MINUTES OF 43rd MEETING OF THE TECHNICAL COMMITTEE HELD ON 12.04.2018 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. Promila Gupta, Director General of Health Services, Nirman Bhawan, New Delhi	Chairman
2.	Dr. Kamlakar Tripathi, Formery, Prof. Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi.	Member
3.	Dr. Nandini Kumar, Former Dy. Director General Sr. Grade, Adjunct Professor, KMC, Manipal, Chennai.	Member
4.	Dr. Yash Paul, Prof. & Head, Dept. of Cardiology, PGIMER, Chandigarh.	Member

Special Invitee:

1. Dr. Sudhir Gupta
   Prof & Head, Government Medical College & Super Specialty Hospital, Nagpur

From CDSCO:

1. Dr. S. Eswara Reddy
   Drugs Controller General (India)

2. Sh. A.K Pradhan
   Deputy Drug Controller (India)

3. Sanjeev Kumar
   Deputy Drug Controller (India)

4. A Senkathir
   Deputy Drug Controller (India)

The Chairman welcomed the members of the committee for the 43rd Technical Committee meeting. Thereafter, total seven proposals which were not considered for approval by the SECs were placed before the committee for consideration..The committee discussed the proposals one after another. The details of the proposals and recommendations of the committee are as under:

Agenda No. 1

Applicant: M/s MSD Pharmaceuticals Pvt. Ltd.

Drug Name: Fixed Dose Combination of Ceftolozane 1gm + Tazobactam 0.5gm Injection

Ceftolozane exerts bactericidal activity by inhibiting essential penicillin-binding proteins (PBPs), resulting in inhibition of cell-wall synthesis and subsequent cell death. Ceftolozane is an inhibitor of the essential Pseudomonas aeruginosa PBP1b, PBP1c, PBP2, PBP3 and PBP4 and Escherichia coli PBP3.

Tazobactam is an irreversible inhibitor of β lactamases and can bind covalently to chromosomal and plasmid-mediated bacterial β-lactamases. In a kinetic study, tazobactam demonstrated reversible binding kinetics prior to irreversible inactivation.

Type of Application: Import and market

Proposed Indication: Indicated for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms:-

- Complicated Intra-abdominal infections
- Complicated Urinary Tract Infections, including Pyelonephritis.

Regulatory Status: The drug is approved in many countries including USA, UK, Austria, Germany etc.

Recommendation of the SEC (Antimicrobial, Antiviral, Antiparasitic and Antifungal) held on 22.09.2016:

The company presented the data of Ceftolozane (1mg) + Tazobactam (0.5gm) Injection. The Committee noted the following:-

1. A Global trial with this formulation was referred to in which more than 1000 patients were recruited in which only 38 were Indian.
2. The Committee is of the opinion that this number of patients is inadequate for approval of the drug in India.
3. A Phase III clinical trial in Indian patients is required.

Accordingly, firm may submit Phase III clinical trial protocol to DCG (I) office.

On subsequent response of the applicant, the proposal was again deliberated in SEC (Antimicrobial & Antiviral) held on 12.12.2017 and the committee recommended that the firm presented their justification for Phase III clinical trial waiver before the committee. The committee observed that the firm did not present any additional data / justification in support of waiver of clinical trial. Therefore, the committee reiterated in its earlier recommendation that firm should conduct Phase III clinical trial in India.

However, the firm did not agree with the recommendation of SEC. Accordingly the proposal was deliberated in the Technical committee meeting.

Recommendation:- The committee after detailed deliberation recommended for grant of permission to import and market the fixed dose combination of Ceftolozane 1gm+ Tazobactam 0.5 gm injection indicated for the treatment of patients 18 years or older with infections caused by designated susceptible microorganisms of Complicated Intra-abdominal infections & Complicated Urinary Tract Infections, including Pyelonephritis in ICU setting only, subject to the condition that the firm should conduct Phase IV clinical trial within 12 months. Accordingly firm shall submit Phase IV clinical trial protocol before launching the product in the market.

Agenda No. 2

Proposal of M/s Natco Pharma Limited for grant of manufacture and marketing permission of Fixed Dose Combination (FDC) of Daclatasvir 60 mg + Sofosbuvir 400 mg film coated tablets with request for waiver of local clinical trial.

Applicant: M/s Natco Pharma Limited

Drug Name: FDC of Daclatasvir 60 mg + Sofosbuvir 400 mg film coated tablets.

