# MINUTES OF 46th MEETING OF THE TECHNICAL COMMITTEE HELD ON 01.07.2019 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:-**

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| 1. | **Dr. S. Venkatesh,**<br>Director General of Health Services,<br>Nirman Bhawan, New Delhi. | Chairman |
| 2. | **Dr. Nandini Kumar,**<br>Former Dy. Director General Sr. Grade,<br>Adjunct Professor, KMC, Manipal, Chennai. | Member |
| 3. | **Dr. Kamlakar Tripathi,**<br>Ex. Prof., Dept. of Medicine,<br>Institute of Medical Sciences,<br>Banaras Hindu University, Varanasi – 221005. | Member |
| 4. | **Dr. P. K. Dalal,**<br>Professor & Head, General Psychiatry & Drug de-addiction,<br>King George's Medical University, Lucknow, U.P. | Member |
| 5. | **Dr. B. L. Sherwal,**<br>Director, Rajiv Gandhi Super Speciality Hospital,<br>Tahirpur, New Delhi-110093. | Member |

**Special Invitees:-**

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| 1. | **Dr. Promila Gupta,**<br>Principal Consultant<br>Directorate General of Health Services,<br>Nirman Bhawan, New Delhi. |
| 2. | **Dr. A. P. Dubey,**<br>Professor of Peadiatrics, ESI PGIMER, New Delhi. |
| 3. | **Dr. Sandeep Bansal,**<br>Professor & Head, Department of Cardiology,<br>Safdarjung Hospital, New Delhi - 110 029. |
| 4. | **Dr. P. Ravindran,**<br>Addl. DDG (EMR)<br>Directorate General of Health Services,<br>Nirman Bhawan, New Delhi |

**From CDSCO:**

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| 1. | **Dr. S. Eswara Reddy,**<br>Drugs Controller General (India). |
| 2. | **Mr. A. K. Pradhan,**<br>Deputy Drugs Controller (India), CDSCO (HQ), New Delhi. |
| 3. | **Mr. Sanjeev Kumar,**<br>Deputy Drugs Controller (India), CDSCO (HQ), New Delhi. |

The Chairman welcomed the members of the committee and special invitees for the 46th Technical Committee meeting. **Thereafter, total 9 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. Bayer Pharmaceuticals Pvt. Ltd. for grant of Import& Marketing permission for additional indication of Rivaroxaban tablets 2.5mg with request for waiver of local clinical trial.**

**Applicant:-** M/s Bayer Pharmaceuticals Pvt. Ltd.

**Drug Name:-** Rivaroxaban tablets 2.5mg (add. Indication)

**Type of Application:-** Import & Marketing permission of Rivaroxaban tablets 2.5mg (additional. Indication).

**Proposed Indication:** Rivaroxaban 2.5mg tablet, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

**CDSCO approval status:-**

1. Rivaroxaban Tablet 10mg indicated For the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery on 03.02.2010.
2. Rivaroxaban tablet 15/20mg (Additional strength/indication) on 02.09.2014, indicated as:-
    a) Treatment of deep vein thrombosis and for prevention of recurrent DVT and pulmonary embolism.
    b) For the prevention of stroke and systemic embolism in patient with non-valvular arterial fibrillation.

3. Rivaroxaban tablet 2.5mg (add. strength), Rivaroxaban 2.5mg tablet, co-administered with Acetylsalicylic acid (ASA) alone or with ASA plus Clopidogrel or Ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated Cardiac biomarkers" on 13/07/2015. (To M/s Bayer Pharmaceuticals Pvt Ltd.).

**International approval status:-**

The firm had stated that the proposed new indication is already approved by EMA in August, 2018.

**SEC Recommendation:-**

**Recommendations of SEC (Cardiology) meeting held on 27.11.2018:-** The committee after detailed deliberation recommended that the firm should conduct Phase III clinical trial in Indian population as there is no clinical data in the proposed indication on patients from South East Asia. Accordingly clinical trial protocol should be submitted for review by the committee."

**Recommendations of SEC (Cardiology) meeting held on 04.01.2019:-** In light of recommendation of the previous SEC meeting held on 27.11.2018, the firm presented their justification for waiver of local Clinical trial for approval of the additional indication Committee however noted that no new justification & rationality was presented by the firm in support of their proposal.

After detailed deliberation, committee reiterated its earlier recommendation that phase III clinical trial should be conducted in Indian patients. Accordingly protocol should be submitted for review by the committee".

**Subsequently, the firm had requested for deliberation in the Technical committee meeting, based on the already available efficacy and safety data of Rivaroxaban 2.5mg tablet for CAD/PAD indication quoting various global clinical trials conducted.**

**Firm has given following rationality/justification for Clinical Trial Waiver for *Rivaroxaban 2.5mg tablet*is as follows:**

- Disease in the coronary arteries (as CAD), peripheral arteries (as PAD), or cerebrovascular arteries (cerebrovascular disease) may be present but remain unrecognized until an affected arterial bed develops the first signs or symptoms, representing the clinical presentation of the disease.
- The life expectancy of patients with cardiovascular disease is decreased by 7.7 years and by 9.2 years for patients with prior MI, as compared to healthy people.

