MINUTES OF 48TH MEETING OF THE TECHNICAL COMMITTEE HELD ON 26.04.2021 AT 04.00 PM UNDER THE CHAIRMANSHIP OF DGHS FOR SUPEVISING CLINICAL TRIALS ON NEW CHEMICAL ENTITIES IN THE LIGHT OF DIRECTIONS OF THE HON'BLE SUPREME COURT OF INDIA ON 03.01.2013

Present:-

1	**Dr. Sunil Kumar** Director General of Health Services, Nirman Bhawan, New Delhi	Chairman
2	**Dr. Nandini Kumar,** Former Dy. Dire. Gen. Sr. Grade, Adjunct Professor, KMC, Manipal, Chennai.	Member
3	**Dr. Kamlakar Tripathi,** Ex. Prof., Dept. of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005.	Member
4	**Dr. Ashok Kumar Das,** Professor of Medicine & Professor and Head of Endocrinology, Pondicherry Institute of Medical Sciences, Pondicherry.	Member
5	**Dr. Nikhil Tandon,** Professor, Dept. of Endocrinology & Metabolism, AIIMS, New Delhi.	Member
6	**Dr. Raju Titus Chacko,** Prof. & Head, Dept. of Medical Oncology, CMC, Vellore.	Member

From CDSCO:

1	**Dr. V.G. Somani** Drugs Controller General (India)
2	**A.K. Pradhan** Deputy Drugs Controller (India), CDSCO (HQ), New Delhi

The chairman welcomed the members of the committee for the 48th Technical committee meeting. Thereafter, total 10 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 Dr. Willmar Schwabe India Private Ltd., India for permission to for Import & Marketing of Lavender oil (Lasea®) 80 mg soft gelatin capsules

Applicant: M/s Dr. Willmar Schwabe India Private Ltd., India.

Drug Name:Lavender oil (Lasea®) 80 mg soft gelatin capsules

M/s Dr. Willmar Schwabe India Private Ltd., India applied for permission to Import & Marketing of Lavender oil (Lasea®) 80 mg soft gelatin capsules for relief of Anxiety with symptoms such as nervous tenseness, irritability and restlessness in adults and adolescents aged 12 year and above.

The proposal of the firm was deliberated in **SEC** (**Neurology and Psychiatry**) along with Phytopharmaceutical Expert in its meeting held on 18.02.2020, in which firmpresented their proposal for import and marketing of the drug along with preclinical and clinical data with request for waiver of local clinical trial.

In light of recommendation of the committee dated 23.10.2019, the firm presented the details of standardization of the product, clinical data from other countries, regulatory status of the product from countries like Germany, UK, Spain, France, Italy, etc.

The committee after detailed deliberation recommended that the firm should conduct Phase III Clinical Trial in Indian population for which protocol should be submitted for review by the committee.

The firm has submitted the justification for the deliberation of proposal in Technical Committee by statingthatthe phytopharmaceutical drug product Lasea® 80 mg capsules contains exclusively plant material as active substance: a high quality essential oil of Lavender Oil (Lasea®) 80 mg. It is produced by steam distillation of the freshly harvested flowering tops of *Lavandula angustifolia* P. Mill. (*L. officinalis* Chaix) and meets the requirements of the European Pharmacopoeia.The raw material selection and manufacturing processes ensure batch-to-batch consistency of the content and quality of active ingredients.

Lasea® 80 mg soft capsules" has been marketed by Dr. Willmar Schwabe GmbH & Co. KG, Germany since 2010 in many countries, i.e. for more than five years. For the period between 2009 and 2017 approximately 285.2 million defined daily doses (DDD) of Lasea® 80 mg soft capsules were placed on the market worldwide (as based on the standard daily dose of 1capsule per day).

Safety and efficacy of Lasea® is extensively and adequately published. Lasea® 80 mg soft capsules is shown to be effective in the proposed indication in three published placebo-controlled trials in patients with mild to moderate anxiety as well as in two reference and / or placebo-controlled trials in GAD. Based on the results of the clinical program the efficacy of **Lasea®**80 mg soft capsules in the indication applied for is regarded as scientifically reasonable and justified.

Apart from the demonstrated efficacy, a major advantage of **Lasea®**80 mg soft capsules compared to other treatment options is the excellent tolerability. The safety data from the published clinical development program including the phase-I-studies, clinical efficacy and safety trials, the scientific literature, and the post-marketing experience show that mainly minor reactions occur as ADRs. The efficacy and safety data indicate that **Lasea®**80 mg soft capsules is well suited for the use as a medicinal product in the proposed therapeutic indication.

The long-term clinical experience with Lavender oil together with the results of product-specific clinical studies show that **Lasea®**80 mg soft capsules is effective and very well tolerated. Serious side effects or other drug associated risks have not become apparent. Overall, the benefit/risk ratio is favourable for Lasea® 80 mg soft capsules.

Taking all above into account, Lasea® 80 mg soft capsules meets all conditions defined by the Gazette notification G.S.R. 918(E) for the waiver of local clinical trial for the phytopharmaceutical drugs.

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and recommended that the firm should conduct Phase III Clinical Trial in Indian population for which protocol should be submitted for review by the SEC.

Agenda no. 2

Proposal of M/s Roche Products (India) Private Limited for Import and market new drug Polatuzumab Vedotin for Injection 140 mg/vial withrequest of waiver for conduct of local clinical Trial – Regarding

Applicant: M/s Roche Products (India) Private Limited
Drug Name: Polatuzumab Vedotin for Injection 140 mg/vial

Subject: Application in Form CT-18 for Import and marketing of new drug Polatuzumab Vedotin for Injection 140 mg/vial withrequest of waiver for conduct of local clinical Trial – Regarding

Firm has applied for Import and market new drug Polatuzumab Vedotin (Polivy®) 140 mg/vial for Injection in single-dose 20 mL vials. Upon reconstitution Polivy concentrate contains 20 mg/mL of polatuzumab vedotin for intravenous infusion. Polatuzumab Vedotin in combination with bendamustine and rituximab is indicated forthe treatment of previously treated adult patients with diffuse large B-Cell lymphoma (DLBCL) who are not candidate for hematopoietic stem cell transplant.

