients with IgA nephropathy and feature suggesting a high risk of progression"

An application from M/s George Institute for Global Health, regarding conduct of clinical study titled "**To evaluate the long- term efficacy and safety of oral Methylprednisolone compared to matching placebo, on a background RAS Inhibitor therapy, in preventing kidney events in patients with IgA nephropathy and feature suggesting a high risk of progression"** was received on 22-07-2013 by CDSCO.

The proposal of M/s. George Institute for Global Health, regarding permission to conduct Phase-III clinical study with Methylprednisolone was deliberated in NDAC/SEC, details of deliberation are as below;

A. Details of SEC/NDAC deliberation:

1. 1st SEC/ NDAC Deliberation on 24-01-2014:

Recommendations: The committee opined that the inclusion criteria include patients with GFR up to 20 ml/min (Stage IV CKD) which is not because of cresentric glomerulonephritis. Steroid alone in stable stage- IV CKD is not appropriate as the risk far more than the potential benefits. One of the exclusion criteria is minimal change disease with IgA deposition. Without electron microscopy this exclusion criteria is invalid to differentiate from IgA with minimal change pathology. There is no investigation mentioned in protocol to diagnose the latent TB which is one of the exclusion criteria. This is an important issue in patients with IgA and CKD, more so in Indian context. For such type of study requiring creatinine and proteinuria estimation and for consistency of the results a central laboratory is essential. In view of the study protocol is not acceptable in this present form.

2. Response of the firm:

The firm submitted revised protocol with following changes:

a) Minimal change renal disease with IgA deposits deleted.

b) Latent infection will be diagnosed on the basis of Mantoux test.

c) Inclusion criteria revision on eGFR and the range of eGFR also changed throughout the protocol.

3. 2nd SEC/NDAC Deliberation on 21-08-2014:

Recommendation:

After detailed deliberation of the revised protocol, the Committee observed that the applicant has deleted the exclusion criteria of minimal change disease. However, just by exclusion, false inclusion of the minimal change disease will mislead the data conclusion. Thus committee recommended exclusion of those cases where electron microscopy is not available. Investigator has included Mantoux test as criteria for

diagnosis of latent TB. However, in Indian context where BCG is universally given, Mantoux test will give false positive results. Further in CKD patients Mantoux will give also false negative test. For both the issues Mantoux test will not be appropriate in this clinical setting. Committee recommended inclusion of Quantiferon Gold Test for diagnosis of latent TB. Committee also wishes to see the change of eGFR criteria to be applicable in global protocol. Investigator has agreed to give documentary evidence for such change globally. Committee wishes to get such evidence as hard copy signed by appropriate global body/person. Accordingly the committee recommended the conduct of the trial subject to the above condition. The above changes in the protocol may be circulated as soft copy to committee members for their remarks.

4. 3rd SEC Deliberation on 25-11-2014:

Recommendation:

After detailed deliberation the committee opined that the written opinion of the TB expert on the following may be obtained: Requirement/status of Quantiferon gold test to rule out latent TB patients from being recruited in this study. The committee recommended that the trial protocol may be approved based on the opinion of the antimicrobial expert on the above mentioned aspect. Regarding the second condition of the electron microscopy the committee agreed with the justification now presented by the applicant that the said test may not be required.

5. 4th SEC Deliberation on 07-04-2015: (Antimicrobial)

Recommendation:

The protocol was referred by the SEC (Cardiology and Nephrology) to examine the requirement of Quantiferon Gold tests to rule out the Latent TB cases from being recruited in this study. After detailed deliberation the committee opined that Quantiferon Gold tests in tube can be done to rule out the latent TB cases.

B. Appeal by M/s George Institute for Global Health to DCG(I) on 23-04-2015 for consideration in Technical Committee based upon following justification:

This not a commercial drug approval study, but an academic investigator initiated trial, funded by Australian National Medical Research Council (a government funding agency). This protocol deliberate thrice in SEC cardiology and nephrology and once in Antimicrobial, most of issues ha been resolved but the use of Quantiferon Gold tests for detection of latent TB, remains unresolved. The study is recruiting globally including in China where over 200 patients have already been randomized. Despite the fact that China is also endemic for TB, there is no requirement of this test there. The firm wishes to contest primarily because it is scientifically unsound and completely invalidates the purpose behind doing study; which is to generate evidence that is generalisable and can be applied to a majority of population with given disease condition. There is sufficient evidence in literature and opinion of

highly regarded clinicians that clearly negates the utility of this suggested test in an endemic area like India.

C. Consideration of proposal by Technical Committee: The applicant made the presentation before the committee. After detailed deliberation, the committee reiterated the recommendation of the SEC and recommended the conduct of the trial subject to the following conditions:

1. Quantiferon Gold tests should be done to rule out the latent TB cases.
2. As one of the exclusion criteria in the clinical trial protocol is minimal change disease with IgA deposition, therefore electron microscopy should be done to differentiate from IgA nephropathy with minimal change pathology.

   The firm agreed with the recommendation of the Technical Committee. Accordingly the firm should submit revised protocol with the inclusion of the above tests for final approval by the DCG (I) office.

The meeting ended with vote of thanks to the Chair.

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Annexure-I

List of 01 case of clinical trial of NCEs along with their evaluations and recommendations of the Technical Committee in its 25th Meeting.

