MINUTES OF 45th MEETING OF THE TECHNICAL COMMITTEE HELD ON 22.01.2019 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. S. Venkatesh,** Director General of Health Services, Nirman Bhawan, New Delhi	Chairman
2.	**Dr. Nandini Kumar,** Former Dy. Director General Sr. Grade, Adjunct Professor, KMC, Manipal, Chennai.	Member
3.	**Dr. Kamlakar Tripathi,** Prof., Dept. of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005.	Member

Special Invitee:-

1.	**Dr. Sameer Bakshi,** Professor, Department of Oncology, AIIMS, New Delhi - 110 029.
2.	**Dr. Devesh Gupta,** Additional DDG (TB), Ministry of Health and Family Welfare.
3.	**Dr. Rupak Singla,** HOD, Department of Tuberculosis & Chest, National Institute of TB and Respiratory Diseases, New Delhi.

From CDSCO:

1.	**Dr. S. Eswara Reddy,** Drugs Controller General (India)	
2.	**Mr. A. K. Pradhan,** Deputy Drugs Controller(India), CDSCO (HQ)	

The Chairman welcomed the members of the committee and special invitees for the 45th Technical Committee meeting. **Thereafter, total 4 proposals were placed before the**

committee for consideration. The committee discussed the proposals one after another. The details of the proposals and recommendation of the committee are as under:

Agenda No. 1

Proposal of M/s MSN Laboratories Pvt. Ltd for Permission to manufacture and market of Fingolimod Bulk and Fingolimod Capsules 0.5mg with clinical trial waiver.

Applicant: M/s MSN Laboratories Pvt. Ltd.

Drug Name: Fingolimod Capsules 0.5mg

Fingolimod is metabolized by Sphingosine kinase to active metabolite, Fingolimod-phosphate. Fingolimod-phosphate is a sphigosine1-phosphate receptor modulator, and bind with high affinity to Sphingosine 1-phosphate receptor 1, 3, 4, and 5. Fingolimod-phosphate blocks the capacity of lymphocytes in peripheral blood. The mechanism by which Fingolimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocytes migration into the central nervous system.

Type of Application: Manufacture and market permission of Fingolimod Bulk and Fingolimod Capsules.

Proposed Indication: Fingolimod Capsules 0.5mm is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Regulatory Status: The drug is approved in Australia, Canada, Europe and the USA.

The firm has requested for waiver of local clinical trial. Accordingly, the firm has submitted the following justification:-

i. The drug is indicated for serious/life threatening conditions.

ii. The drug is indicated for a disease of special relevance to the Indian scenario.

iii. The drug is indicated for a disease for which there is no or limited satisfactory therapeutic options.

iv. The drug is indicated for a rare disease or a disease in which patient population is scanty and conducting clinical trial will take long time.

v. Existence of significant unmet medical needs or significant public health issue.

vi. Multiple sclerosis is one of the most serious conditions. There are no satisfactory treatment options available in India for this serious conditions, but there is no improvement in limitation of these treatments

vii. Fingolimod has been approved in various Europe as an orphan drug for the treatment of rare disease

viii. There are numbers of evidence on the safety profile of Fingolimod long term clinical studies on which basis it was approved.

The proposal was earlier examined in consultation with Subject Expert Committee (Neurology and Psychiatry) in its meeting held on 11.04.2018.

Recommendation of the Subject Expert Committee (Neurology and Psychiatry) dated 11.04.2018:- The firm presented their proposal along with BE study report before the committee. The committee noted that the drug is approved in Australia, Canada, Europe and US. The committee also noted that in case of Teriflunamide used for same indication, the Technical Committee in its 39th meeting held on 06.09.2017 had recommended for approval of the drug with waiver of local clinical trial subject to condition to conduct the Phase IV clinical trial in the country. After detailed deliberation, the committee recommended for grant of permission to manufacture and market the drug subject to the condition that the firm should conduct a Phase IV clinical trial. Accordingly, the firm should submit the protocol for review by the committee before launching the product in the market. The drug should be sold by retail only on prescription of Neurologists.

It has been decided to refer the matter to Technical Committee for deliberation, whether based on the justification submitted by the firm and recommendation of SEC (Neurology and Psychiatry) dated 11.04.2018, permission to manufacture and market Fingolimod Capsules 0.5mg can be given to the firm with local clinical trial waiver.