- The Registrar General of India reported that CHD led to 17% of total deaths and 26% of adult deaths in 2001-2003, which increased to 23% of total and 32% of adult deaths in 2010-2013
- The patients with CAD/PAD are at high risk for developing acute thrombosis in form of stroke, MI or CV death despite current optimal medical therapy including anti-hypertensive, lipid-lowering and antiplatelet drugs.
- CAD is one of the most important causes of mortality and morbidity in India. The prevalence of CAD ranged from 2.5% to 12.6% was observed in urban parts of India between 1990 and 2012. Therefore to counter the burgeoning epidemic of CAD in India, we urgently need effective and improved treatments for prevention of CAD complications.
- Although ASA is the cornerstone in the long term treatment of CAD/PAD, a high residual risk for atherothrombotic events exists in patients with CAD/PAD despite intensive antiplatelet therapy.
- Thrombogenesis is a complex process that includes adhesion, activation, and aggregation of platelets and thrombus propagation. Therefore the role of antiplatelet and anticoagulant therapy is reasonable.
- Rivaroxaban has the potential to address this unmet need and could significantly reduce the CV events of death, MI and stroke when used in conjunction with the current standard of care.
- In the study population of COMPASS(n = 27395), which included subjects with objectively established CAD or PAD who had no requirement for dual antiplatelet therapy and no requirement for full anticoagulation, the primary efficacy objective for superiority was met for rivaroxaban 2.5 mg bid/ASA 100 mg od compared with ASA 100 mg od alone for the prevention of the composite primary outcome of MI, stroke, and CV death(HR 0.76; 95% CI 0.66-0.86; p value <0.00004).
- The positive treatment effect was also seen in consistent and clinically meaningful relative risk reductions in all components of the composite: 14% for MI (HR 0.86; 95% CI 0.70-1.05), 42% for stroke (HR 0.58; 95% CI 0.44-0.76) and 22% for CV death (HR 0.78; 95% CI 0.64-0.96).
- In addition, two important secondary endpoints were also reduced. All-cause mortality showed a relative risk reduction of 18% and acute limb ischemia showed a relative risk reduction of 45%.
- The benefit was observed early with a constant treatment effect over the entire treatment period.

- Significant 1.7-fold increase of the primary safety outcome (modified ISTH major bleeding events) was observed in patients treated with rivaroxaban 2.5 mg bid in combination with ASA 100 mg od compared to patients who received ASA 100 mg od.
- The incidence rates for fatal bleeding events, non-fatal symptomatic bleeding into a critical organ as well as intracranial bleeding events showed no statistically significant difference.
- Rivaroxaban 2.5 mg has been studied in Indian patients (n = 1469)with recent acute coronary syndromes to reduce the risk of composite end point of death from cardiovascular causes, myocardial infarction, or stroke(ATLAS ACS 2-TIMI 51, phase III trial)enrolled and randomized at 53 study sites. The results of the subgroup analyses for the India cohort were generally consistent with the results of the overall primary efficacy and safety endpoint analysis, on the basis of the same Rivaroxaban2.5mg was approved by Indian health authority for use after ACS.
- In COMPASS trial, the pre-specified composite outcome for net clinical benefit (cardiovascular death, myocardial infarction, stroke, fatal or symptomatic critical-organ bleeding events) was reduced with rivaroxaban 2.5 mg bid in combination with ASA 100 mg OD.

The firm presented their proposal before the Technical committee.

**Recommendation**:- The Committee, after detailed deliberation, recommended for grant of permission to import and market the drug Rivaroxaban 2.5mg tablet for additional indication - co-administered with acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events, with local clinical trial waiver subject to the condition that the firm should conduct a Phase IV clinical trial. Accordingly, the firm should submit the protocol for the Phase IV trial within three months of approval of the additional indication for review.

## Agenda No. 2

**Proposal of M/s. Novartis Pharmaceuticals Ltd. for grant of Import & Marketing permission of Nepafenac Ophthalmic Suspension 0.3% w/v (Additional indication) with request for waiver of local clinical trial.**

Applicant:- M/s. Novartis Pharmaceuticals Ltd.

**Drug Name:** Nepafenac Ophthalmic Suspension 0.3% w/v

**Type of Application:** Permission for Import & Marketing of Nepafenac Ophthalmic Suspension 0.3% w/v (Additional indication)

**Proposed Additional Indication:-**

1. Reduction in the risk of postoperative macular edema associated with cataract surgery in diabetic patients.

**CDSCO approval status:-**

1. This directorate has approved Nepafenac Ophthalmic suspension 0.1%w/v (1mg/ml) on 31.03.2008 indicated for the treatment of pain and inflammation associated with cataract surgery.
2. Nepafenac Ophthalmic Suspension 0.3% w/v is approved on 13.07.2018 Indicated for the treatment of pain and inflammation associated with cataract surgery.
3. Nepafenac Ophthalmic Suspension 0.3%w/v (Additional Indication) is approved on 09.11.2018, Indicated for the treatment of post-operative pain and inflammation associated with cataract surgery.