Earlier SEC deliberations:

First SEC meeting held on 21 October 2019, the recommendations were as follows:
"Firm presented their proposal for permission to import and marketing of the drug for the indication "Polatuzumab Vedotin in combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-Cell. Lymphoma (DLBCL) who are not candidate for hematopoietic stem cell transplant" with waiver of Phase III and Phase IV clinical trial in the country. Committee noted that the drug has been approved by USFDA through accelerated approval process based on Phase II study on limited number of patients for the indication in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.

As per USFDA approval, the firm is required to conduct two Phase III studies. Committee opined that although the proposed indication is a rare disease, considering the safety profile of the drug (Grade III/IV toxicities of 84.6%), Phase III clinical trial data is required for further consideration. Committee also noted that efficacy data has been generated in the Phase II study with relatively weak comparator arm. Therefore, the committee recommended that the firm should submit Phase III clinical trial data of the drug."

Roche has submitted a request for reconsideration of their application firm was invited in SEC meeting held on 3rd July 2020.

Second SEC meeting held on 03 July 2020 the recommendations were as follows:
"In-light of the recommendations of the SEC meeting held on 21.10.2019, the firm presented safety data and requested for grant of marketing authorization with local Phase III clinical trial waiver.
The committee noted that with the available safety data, the risk to benefit ratio is not compelling for waiver of local Phase III clinical trial. After detailed deliberation, the committee reiterated its earlier recommendation to conduct local Phase III clinical trial with the drug".

The firm has filed an appeal for "Technical Committee" regarding their proposal requesting permission to Import and Market the subject drug **as an Orphan drug, Treatment for Rare Disease, Unmet Medical Need.**

Firm has submitted following justifications:

1. **Transplant-ineligible R/R DLBCL is a Rare disease.**
2. **Currently, there is a huge unmet need in patients with r/r DLBCL Transplant ineligible.**
3. **Compliance to New Drugs and CT Rules – CT waiver criteria, [refer Rules 80(7)],**
    - As on date, Polatuzumab Vedotin for Injection 140 mg/vial [Polivy®] is approved in approx. 47 countries including USA, EU, Canada, Australia etc. and Approx. 7200 patients are treated globally.
    - India is under consideration as one of the potential participating countries in the global clinical trial Phase III [Protocol No - MO40598]. Currently site feasibility is underway. However, firm inform that, Roche India has participated in the global Compassionate Use (CU) program where 38 Indian patients were treated with Polivy®. There were no new safety signals reported.
    - An undertaking to conduct Phase IV clinical trial is submitted.
4. **Molecule has a good Risk Benefit ratio**
5. **Roche India is committed to submit the CSRs for the ongoing Global Phase III clinical trials as & when available** [approx.. timelines are study 1: Q3-2022 and study 2: Q2-2024].
6. **Local Phase III in India will delay the approval of the product by further 3 years denying the access to newer therapy to patients who have failed to respond to existing treatment options in DLBCL.**

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and recommendedto conduct local Phase III clinical trial with the drug.

Agenda no 03

Proposal of M/s Sanofi-Synthelabo (India) Private Limited for import and market Dupilumab 150 mg/ml (300 mg in 2 mL), solution for s.c Injection (Prefilled syringe and Prefilled syringe with needle shield) based on local Phase III clinical trial waiver.

Applicant - M/s Sanofi-Synthelabo(India) Private Limited

Drug Name: Dupilumab 150 mg/ml (300 mg in 2 mL), solution for s.c Injection (Prefilled syringe and Prefilled syringe with needle shield)

Objective – Application for grant of permission to import and market Dupliumab 150 mg/ml (300 mg in 2 mL), solution for s.c Injection (Prefilled syringe and Prefilled syringe with needle shield) based on local Phase III clinical trial waiver - reg

It is stated that M/s Sanofi-Synthelabo(India) Private Limitedsubmitted application on 31st January 2019 for grant of marketing authorization (permission to Import and market) for Dupilumab (BRNAD name – Dupixent) 150 mg/ml (300 mg in 2 mL), solution for SC Injection (PFS and PFS with needle shield).

The drug is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical therapy.

Pack presentation - single-use pre-filled syringe with needle shield contains 300 mg dupilumab in 2 mL solution.

Recommended dose of Dupixent for adult patients - initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.

Based on individual therapeutic response, the dosage may be increased to 300 mg given weekly

1st SEC meeting held on 12th Sept 19 –

Firm presented their proposal for grant of marketing authorization with local clinical trial waiver. The committee opined that there was no clinical data available on this drug in Indian patients and alternative therapies are available for the proposed indication. After detailed deliberation, the committee recommended that the firm should conduct local Phase III clinical trial to assess the safety and efficacy profile of the drug in Indian patients and submit the protocol for review.

In-light of the minutes reproduced above, on **30th Sept 2019** CDSCO informed the firm to submit Phase-III CT protocol for taking further action in this regard.

On 8th Nov 2019, firm submitted request for reconsideration of phase III waiver requestin light of the New Drug and CT Rules 2019 as specified in Chapter X Rule 75 (7) under provided criteria i, ii, iii and iv.

As per Criteria (i), firm clarified that the drug Dupixent is approved in over 40 countries worldwide (US, EU, Australia, Japan, Canada etc.) with no major unexpected AE reported in post marketing phase.

Dupixent is the first biologic drug approved for patients with Moderate to severe AD who failed topical therapies and has proved efficacy with mild and manageable side effects. Extensive clinical evidence and Real World experience.

Criteria (ii): Firm informed that, there is ongoing Phase III global clinical study of Dupixent for the asthma indication in which India is participating with proposed patients no. is 100.

Criteria (iii): Analysis from 3 Phase III clinical trial have confirmed low ethnic sensitivity.

Criteria (iv): Firm commits to do Phase IV study with safety as a primary endpoint (Undertaking submitted). Firm has also shared Unmet need and limitation in existing systemic therapies available for patients with moderate to severe atopic dermatitis.