The firm presented their proposal for approval of the drug with local CT waiver. The firm has already conducted the BE study with their formulation and submitted the same to USFDA as part of ANDA and the USFDA has already granted tentative approval for the same. The firm has also presented their justification that as per ICMR definition, a disease is defined rare in India when it affects fewer than 1 in 2500 individual (i.e., 40 in 1 lakh individuals). As per multiple sclerosis society of India, 2 lakh MS people are there in India. Considering Indian population 1.33 billion, there are 15 MS people in 1 lakh individuals. Thus, MS can be considered as rare disease in India.

Recommendation:- The committee after detailed deliberation agreed with the recommendations of SEC and recommended for grant of permission to manufacture and market Fingolimod 0.5mg Capsules for the proposed indication subject to the condition that the firm should conduct a Phase IV clinical trial as recommended by SEC. Accordingly, the firm should submit the protocol for review by the SEC before launching the product in the market. The drug should be sold by retail only on prescription of Neurologists/Internal medicine Specialists. The committee also recommended that the firm should specifically mention the following in the prescribing information:

i. The patient should be monitored for Bradyarrhythmia and Atrioventricular blocks during Fingolimod treatment initiation.

ii. Patients with symptoms and signs consistent with *Herpes Viral Infection* should undergo prompt diagnostic evaluation and appropriate treatment.

Agenda No. 2

Proposal of M/S Sanofi –Synthelabo (India) Pvt. Ltd. for Permission for import and marketing of Refapentine film coated tablet 150mg (PRIFTIN®) with clinical trial waiver.

Applicant: M/S Sanofi –Synthelabo (India) Pvt.Ltd.

Drug Name: Refapentine Film Coated Tablet 150mg (PRIFTIN®).

Type of Application: Import and marketing permission of Refapentine film coated tablet 150mg (PRIFTIN®).

Proposed Indication: Refapentine is indicated for the treatment of latent tuberculosis infection caused by Mycobacterium tuberculosis in adults and children 2 years and older who are at high risk of progression to tuberculosis disease (Including those in close contact with active tuberculosis patient, recent conversion to positive tuberculin skin test, HIV infected patients or those with pulmonary fibrosis on radiograph). Active TB should be ruled out before imitating treatment for latent TB infection.

Regulatory Status: It is reported that the Refapentine(Priftin) was approved by USFAD for LTBI indication in 2014. Later it is also approved in Taiwan on 31-08-2017, Hongkong on 19-12-2017 and Philippines on 18-05-2018.

The proposal was examined in consultation with Subject Expert Committee (Antimicrobial & Antiviral) in its meeting held on 10.10.2018.

Recommendation of the Subject Expert Committee (Antimicrobial & Antiviral) dated 10.10.2018:- Firm presented their proposal along with non-clinical & clinical data generated outside India in support of drug for treatment of latent TB infection with a request for local Clinical Trial waiver.

The committee noted that India aims to eliminate TB by 2025. Treatment of LTBI is an important component for elimination of TB in India. The Rifapentine is included in WHO Essential Medicines List. The drug is reported to have advantage of once weekly regimen for 3 months for treatment of LTBI. After detailed deliberation the committee considered that there is an unmet need of this drug for treatment of LTBI & recommended that in public interest permission to import & market the drug should be granted with local clinical trial waiver for the treatment of LTBI subject to the following conditions:

I. This drug should be available only through National TB control program in the treatment of LTBI.

II. Phase IV clinical trial shall be conducted by the firm through the programme, for which protocol should be developed in consultation with the programme expert & submitted to CDSCO for review through SEC.

It has been decided to refer the matter to Technical Committee for deliberation, whether based on the justification submitted by the firm and recommendation of SEC (Antimicrobial

& Antiviral) dated 10.10.2018, permission to manufacture and market Refapentine film coated tablet 150mg can be given to the firm with clinical trial waiver.

Firm presented their proposal along with non-clinical & clinical data generated outside India in support of the drug for treatment of latent TB infection with a request for local Clinical Trial waiver.

Recommendation:- The committee after detailed deliberation agreed with the recommendation of the Subject Expert Committee (Antimicrobial & Antiviral) dated 10.10.2018 and recommended for grant of permission to import and market the drug in the country with local clinical trial waiver subject to the same conditions as recommended by the SEC.

Agenda No. 3

Proposal of M/s. Lambda Therapeutic Research Ltd for Permission to conduct Comparative Bioavailability study of Rigosertib soft gelatin capsule 280 mg with Rigosertib oral solution 75mg/ml (3.73 mL) [At a dose of 280 mg]; Protocol No. 0547-17 for export purpose only-regarding.