**International approval status:**

| S. No. | Approval Country | Strength | Approved Therapeutic Indication |
|---|---|---|---|
| 1 | US | Ophthalmic suspension 0.1% (1mg/ml) | NEVANAC ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery |
| 2 | US | Ophthalmic suspension 0.3% (3mg/ml) | ILEVRO (nepafenac ophthalmic suspension), 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery. |
| 3 | UK | Ophthalmic suspension 0.1% (1mg/ml) | 1. to prevent and relieve eye pain and inflammation following cataract surgery on the eye<br>2. To reduce the risk of macular edema (swelling in the back of the eye) following cataract surgery on the eye in diabetic patients. |
| 4 | UK | Ophthalmic suspension 0.3% | 1. To prevent and relieve eye pain and inflammation following cataract surgery on the eye. |

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| | | (3mg/ml) | 2. To reduce the risk of macular edema (swelling in the back of the eye) following cataract surgery on the eye in diabetic patients. |

**SEC Recommendation:-**

**Recommendation of SEC (Ophthalmology) meeting held on 13.03.2018:-** The firm presented their proposal for additional strength and additional indication of Nepafenac ophthalmic suspension 0.3% w/v before the committee and requested for clinical trial waiver.

After detailed deliberation, the committee recommended that the firm should conduct the clinical trial to generate the safety and efficacy data in Indian patients for the proposed indication. Accordingly, protocol should be submitted for review by the committee.

**Recommendation of SEC (Ophthalmology) meeting held on 16.08.2018:-** The firm presented their proposal for Nepafenac ophthalmic suspension 0.3% w/v before the committee for two indications

1. Prevention and treatment of postoperative pain and inflammation associated with cataract surgery.
2. Reduction in the risk of postoperative macular edema associated with cataract surgery in diabetic patients.

The Nepafenac ophthalmic suspension 0.3% w/v is already approved for treatment of postoperative pain and inflammation associated with cataract surgery. After detailed deliberation, the committee recommended for grant of permission to market Nepafenac ophthalmic suspension 0.3% w/v for prevention and treatment of postoperative pain and inflammation associated with cataract surgery. As regards the other indication the committee opined that there is therapy available for diabetic macular edema. Therefore, the committee recommended that the firm should conduct Phase III clinical trial for the same indication.

**Firm has given the rationality/justification for clinical trial waiver and additional indication as follows:-**

1. **Indication in the same set of patients**
   a) The formulation Nepafenac Ophthalmic Suspension 0.3% w/v is already approved for post cataract surgery use and the proposed additional indication is for same type of patients i.e. posts cataract surgery patients.
2. **Unmet need**
   a) No therapy approved in India for "Reduction in the risk of postoperative macular oedema following cataract surgery in diabetic patients.

b) There is a high disease burden of Cystoid Macular Oedema in Indian diabetic patients who undergo cataract surgery (upto 50%).
c) Cystoid Macular Oedema (CME) is the most frequent cause of visual decline post cataract surgery.

3. **Indication is globally approved**
   a) Approved in ICH countries i.e. EU (28 countries) since July 2016.

4. **Clinical evidence**
   a) Published evidence from clinical trials (3152 patients) conducted across the world have shown that Nepafenac 0.3 % has proven efficacy in reducing the risk of postoperative Macular Oedema (ME) and in improving vision in patients with diabetes.
   b) Safety profile was similar to Nepafenac 0.1%.

5. **Latest Periodic Safety Update Report (PSUR) does not indicate any major safety concern.**

The firm presented their proposal before the Technical committee.

**Recommendation**:- The Committee, after detailed deliberation, agreed with the recommendation of the Subject Expert Committee (Ophthalmology) dated 16.08.2018 and recommended that the firm should conduct Phase III clinical trial with the drug as recommended by the SEC.

## Agenda No. 3

**Proposal of M/S Novartis healthcare Private Limited for grant of manufacturing and marketing permission of FDC of Vildagliptin 50mg + Metformin 850mg + Glimepiride 2mg Tablets**

**Applicant: M/S Novartis healthcare Private Limited**

**Drug name:** Fixed dose combination of Vildagliptin 50mg + Metformin 850mg + Glimepiride 2mg Tablets

**Type of Application:** Manufacturing and Marketing

**Proposed Indication:** As an adjunct to diet and exercise in patients inadequately controlled with Metformin and sulfonylurea.

**Regulatory Status:** FDC is not yet approved in any country.

**Recommendations of SEC (Endocrinology & Metabolism) held on 28.08.2018;**

The committee opined that there is no rationality in combining two insulin secretagogues in one FDC. Moreover, the committee also noted that the clinical study data presented by the firm is not on the proposed FDC. Further the firm informed the committee that proposed FDC is not marketed anywhere in the world. Hence, the committee did not recommend for the proposed FDC.

**On subsequent response of the applicant, the proposal was again deliberated in SEC (Endocrinology & Metabolism) held on 11.12.2018.**

**Recommendations of SEC (Endocrinology & Metabolism) held on 11.12.2018;**

The committee opined that although SU & DPP-IV inhibitors act differently, the outcome of both the drugs is to stimulate insulin secretion. The justification that this FDC will be useful for patients who require 3 drugs as add-on therapy and hence FDC of the 3 drugs will be useful was not justified with adequate data. The clinical trial data presented is on the 3 drugs given as add-on therapy and not with the proposed FDC. The committee also noted that the proposed FDC is not approved in any country. In view of above, committee after detailed deliberation reiterated its earlier stand and didn't recommend approval of the proposed FDC.

