MINUTES OF 49th MEETING OF THE TECHNICAL COMMITTEE HELD ON 18.01.2022 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. **Prof. (Dr.) Sunil Kumar ,** Chairman
   Director General of Health Services,
   Ministry of Health and Family Welfare
2. **Dr. Yash Paul Sharma,** Member
   Prof. & Head, Dept. of Cardiology,
   PGIMER, Chandigarh.
3. **Dr. Kamlakar Tripathi,** Member
   Former Prof., Dept. of Medicine,
   Institute of Medical Sciences, BHU, Varanasi.
4. **Dr. B. L Sherwal,** Member
   Director, Rajiv Gandhi Super Speciality Hospital
   Tahirpur, New Delhi-110093
5. **Dr. Nandini Kumar,** Member
   Former Dy. Dire. Gen. Sr. Grade, Adjunct Professor, KMC, Manipal, 5/1 (New) Padmalaye Apt. Chennai.
6. **Dr. Raju Titus Chacko,** Member
   Prof. & Head, Dept. of Medical Oncology,
   CMC, Vellore.
7. **Dr. Ashok Kumar Das,** Member
   Professor of Medicine & Professor and Head of Endocrinology, Pondicherry Institute of Medical Sciences, Pondicherry.
8. **Dr. Nikhil Tandon,** Member
   Professor, Dept. of Endocrinology & Metabolism,
   AIIMS, New Delhi.

From CDSCO:

1. Dr. V. G. Somani, Drugs Controller General (India)
2. Dr. A. K. Pradhan, Joint Drugs Controller (India)

49th Technical Committee Meeting -18.01.2022

The Chairman welcomed the members of the committee for the 49th Technical Committee meeting. Thereafter, total 9 proposals were placed before the committee for consideration. The committee discussed the proposals one after another and gave its recommendation. The details of the proposals and recommendation of the committee are as under:

Agenda No. 1

Proposal of M/s Pfizer Products India Pvt. Ltd for import and market Crisaborole Ointment 2% with local Phase III clinical trial waiver.

File No: - ND/IMP/20/000098

Firm name: -M/s Pfizer Products India Pvt. Ltd

Product name: - Crisaborole Ointment 2%

Indication: Crisaborole ointment is indicated for topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 2 years of age & older.

Request of the firm: Import and market Crisaborole Ointment 2% with local Phase III clinical trial waiver.

Approval Status Globally: -Crisaborole Ointment 2% [Staquis®]received first approval from US FDA on 14thDecember 2016post which it also received approval from Canada, European Union (27 member states), Australia, Colombia, China & Hong Kong.

The proposal of the firm has been deliberated in the SEC (Dermatology and allergy) twice.

Recommendations of the SEC (Dermatology & Allergy) held on 12.01.2021

The firm presented their proposal for import & market of the drug along with local clinical trial waiver before the committee. Committee noted that firm has presented inadequate data as well as justification for local clinical trial waiver as per requirements. After detailed deliberation, the committee recommended that the firm should conduct the phase III clinical trial and accordingly firm should submit the phase III clinical trial protocol to CDSCO for further review by the committee.

Recommendations of the SEC (Dermatology & Allergy) held on 11.02.2021

In light of earlier recommendation dated 12-01.2021, firm presented their proposal before the committee. After detailed deliberation committee reiterated its earlier recommendation dated 12.01.2021.

Now the firm submitted application and requested to deliberate the proposal in the upcoming Technical committee meeting.

M/s Pfizer has submitted justification for their proposal as under.

Provision of New Drugs & Clinical Trial Rules 2019, Rule 75 of which states that provided there is no probability of evidence of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug and no major unexpected serious event being reported, requirement of local clinical trial can be waived provided applicant undertakes to conduct local Post Marketing Phase IV study for said new drug.

In line to said provisions, they have furnished following points for your kind perusal

1. Crisaborole ointment is topical formulation hence has very low probability of systemic pharmacology
2. Crisaborole has been studied for maximal usage (4-5 fold higher % treated BSA as compared to typically observed mild-moderate AD case) in patients of 2-17 years' age as results of which, no significant differences were observed in PK parameters between the cohorts
3. Crisaborole is metabolized by oxidation deboronation which is catalyzed by multiple oxidative enzymes, including both cytochrome P450 isoenzymes and other oxidases which produce H_2O_2 therefore there is no difference in enzymes or genes involved in metabolism and thereby it is highly unlikely to be impacted by race or ethnic differences to produce clinically significant differences in systemic exposure
4. Crisaborole is non-steroidal therapeutic option to treat mild to moderate Atopic Dermatitis which is studied for longer treatment duration (up to 28 days) and can also be used on sensitive skin areas e.g. face, intertriginous areas, genitals, flexor areas as compared to existing steroidal treatments (e.g. TCI, TCS, biologicals, etc.) posing safety risks that limits their continuous use (especially on sensitive skin areas).
5. White petrolatum is the main excipient and base of Crisaborole ointment 2%, which was selected for its optimal properties such as efficient drug delivery, sustained drug substance level in the target tissue area, drug product stability, emollient effect, and patient acceptability.