Type of Application: Manufacture and market

Proposed Indication: It is indicated for treatment of all genotypes chronic Hepatitis C virus (HCV) infection.

Recommendation of the SEC (Antimicrobial, Antiviral, Antiparasitic, Antifungal) held on 22-09-2016:

The proposal was deliberated by the Committee on 23.3.2016 and the same was deferred to next meeting and the Committee recommended for approval of the FDC with Bioequivalence Study.

Subsequently it was felt that a wider consultation is required as this FDC which is not approved anywhere in any developed country and there could be safety concern when these two drugs are combined together. The proposal was re-examined and in the meanwhile the firm also proposed for Phase-III Clinical trial. The Committee deliberated on the issue and recommended that:-

i. In all the FDCs/Combikit, Firm should conduct Bioequivalence Study as well as Phase-III Clinical Trials for which protocol may be submitted.

ii. M/s Natco Pharma informed the committee that they have already conducted a Bioequivalence Study on 24 healthy subjects for export purpose. The firm was asked to submit the BE Study data to the office of DCG(I).

iii. M/s Natco Pharma also presented a Phase-III Clinical trial protocol in which following recommendations were made:

a) Before the start of Clinical trial, BE Study data shall be evaluated by the office of DCG(I) and if found satisfactory CT permission may be issued.

b) In the proposed Clinical trial protocol, CKD patients with Creatinine >1.5 mg should be excluded.

c) The patients receiving Amiodarone should be excluded.

d) Cardiac evaluation including ECG and Echocardiogram should be conducted at baseline, 2weeks, 4weeks, 12 weeks and 24 weeks.

e) Study duration shall be 24 weeks.

f) Study shall be conducted in the sites geographically distributed in the country.

Accordingly, the firm shall revise the Clinical trial protocol. The other two firms M/s Hetero and M/s Mylan also are required to follows the same recommendations as recommended for M/s Natco for conducting CT/BE Study. It was also observed that M/s Hetero does not have approval for Daclatasvir 30mg tablets.

On subsequent response of the applicant, the proposal was again deliberated in SEC (Antimicrobial, Antiviral, Antiparasitic, Antifungal) held on 11-04-2017

Recommendation of the SEC (Antimicrobial, Antiviral, Antiparasitic, Antifungal) held on 11-04-2017:

The firm presented the BE study data conducted for export purpose as recommended by the Committee in the previous meeting held on 22.09.2016. The committee reviewed and found the BE data satisfactory. Further the firm also requested for the CT waiver based on the recent circular issued by DCG(I) on 20.03.2017. The Committee did not recommended for the CT waiver as the proposed drug does not fall under the category of extreme urgency.

The firm has made representation before DCG(I) that similar FDC of Sofosbuvir + Velpatasvir has been considered by SEC (Gastroenterology and Hepatology) in its meeting held on 23.03.2017 and the committee has recommended for import and marketing of this FDC with local clinical trial waiver subject to Phase IV clinical trial.

It may please be noted that based on the SEC recommendation permission was granted to import/ manufacture and marketing of the drug FDC of Sofosbuvir + Velpatasvir on 04.05.2017 with local clinical trial waiver.

Justification for clinical trial waiver submitted by the firm:-

- Daclatasvir is approved in India for use with Sofosbuvir for the treatment of genotype 3 patients with chronic hepatitis C virus (HCV) infection.
- Daclatasvir must be concomitantly used with Sofosbuvir and cannot be used independently.
- Fixed Dose Combination of Daclatasvir 60 mg + Sofosbuvir 400 mg will be convenient for the patients, thus improving the compliance as well as intended therapeutic effect.
- To achieve better SVR, it is important for the patients not to miss any of the two drugs. Hence, the FDC can be very useful in this aspect.
- The FDC of Daclatasvir 60 mg & Sofosbuvir 400 mg complies with WHO's Guidelines for Registration of FDC Medicinal Products.
- This FDC also qualifies the waiver criteria issued by the DCGI on March 20, 2017.
- Daclatasvir and Sofosbuvir are designated as Essential Medicines in the WHO Model List of Essential Medicines.
- The potential benefits of the FDC of Daclatasvir 60 mg & Sofosbuvir 400 mg significantly outweigh any risk involved.
- As Daclatasvir 60 mg & Sofosbuvir 400 mg are already approved for use concomitantly, we request the approval of the FDC on the basis of a Bioequivalence Study in healthy volunteers.