Based on firm's request, proposal was re-deliberated in the 44th SEC (Dermatology & Allergy) held on 17th January 2020–

Firm presented its proposal for grant of marketing authorization with local Phase III clinical trial wavier. The committee noted that the proposal was earlier deliberated on **12.09.2019** wherein the committee recommended that the firm should conduct local Phase III clinical trial to assess the safety and efficacy profile of the drug in Indian patients and submit the protocol for review as there is no clinical data available on this drug in Indian patients and alternative therapies are available for the proposed indication. After detailed deliberation, the committee reiterated its recommendation as per the SEC meeting dated 12.09.2019. Accordingly, the firm should conduct local Phase III clinical trial to assess the safety and efficacy of the drug in Indian patients.

The firm has requested for the matter to be deliberated in Technical committee for considering its proposal for marketing authorization based on waiver of local clinical trial (Phase III) while committing to do Phase IV study.

Firm has submitted letter from SKIN ALLERGY RESEARCH SOCIETY which is registered in Maharashtra. The letter reads "we are surprised and concerned to note that such an important and transformative therapeutic option and which is available in all major countries of the world has still not been made available to patients with AD in India". This is only one representation submitted in the matter.

WRT to ongoing GCT to evaluate the efficacy of dupilumab in patients with persistent asthma, firm has clarified that out of 26 patients 12 has completed the trial (52 weeks duration).

Since the study does not have any formal interim analysis planned hence unblinded data is currently unavailable.

Firm has informed that after close to 5 months of mean exposure, there were no serious adverse events (SAEs) or adverse events of special interest (AESI) observed in any of the 26 subjects in the study. However, total of 46 AEs was reported in 16 subjects 45 of

which were not related to study medication but one AE (fever) was marked as related to study medication by the investigator and one AE (Vaginal pustule) which was not related to study medication led to IP discontinuation.

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and recommended that the firm should conduct local Phase III clinical trial to assess the safety and efficacy of the drug in Indian patients.

Agenda no. 4

Proposal of M/s Pfizer Products India Private Ltd, for wavier for Phase IV trial, condition for the product Lorlatinib Tablets 25mg permission.

Name of Applicant:. M/s Pfizer Products India Private Ltd

Drug Name/indication:Lorlatinib Tablets 25mg, for the treatment of ALK fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)

Recommendations of SEC (Oncology & Haematology) meeting held on 28.03.2019:-

The firm presented their proposal for import& marketing of the drug before the committee.
The committee noted that the drug is indicated for a disease condition which is rare & it has activity against brain metastasis & resistant mutation in Advance/Recurrent NSCLC& there is unmet medical need. The drug is approved in US, Canada, Japan & other countries based on phase II clinical trial data. USFDA while approving the drug under their accelerated approval regulations has also required further adequate well control clinical trials to verify & describe clinical benefit. Phase III trial of the drug is ongoing in many countries including India.

Considering the above aspects, after detailed deliberation the committee recommended for grant of permission to import & market the drug subject to condition that the firm should conduct a phase IV CT on about 100 patients for which protocol should be submitted within 3 months of approval and results should be submitted for review within 2 years of the approval of the phase IV Clinical trial.

Recommendations of SEC (Oncology & Haematology) meeting held on 26.06.2020:-

Applicant presented their proposal for Phase IV study before the committee.

After detailed deliberation, the committee recommended for grant of permission to conduct the phase IV trial as per the protocol presented. As per conditions of import permission firm should submit results of the trial within 2 years for review.

As per Market Authorization condition, firm was asked to conduct Phase IV CT on about 100 patients andpermission for conduct of phase IV clinical trial has been granted to the firm with permission no. CT/ND/55/2020, dated 02-07-2020.

Now the firm has requested to refer their proposal to Technical committee for waiver of phase IV clinical trial. The firm has submittedjustification for the same as given below-

1. The overall estimated lung cancer mortality in India in 2018 was 63,475 cases, making it the third most common cause of cancer-related mortality in India after breast and oral cancers. In India, NSCLC is reported to be around 80-92% of all cases of lung cancer and adenocarcinoma histology is around 26% to 52.9%. ALK positivity in India varies from 2.1 % to 13.5% in NSCLC patients which will be approx. 4000 to 5000 patients per year based on Population Based Cancer Registry. This fulfills the definition of a rare disease in India. Hence Lorlatinib falls under the Orphan Drug category based on the definition provided by New Drugs and Clinical Trials Rules, 2019. Other companies have also been granted clinical trial wavier for drugs falling under Orphan Drug criteria. Due to the low 5 year survival rate for all patients with NSCLC (21.6%, 4.9% for metastatic disease), Lorlatinib fulfills an unmet medical need.

2. Lorlatinib had also been granted orphan drug status in the US on 23 June 2015 for the treatment of ALK-positive or ROS1-positive NSCLC. US FDA had also granted Lorlatinib Breakthrough Therapy Designation (BTD) on 26 April 2017 for the treatment of patients with ALK-positive metastatic NSCLC previously treated with one or more ALK inhibitors. BDT is the official recognition of the fact that the drug demonstrates substantial improvement over available therapy.

3. ALK positive NSCLC patients can be treated with crizotinib or the second generation ALKTKIs, alectinib and ceritinib, as the first line treatment option. However, approximately 53-71% ALK positive patients treated with second-generation ALK TKIs such as ceritinib, alectinib, who initially experience benefit invariably develop resistance mutations or progress due to the emergence of brain metastases. Our drug Lorlatinib is for patients who have failed first line therapy, hence the number of patients who will fall under the criteria of the approved indication will be even smaller.

4. Lorlatinib is a third-generation ALK TKI that was specifically developed to have broad activity against ALK resistance mutations, including the most commonly observed G1202R. Lorlatinib has strong intracranial activity, consistent with its ability to cross the blood-brain-barrier and therefore has a high potential to treat patients with CNS metastases. With the above attributes, Lorlatinib represents a viable option for patients with resistance or intolerance to first line ALK TKI.