6. CDSCO has approved white petrolatum based topical steroidal formulation in past; initially on October 1979 and further for treatment of psoriasis, contact dermatitis, atopic dermatitis neurodermatitis (Refer Annexure 2).
7. No serious safety concerns have been reported with use of white petrolatum based topical formulations approved in India for skin ailment including atopic dermatitis since their initial approval
8. Crisaborole ointment is not protected under Indian Patent Act and there are generics available in other markets including Bangladesh. Pfizer's Crisaborole is marketed in other countries for more than four years with no major safety concerns therefore, various other Indian companies are potentially in process of submitting their application to secure approval from your kind Directorate.
9. Crisaborole Ointment 2% formulation has been already developed in & approved by Bangladesh which has similar climatic conditions as India and said formulation is potentially available for marketing in neighbouring countries. (Enclosure 3 for details on said formulation).
10. Local Phase III study would result to prolong drug availability of Crisaborole Ointment and thereby would deprive needy Indian patients of this novel, first in class, nonsteroidal treatment option having comparatively well tolerated safety profile by approximately 2-2.5 years; instead Pfizer request approval to import and market Crisaborole Ointment 2% in India with waiver of Phase III with an undertaking to conduct local post marketing Phase IV study per the regulations.

The firm presented their justification of waiver of clinical trial before the technical committee highlighting the following: -

1) Crisaborole is a novel, nonsteroidal, topical, anti-inflammatory PDE4 inhibitor
2) The drug is approved by US FDA on 14 December 2016 followed by 20 other countries including Canada, EU, France, Israel, Australia, Lebanon, UAE, United Kingdom and Asian countries - China, Hong Kong, Thailand & Taiwan
3) There have been no new safety signals noted with use of Crisaborole & overall Crisaborole benefit-risk profile remains favorable
4) Atopic Dermatitis is a multifactorial disease with heterogenous presentation and severity affecting up to 20% children & 1%-3% of adults globally

5) Studies report Indian prevalence rate for Atopic Dermatitis as 0.55% (eastern India) v/s incidence of 29.9% (northern India). Patients with Atopic Dermatitis experience higher emotional distress, sleep disturbances, limited physical function, and risk of comorbid diseases. Current approved therapies (TCS/TCIs, biologicals, etc) carry significant risk and there is need to newer treatment options
6) Crisaborole ointment being a topical formulation has very low probability of systemic circulation. Statistically significant success rates were demonstrated for all 5 signs of Atopic Dermatitis in Study AN2728-AD-302 and for the pooled studies
7) Crisaborole reversed biomarker profiles indicative of skin inflammation and barrier dysfunction (FLG and Keratin 16), with associated improvements in clinical efficacy measures. Safety findings of Crisaborole Atopic Dermatitis program did not include evidence of sustained cutaneous reactions at the application site (i.e. atrophy, telangiectasia, or hypopigmentation as described with use of TCSs) or PG-related adverse events, such as cardiac/neurologic disorders.
8) There is no cure for Atopic Dermatitis; treatment focus on alleviating the debilitating signs/symptoms and gaining control over recurrent flares
9) Available treatment options for Atopic Dermatitis pose potential safety concerns that limit their continuous use (especially on sensitive skin areas)
10) Crisaborole can be used to treat Atopic Dermatitis on all body regions including sensitive skin areas having substantial impact on a patient's quality of life. Local tolerability and limited systemic exposure of Crisaborole combinedly offer a safety profile that differentiates it from the currently available treatment options for mild to moderate Atopic Dermatitis.

Recommendation of the Technical Committee: After detailed deliberation the committee recommended for grant of permission to import and market Crisaborole ointment 2% subject to the Condition that the firm should conduct a phase IV clinical trial for which protocol should be submitted for review by the SEC within 3 months of approval of the drug.

Agenda No. 2

M/s. Pfizer requested for technical committee review for their proposal to amend condition No:-04 of permission IMP/ND/47/2016(in Form-45) & Condition No:-III of permission No:-IMP/SND/20/000060 & IMP/SND/21/000091 – Reg.

File No: - 12-01/19-DC (Pt.308)

Firm name: -M/s Pfizer Products India Pvt. Ltd

Product name: - Tofacitinib Tablets 5mg

Indication: *"for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to Methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs)".*

Request of the firm: Requesting amendment in condition No:-04 of permission IMP/ND/47/2016(in Form-45) & Condition No:-III of permission No:-IMP/SND/20/000060 & IMP/SND/21/000091 as follows:

"To be sold on the retail on the prescription of "Registered Medical Practitioner only"

Or

To be sold on the retail on the prescription of "Registered Medical Practitioner only "Rheumatologist" or specialist in internal medicine" or "Dermatologist or gastroenterologist" or Hepatologist or "Orthopedician"

This office has already granted permission for import and marketing of the drug for Rheumatoid arthritis, Psoriatic arthritis and ulcerative colitis with the following warning.