This office has received an application for the grant of permission to conduct Comparative Bioavailability study of Rigosetib soft gelatin capsule 280 mg with Rigosertib oral solution 75mg/ml (3.73 mL) [At a dose of 280 mg]; Protocol No. 0547-17 for export purpose only.

Applicant: M/s. Lambda Therapeutic Research Ltd.

Drug Name: Rigosertib soft gelatin capsule 280 mg & Rigosertib oral solution 75mg/ml (3.73 mL) [At a dose of 280 mg].

Rigosertib is being developed as a new therapy for the treatment of MDS (myelodyspiastic syndrome) and other hematologic malignancies, and as an anti-cancer agent in advanced cancer and solid tumors. Rigosertib is a small molecule that binds to a key regulatory domain contained in all rat sarcoma (Ras) effector proteins. Binding to this domain, also called the Ras binding domain (RBD), prevents the interaction of effector molecules with Ras, thus blocking their activation.

Type of Application: For Permission to conduct Comparative Bioavailability study.

Proposed Indication: Rigosertib is being developed as a new therapy for the treatment of MDS (myelodysplastic syndrome) and other hematologic malignancies, and as an anti-cancer agent in advanced cancer and solid tumors.

Regulatory Status: It is reported that the drug Rigosertib in any dosage form is not marketed in any country and it is under late stage clinical development phase. Sponsor (Onconova Therapeutics, Inc.) has conducted Phase I/II/III studies on Rigosertib Parenteral and oral formulation in India in past as a part of Global Clinical Trial.

The firm has proposed to conduct Comparative Bioavailability study entitled **"An open label, randomized, two-period, two-sequence, single oral dose, crossover, comparative bioavailability study of Rigosertib soft gelatin capsule 280 mg with**

Rigosertib oral solution 75mg/ml (3.73 mL) [At a dose of 280 mg] in normal, healthy, adult, human male subjects under fasting condition". 12 normal, healthy, adult, human male subjects will be enrolled in this study at 01 site with total duration for the study from check in of period-I till the end study examination is planned to be at least 07 days.

The objective of this Comparative Bioavailability study is to determine Primary pharmacokinetics (PK) Parameters i.e. AUC0-t and AUC0-∞ & Secondary pharmacokinetic (PK) Parameters i.e. Tmax, Cmax, AUC_% Extrap_obs, R^2 adjusted, z and $t_{1/2}$.

The proposal was examined in consultation with Subject Expert Committee (Oncology & Haematology) in its meeting dated 06.02.2018.

Recommendation of the Subject Expert Committee (Oncology & Haematology) dated 06.02.2018:- The firm had presented the proposal before the committee. After detailed deliberation the committee raised the following concerns:-

1. This drug is an anticancer drug and is under consideration for indications of MDS, pancreatic and ovarian cancer.
2. The committee also noted that this drug has adverse effects which occur in up to 20-25% subjects. In view of this, the issue of subjecting the healthy volunteers to this drug is a safety concern. Hence, the committee did not recommend the proposal.

Firm submitted their reply and stated that:

1. Rigosertib is an anti-cancer agent for advanced cancer and solid tumors, and other hematologic malignancies. It acts by binding to the Ras-binding domain of tumor cells in various solid tumors and hematological malignancies. Rigosertib binding to Ras effector proteins results in inactivation of these proteins, which leads to mitotic arrest and apoptosis of tumor cells. *In vitro* studies demonstrated that rigosertib had differential effects on cell cycle progression in tumor cells versus normal cells. In normal cells, cell cycle progression was reversibly arrested at the G1 stage, with minimal apoptosis. Thus, Rigosertib interacts with cancer cells and less so with healthy cells due to its unique mechanism of action. As the proposed study is designed for healthy human volunteers and for them to receive a sub-therapeutic single dose of oral rigosertib, we do not foresee any significant risk to them by the subject drug. Furthermore, it is a standard practice globally to establish pharmacokinetic parameters in healthy volunteers once the risk benefit profile of the drug has been established in patients. Finally, it would be unethical to expose end-stage cancer patients to a sub-therapeutic single dose of a drug.
2. They have further explained that the adverse events occurred during previous clinical trials were: Fatigue, Nausea, Diarrhea, Vomiting, Constipation etc. which should not be considered as major or serious adverse events and can be managed easily during the course of trial. These adverse events were also seen in cancer patients with co-morbidities and confounding medications which may explain these adverse events and thus they may not be uniformly related to Rigosertib. In

addition, these adverse events were only seen after repeated dosing, higher drug exposures, and multiple cycles; not with a single sub-therapeutic dose.