5. A total of 8 global studies supporting the regulatory submission in India of lorlatinib for the treatment of patients with ALK-positive NSCLC have been conducted, including a total of 334 patients (55 patients in Phase 1, 276 patients in Phase 2, and 3 patients in the Japan Lead-in Cohort) enrolled in the Phase 1/2 Study).

6. Lorlatinib is approved in many countries and no new safety concerns were identified from post-marketing experience.

7. Pfizer has already made this drug available on name patient bases over the period of last two and half years.

The firm has proposed the following measures to generate additional safety data for the product:

- Active surveillance to submit safety data from the first 50 patients treated with Lorlatinib Tablets, post marketing.
- Submission of regular periodic safety updates (PSUR) reports for the extended period of four years.

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and recommended for conduct of phase IV clinical trial as per conditions of import permission

Agenda no. 5

Proposal for Post Marketing Surveillance (Protocol No. CIGE025EIN01) to evaluate the safety and effectiveness of Omalizumab in Indian patients with Chronic Spontaneous Urticaria refractory to standard of care

Applicant - M/s Novartis Healthcare Pvt. Ltd.
Drug Name: Omalizumab

Post Marketing Surveillance (Protocol No. CIGE025EIN01) to evaluate the safety and effectiveness of Omalizumab in Indian patients with Chronic Spontaneous Urticaria refractory to standard of care . Firm was granted approval for additional indication on dated 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. If it is not submitted, the conditional approval will be withdrawn.

As per the said condition firm has submitted the study protocol CIGE025EIN01 version 00 dated 16.06.2015, CRF, patients information sheet etc. with the assurance that, after

completion of the study, full clinical study report (CSR) of the said PMS will be submitted.

Further on 08.01.2016, firm informed that, first patients has been enrolled in the study on 16.12.2015 and study will be completed around April 2018. However, on 10.04.2017 firm requested to extend the time line by Dec 2018 to submit the CSR report.

Firm has submitted the PMS report entitled "A Prospective, Post Marketing Surveillance Study to Study the Safety and Effectiveness of Omalizumabin Indian Patients with Chronic Spontaneous Urticaria Refractory to Standard of Care." vide application dated 24.12.2018

Minutes of SEC meeting dated 14.03.2019
"The firm presented their Phase IV clinical study of Omalizumab. After detailed deliberation, the committee recommended that the firm should present detailed dose - response and dose - safety data of the said study before the committee"
Accordingly, firm presented dose - response and dose - safety data on SEC dated 05.11.2019 and the committee recommended following:

Minutes of the SEC meeting dated 05.11.2019
"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.

Firm has submitted proposal for re-deliberation vide application dated 27.02.2020. The proposal was again deliberated in SEC meeting dated 13.07.2020."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 the above, firm has filed an appeal vide application dated 03.11.2020 for Technical Committee Meeting for not continuing the PMS study on additional 200 Indian patients, based on the following rationale:

1. **Regulatory Approval Status of Omalizumab globally and in India**
   - Indication: Moderate To Severe Persistent Allergic Asthma: Approved (in Oct 2005) and marketed in India for more than 14 years. Globally approved (since 2002) in 99 countries.

- Indication: Chronic Spontaneous Urticaria: Approved (in Oct 2014) and marketed in India for more than 6 Years. Globally approved (since Sep 2013) in 93 countries.

2. Data on anaphylactic reaction from the current PMS study

- Firm presented the safety and efficacy data, as obtained from the PMS study of Omalizumab 150mg and 300mg doses to the Dermatology & Allergy SEC members on 5 Nov 2019.
- Firm presented 1 anaphylactic reaction (1 out of 143 patients = 0.7%), suspected to be related to the drug and occurred in a single patient (Rash, urticaria, dyspnea, peripheral swelling and cyanosis were of mild intensity; angioedema was severe). The study drug was discontinued in this patient and the patient recovered.

3. Omalizumab and Anaphylactic Reaction - Prescribing Information

- Anaphylactic reaction is a known rare adverse drug reaction associated with Omalizumab administration in clinical studies.
- India specific prescribing information states that:

"Anaphylactic reactions are expected ADRs, as with any protein. Therefore, medications for the treatment of anaphylactic reactions should be available for immediate use following administration of Omalizumab. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur".

4. Omalizumab and Anaphylactic Reaction - India Safety Data

- Omalizumab was launched in India in 2005.
- There have been three AE reports of anaphylactic reaction of which one case of anaphylactic reaction was associated with Omalizumab administration.
- Anaphylactic reactions related to Omalizumab in India remain consistent with the overall global safety data.
- No changes to the safety profile concerning the topic of the identified risk 'Anaphylactic reactions' have been identified.

5. Omalizumab and Anaphylactic Reaction - Global PSUR data

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

6. Omalizumab and Anaphylactic Reaction - Review of Literature

- Literature suggests that anaphylactic reactions have been reported following the administration of Omalizumab.
- In post marketing spontaneous reports, the frequency of anaphylaxis attributed to Omalizumab use was estimated to be in at least 0.2% of patients. This rate of anaphylaxis has been known and is clearly outlined in the package insert of the product as well.
- Omalizumab should only be administered by a physician or health care professional, who is trained in the recognition and treatment of anaphylaxis, in a setting where the appropriate medications and equipment are available to respond to an episode of anaphylaxis. (IndianDermatol Online J. 2016 Jan-Feb; 7(1): 6-11; Indian J Dermatol. 2018 Jan-Feb; 63(1): 66-69.)

Based on above information, firm informed that, the frequency of anaphylactic reactions reported in the PMS study are in accordance to the prevalence reported in

literature and clinical studies. The same has been specified in the India Package Insert. The firm has a robust pharmacovigilance program in place with a RMP. Considering all the cited points, continuation of the PMS study is not warranted for Omalizumab in chronic spontaneous urticaria.

Recommendation of the Committee: 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.