To be sold on the retail on the prescription of "Registered Medical Practitioner only "Rheumatologist" or specialist in internal medicine" or "Dermatologist or gastroenterologist" or Hepatologist.

Recommendation of the Technical Committee: : After detailed deliberation the committee recommended for addition of Orthopedician as additional prescriber for the drug and the condition of the permission should be amended accordingly.

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

Firm name: -M/s Novartis Healthcare Pvt Ltd

Product name: - Fixed dose combination of Vildagliptin 50mg + Metformin 850mg + Glimepiride 2mg Tablets.

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

Request of the firm: manufacturing and marketing permission for the said FDC for the proposed indication.

The proposal was earlier deliberated in the SEC meeting. The recommendations are as under:-

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.

On subsequent response from the applicant, the proposal was placed in 46th Technical Committee meeting held on 01.07.2019.

Recommendations of 46th Technical Committee meeting held on 01.07.2019;

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 for the FDC.

On subsequent response from the applicant, the proposal was re-deliberated in 47th Technical Committee meeting held on 19.02.2020.

Recommendations of 47th Technical Committee meeting held on 19.02.2020;

The committee, after detailed deliberation, recommended that proposed prescribing information with detailed information in respect of specific conditions, indication, dosage etc. for which the FDC is intended to be used supported by justification/rationality along with risk management plan for the proposed FDC for further review by the Technical Committee.

Accordingly the firm presented their proposal before along with global clinical trial data.

Recommendation of the Technical Committee: The firm presented their proposal before the Technical committee. The committee after detailed deliberation agreed to the recommendations of the SEC and did not recommend for approval of the FDC with given justification due to possibility of hypoglycemia and difficulties for dose titration for such patients.

Agenda No. 4

Proposal of M/s Novartis India Limited, for Re-deliberation - Post Marketing Surveillance Study to Study the Safety and Effectiveness of Omalizumab in Indian Patients with Chronic Spontaneous Urticaria Refractory to Standard of Care.

Applicant Name - M/s Novartis India Limited

Drug Name – Omalizumab

The firm was granted marketing authorization for Omalizumab 75 mg and 150 mg vide permission no. Import-6200/05 dated 26.10.2005 for Moderate to Severe Persistent Allergic Asthma.

Further, the firm was granted approval for additional indication on 22.10.2014 "for treatment of adults and adolescence (12 years of age and above) with chronic spontaneous urticaria refractory to standard of care" subject to submission of PMS

data for 2 years to this office which would be presented before the SEC committee for final approval.

Accordingly, the firm presented the Clinical Study Report of conducted PMS study before the SEC in its meeting dated 05.11.2019. The committee recommended that the firm should continue the PMS study and generate safety data on additional 200 Indian patients and submit the data before the committee.

Earlier SEC recommendations on the requirement of PMS data are as under:-

First SEC meeting held on 05.11.2019. The SEC recommendations were as follow:

"The firm presented dose-response and safety data of the product for Chronic Spontaneous Urticaria in Indian Patients. The committee noted that there is 01 SAE (Anaphylactic shock) reported out of 142 patients and therefore more safety data need to be generated in Indian patients.

After detailed deliberation, the committee recommended that the firm should continue the PMS study and generate safety data on additional 200 Indian patients and submit the data before the committee"

M/s Novartis submitted a request for reconsideration of their proposal to consider the data already generated through the PMS study. Based on firm's request, firm was invited in the SEC meeting held on 13.07.2020.

Second SEC meeting was held on 05.11.2019. The recommendations were as follow:

"In light of earlier recommendation dated 05.11.2019, firm has presented justification for not continuing the PMS study on additional 200 Indian patients. After detailed deliberation, the committee reiterated its earlier recommendation to continue PMS study in additional 200 Indian patients."

In view of above , the firm filed an appeal for Technical committee regarding their proposal.

The proposal was deliberated in the 48th Technical Committee Meeting held on 26.04.2021. The recommendations of said Technical Committee were as follows-.

"The committee after detailed deliberation agreed with the recommendations of SEC and recommended that, the firm should continue the PMS study and generate safety data on additional 200 Indian patients and submit the data before the SEC."

Accordingly, firm was informed vide this office letter dated 11.08.2021 to continue the PMS study and generate safety data on additional 200 Indian patients and submit the data before the SEC.

In view of above the firm has again requested to re-consider their proposal for deliberation in the Technical Committee Meeting.