**Justification submitted by the firm:-**

In fact, as per IQVIA September 2018 data, as many as 16% prescriptions of OADs comprise of triple drugs. Report also suggests that 40% co-prescriptions of Galvus (Vildagliptin) are with an SU + Metformin and 22% co-prescriptions of GalvusMet (Vildagliptin + Metformin) are with an SU. This data is indicative and conclusive of the fact that 50% of patients are presently already on a Vildagliptin (DPP-4 inhibitor) + Metformin + SU.

The guidelines recommend adding a DPP-4 inhibitor to Metformin and SU or, an SU to Metformin + DPP4 inhibitor combination in case of inadequate glycemic control while on either of the combinations and it is evident from IQVIA data that significant number of prescriptions are of triple drugs.

The proposed FDC will ensure improved adherence for achievement of long-term treatment goals. Polypharmacy with increased pill burden and dosing frequency are identified as factors responsible for poor adherence to oral hypoglycemic therapy. In a study of 2741 patients on oral antidiabetic drug (OAD), there was an inverse relationship between OAD adherence and HbA1c; controlling for baseline HbA1c and therapy regimen, each 10% increase in oral diabetes medication adherence was associated with a 0.1% HbA1c decrease (=0.0004), suggesting that adherent patients are more likely to achieve glycemic control than the nonadherent ones.

The firm presented their proposal before the Technical committee.

**Recommendation**:- The Committee, after detailed deliberation, agreed with the recommendation of the Subject Expert Committee (Endocrinology & Metabolism) dated 11.12.2018 and didn't recommend for approval of the proposed FDC.

## Agenda No. 4

**Proposal of M/S Johnson & Johnson Private Limited for considering waiver for Phase –IV clinical trial for of FDC of Canagliflozin 50mg/ 150mg/ 50mg/ 150mg/ 50mg/ 150mg + Metformin 500mg/ 500mg/ 850mg/ 850mg/ 1000mg/ 1000mg film coated tablets.**

**Applicant:** M/s Johnson & Johnson Private Limited

**Drug name:** Fixed dose combination of Canagliflozin 50mg /150mg /50mg /150mg/50mg/150mg + Metformin 500mg/500mg/850mg/850mg/1000mg/1000mg film coated tablets.

**Type of Application:** Import and Marketing

**Proposed Indication:**

Indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct and exercise to improve glycemic control:

- In patients not adequately controlled on their maximally tolerated doses of Metformin alone.
- In patients on their maximally tolerated doses of Metformin alongwith other glucose –lowering medicinal products including insulin, when these do not provide adequate glycemic control.
- In patients already being treated with the combination of Canagliflozin and Metformin as separate tablets.
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**Regulatory Status:** FDC is approved by this office in 27.03.2018 to the firm with the condition that the firm should conduct a Phase IV clinical trial.

Recommendations of SEC (Endocrinology & Metabolism) held on 13.02.2018;

The firm presented their proposal for the FDCs Canagliflozin 50mg/ 150mg/ 50mg/ 150mg/ 50mg/150mg + Metformin HCl 500mg/500mg/850mg/850mg/1000mg/1000 mg Film coated tablet along with data of global clinical trial conducted in which Canagliflozin was used as an add-on therapy in patients with Metformin and India was one of the participating country. The firm also presented that Pharmacokinetics of both Canagliflozin and Metformin were bioequivalent when administered as fixed dose combination or as individual components. After detailed deliberation the committee

recommended for approval of grant of permission to import and market the FDC subject to condition that the firm should conduct a Phase IV clinical trial. Accordingly, the protocol should be submitted before launching the product in market, for review by the committee.

**On subsequent response of the applicant, the proposal was again deliberated in SEC (Endocrinology & Metabolism) held on 28.08.2018.**

**Recommendations of SEC (Endocrinology & Metabolism) held on 28.08.2018;**

The firm presented their proposal before the committee. After detailed deliberation, the committee recommended that the firm should submit Phase IV clinical trial protocol for review by the committee

**On subsequent response of the applicant, the proposal was again deliberated in SEC (Endocrinology & Metabolism) held on 22.01.2019**

**Recommendations of SEC (Endocrinology & Metabolism) held on 22.01.2019;**

The firm presented their request for Phase-IV CT waiver before the committee. After detailed deliberation, the committee upheld its decision made in its meeting held on 13.02.2018 & 28.08.2018 for requirement of conducting phase-IV clinical trial. Committee opined that this more imperative in view of the recent ADRs reported with such class of drugs.