Agenda no. 06

Proposal of M/s Sanofi Pasteur India Pvt. Ltd. Mumbai for the grant of permission for the import of Quadrivalent Influenza vaccine (QIV) [Brand name: Vaxigrip Tetra] in Form CT-20 from M/s. Sanofi Pasteur, Parc Industriel D, Incarville Val De Reuil, France with Phase III clinical trial waive off along with Phase IV condition.

Applicant : M/s Sanofi Pasteur India Pvt. Ltd.
Drug Name: Quadrivalent Influenza vaccine (QIV) [Brand name: Vaxigrip Quadri]

This Directorate has received an application from M/s Sanofi Pasteur India Pvt., Ltd., Mumbai for the grant of permission for the import of Quadrivalent Influenza vaccine (QIV) [Brand name: Vaxigrip Tetra] in Form CT-20 from M/s. Sanofi Pasteur, Parc Industriel D, Incarville Val De Reuil, France with Phase III clinical trial waive off along with Phase IV condition.

Type of application: Market authorization application for grant of import permission in Form CT-20 for Quadrivalent Influenza Vaccine (Split Virion, Inactivated) [Brand Name: Vaxigrip Tetra] imported from M/s. Sanofi Pasteur, Parc Industriel D, Incarville Val De Reuil, France with Phase III clinical trial waive off along with Phase IV condition.

CDSCO approval status: Earlier this office had granted import permission in Form 45 for Quadrivalent Inactivated Influenza Vaccine (split virion) I.P. [Brand Name: FLUQUADRI] vide permission no.: IMP-119/2017, dated: 30.05.2017 with the indication for the prevention of influenza disease caused by influenza types A and B viruses contained in the vaccine. FluQuadri® is approved for use in persons 6 months of age and older imported from M/s Sanofi Pasteur Inc., Discovery Drive, Swiftwater PA 18370, USA.

International approval status: France (2016), Australia Switzerland, United Kingdom (UK), South Africa, Hong Kong, Malaysia, Singapore, Philippines, Korea, Thailand Bangladesh, Turkey, Brazil et al.

SEC (Vaccine) Recommendations:

SEC meeting	Recommendations
SEC (Vaccine) meeting dated 06.07.2020	• The firm presented its proposal for grant of marketing authorization of Quadrivalent Influenza (Vaxigrip Tetra) Vaccine with local clinical trial waiver. • The committee noted that Quadrivalent Influenza Vaccine

	(QuadriFlu) of the same firm is already being marketed in the country the proposed vaccine differs with the already marketed vaccine in terms of dose, indication, composition & manufacturing site. • After detailed deliberation, the committee recommended that firm should conduct local clinical trial as per requirements.

Now, firm has submitted an application for grant of import permission in Form CT-20 for Quadrivalent Influenza Vaccine (Split Virion, Inactivated) [Brand Name: Vaxigrip Tetra] imported from M/s Sanofi Pasteur, Parc Industriel D, Incarville Val De Reuil, France with Phase III clinical trial waive off along with Phase IV condition. In this regard, firm has submitted the various clinical trials conducted outside India.

Justification for local clinical trial waiver with Phase IV condition:

- VaxigripTetra has been approved in over 90 countries worldwide including in 2016 (July) United Kingdom (UK); 2016 (Aug) in France; 2019 (May) In Australia; 2017-2019 In Malaysia, Philippines, Singapore etc. Vaxigrip Trivalent Influenza Vaccine.

S. No.	Name of country where Clinical Trial Conducted	Phase of clinical trial	Dose	Age group (with/without pregnant lady)	Safety Summary	Efficacy Summary
1	Finland, Poland, Mexico, Taiwan	III	1 dose 0.5 mL and 2nd dose of 0.5ml on Day 28 for (unprimed individuals) who were not vaccinated in prior season with 2 doses	3–8 years Children aged 3 to 8 years, previously vaccinated against influenza or not	Similar frequencies of solicited reactions and unsolicited AEs between vaccine groups. The study showed that the QIV was well tolerated.	As immunogenic as TIV for the shared strains Produces superior immunogenicity for the additional B strain Induced a significant immune response against the 4 strains in - Primed* subjects who received 1 injection (0.5 mL), and - In unprimed* subjects who received 2 injections 28 days apart Induced immune responses in a subgroup of subjects with underlying chronic illness comparable to the overall population

2	Taiwan	III	1 dose (0.5 Ml)	9–17yr Children / Adolescents aged (09 to 17 years)	The study showed that the QIV was well tolerated.	This study showed that despite high baseline HAI titers, the 2013–2014 Northern Hemisphere formulation of the QIV was immunogenic in children and adolescents 9–17 years of age.
3	Belgium, France, Germany, Poland	III	1 dose (0.5 mL)	≥ 18yr Adults aged 18 to 60 years and elderly aged over (60 years)	VaxigripTetra® is well-tolerated, immunogenic, in both non-elderly and elderly adults. Vaccination with VaxigripTetra® could help address an unmet need due to mismatched B strains in previous influenza vaccines	For all matched strains, antibody responses to VaxigripTetra® were non-inferior to responses to trivalent vaccines Antibody responses against the B strains not contained in the trivalent vaccine comparators were superior with VaxigripTetra
4	France, Spain, Greece, Germany, Italy, Philippines, South Africa, Dominican Republic, Honduras	III	2 doses 0.5 mL (28 days apart)	6–35 months Children Aged 6 to 35 Months, not previously vaccinated against influenza	Vaxigrip Tetra prevents 56.6% of severe laboratory-confirmed influenza illnesses due to any strain, and 71.7% of severe laboratory-confirmed influenza illnesses due to vaccine-similar strains (pre-defined complementary analysis) In addition, subjects receiving Vaxigrip Tetra	The efficacy of VaxigripTetra against laboratory confirmed influenza due to any influenza A or B types was 52.03% and against laboratory confirmed influenza due to influenza strains similar to those contained in the vaccine 69.33% (co-primary endpoints).