The firm presented their justification before the technical committee as under:-

Omalizumab has been approved in India since October 2005 for the indication "Moderate to Severe Persistent Allergic Asthma". The indication of CSU was approved by the DCGI office dated 22 Oct 2014. Hence, the drug Omalizumab has been marketed in India for over 16 years now.

Omalizumab is approved in India for more than 16 years (since 2015) and for CSU indication in India dated 22 Oct 2014 (approved for 7 years) and globally in 93 Countries (including key countries like EU – 31 member countries, Switzerland, Canada)

The frequency of anaphylactic reactions reported in the PMS study (0.3%) are in accordance with the prevalence reported in package insert, literature and clinical studies (0.2%). Anaphylactic reactions related to Omalizumab in India remain consistent with the overall global safety data. This rate of anaphylaxis has been known and is clearly outlined in the package insert of the product as well.

No changes to the safety profile concerning the topic of the identified risk 'Anaphylactic reactions' have been identified. Omalizumab has more than 1.3 million Patient Treatment Years of exposure.

The firm also presented the AEs and SAEs that occurred in the PMS study "A prospective, Post Marketing Surveillance study to Evaluate the safety and effectiveness of omalizumab in Indian patients with Chronic Spontaneous Urticaria refractory to standard of care"

Further the firm also provided a commitment to conduct an Active Surveillance study for AEs with Omalizumab wherein the active surveillance will be implemented by Novartis Field Associates (NFA) across all the zones (east, west, south, north) in

India. NFAs will be trained on risk management plan for omalizumab including all the Adverse Events (AEs). All individual clinicians will be contacted regularly at least once in 3 months to collect information on the occurrence of all AEs in the surveillance period" NFAs will thoroughly train treating physicians on Adverse Event Profile of omalizumab. AE reporting forms will be made available to all the treating doctors for reporting any AE. All the AEs reported will be collected by Pharmacovigilance team (PV) of Novartis and collated data will be submitted to DCGI by Novartis Regulatory team on an annual basis for 2 years.

Recommendations of the Technical Committee: The committee after detailed deliberation, recommended that, in place of active PMS study on additional 200 patients, the firm should conduct an active surveillance study for AEs to be implemented by Novartis field associates as committed by the firm.

Agenda No. 5

Proposal of M/s Sandoz Private Limited, for wavier for Phase IV trial, condition for the product Erenumab 70 mg/ml Pre-filled syringe permission.

Name of the applicant - M/s Sandoz Private Limited

Drug Name Erenumab 70 mg/ml Pre-filled syringe

M/s Sandoz Private Limited was granted import and marketing authorization for Erenumab 70 mg/ml Pre-filled syringe by this office on 17th February 2020 for "Prophylaxis of migraine" with the condition that firm shall initiate Phase IV clinical trial before the launching the subject drug in the India Market. Accordingly, firm shall submit the Phase IV clinical trial protocol for approval.

The above said drug was approved based on the recommendations of the SEC in its minutes dated 12.06.2019. The recommendations of the SEC were under: -

In light of recommendation meeting dated 08.08.2018, the firm presented their justification for waiver of local clinical trial along with interim safety profile on 296 Indian patients from the ongoing global clinical trial. On the safety profile, it was presented that there was no SAEs. The firm also presented that the Global clinical trial data generated so far have not indicated any ethnic difference between Caucasian & Asian patients. After detailed deliberation, committee recommended for grant of permission to import & market the drug with local clinical trial waiver subject to the condition the firm should conduct phase IV trial in 500 patients in addition to

ongoing Global clinical trial in India& accordingly the firm should submit the phase IV protocol before grant of marketing approval.

Subsequently, firm approached the CDSCO for waiver of Phase IV condition reasoning that the condition in MA that "Firm shall initiate Phase IV clinical trial before the launching the subject drug in the India Market" is hindering its drug launch and marketing in the country.

The firm justified that the Erenumab is approved and marketed in 52 countries including ICH countries and it has already completed a global Phase III study EMPOWER (CAMG334A2302) which had 351 Indian subjects randomized across 27 sites in India. The said GCT was conducted in 11 countries in 900 subjects. The study was completed on 13.01.2020.

It was a 12-week double-blind, randomized, multi-center study comparing the efficacy and safety of once monthly subcutaneous Erenumab against placebo in adult episodic migraine patients (EMPOwER). Both the primary & secondary efficacy results for Indian sub-population were in line with the global results.

Firm presented the results from the above said study with request for Phase IV waiver in SEC meeting dated 17.11.2020

However, the committee did not consider firm's request for waiver. The recommendation of the SEC was as follows -

Firm presented their proposal for waiver of condition in marketing authorization to conduct Phase IV clinical trial. After detailed deliberation the committee observed that migraine is common ailment and requires more safety data, therefore the committee didn't recommend for waiver of Phase IV Clinical Trial.