However, the firm did not agree with the recommendation of SEC and the proposal was deliberated in Technical Committee meeting held on 25.09.2017. The committee discussed the justification submitted by the firm for clinical trial waiver. After detailed deliberation, the committee opined that two hepatologist may be invited in next meeting for deliberation on the issue and firm may be invited in the next meeting for deliberation on the issue and firm may be asked for presentation of the justification along with clinical trial data, if any.

Accordingly the proposal was deliberated again in the Technical Committee meeting on 12.04.2018.

Recommendation:- The committee noted that Daclatasvir Dihydrochloride Tablet 30mg/60mg has been approved in the country on 14.12.2015 for use with Sofosbuvir for the treatment of patient with chronic hepatitis C virus (HCV) genotype 3 infection. The firm has already conducted bioequivalence study with the FDC.

The committee after detailed deliberation recommended for grant of permission to manufacture and market Fixed Dose Combination (FDC) of Daclatasvir 60 mg + Sofosbuvir 400 mg film coated tablets with waiver of local clinical trial subject to condition that the firm should conduct the Phase IV clinical trial. Accordingly, Phase IV clinical trial protocol should be submitted before launching the product in the market.

Agenda No. 3

Proposal of M/s Claris Otsuka Private Limited for grant of import and marketing permission of Fixed Dose Combination (FDC) of FDC of % amino Acid and 7.5% Glucose with Electrolytes and Vitamin B1 Injection with request for waiver of local clinical trial.

Applicant: M/s Claris Otsuka Private Limited

Drug Name: FDC of % amino Acid and 7.5% Glucose with Electrolytes and Vitamin B1 Injection.

Type of Application: Import and market

Proposed Indication: It is indicated for supply of amino acids, electrolytes, vitamin B1 and water in patients with conditions like mild hypoproteinemia or mild malnutrition due to inadequate oral intake before and after surgery.

Regulatory Status: The drug is registered in Japan, Taiwan, Thailand, Hongkong, Vietnam & Philippines and launched in Japan, Taiwan, Thailand and Hongkong.

Recommendation of the SEC (Gastroenterology & Hepatology) held on 23-05-2017:

The firm presented the proposal before the Committee and has requested for CT waiver. The product [BFLUID] is different from available products in respect to presence of Vit B1. The trial data presented by the firm comparing the two products showed that B1 levels were maintained in BFLUID group vs the AMINOFLUID group. However, there was no improvement in other biochemical nutritional parameters. Also, it did not translate into the hypothesized benefits of reduction in lactic acidosis, Wernicke's encephalopathy and injection site phlebitis. The committee recommended that the firm should conduct a Clinical trial in India which should be in appropriate patient groups [like alcoholics or other groups with nutritional deficiencies] and well defined clinical endpoints.

On subsequent response of the applicant, the proposal was again deliberated in SEC (Gastroenterology & Hepatology) held on 22-06-2017

Recommendation of the SEC (Gastroenterology & Hepatology) held on 22-06-2017:

The firm presented information about the product and data on its use in other countries. The product has mostly been used in Japan and use in other south east Asian countries is very minimal. The product is an intravenous fluid containing glucose, aminoacids and thiamine. The medical advantage of this product over the currently available simple intravenous fluids was considered as minimal because

i. Amino acids are unlikely to be used for anabolism when calories are inadequate;
ii. The advantage of fixed dose combination thiamine over separate administration of thiamine is minimal.

In view of the above, the criteria for waiver of Clinical Trial were not met. Hence, the committee reiterated previous recommendations of the committee.

However, the firm did not agree with the recommendation of SEC. Accordingly the proposal was deliberated in the Technical committee meeting.

Recommendation:- The Committee after detailed deliberation recommended that firm shall conduct the Phase III clinical trial as per SEC recommendation.

Agenda No. 4

Proposal of M/s Eli Lilly and Company (India) Private Limited for grant of import and marketing permission of Ixekizumab injection 80mg/ml in Prefilled Autoinjector and Prefilled Syringe with request for waiver of local clinical trial.

Applicant: M/s Eli Lilly and Company (India) Private Limited

Drug Name: Ixekizumab injection 80mg/ml in Prefilled Autoinjector and Prefilled Syringe

Type of Application:- Import & market

Proposed Indication: Ixekizumab is indicated for treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy of phototherapy.

Regulatory Status:- Taltz (Ixekizumab) has been approved in US in Mar-2016, EU in Apr 2016 and Japan in Jun 2016.

Recommendation of the SEC (Dermatology & Allergy) held on 27-07-2017:

Firm presented their proposal for seeking marketing authorization with local clinical trial waiver. After detailed deliberation committee noted that, there is no data on Indian population. Therefore, the committee recommended for conduct of Phase III clinical trial in a sizable number of Indian patients.