**Justification submitted by the firm;**

1. The combination of Canagliflozin and Metformin has been approved globally in 54 countries including US, EU etc., and is marketed since Aug 2014.firm stated that they have already submitted report entitled Approval of FDCs by US FDA and with Vokanmet as a case study which captures regulations of approval of FDCs by US FDA and EMA and, the submissions and rationale submitted by Janssen to approve the product.
2. 1131 Indian patients have participated in total 9 Phase 2/Phase 3 studies that evaluated the administration of Canagliflozin 100mg 0r 300mg in subjects with T2DM.of these patients , 839 patients were already on the background of Metformin.
3. Apart from rigorous data form phase 3 abundant data about real world experience has also been published. Use of Canagliflozin relative to the use of SGL T2i and found no statistically or clinically significant differences in any database in either the on treatment or intent-to treat analyses.
4. The safety concerns raised have been attributed to the class effect of sodium-glucose contansporter 2 inhibitors and are restricted to Cangliflozin alone etc.

The firm presented their proposal before the Technical committee.

**Recommendation**:- The Committee, after detailed deliberation, agreed with the recommendation of the Subject Expert Committee (Endocrinology & Metabolism) dated 22.01.2019 and recommended that the firm should conduct Phase IV clinical trial with the drug as recommended by the SEC.

## Agenda No. 5

**Proposal of M/s Zuventus Healthcare Ltd., Mumbai for grant of market authorization in Form 45 for Trivalent Inactivated Influenza vaccine (Split Virion) to be imported from M/s Hualan Biological Bacterin Co.,Ltd. Jia No.1-1, Hualan Ave., Xinxiang, Henan, China, Zip Code: 453003 without conduct of clinical trial in India.**

**Applicant:** M/s Zuventus Healthcare Ltd., Mumbai
**Drug Name:** Trivalent Inactivated Influenza vaccine (Split Virion) [Single dose in Pre filled syringe for 0.25ml (Pediatric dose) & 0.5ml (Adult dose)]

**Type of application:** Market authorization in Form 45 for import of Trivalent Inactivated Influenza vaccine (Split Virion) without conduct of clinical trial in India.

**Proposed Indication:** For active immunization against influenza disease caused by influenza virus subtypes A and B contained in the vaccine for prophylaxis of the influenza caused by the contained vaccine strain.

**CDSCO approval status:** The vaccine manufactured by M/s Hualan Biological Bacterin Co., Ltd. China is not approved by CDSCO.

**International approval status:** The vaccine is approved in China.

**SEC (Vaccine) Recommendation dated 18.03.2019:** In light of recommendation of the SEC meeting held on 18.03.2019, the firm presented the safety and efficacy data generated in China for grant of Market Authorization with phase III clinical trial waiver. After detailed deliberation, the committee recommended that the firm should conduct Phase III clinical trial and protocol etc. may be submitted for evaluation.

**Subsequently, the firm had made a request for reconsideration of the proposal for Technical Committee meeting for grant of Market Authorization of Trivalent Inactivated Influenza vaccine (Split Virion) without conduct of clinical trial in India.**

**Justification submitted by the firm for clinical trial waiver:-**

- Inactivated Influenza vaccine (Split Virion) is a WHO pre-qualified vaccine and WHO prequalification assures the vaccine procured by UNICEF and GAVI meets the highest international quality standards and conducting Clinical trial may not yield any additional information and granting a waiver can help to bring the vaccine in the country immediately.
- Due to shortage of the vaccine, the department of Pharmaceuticals vide letter dated 14.02.2019 had directed to all the importers/manufacturers to submit a report on product, sale and stock position of the flu vaccines/tablet/inhalation to Government.
- It was mentioned that India is currently facing shortage in Trivalent Vaccine and stated that this case if approved by the Technical Committee can be qualified for consideration of Clinical trial waiver; as it pertains to National emergency/extremely emergency category, Firm submitted news articles on prevalence report on Flu out breaks/other reports for consideration.

Earlier, firm had submitted the clinical trial reports of Inactivated Influenza vaccine (split virus) conducted in China as below:

- Phase III clinical trial (single center, randomized, double-blind and parallel Control) Paediatric Inactivated Influenza vaccine (split virus) in 6 months 36 months age group (2doses 4 weeks apart): A total of 769 people (including 514 in test group, 255 in control group) of the Paediatrics influenza vaccine by comparing with VAXIGRIP of M/s Shenzhen Aventis Pasteur Biological Products Co., Ltd. Conducted in 2006 at Jintan City, Jiangsu province. The clinical trial results indicated that the antibody seroconversion rate of H1N1, H3N2, and B were 93.58%, 88.72%, and 81.32%; with GMT increase of 51.1, 20.9, and 15.7 respectively. It has been reported that there were expected adverse reaction in test group and control group are 22.59% and 22.96% respectively.
- Another Phase III clinical trial in adults (16-60 years age), children (6 to 12 years age), and infants (6 months to 3 years age) age group: 60 subjects were included in the first stage and divided into three age groups, 20 subjects for each age group. A total of 840 subjects were included in the second stage and divided into four age groups, 360 subjects in the elderly and infant groups (240 subjects in test group and 120 in the control group); 480 subjects were included up in the adult and children groups (320 subjects in the test group and 160 in the control group). The eligible subjects were randomly divided into the test group and the control group in proportion of 2:1. The results of this phase III Clinical trial is as below:

  **Safety results:** There was no statistically significant difference in cases and incidence of adverse reactions in each age group of the test and Control groups; and there was also no statistically significant difference in severity distribution between the two groups. It showed that the influenza vaccine of

Hualan Bio had a good safety compared with the control vaccine. There were 4 cases of serious adverse reactions in the test group and 1 case in the Control group. Cases and incidence of systemic and local reactions of the test vaccine were higher than those of the Control group, but there was no statistically significant difference.