In the same meeting the firm also informed that they have also obtained permission for conduct of another GCT; phase III study (DRAGON) which is also a GCT approved by this office in July 2020 & has committed to submit the report to this Directorate

Aggrieved by the decision of SEC meeting dt. 17.11.2020, the firm had approached CDSCO to reconsider its decision and waiver of Phase IV study and requested for deliberation of their proposal in Technical committee.

The firm presented their proposal before the Technical committee as under:-

Erenumab is approved & marketed for ~3 years in 52 countries including ICH countries like US, EU (27 member countries), Switzerland, Canada and Singapore for treatment of prophylaxis of migraine.

Firm has already submitted data generated from global Phase III study in 351 Indian patients (40% of global population) across 27 sites in India. The efficacy & safety results for Indian sub-population are in line with the global results. MA was accorded based on the GCT results.

In addition, to continue to evaluate the safety and efficacy, a second Phase III trial (DRAGON) was conducted with Erenumab with 30 Indian patients across 5 sites. The study met the primary endpoint demonstrating erenumab 70mg had significantly greater reduction over placebo on monthly migraine days. No new safety findings were observed.

In the Post marketing experience of 6.32 lakh patient years; from PSUR (17 Nov 2020 to 16 May 2021), no new risk was detected for Erenumab.

Despite huge data from Indian patients in Phase III study, there was no scientific rationale for an additional post marketing Phase IV study in 500 patients.

Recommendations of the Technical Committee: The committee after detailed deliberation agreed for grant of waiver to conduct the Phase IV study and the condition stipulated in the marketing authorization for conduct of Phase IV study should be omitted.

Agenda No. 6

Proposal of M/s Johnson & Johnson Pvt. Ltd, Application in for grant of permission to Import and Market of Ustekinumab Solution for injection for SC administration in PFS 45 mg/0.5 ml, 90 mg/ml and Ustekinumab Solution for IV infusion in single use vial 130 mg/ 26 ml with waiver of conduct of local Clinical trial

Name of the applicant - M/s Johnson & Johnson Pvt. Ltd.

Drug Name - Ustekinumab Solution for injection for SC administration in PFS 45 mg/0.5 ml, 90 mg/ml and Ustekinumab Solution for IV infusion in single use vial 130 mg/ 26 ml

M/s Johnson & Johnson Pvt. Ltd. has applied for permission to Import and Market the subject drug with waiver of conduct of local clinical trial for following indication.

For inducing and maintaining clinical response, inducing and maintaining clinical remission, eliminating corticosteroid use, inducing endoscopic healing, improving health-related quality of life in adults with moderately to severely active Crohn's disease who: have failed or were intolerant to immunomodulators or corticosteroids or were corticosteroid dependent or have failed or were intolerant to one or more anti-TNF treatment" with Ustekinumab in India.

On 16th Sep 2020 the firm's request for MA with waiver of local Phase III and Phase IV clinical trial was deliberated and the SEC and the committee didn't recommend for waiver of local clinical trial. The recommendations of the SEC are as follow:

"The firm presented their proposal before the committee. The committee noted that, the firm could not justify and also not fulfilled the conditions for waiver of local Phase III & Phase IV Clinical Trial. After detailed deliberation, the committee did not recommend for the grant of permission for market the drug with waiver of local Clinical Trial."

On 17th Dec 2020, the firm again requested for local Phase III clinical trial waiver with commitment to conduct Phase IV study. However, the SEC did not recommend for waiver of local Phase III clinical trial. The recommendations of the SEC are as follow:-

"In light of earlier SEC recommendation dated 16.09.2020, firm presented their proposal for marketing authorization with the request for local Phase III clinical trial waiver and a commitment to conduct Phase IV study. The committee noted that the justification submitted by the firm for local clinical trial is inadequate. After detailed deliberation, the committee didn't recommend for grant of marketing authorization with local clinical trial waiver."

On 17th Mar 2021, the firm again requested for waiver of local Phase III study with submission of real-world evidence data and reference guidelines for the use of Ustekinumab in CD before the SEC. However, the committee did not recommend for waiver of the need for local Phase III clinical trial. The recommendations of the SEC are as follow:-

"In-light of the SEC recommendations dated 17.12.2020, the firm presented real-world evidence data and reference guidelines for the use of Ustekinumab, to the committee. The committee observed that there are no safety and efficacy data from

Indian patients on this drug. After detailed deliberation, the committee did not recommend for waiver of the need for local Phase III clinical trial."

Accordingly, firm was informed that, local Phase III CT waiver cannot be considered as there is no safety and efficacy data from Indian patients on this drug in line with SEC dated 17.03.2021.