However, the firm did not agree with the recommendation of SEC. Accordingly the proposal was deliberated in the Technical committee meeting.

Recommendation:- The Committee after detailed deliberation recommended that there is no unmet need for plaque Psoriasis in the country. There are plenty of patients available with plaque Psoriasis. Therefore the firm should conduct Phase III clinical trial in Indian patients as per SEC recommendation.

Agenda No. 5

Proposal of M/s Reliance Life Sciences Private Limited for grant of manufacture and marketing permission of Recombinant human growth hormone (Somatropin) (R-TPR-007) drug substance (bulk 4mg/ml to 8mg/ml) and its formulation (3.33mg/ml) based on clinical trial data generated in 24 patients.

Applicant: M/s Reliance Life Sciences Private Limited

Drug Name: Recombinant human growth hormone (Somatropin) (R-TPR-007) drug substance (bulk 4mg/ml to 8mg/ml) and its formulation (3.33mg/ml).

Type of Application:- Manufacture & market

Proposed Indication:

For Paediatric Patients:

1. For the treatment of paediatric patients with growth failure due to inadequate secretion of endogenous growth hormone (GH).
2. For the treatment of paediatric patients with short stature associated with Noonan Syndrome
3. For the treatment of paediatric patients with short stature associated with Turner Syndrome.
4. For the treatment of paediatric patients with short stature born small for gestational age (SGA) with no catch-up growth by age 2 to 4 years.

For Adult Patients:

For the replacement of endogenous GH in adults with growth hormone deficiency (GHS) who meet either of the following two criteria:

1. Adult Onset (AO): Patients who have GHS, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or
2. Childhood Onset (CO): Patients who were GH deficient during childhood as a result of congenital, genetic, acquired or idiopathic causes. Patients who were treated with rhGH for GHD in childhood and whose epiphyses are closed should be reevaluated before continuation of rhGH therapy at the reduced dose level recommended for GHD adults. According to current standards, confirmation of the diagnosis of adult GHD in both groups involves an appropriate growth hormone provocative test with two exceptions:

   (i) patients with multiple other pituitary hormone deficiencies due to organic disease; and

   (ii) Patients with congenital/genetic growth hormone deficiency.

Regulatory Status:- Recombinant human growth hormone is already approved in India

Firm was granted Phase III clinical trial permission on 03.07.2014 to conduct Phase III clinical trial in 24 patients.

Recommendation of the SEC (Endocrinology and Metabolism) held on 13-02-2018:

The firm made a detailed presentation before the committee. After detailed deliberation the committee opined that-

1. The study is not conducted in any government hospital.
2. The data generated (Clinical, PK, PD) from the study is not adequate to reach conclusion w.r.t the assessment of safety and efficacy parameters.

In view of above, the committee did not recommend for manufacture and market of the drug The committee opined that the firm should generate additional safety and efficacy data of their product.

However, the firm did not agree with the recommendation of SEC. Accordingly the proposal was deliberated in the Technical committee meeting.

Recommendation:- The Committee after detailed deliberation recommended for grant of manufacture and marketing permission of Recombinant human growth hormone (Somatropin) (R-TPR-007) for the proposed indication for paediatrics subject to the condition that the firm should conduct phase IV clinical trial in Paediatrics patient. Accordingly the firm should submit Phase IV clinical trial protocol before launching the product in the market.

Agenda No. 6

Proposal of M/s Sun Pharma Laboratories Limited for grant of manufacture and marketing permission of Prednisone delayed release tablet 5 mg with request for the waiver of the requirement of evaluating the HPA axis suppression in the remaining of the 270 patients in the clinical trial.

Applicant: M/s Sun Pharma Laboratories Limited

Drug: Prednisone delayed release tablet 5 mg.

Prednisone is a synthetic corticosteroid drug that is particularly effective as an immunosuppressant drug. It is used to treat certain inflammatory diseases (such as moderate allergic reactions), some autoimmune diseases, and (at higher doses) some types of cancer, but it has significant adverse effects.

Type of Application: Manufacture and market

Proposed Indication: For the treatment of moderate to severe active rheumatoid arthritis in adults particularly when accompanied by morning stiffness.