**Immunogenicity results:** The results of the clinical trial showed that: after administering the test vaccine, the antibody seroconversion ratios (4-fold increase) of different subtypes of each age group were higher than 80%, far exceeding the European specification (40%); the positive rates (the proportion of subjects with HI antibody GMT≥1:40 after immunization) of different subtypes of each age group were high, exceeding the highest European specification (70%).The antibody GMT of all different subtypes of each age group after immunization increased, especially subtype H1N1 and subtype B. The subtype H3N2 antibody was at a higher level before immunization, so the increase after immunization was limited. With the age increase, the increase of antibody after immunization became slow. The immunogenicity results showed that the influenza vaccine of Hualan Bio had a good immunogenicity performance in the proportion of subjects with the seroconversion ratios and HI antibody GMT ≥ 1:40 after vaccination in each age group, especially the elderly and infant groups. It was concluded that the influenza vaccine of Hualan Bio is safe and immunogenic in the age group of 6 months of age and over.

The firm presented their proposal before the Technical committee.

**Recommendation**:- The Committee, after detailed deliberation, recommended that, CDSCO should obtain opinion from ICMR and Dr. Lalit Dar, Professor, Department of Microbiology, Head, Virology Section, AIIMS, New Delhi and place the opinions before the Technical Committee for further consideration.

## Agenda No. 6

**Proposal of M/s Synokem Pharmaceuticals Limited for grant of manufacturing and marketing permission of FDC of Teneligliptin 20mg/20mg + Pioglitazone 15mg/30mg Tablets .**

**Applicant:** M/S Synokem Pharmaceuticals Limited

**Drug name:** Fixed dose combination of Teneligliptin 20mg/20mg + Pioglitazone 15mg/30mg

**Type of Application:** Manufacturing and Marketing

**Proposed Indication:** In the treatment of type 2 diabetes mellitus.

**Regulatory Status:** FDC not approved in any country.

**The proposal was placed before 53rd SEC (Endocrinology & Metabolism) in its meeting held on 19.02.2019**

**Recommendations of 53rd SEC (Endocrinology & Metabolism) meeting held on 19.02.2019;**

The firm presented the Bioequivalence study results along with protocol for clinical trial. The Committee observed that abnormal laboratory values in respect of Hb, PCV, RBC, WBC and Platelets in one subject enrolled in the bioequivalence study were inconsistent with each other. Therefore, the committee recommended that the firm should submit raw data of all the subjects along with accreditation/ approval status of the bio analytical lab used for BE study for the review by the committee. The committee also opined that the CT protocol presented is highly inadequate in terms of objectives, inclusion/ exclusion criteria, discontinuation/ rescue criteria etc.

**On subsequent response of the applicant, the proposal was again deliberated in 55th SEC (Endocrinology & Metabolism) meeting held on 21.05.2019.**

**Recommendations of 55th SEC (Endocrinology & Metabolism) meeting held on 21.05.2019;**

In light of the earlier recommendations of the committee dated 19.02.2019, the firm presented the raw data. The committee noted that there is a gross inconsistency in the laboratory results of patient no. 1 compromising the reliability of the data of the study. Therefore, the committee recommended to repeat the bioequivalence study with the already approved protocol.

However, the firm did not agree with the recommendations of SEC and had requested to deliberate the proposal in Technical Committee.

The firm presented their proposal before the Technical committee.

**Recommendation**:- The Committee, after detailed deliberation, recommended that, CDSCO shall conduct inspection at the BA –BE study centre to verify the raw data, changes of the researchers, if any, during the conduct of the study at the site etc. for further consideration.

## Agenda No. 7

**Proposal of M/s Sanofi-Synthelabo (India) Private Limited for grant of permission to conduct Phase III clinical trial with SAR341402 Mix 70/30.**

**Name of Applicant:**. Sanofi-Synthelabo (India) Private Limited.

**Drug Name:** Comparison of SAR341402 Mix 70/30 to NovoMix®30

**Proposed Indication:** Antidiabetic for the treatment of Diabetes mellitus.

**Protocol Title:** A 26-week, Randomized, Open-label, Parallel-group Comparison of SAR341402 Mix 70/30 to NovoMix®30 in Adult Patients with Diabetes Mellitus using Pre-mix Insulin Analogs.

**The proposal was placed before SEC (Endocrinology & Metabolism) in its meeting held on 19.03.2019**

**Recommendations of SEC (Endocrinology & Metabolism) meeting held on 19.03.2019;**

Recommendations of the SEC (Endocrinology &Metabolism) made in its 54th meeting held on 19.03.2019 at CDSCO HQ New Delhi. After detailed deliberation, the committee recommended for the grant of permission to conduct the Phase III clinical trial study subject to following conditions:

1. The firm should also assess the PK/PD of an adequate number of Indian subjects as part of the study.
2. The upper age limit of subjects should be 65 years
3. The Investigators should be at least MD/DNB (Medicine).