On 20.04.2021 and 17.06.2021, firm had appealed for deliberation in Technical Committee meeting being aggrieved by the recommendation of SEC with following justifications –

Overall, Stelara has 10+ years of experience across all indications; 4+ years' experience in Crohn's Disease

Under clinical settings:

a. >2.2 million patient-years exposure to Stelara since the launch of its first indication, till date

b. >12,000 patients exposed to Stelara in Clinical trials with approximately 25% patients exposed in Crohn's Disease in these clinical trials

c. STELARA® CD: Phase III Program included two induction studies that enrolled 741 & 628 patients and one 44-week maintenance study that enrolled 397 patients (Clinical study reports submitted)

d. One long term extension 272 weeks maintenance study in 1281 subjects

4 RWE studies in 1000+ patients demonstrated 'Response rates' consistent with those found in clinical trials

Latest American Gastroenterological Association (AGA) (2020), European Crohn's Colitis Organization (ECCO) (2020) and National Institute for Health and Care Excellence (NICE) Guidelines (2019) all recommend ustekinumab for induction and maintenance of remission in both biologic-naïve and biologic inadequate responder Crohn's Disease patients

Asian Pacific Association of Gastroenterology (2020) recommends ustekinumab as a better alternative to anti-TNFs given the low immunogenicity

Asian Pacific Association of Gastroenterology (2020) recommends ustekinumab as a preferred biologic in higher risk elderly patients underscoring its safety. Indian medical experts as part of the team that developed these guidelines.

Stelara is a new effective treatment option with a novel mechanism of action.

- All the international treatment guidelines consider ustekinumab as superior to vedolizumab in terms of strength of recommendation and quality of evidence except for fistulizing CD, where both are placed equally.

Further, the local clinical trial waiver has been requested under the provisions prescribed in Rules 75 (7) (i, iii and iv) of New Drugs and Clinical Trials Rules, 2019 as below.

I. Stelara has been approved for CD in 47 countries globally including United States of America, European Union, Canada, Japan (Initial approval in USA: 2016)

II. "Orphan" designation of this drug - While the disease burden of IBD in India is one of the highest globally; as per the World Gastroenterology Organisation Global Guidelines 2015, UC accounts for a higher proportion of IBD patients than CD with a documented UC/CD ratio of 8:1 (previously 10:1). Ahuja et al in their publication in 2017 outlined that the estimated prevalence of UC is 44.3 per 100,000 population which makes the estimated prevalence of CD in India close to 5.55 per 100,000 inhabitants. In other words, approximately 75,000 patients are currently suffering from CD among our population of 1.38 billion (2020 population estimates). Crohn's Disease thus is an orphan disease in India as per available literature, in accordance with the defined criteria in New Drugs and Cosmetic Rules 2019 (Enclosure 2 – published literature).

III. Stelara has been shown to lack ethnic sensitivity as per ICH E5 Guidance.

IV. Declaration to Undertake Phase IV clinical trial to support generation of local clinical safety data. Declaration along with protocol element document for proposed Phase IV trial.

Recommendation of the Technical Committee: The committee, after detailed deliberation recommended for grant of permission to import and market the drug subject to conditions that the firm should conduct a phase IV clinical trial for which protocol should be submitted to CDSCO for the review by the SEC within 3 months of approval of the drug.

Agenda No. 7

Proposal of M/s Biotechnos Pvt. Ltd., for grant of permission to conduct Phase III clinical trial on FDC of Bioactive concentrate from small marine fish 0.1ml + water for injection (WFI) 1ml solution for injection administered intramuscularly in subjects with osteoarthritis of knee joints.

Applicant: M/s Biotechnos Pvt. Ltd.

Drug name: FDC of Bioactive concentrate from small marine fish 0.1ml + water for injection (WFI) 1ml solution

Regulatory Status: As per the firm, the FDC is in the market since 1993 and is currently being marketed in 14 countries including Romania. However, the FDC is not yet approved in the country.

The proposal of the firm was deliberated in SEC (Analgesic & Rheumatology) in its 72nd meeting held on 24.06.2021 & 25.06.2021 wherein the firm presented their proposal before the committee. The committee noted that the firm needs to present the full text of published articles in support of proposed FDC. On the request of the firm, the proposal was deferred for the next meeting

Accordingly, the proposal was re-deliberated in SEC (Analgesic & Rheumatology) in its 74th meeting held on 11.08.2021 wherein in light of earlier recommendations of SEC, the firm presented their proposal before the committee.

After detailed deliberation, the committee opined that the data presented was not from high impact peer reviewed journals and proposal requires wider deliberation in the presence of more number of experts (orthopedics and rheumatologist).

Then, the firm presented their proposal before 76th SEC (Analgesic & Rheumatology) in its meeting held on *12.10.2021* wherein in light of earlier recommendation, the firm presented their proposal before the committee. After detailed deliberation, the committee opined that;

1. The firm did not present any scientific rationale of the proposed FDC in the management of osteoarthritis of knee joints.

2. The data presented was inadequate and not convincing for the proposed indication.

3. The proposed FDC has not been recommended in any standard treatment guidelines.

In view of above, the committee did not recommend for approval of the proposed FDC.