Thus; adverse events reported were only observed in the studies with repeated oral dose of Rigosertib **560 mg or 700 mg BID.** Whereas; the proposed study is to be conducted with **Single oral dose of Rigosertib 280 mg** which is at least 75% less than above mentioned doses. Also, please note that above mentioned adverse events were reported in patients after long duration of treatment. Hence; single oral dose of 280 mg Rigosertib in healthy humans is not anticipated to cause any harm to the subjects.

The proposed study is to be conducted in 12 healthy subjects. Subjects will be monitored closely and if we find any issue in the first period of the study then we would not dose the additional subjects. We will have the Data and Safety Monitoring Board (DSMB) to evaluate the AEs/ SAEs if any are observed during first period; if agreed and determined this is acceptable for this important trial to move forward. In such case, they would carry out the dosing in second period only after approval from DSMB. They have assured assure to take all the precautionary measures for the safety of the subjects in the study.

The proposal was deliberated in Grievance Committee held on 31.07.2018, CDSCO, (HQ), based on the justification submitted by the firm, After detailed deliberation the grievance committee recommended that, this proposal may be redeliberated in upcoming SEC (Oncology & Haematology).

Accordingly, the proposal was again deliberated in SEC (Oncology & Haematology) in its 74th meeting held on 30.08.2018:

Recommendation of the SEC (Oncology & Haematology) dated 30.08.2018:- The drug was developed in USA and also proposed to be studied on healthy subjects. Further, the drug is an anti-cancer drug. In view of the above, the committee recommended that the application to conduct Phase I clinical trial on healthy volunteers in India may not be considered.

However, the firm did not agree with the recommendation of SEC and had requested to deliberate the proposal in Technical Committee for grant of permission to conduct Comparative Bioavailability Study of Rigosertib Soft Gelatin Capsule 280 mg with Rigosertib oral solution 75mg/ml (3.73 mL) [At a dose of 280 mg]; for export purpose only.

The firm presented their justification for conducting Comparative Bioavailability Study of Rigosertib Soft Gelatin Capsule 280 mg with Rigosertib oral solution 75mg/ml (3.73 mL) [At a dose of 280 mg]; for export purpose in healthy subjects in India.

Recommendation:- After detailed deliberation, the committee agreed with the recommendation of the SEC that the proposed study in 12 healthy volunteers only in India should not be approved. The committee however opined that in case, the study is proposed to be conducted both in USA and India (on 6 healthy volunteers in each country), the proposal can be taken up for further consideration. In such a scenario, the firm should submit their proposal along with the approval from USFDA for the proposed study for review.

Agenda No. 4

Proposal of M/S Sun Pharma Laboratories Limited for grant of manufacturing and marketing permission of FDC of Cephalexin Extended release and Clavulanate Potassium Tablets (375mg+125mg) and (750mg+125mg).

Applicant: M/S Sun Pharma Laboratories Limited.

Drug name: Fixed dose combination of Cephalexin Extended release and Clavulanate Potassium Tablets (375mg+125mg) and (750mg+125mg).

Type of Application: Manufacturing and Marketing.

Proposed Indication: In the treatment of Upper Respiratory Tract infections (URTI) and in treatment of uncomplicated skin and soft tissue infections.

Regulatory Status: FDC not approved in any country.

Earlier, the firm conducted a non-comparative clinical trial and results of the study was placed before NDAC in its meeting held on 25.05.2012.

Recommendations of NDAC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) dated 25.05.2012:- FDC is not approved in any country and further the clinical trial data generated by the firm is not adequate to support the efficacy of the formulation. Therefore, the committee did not recommend for the FDC.

On subsequent response of the applicant, the proposal was again deliberated in NDAC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) held on 12.04.2013.

Recommendations of NDAC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) dated 12.04.2013:- Committee recommended that a comparative double blind trial of Cephalexin+ Clavulanate Potassium vs Cephalexin should be conducted to show the superiority of the FDC. Protocol etc. should be submitted to the committee for examination.

On subsequent response of the applicant, the proposal was again deliberated in NDAC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) held on 18.06.2014.