**The proposal was placed before SEC (Endocrinology & Metabolism) in its meeting held on 21.05.2019**

**Recommendations of SEC (Endocrinology & Metabolism) meeting held on 21.05.2019;**

Recommendations of the SEC (Endocrinology & Metabolism) made in its 55thmeeting held on 21.05.2019 at CDSCO HQ New Delhi. In light of recommendation of the committee dated 19.03.2019, the firm presented their justification for waiver of PK/PD study & upper age limit of 65 years in the proposed clinical trial.

The committee after detailed deliberation reiterated its earlier recommendation that PK/PD study should be conducted in Indian subjects as part of the trial. The committee however recommended for relaxation of upper age limit of 65 years subject to condition that the firm should ensure stringent monitoring of such subjects in the trial.

The committee recommended for grant of permission to conduct the trial with above conditions.

The firm presented their justification for not conducting the PK/PD study on Indian subjects as part of the global trial, before the Technical committee

**Recommendation**:- The Committee, after detailed deliberation, agreed with the recommendation of the Subject Expert Committee (Endocrinology & Metabolism) dated 21.05.2019 and recommended that the firm should conduct the PK/PD study on adequate number of Indian subjects as part of the global trial, as recommended by the SEC.

## Agenda No. 8

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

**Applicant:** M/s Sun Pharma Laboratories Limited

**Drug Name:** Fixed dose combination of Cephelexin 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 Dental infections.

**Regulatory Status:** FDC is 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) meeting held on 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) meeting held on 12.04.2013.**

**Recommendations of NDAC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) meeting held on 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) meeting held on 18.06.2014.**

**Recommendations of NDAC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) meeting held on 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) meeting held on 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) meeting held on 12.12.2017.**

**Recommendations of SEC (Antimicrobial, Antiparasitic, Antifungal and Antiviral) meeting 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 ratio6:1 and 3:1 against Beta-Lactmase producing eighty two strains of clinical isolates taken in the study.

**The proposal was deliberated in Technical Committee in its meeting held on 05.09.2018.**

**Recommendations of the Technical Committee meeting dated 05.09.2018:-** The firm presented the clinical trial 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, firm submitted In-vitro study protocol and Phase IV clinical trial protocol, which were deliberated in Technical Committee in its meeting held on 22.01.2019.**

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

**Recommendations of the Technical Committee meeting dated 22.01.2019** - 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.

Subsequently, the firm has submitted reports of *In-vitro* study and requested for manufacturing and marketing permission of FDC of Cephelexin Extended release and Clavulanate Potassium Tablets (375mg + 125mg) and (750mg + 125mg).

The firm presented their proposal alongwith the results of the *In vitro* study before the Technical committee. As per the results presented, there was more than 4 fold decrease in MIC of MSSA clinical isolates in Cephalexin + Clavulanate (3:1) and Cephalexin + Clavulanate (6:1) in comparison with Cephalexin alone.

**Recommendation**:- The Committee, after detailed deliberation, recommended for grant of permission to manufacture and market the drug for the treatment of upper respiratory tract infections (URTI) and uncomplicated skin and soft tissue infections subject to condition that the firm should conduct a Phase IV clinical trial. Accordingly, the firm should submit the protocol Phase IV Clinical Trial within three months of the approval of the drug for review by the SEC.

## Agenda No. 9

**Consideration of regulatory provisions allowing Independent (Non-institutional) Ethics Committee constituted under Rule 7 of New Drugs and Clinical Trials Rules, 2019 to review and accord approval of clinical trial where a clinical trial site does not have its own Ethics committee.**

**The Technical Committee was apprised as under:-**

1. The Ethics Committees play a very crucial role in the conduct of clinical trial. The Drugs and Cosmetics Rules was amended vide G.S.R No. 72(E) dated 08.02.2013

specifying requirements and guidelines for registration of Ethics Committee. Accordingly Rule 122DD was inserted to the Drugs and Cosmetics Rules.

**2.** There are two types of Ethics Committee functioning in the country which are referred as Institutional Ethics Committee and Independent (Non-institutional) Ethics Committee.

**3.** As per 2nd meeting of the **Apex Committee** held on 28.03.2013 under the Chairmanship of Secretary, Health and Family Welfare for supervising clinical trials on new chemical entities in the light of directions of the Hon'ble Supreme Court of India directives dated 03.01.2013, it was decided that **Institutional Ethics committee should review and accord approval to any clinical trial protocol for the respective Institute. For the Bioequivalence/Bioavailability (BA-BE) studies conducted at Bioequivalence study centers in various parts of the country, the study proposals should be reviewed and approved by the Institutional Ethics committees of medical college/Hospitals/Institutions located in the same area where the Bioequivalence study centers are located. The practice of review and approval of BA-BE study protocols by Independent Ethics committees functioning outside any Institutions should be discontinued within 60 days.**

**4.** In 4th meeting of the **Apex Committee** held on 31.05.2013 under the Chairmanship of Secretary, Health and Family Welfare, as regards the registration of Independent Ethics committee, the committee members were informed that as already decided, the Independent Ethics committees were being registered with CDSCO subject to the condition that they will review and accord approval to only the BA-BE studies of approved new drug molecules. However concerns were raised with respect to the periodic review of ongoing clinical trials already approved by such Independent Ethics committees. The Technical committee deliberated the issue and recommended that the Independent Ethics committees should be allowed to make periodic review of the clinical trials already approved by them. However no new clinical trials should be reviewed and approved by such Independent Ethics committees. The Apex committee agreed to the above recommendation of the Technical committee.