					were 59.2% less likely to experience an influenza illness leading to a medical visit than subjects receiving Placebo (pre-defined complementary analysis)	
5	Finland	III	1 dose (0.5 mL)	Pregnant adults 18 years and older	All birth outcome reported were live births. The majority of babies (96.9%) were born with no congenital abnormalities. No death was reported 21 SAEs were reported in 20 babies in the QIV group. 18 SAEs were reported in 16 babies in the TIV group. None of them were considered as related tothe study drug. <u>Within 21 days after vaccination</u>: -No immediate AEs were reported. 93% subjects in the QIV group and 92.2% subjects in the TIV group	A/H1N1: In PPAS, the majority of subjects (99.5%) had 21 days post-vaccination titers ≥ 40 and a majority of subjects (95.4%) had titers ≥ 160 A/H3N2:In PPAS, the vast majority of subjects (95.8%) had 21 days post-vaccination titers ≥ 40 and a majority of subjects (77.1%) had titers ≥ 160 *B/Brisbane (B/Victoria lineage):* In PPAS, the vast majority of subjects (100%) had 21 days post-vaccination titers ≥ 40 and a majority of subjects (94.5%) had titers ≥ 160 *B/Phuket (B/Yamagata lineage):* In PPAS, the vast majority of subjects (100%) had 21 days post-vaccination titers ≥ 40 and a majority of subjects (86.2%) had titers ≥ 160

					reported solicited reactions. Injection site Pain and Headache were the most reported in both the groups. -2 SAEs reported by 2 subjects in the QIV group. -No AESIs and deaths were reported.	
6	France, Germany	III	1 dose 0.5 mL	≥ 18yr Adults aged 18 to 60 years and elderly aged > 60 years	This study confirmed that the inactivated QIV is well tolerated, immunogenic, and meets EMA immunogenicity criteria in both non-elderly and elderly adults.	Vaccination with this QIV could help address an unmet need due to mismatched B strains in previous influenza vaccines. The results support a switch from TIV to QIV in adults.
7	Australia, Italy, France, Spain, Greece Germany Philippines	III	1 dose 0.5 mL	9–60yr Children/ adolescents aged 9 to 17 years and adults aged 18 to 60 years	A single dose of QIV provides sufficient immunity for adults and for children as young as 9 years old Vaccination with QIV offers a broader immune response to influenza B than with TIV and might help reduce influenza-related hospitalizations, costs, and deaths	Comparable response and safety profiles of QIV to TIV in both age groups. QIV induced robust antibody responses for all 4 strains in both groups. QIV met all adult EMA immunogenicity criteria (seroprotection, GMTR, and seroconversion) for all 4 strains. • There are no EMA criteria for children or adolescents, but all EMA criteria responses were higher in 9–17 years than in adults QIV lot-to-lot

						consistency demonstrated.
8	Nepal	IV	1 dose (0.5 mL)	Pregnant women and Infants	The rate of small for gestational age infants was not modified by immunisation. The number of adverse events was similar regardless of immunisation status. No serious adverse events were associated with receipt of immunisation.	Study assessed vaccine immunogenicity, safety, and three primary outcomes: the incidence of maternal influenza-like illness in pregnancy and 0–180 days postpartum, the incidence of low birthweight (<2500 g), and the incidence of laboratory-confirmed infant influenza disease from 0 to 180 days.
9	Mali	IV	1 dose (0.5 mL)	Pregnant women and infants	No serious adverse events in infants were related to maternal vaccination.	This study unequivocally demonstrates efficacy of maternal immunisation against laboratory-confirmed influenza among infants and mothers, and shows high acceptability and logistical feasibility, thereby paving the way for a larger trial to assess prevention of severe laboratory-confirmed influenza leading to hospital admission in infants.

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and recommended that the firm should conduct local clinical trial as per requirements.

Agenda No. 7

Proposal of M/s Sun Pharmaceuticals Industries Ltd. for Import and marketing of Ferric Pyrophosphate citrate solution, for parenteral administration with bicarbonate concentration, 27.2 mg Fe/5 mL with waiver of Local Clinical trial.

Applicant: M/s Sun Pharmaceuticals Industries Ltd

Drug Name: Ferric Pyrophosphate Citrate solution, for parenteral administration with bicarbonate concentration, 27.2 mg Fe/5 mL and 272 mg Fe/50mL

International Approval Status: Approved only in USA

CDSCO Approval Status: Not yet approved by CDSCO

This Directorate has received an application from M/s Sun Pharma Lab. Ltd. for permission to Import and marketing of Ferric Pyrophosphate citrate solution, for parenteral administration with bicarbonate concentration, 27.2 mg Fe/5 mL with waiver of Local Clinical trial.

Till date, the proposal of local CT waiver for this product, Ferric Pyrophosphate Citrate solution has been deliberated in the SEC committee **thrice**. The recommendations of SEC are as follows: -

1. **M/s. Rockwell Medical India Pvt. Ltd**

   I. **Recommendation of SEC (Oncology and Haematology) held on 13.04.2017**

   Firm has submitted application for the grant of permission Import and marketing of New drug product, Ferric Pyrophosphate Citrate solution, for parenteral administration with bicarbonate concentration, 27.2 mg Fe/5 mL and 272 mg Fe/50mL which is indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis –dependent chronic kidney disease (HDD-CKD). Firm presented the proposal with a request for waiver of local clinical trial in the country. The committee noted that there are available alternatives for the proposed indication in the country. Therefore, after detailed deliberation the committee recommended that the firm should conduct a local Phase III clinical trial in the country and accordingly protocol etc. should be submitted to the office of DCG (I) for the consideration

   II. **Recommendations of the SEC (Cardiovascular & Renal) held on 25.07.2017**

   The firm presented their proposal with clinical data, claiming that this is a drug for unmet need in patient with CKD on haemodialysis in India and the disease is a rare disease. However, the committee after detailed deliberation opined that CKD on

haemodialysis is not a rare disease in India and alternative therapies are available. The committee recommended that local Clinical Trial Phase III should be conducted.