Proposal No.		Assessment of the Proposal *vis –a vis* specified Parameters	Recommendation 1. Technical Committee 2. Subject Expert Committee
1	**Title**: A multicenter study to evaluate safety and tolerability in patients with chronic heart failure and reduced ejection fraction from PARADIGM-HF receiving open label **LCZ696**" **Protocol No**: CLCZ696B2317 **Name of the Drug:** LCZ696 **Phase of the Study:** Phase III **Applicant Name and Address**: Novartis Healthcare Private Limited. Sandoz House, Shiv Sagar Estate, Dr. Annie Besant Road, Worli, Mumbai **Sponsor Name and Address**: Novartis Healthcare Private Limited. Sandoz House, ShivSagar Estate, Dr. Annie Besant Road, Worli, Mumbai **Manufacturer Name and Address**: Novartis Pharma Stein AG Schaffhauserstrasse CH-4332 Stein, Swizerland	**Assessment of Risk vs. Benefit to the patients**: The safety profile of the study drug from preclinical pharmacology, repeat dose toxicity, reproductive toxicity, genotoxicity, juvenile toxicity studies and phase I, II clinical studies justify the conduct of the trial. **Innovation vis-à-vis Existing Therapeutic Option:** The purpose of the study is to evaluate safety and tolerability in patients with chronic heart failure and reduced ejection fraction from PARADIGM-HF receiving open label LCZ696. **Unmet Medical Need in the country:** The test drug may potentially provide alternative option for the treatment of heart failure with reduced ejection fraction.	**Recommendation of the Technical Committee:** After detailed deliberation the Committee recommended that the applicant shall make detail presentation before the Committee. **SEC Recommendation Dated 01-05-2015:** The firm expressed their inability to conduct ECHO cardiography assessment at base line and at follow up, as more than 150 patient have already been recruited in the study and difficult to amend global protocol. After detailed deliberation the committee approves the existing protocol. **SEC Recommendation Dated 26-02-2015:** After detailed deliberation the committee opined that the protocol should include base line data of patient, CRF should include Echo Cardiographic assessment at base line and all follow up. Accordingly revised CRF and protocol should be submitted to this office for further review.

Annexure-II

List of 12 cases of clinical trial proposals other than GCT/NCE along with evaluations and recommendations of the Technical Committee in 25th Meeting.

Sl No	Name of the Drug	Firm Name	Recommendation of the Technical Committee
1.	Varicella Vaccine (Live Attenuated, Freeze dried IP)	M/s Cadila Healthcare Ltd	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
2.	Permethrin 5% Cream	M/s Cadila Healthcare Ltd	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
3.	Tacrolimus 0.03%	M/s Intas Pharmaceuticals Limited	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
4.	Tacrolimus ointment 0.1%	M/s Intas Pharmaceuticals Limited	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
5.	Ebastine	M/s Micro Labs Ltd	After detailed deliberation, the Committee opined that opinion of Pulmonary/ ENT experts may be taken to decide further.
6.	Methylcobalamin	M/s Troikaa Pharmaceuticals Limited	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation subject to the condition that the study shall be conducted in minimum 100 patients.
7.	Recombinant Human Granulocyte Colony Stimulating Factor	M/s Bio Genomics Limited	The Committee after deliberation observed that the study is proposed to be carried out in healthy volunteers. Therefore, the Committee opined that the firm shall submit published report of PK/PD and safety studies carried out in healthy human volunteers with this drug for further deliberation by the Technical Committee.
8.	Neutrogen (GCSF)	Virchow Biotech Private Limited	The Committee after deliberation observed that the study is proposed to be carried out in healthy volunteers. Therefore, the Committee opined that the firm shall submit published report of PK/PD and safety studies carried out in healthy human volunteers with this drug for further deliberation by the Technical Committee.

9.	PEG Neutrogen (PEG GCSF)	Virchow Biotech Private Limited	The Committee after deliberation observed that the study is proposed to be carried out in healthy volunteers. Therefore, the Committee opined that the firm shall submit published report of PK/PD and safety studies carried out in healthy human volunteers with this drug for further deliberation by the Technical Committee.
10.	Zilver PTX Drug-Eluting Peripheral Stent	Cook India Medical Devices Pvt Ltd,	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
11.	Tacrolimus 0.1% Topical ointment (Export purpose)	M/s Intas Pharmaceuticals Limited	After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
12.	Darbepoetin Alfa	M/s Hetero Drugs Limited,	The firm submitted the published report of Pharmacokinetics studies of Darbepoetin Alfa in healthy volunteers published in international journal. After review of the same, the Committee noted that there was no safety report in healthy volunteers in the submitted published report. Therefore, the Committee recommended that the firm should submit published safety report in healthy human volunteers before the Committee for further deliberation.

Annexure-III

Recommendation of the SEC and Technical Committee:

Sr. no.	Drug Name	Name of the Firm	Indication	Recommendations
1.	Hydroxy Chloroquine Sulfate Tablet 300mg	M/s Ipca Laboratories Ltd	For the treatment of patients with lower body weight i.e) 45 to 60kg in Rheumatoid arthritis, systemic Lupus Erythematous & Polymorphic light Eruption	**Recommendation of the Technical Committee:** The Committee opined that firm may be requested to make a presentation before the committee to decide further for considering Phase IV trial waiver. **Recommendation of the SEC dated 19.02.2014:** The Committee opined that the proposed strength of 300mg may be given for the patients with lower body weight i.e 45 to 60kg. The committee opined that Phase IV trial protocol shall be submitted within 6 months. As per the NDAC recommendation our Directorate issued a Form 46 permission (MF188/2014) on 08-09-2014 for the above mentioned indication with the condition of conductance of Phase IV clinical trial. The firm requested CDSCO to consider waiver for conduct of Phase IV trial and the proposal was deliberated in 16th SEC (Analgesic, Anaesthetic & Rheumatology) held on 23-01-2015. **Recommendation of SEC dated 23.01.2015:** The Committee recommended that firm should conduct Phase- IV clinical trial within the stipulated time. The firm again submitted a request letter to CDSCO on 05-03-2015 to consider waiver to conduct Phase IV trial for above formulation.

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