**5.** In 7th meeting of the **Apex Committee** held on 30.08.2013 under the Chairmanship of Secretary, Health and family Welfare, while deliberating the clinical trial proposals,

the members had pointed out that clinical trials should not be allowed to be conducted at the sites which were having Independent Ethics Committees for the review and approval of clinical trials. Further in the said meeting it was decided that clinical trial sites which were multispecialty hospitals/ institutes having emergency facilities and Institutional Ethics Committee registered with CDSCO should only be recommended for the conduct of clinical trial.

**6.** In the **14th meeting of the Technical Committee held on 28.04.2014**, after deliberation, the Committee recommended that the clinical trial sites should have minimum of 50 numbers of beds in the Institute/ hospital with emergency medical care facilities.

**7.** In the **15th meeting of the Technical Committee held on 04.06.2014**, the committee noted that CDSCO had been registering Institutional Ethics committees for oversight of clinical trials and Independent ECs for oversight of BA-BE studies with old molecules. The committee was appraised of the request from the Ethics committee based at OPD clinics and Nursing homes etc. (having less than 50 bed strength) seeking approval for oversight on clinical trials. The committee opined that only those sites that are having a minimum of 50 bed strength will be treated as clinical trial sites and **accordingly such sites must have an Institutional Ethics committee, while Ethics committee constituted by OPD clinics and nursing homes having less than 50 bed strength** must be treated as Ethics Committees for oversight on BA/BE studies.

**8.** In the **17th meeting of the Technical Committee held on 04.08.2014,** Conversion of status of registered **Independent Ethics committees to Institutional** for review and approval of clinical trials was deliberated. It was mentioned in the minutes that the Ethics committees which were constituted by following types of institutes were registered as Institutional Ethics Committees.

a) Hospital/Medical facilities having emergency management services/ICU
b) Dental Hospital
c) Medical Colleges
d) Research organization such as ICMR, National Labs of the Govt.

The Ethics committees which were not constituted by institutes mentioned above were registered as the Independent Ethics Committees. Institutional Ethics committees were allowed to review and accord its approval to clinical trial protocols. Independent Ethics committees were allowed to review and approve protocols for Bioavailability/Bioequivalence (BA/BE) studies of approved drug molecules only.

Certain Ethics committees which were already registered as Independent Ethics Committees represented to convert their status to Institutional Ethics Committee.

The Committee deliberated the matter in detail and reiterated its earlier recommendations made during its 2nd, 4th, 7th, 14th & 15th meetings.

**9.** Further in the **28th Meeting of the Technical Committee** held on 21.08.2015, the requirement of 50 bedded sites for clinical trial was deliberated in detail and recommended that Ethics Committee should examine & decide whether the clinical trial site is suitable for trial or not irrespective of number of bed. The site should have emergency rescue and care along with all other necessary arrangement required for conduct of clinical trial.

**10.** CDSCO has received requests from some of the Ethics Committees which are registered as Independent Ethics Committee for review of BA-BE to upgrade them as Institutional Ethics Committee for oversight of clinical trials.

**11.** Recently, New Drugs and Clinical Trials Rules, 2019 have been notified by Government of India with effect from 19.03.2019.

Detailed guidelines and requirements for registration/renewal of Ethics Committee are specified in Chapter III of the said rules. In addition to that it has been mentioned in Rule 25, Part A of Chapter V that permission granted by the Central Licencing Authority to conduct clinical trial under this Chapter shall be subject to following conditions, namely:

i. clinical trial at each site shall be initiated after approval of the clinical trial protocol and other related documents by the Ethics Committee of that site, registered with the Central Licencing Authority under rule 8;

ii. where a clinical trial site does not have it's own Ethics Committee, clinical trial at that site may be initiated after obtaining approval of the protocol from

the Ethics Committee of another trial site; or an independent Ethics Committee for clinical trial constituted in accordance with the provisions of rule 7:

Provided that the approving Ethics Committee for clinical trial shall in such case be responsible for the study at the trial site or the centre, as the case may be:

Provided further that the approving Ethics Committee and the clinical trial site or the bioavailability and bioequivalence centre, as the case may be, shall be located within the same city or within a radius of 50 kms of the clinical trial site.

In view of the recent regulatory provision, the committee deliberated the matter in detail.

**Recommendation**:- The Committee, after detailed deliberation, noted that, as per the recent regulatory provisions under the New Drugs and Clinical Trials Rules, 2019, Independent Ethics committees constituted under Rule 7 can review and accord approval of clinical trial where a clinical trial site does not have its own Ethics committee subject to the various conditions as prescribed under the new Rules.

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