2. **M/s Sun Pharma laboratories ltd.**

III. Recommendations of the SEC (Cardiovascular & Renal) held on 25.07.2020

The firm presented their proposal along with justification of clinical trial waiver. The committee after detailed deliberation reiterated its recommendation made earlier for application of M/s Rockwell that there is available alternatives for the proposed indication and therefore the firm should conduct a local Phase III clinical trial and accordingly protocol etc. should be submitted for review.

Now the firm has requested this office to refer their proposal to Technical committee and provide an opportunity to present their proposal of local clinical trial waiver.

Summary for seeking waiver from conducting local Phase III clinical trial:

- Ferric Pyrophosphate Citrate Solution, 27.2 mg Fe/ 5 ml is the only iron product that is US FDA approved for delivery via dialysate indicated for the replacement of iron to maintain haemoglobin in adult patients with HDD-CKD.

- Ferric Pyrophosphate Citrate Solution of Rockwell Medical is approved by US FDA on 23rd January 2015 and is commercially launched in USA in September 2015.

- There are no unexpected serious adverse events reported with Ferric Pyrophosphate Citrate Solution in USA since its launch.

- Ferric pyrophosphate citrate is the first iron salt devoid of carbohydrate to be considered for parenteral administration in over 100 years.

- No approved IV iron product has an indication for a continuous maintenance regimen in haemodialysis-dependent chronic kidney disease patients in India. Therefore, there is an unmet need in haemodialysis-dependent chronic kidney disease patients.

- Ferric Pyrophosphate Citrate Solution is indicated ONLY for Haemodialysis-dependent chronic kidney disease patients which is rare disease/condition in India.

- There is an unmet need for Ferric Pyrophosphate Citrate Solution in India as currently there is no available therapy which is indicated for the maintenance of Haemoglobin in haemodialysis-dependent chronic kidney disease patients.

- Currently used intravenous iron agents, iron sucrose and iron carboxymaltose, are used on a weekly-monthly schedule even though efficacy and safety of these agents have never been demonstrated in long term studies.

- The safety and efficacy of Ferric Pyrophosphate Citrate Solution in patients with HDD-CKD was assessed in two randomized, single blind, placebo-controlled clinical trials (SFP-4-RC and SFP-5-RC). Study was conducted in 305 patients and 294 patients in SFP-4-RC and SFP-5-RC respectively.

- There were no deaths or events of suspected hypersensitivity reactions due to Ferric

Pyrophosphate Citrate Solution in these studies.

- A number of clinical studies (including phase I, II and III) have been conducted to evaluate the safety and effectiveness of Ferric Pyrophosphate Citrate Solution (27.2 mg Fe/5 ml) in USA and Canada on different race categories including Caucasians, African Americans, Hispanics and some Asians and American Indians.

- The clinical trials performed on Ferric Pyrophosphate Citrate Solution fulfils the ICH requirements (ICH Guideline E5 (R1) On 'Ethnic Factors in the Acceptability of Foreign Clinical Data') of extrapolating the clinical data to the new region (in this case, India).

- Ferric Pyrophosphate Citrate is insensitive to ethnic factors and that the clinical studies that were concluded in the American population in the USA are valid for Indians.

- As of 31 December 2019, there were 40,200 patient days of exposure (110 patient-years of exposure) to Triferic ampules. There has been a total of 1,442,000 patient days for all dialysate Triferic based on based on commercial sales distribution.

- Chronic Kidney Disease is classified as Rare Disease in India as per Organization for Rare Disease India (ORDI). Haemodialysis therapy is much more rare than Peritoneal dialysis.

- As per an Office Memorandum dated 1st February 2019 issued by Ministry of Health and Family Welfare, Haemodialysis is considered as a Rare Disease in India.

- As per published article in 2018, India is expected to have 1,20,000 patients on Haemodialysis and as per New Drug Clinical Trial Rules 2019, Orphan drug means a drug intended to treat a condition which affects fewer than two lac person in India. From the above factor we can deduce that Ferric Pyrophosphate Citrate solution can be an orphan drug in India.

- As per Rule 75 (7) of New Drugs and Clinical Trials Rules, 2019, if the new drug is approved and marketed in other countries internationally, the local clinical trial may not be required.

- In the past, based on recommendation of Technical Committee in its 44th meeting held on 05th September 2018 recommended for CT waiver and accordingly drug product Sucroferric Oxyhydroxide bulk & Sucroferric Oxyhydroxide Chewable tablets 500 mg for the control of serum phosphorous levels in patients with chronic kidney disease on dialysis was approved in India on 18.04.2020 with a local clinical trial waiver.

  In lieu of all above, as the drug product is internationally available in well-regulated country like USA, number of well-controlled studies conducted with the drug and it fulfills the criteria of non-sensitivity to ethnical factor, we strongly believe that the internationally conducted clinical studies can be considered as valid for Indian population. Also the drug fulfills the criteria of local clinical trial waiver as per New Drugs and Clinical Trials Rules, 2019. Hence, we seek wavier from conducting local clinical trial.

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and recommended that the firm should conduct a

local Phase III clinical trial and accordingly protocol etc. should be submitted for reviewby the SEC.

Agenda no.8

Proposal for grant of permission to conduct clinical trial of a novel phytopharmaceutical - aqueous extract of Cocculus hirsutus (AQCH)

Applicant : M/s Sun Pharmaceutical Industries Ltd.
Drug Name: Novel phytopharmaceutical – purified aqueous extract of Cocculus hirsutus (AQCH) tablets 400mg

This office has received an application for grant of permission to conduct clinical trial of a novel phytopharmaceutical - aqueous extract of Cocculus hirsutus (AQCH) tablets titled "An open label, multicenter, non-randomized clinical trial to evaluate the efficacy and safety of AQCH tablet in treatment of COVID -19" study phase: Proof of Effectiveness, proposed to be conducted in 100 participants. The Primary Objective of the study is to evaluate the efficacy of Cocculus hirsutus-based phytopharmaceutical drug AQCH for treatment of COVID-19 and Secondary Objective is to evaluate the safety of Cocculus hirsutus-based phytopharmaceutical drug AQCH for treatment of COVID-19.