Recommendations of NDAC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) dated 18.06.2014:- As per the recommendations of the NDAC previously, firm presented the protocol before the committee for conducting the clinical trial. The committee recommended for conducting the proposed trial. In terms of Risk/ Benefit, the committee opined that the FDC will have superiority over Cephalexin alone. Regarding unmet need and Innovation vis a vis current therapy, the committee opined that the proposed FDC will

be useful in the said resistant patients. The committee also recommended including at least one site from North-East region of India.

However, firm vide letter dated 20.06.2014 informed that experts during NDAC meeting held on 18.06.2014 agreed that the comparative trial will not show any significant superiority of FDC over cephalexin alone on the basis of scientific explanation submitted by the firm.

The proposal was also placed before Technical committee in its meeting held on 17.11.2014. Accordingly the firm was granted permission to conduct Phase III clinical trial with FDC of Cephalexin Extended Release (375 mg) and Clavulanate Potassium (125 mg) tablets with Cephalexin Extended release (375 mg) tablets – A randomized Double-blind study on 18.12.2014.

Subsequently, the firm has submitted the clinical report to this office on 05.04.2017 and the clinical report was placed in SEC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) meeting held on 22.09.2017.
Recommendations of SEC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) dated 22.09.2017:- "The firm presented the results of two phase III clinical trials of FDC of Cephalexin + Clavulanate Vs Cephalexin alone. Committee observed that there was no statistically significant difference of efficacy between the two groups. Hence based on these data there is no justification for this combination".

On subsequent response of the applicant, the proposal was again deliberated in SEC (Antimicrobial, Antiparasitic, Antifungal and Antiviral)held on 12.12.2017.

Recommendations of SEC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) held on 12.12.2017:- "The firm presented their justification for approval of the product based on clinical trial data generated. The Committee deliberated in detailed and reiterated its earlier stand that there was no statistically significant difference of efficacy between the two groups. Hence based on these data there is no justification for this combination".

However, the firm did not agree with the recommendations of SEC and has requested to deliberate the proposal in Technical Committee for considering the application for grant of manufacturing and marketing permission of the FDC of Cephalexin Extended release and Clavulanate Potassium Tablets (375mg+125mg) and (750mg+125mg). The firm has mentioned that:

1. The trial proposal was evaluated by the NDAC and approval was granted.
2. The trial was not a superiority trial and hence showing statistical significant difference of FDC was not possible. The result of the clinical trials are comparable and in lines with the approved protocol with non-inferiority design.

3. Various guidance documents of United States Food and Drug Administration (USFDA) and European Medicine Agency (EMA) recommend non-inferiority design for conducting clinical trials with antimicrobials.
4. Antimicrobials are also approved internationally based on non-inferiority clinical trial.
5. CDSCO guideline on FDC product also recommends non-inferiority clinical trial design in case of combination with clavulanic acid.
6. **In-vitro study proved that the combinations shows MIC >4 fold fall as compared to Cephalaxin at MIC50 and MIC90 in both combination ratio 6:1 and 3:1 against Beta-Lactmase producing eighty two strains of clinical isolates taken in the study.**

On subsequent response of the applicant, the proposal was placed in 44th Technical Committee meeting held on 05.09.2018.

Recommendations of 44th Technical Committee meeting held on 05.09.2018:- The firm presented the clinical data as well as some in vitro data in support of efficacy of the FDC in resistant strain of MSSA (Methicillin-Susceptible Staphylococcus aureus) before the committee. After detailed deliberation the committee recommended that firm should conduct an in vitro study to assess the efficacy of the FDC in resistant strain of MSSA in community setup with statistically justified sample size. Accordingly, the firm should submit a protocol for the in-vitro study with statistical justification on sample size along with Phase-IV clinical trial protocol for review by the Technical Committee. If the results in-vitro study is found satisfactory, the FDC may be considered for approval subject to the Phase-IV clinical trial.

As per the recommendation of Technical Committee the applicant has now submitted In-vitro study protocol and Phase IV clinical trial protocol.

The firm presented *In-vitro* study protocol as well as Phase IV clinical trial protocol before the committee.

Recommendation:- The committee after detailed deliberation recommended for grant of permission to conduct the proposed *In-vitro* study as per the protocol presented. The firm should submit their proposal along with the in-vitro study results for further consideration of approval of the said FDC. The Phase IV clinical trial protocol should be deliberated in the SEC once the proposal is considered for approval.

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