However, the firm did not agree with the recommendations of Subject Expert Committee and the firm had requested to place this proposal in the Technical Committee for deliberation.

Recommendation of the Technical Committee: After detailed deliberation, committee recommended for grant of permission to conduct the proposed Phase III Clinical Trial of the drug.

Agenda No. 8

Application from M/s GlaxoSmithKline Pharmaceuticals Limited, Mumbai for the grant of permission for import in Form CT-18 for Herpes zoster vaccine (recombinant, adjuvanted) imported from M/s. GlaxoSmithKline Biologicals S.A., Parc de la Noire Epine Avenue Fleming 20, 1300 Wavre Belgium with indication for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older with requesting waiver for clinical trial in the country and commits to conduct a Phase IV study of the Shingrix vaccine in the Indian population as per the provisions of Rule 75, sub-rule 7 of NDCT Rules, 2019.

Drug Name: Herpes zoster vaccine (Recombinant, Adjuvanted)

File No: - BIO/IMP/20/000041

Type of Application: Market authorization application for grant of import permission in Form CT-20 for Herpes zoster vaccine (Recombinant, Adjuvanted) imported from M from M/s. GlaxoSmithKline Biologicals S.A., Parc de la Noire Epine Avenue Fleming 20, 1300 Wavre Belgium with Phase III clinical trial waive off along with Phase IV condition.

International approval status: Herpes zoster vaccine (recombinant, adjuvanted) is currently approved in the United States (USA), all European Economic Area (EEA) countries and Japan, as well as in three other countries (Canada, Australia and China).

Details of the Herpes zoster vaccine (recombinant, adjuvanted) are as below:

The Varicella Zoster Virus (VZV) glycoprotein E (gE), presented in a monodose 3 mL glass vial, contains the lyophilized gE antigen. This antigen is mixed

extemporaneously prior to administration with the liquid AS01B Adjuvant System, also presented in a monodose 3 mL glass vial, to form the gE/AS01B Reconstituted Vaccine (RV).

Route of Administration: Intramuscular injection.

Dosage form & Route of administration: Suspension for injection after reconstitution.

Commercial presentation: 1 vial of powder plus 1 vial of suspension or 10 vials of powder plus 10 vials of suspension.

Indications: for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older.

Storage Condition: Between +2ºC and +8ºC, protect from light & do not freeze.

Earlier the proposal was deliberated in the SEC as well as in technical committee, the recommendations are as under: -

Meeting	**Recommendations**
Technical committee meeting dated 26.04.2021	Technical committee after detailed deliberation agreed with the recommendations of SEC meeting & recommended that the firm should conduct local clinical trial as per requirements.
SEC (Vaccine) meeting dated 06.07.2020	Firm presented its proposal for grant of marketing authorization of Herpes Zoster Vaccine (Recombinant) with local clinical trial waiver. After detailed deliberation, the committee recommended that firm should conduct local clinical trial as per requirements.

Subsequently, however, based on the application of firm, CDSCO has granted permission to M/s GSK on 16.09.2021 to conduct Phase III clinical trial of Herpes zoster vaccine (recombinant, adjuvanted) firm has stated that the trial will be initiated in Jan 2022 & clinical trial data will be available in 2023.

Now, the firm has requested for grant of conditional marketing authorization for Herpes zoster vaccine (recombinant, adjuvanted) in parallel to ongoing local Phase

III clinical trial to increase timely access to the vaccine during current COVID-19 pandemic situation. Firm has submitted justification for the same as given below:Herpes zoster or Shingles disease burden in India.

1. Unmet need existing treatment and its complications & non availability of other vaccines.
2. Shingrix is approved in 36 countries including US, EU, Canada, Australia, New Zealand, Japan and China.
3. Shingrix fulfils Unmet Need in the country. Due to limitations of treatment of Herpes Zoster (HZ) and its complications, and since it is known that an impaired immune response increases the risk of HZ, prevention of HZ by a vaccine is the optimal approach for limiting the burden of illness caused by HZ and its years of age.

The firm made a presentation before the technical committee and presented the justification for grant of conditional marketing authorization for Herpes zoster vaccine (recombinant, adjuvanted) in parallel to ongoing local Phase III clinical trial to increase timely access to the vaccine during current COVID-19 pandemic situation.

Recommendation of the Technical Committee: The committee after detailed deliberation committee opined that there is an unmet need as Herpes Zoster infection is a painful condition and at times patients attempt to commit suicide due to suffering**.** Therefore the committee recommended for grant of permission to import and market Herpes zoster vaccine (recombinant, adjuvanted) with the condition to submit Phase III clinical trial report on completion of the study at the earliest and early supportive safety data.