Recommendation of the SEC (Analgesics, Anesthetics and Rheumatology) held on 23.01.2015:

The committee recommended the proposed BE/CT studies. However Committee opined that firm shall also establish the effect of MR Prednisolone and plain prednisolone on HPA Axis in atleast first 30 patients and the interim results shall be submitted to CDSCO for further apprising the committee before continuing the trial further on the rest of the patients.

Interim Phase III clinical trial report and bioequivalence report was deliberated in SEC (Analgesic & Rheumatology) held on 09.10.2017 and recommended the following:

The firm presented the interim CT report on 30 patients. The committee observed that in some patients there were significant depression of cortisol level at 30, 60 and 120 mins at end of intervention.

The committee after detailed deliberation, recommended for continuation of the trial on remaining 270 patients subject to following conditions:

1. The sites should be geographically distributed across the country with more Government sites.
2. The measure should be taken to ensure authenticate laboratory investigations for estimation of serum cortisol levels.
3. All patients should be followed for serum cortisol level estimation on the 14th day after intervention.
4. All patients, in which suppressed serum cortisol level is noted, should be followed weekly for the cortisol level till recovery"

The firm had made an appeal to waive off the requirement of evaluating the HPA axis in the remaining of the 270 patients in clinical trial and proposal was deliberated in SEC (Analgesics, Anesthetics and Rheumatology) held on 14.12.2017.

Recommendation of the SEC (Analgesics, Anesthetics and Rheumatology) held on 14.12.2017:

The firm presented the proposal for the waiver of the requirement of evaluating the HPA axis suppression in the remaining of the 270 patients in the clinical trial. After detailed deliberations the committee did not find any reason to change its earlier decision taken during SEC meeting held on 09/10/2017. Hence the waiver requested cannot be granted.

However, the firm did not agree with the recommendation of SEC. Accordingly the proposal was deliberated in the Technical committee meeting.

Recommendation:- The Committee after detailed deliberation recommended that the firm should follow up more patients so as to cover total 30% of patient for serum Cortisol level estimation on 14

day after intervention. Accordingly, the firm should follow-up 60 more patients for serum Cortisol level estimation on 14 day after intervention

Agenda No. 7

Proposal of M/s MSD Pharmaceuticals Private Limited for grant of permission to conduct Phase IV clinical trial entitled, "A prospective, open-label, Phase IV study to evaluate the safety of Pembrolizumab (KEYTRUDA) in subjects with Unresectable or Metastatic Melanoma or PD-L1 positive Non-small Cell Lung Cancer (NSCLC) in India" in 100 combined subjects of Melanoma & NSCLC.

Applicant: M/s MSD Pharmaceuticals Private Limited
Drug: Pembrolizumab Injection 100mg/ml (25 mg/ml in single vial).
Type of Application: Phase IV clinical trial
Proposed Indication: For the treatment of unresectable or metastatic melanoma.
Regulatory Status: Pembrolizumab Injection 100mg/ml (25 mg/ml in single vial) was approved by CDSCO on 16.06.2016.

Recommendation of the SEC (Oncology & Hematology) held on 08.08.2017:
The firm was granted the permission to import and market the drug in June 2016. However, the firm has presented the Phase IV study protocol before SEC today. After detailed deliberation the committee noted that, the proposed no. of subjects of 15 are too less. The committee recommended that the Phase IV trial should be conducted in atleast 100 subjects as availability of patients is not a problem in India.
Firm has submitted revised Phase IV clinical trial protocol, which was deliberated in SEC (Oncology & Hematology) held on 21.03.2018.

Recommendation of the SEC (Oncology & Hematology) held on 21.03.2018:
The firm presented the modified Phase IV protocol for conducting the study for 100 combined subjects of Melanoma & NSCLC before the committee. The committee noted that the NSCLC is not yet approved for this drug. The committee also noted that this drug was granted approval with the condition to conduct a Phase IV trial in 100 subjects on 16.06.2016, and that the firm has not complied with the same. The committee recommended that firm should conduct Phase IV clinical trial in 100 patients of Melanoma as was the decision in the earlier SEC meeting held on 08.08.2017.

However, the firm did not agree with the recommendation of SEC. Accordingly the proposal was deliberated in the Technical committee meeting.

Recommendation:- The Committee after detailed deliberation recommended for grant of permission to market the drug for approval of additional indication of Non Small Cell Lung Cancer (NSCLC) with the waiver of local clinical trial subject to the condition that the firm should conduct phase IV clinical trial in total 150 patients including not less than 25 melanoma patients. Accordingly, Phase – IV protocol should be submitted before launching the product for NSCLC.

The meeting ended with vote of thanks to Chair.

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