Agenda No. 9

Proposal of M/s Eli Lilly and Company (India) Pvt. Ltd., for grant permission to Import and Market the drug Ixekizumab Injection 80 mg/mL (Prefilled Auto injector and Prefilled Syringe) for the treatment of adult patients with active psoriatic arthritis and moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

File No. BIO/IMP/20/000058

Appl. Date - 26-JUN-2020

Name of Firm - M/s Eli Lilly and Company (India) Pvt. Ltd.

Drug Name - Ixekizumab Injection 80 mg/mL (Prefilled Auto injector and Prefilled Syringe)

M/s Eli Lilly and Company (India) Pvt. Ltd., has submitted application on 26-JUN-2020 for Marketing authorization of Ixekizumab Injection 80 mg/mL (Prefilled Autoinjector and Prefilled Syringe) for following indication:

Proposed Indication: For the treatment of adult patients with active psoriatic arthritis and moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The firm has conducted Global Clinical Trial titled "A 52-Week Multicenter, Randomized, Open-Label, Parallel Group Study Evaluating the Efficacy and Safety of Ixekizumab versus Adalimumab in Patients with Psoriatic Arthritis Who Are Biologic Disease-Modifying Anti-Rheumatic Drug Naïve" vide protocol number: 1F-MC-RHCF (Phase: 3b/4) including India as participating country. The trial was approved by this office letter dated 06.09.2017. This Global Clinical Trial includes total of 566 randomized patients. Out of these, 20 Indian patients in ixekizumab arm and 26 Indian patients in adalimumab arm (total 46 Indian patients) were randomized as the ITT Population.

- On 06th Oct 2020 the firm presented their proposal for Marketing Authorization before the SEC with data presented of Indian subset and other global studies. However, the committee recommended that, the firm should generate more safety and efficacy data in Indian population for grant of Marketing Authorization. The recommendation of committee were are as follow:

  "Firm presented their proposal for import and marketing the drug before the committee. The committee noted that safety data is available in only 46 Indian patients. Additional safety data in Indian patients needs to be generated. After detailed deliberation, the committee recommended that the firm should generate more safety and efficacy data in Indian population for grant of marketing authorization."

- Subsequently, on 10th Dec 2020, firm had presented comparison of efficacy and safety data of Indian patients with of Global studies and to re-consider their proposal with respect to rule 75 of New Drugs and Clinical Trials Rules 2019. However, the committee didn't recommend for grant of marketing authorization as the efficacy and safety data generated in Indian patients is not adequate for

consideration of marketing authorization. The recommendation of the are as follow:

"In-light of recommendations dated 06.10.2020, firm presented their proposal for import and marketing the drug in India. Firm presented comparison of efficacy and safety data generated in 46 India patients (which included only 20 patients in test arm) with data generated in global studies. The committee noted that, no additional data was presented by the firm. Further, the efficacy and safety data generated in Indian patients is not adequate for consideration of marketing authorization. After detailed deliberation, the Committee did not recommend for grant of marketing authorization based on the presented data"

Firm has appealed for deliberation in Technical Committee meeting being aggrieved by the recommendation of SEC with following justifications –

1. Unmet need of the subject drug: Psoriasis is a common inflammatory disease affecting approximately 2–3% of the world population. In India, the prevalence of psoriasis in adults varies from 0.44 to 2.8%
2. Ixekizumab is approved in 72 countries for Psoriasis indication as of November 2020.
3. Ixekizumab has been studied in 17 clinical trials (Psoriasis and Psoriatic Arthritis) in 6892 adult patients with exposures up to 5 years.
4. Ixekizumab has consistently higher rates of PASI 100 at the primary time point in 5 head-to-head trials vs several biologics (Etanercept, Ustekinumab, Guselkumab Adalimumab), with noticeable improvements in the first week of treatment and almost 60% of patients having completely clear skin through 60 weeks
5. Cumulative global exposure of Patients (post marketing) is 1,75,000.
6. Overall safety data from global exposure of patients on Ixekizumab is similar to safety data generated from clinical studies.
7. India participated in Phase III global clinical trial for Ixekizumab with Primary and secondary endpoints supporting- Psoriatic Arthritis and Psoriasis; 46 Indian patients- participated across 13 Indian sites in global Phase III study (I1F-MC-RHCF)

8. The efficacy and safety of ixekizumab in the RHCF India subset were consistent with the overall population in the RHCF study as well as that observed in the pivotal PsO studies (RHAZ, RHBA, and RHBC) and PsA study (RHAP)
9. Challenges associated with commonly used systemic agents in India like Methotrexate, Cyclosporine, Etanercept, infliximab include
10. Ixekizumab provided rapid onset of efficacy in patients with moderate-to-severe psoriasis

Recommendations of the Technical Committee: The committee after detailed deliberation recommended for grant of permission to import and market the drug with waiver of clinical trial subject to condition that the firm should conduct Phase IV Clinical trial in the country for which protocol should be submitted within 3 months of approval of the drug.

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