Based on SEC recommendations, this office has issued permission in Form CT-06 for conduct of the Phase II Clinical trial vide No. CT-ND/33/2020 dated 08.05.2020.

Later, the applicant has submitted an application for manufacturing and marketing of Purified aqueous extract of Cocculus hirsutus tablets 400mg for treatment of moderate COVID-19 disease under the Emergency Use Authorization along with Phase II CT report.

Recommendations of SEC (Antimicrobial & Antiviral) meeting held on 29.10.2020:-

The firm presented their proposal for approval of the drug for restricted emergency use along with Phase II clinical trial results, before the committee.

The committee observed that the trial results have failed to meet the primary efficacy end points. Even in the secondary end point although there was some efficacy in respect of viral clearance in day 7 and median time to clinical improvement, overall clinical data was not satisfactory.

Therefore the committee did not recommend for approval of the product for emergency use.

Recommendations of SEC (Antimicrobial & Antiviral) meeting held on 18.12.2020:-

In light of earlier SEC recommendation, the firm presented their reanalysed results with the request for grant of emergency use authorization.

After the presentation of reanalysed data committee observed that the results of the study did not meet the efficacy criteria of primary end point.

Therefore committee has not recommended for grant of approval of emergency use authorization at this stage.

The firm has submitted response to SEC recommendation dated 17.12.2020 and 18.12.2020 along with the justification on their proposal to grant Emergency Authorisation Approval for Phytopharmaceutical drug, AQCH tablets 400mg, for the treatment of moderate Covid and requested to refer their proposal to upcoming Technical committee meeting.

The justification submitted by the firm is as follows:

A. **"Comment:**The results of the study did not meet the criteria of primary efficacy defined as "Proportion of patients showing clinical improvement on Day 14, using 7-point Ordinal scale.

   Response: While the SEC is correct in their observation, we would like to point out that significant differences were observed between day 7 and 13 of treatment, which are clinically important and should not be ignored. The details are:

   1. Patients in the AQCH arm have 56% chance of early clinical improvement compared to the SOC arm.
   2. Using 2-point Ordinal scale, significantly higher proportion of patients demonstrated clinical improvement in the AQCH+SOC arm from day 8 to 13 vs. SOC arm (p values ranged from 0.02-0.03).
   3. Using 1-point Ordinal scale, significantly higher proportion of patients demonstrated clinical improvement in the AQCH+SOC arm from day 6 to 12 vs. SOC arm (p values ranged from 0.0002-0.0020.
   4. In the time to clinical cure (post hoc) analysis, we have found that patients in the AQCH+SOC arm have 57% chance of early clinical cure compared to the SOC arm.
   5. Day wise analysis of proportion of patients with clinical cure has revealed that significantly more proportion of patients had clinical cure in the AQCH+SOC arm vs. SOC arm on day 4,11-13. (p value ranged from 0.01-0.002)

B. **Comment:** No difference in the time of viral clearance as noted on day 14.

   Response: The SEC members are absolutely correct that there was no observed difference between the AQCH and SOC arms for viral clearance on day 14, but the significant time of viral clearance from day 7 to 9 are noteworthy: The data reveals that the actual effect of AQCH was evident much before day 14.

This result is important and highly relevant feature of the AQCH drug, which reveals its value as an anti-viral drug. The details are:

1. Patients in the AQCH arm have 56.3% chance of early RT-PCR negativity compared to the SOC arm.
2. Significantly more proportion of patients became RT-PCR negative in AQCH+SOC arm compared to the SOC arm (p values ranged from 0.0004-0.0006).

Other information:

C. **Time to normalization of fever:** The results of clinical trial have revealed that:

1. Patients in the AQCH+SOC arm have 56% chances of early normalization of fever without antipyretics as compared to the SOC arm.
2. Significantly more population of patients achieved early normalization of fever without antipyretics in the AQCH+SOC arm vs SOC arm on day 4,6,12 and 13 (P values ranged from 0.01-0.05).

D. **Time to hospital discharge:** The results of clinical trial have revealed that:

1. Cumulatively, more proportions of patients consistently received discharge from day 8 to 13 in the AQCH+SOC arm vs SOC arm.

E. **Results of small animal tox studies:**The following results are significant:

1. Based on the results of in-vitro Ames Test, the drug was found to be non-mutagenic at the tested concentrations.
2. Based on the in-vitro chromosomal aberration test, the drug is considered as non clastogenic.
3. Based on the results of in-vivo micronucleus test in mice, the drug is considered as non-clastogenic.
4. We would also like to point out that based on allometric scaling using body surface area, the NOAEL dose from repeated dose toxicity studies in rats and rabbits exceed the proposed human therapeutic dose of 400 mg TID by 2.5 to 3.2-fold.

The above information clearly establishes safety and efficacy as a drug for treatment of moderate COVID, which can be used both for both in-patient and out-patient use.

The studies of clinical trial have shown that significantly more proportion of patients became RT-PCR negative in AQCH+SOC arm compared to the SOC arm (p values ranged from 0.0004-0.0006).

Firm has also submitted that they are prepared to conduct additional studies that may be considered appropriate for use of this drug, which may include studies at higher dose and paediatric formulations after the grant of Emergency Authorization Use of the drug for treatment of moderate COVID."

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and recommended that the approval of emergency use authorization for the drug at this stage may not be granted.

Agenda No 09

Proposal for M/s GlaxoSmithKline Pharmaceuticals Limited, Mumbai for the grant of permission for import and market 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.

Applicant - M/s GlaxoSmithKline Pharmaceuticals Limited
Drug Name: Herpes zoster vaccine (Recombinant, Adjuvanted)
This Directorate has received an 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 fromM/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.

Type of Application: Market authorization application for grant of import permission in Form CT-20 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 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).

SEC (Vaccine) Recommendations:

SEC Meeting	Recommendations
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.

Further, firm in its response has requested for re-deliberation in the Technical Committee meeting providing justification for waiver for local clinical trial waiver as below:

1. Shingrix is approved in 36 countries including US, EU, Canada, Australia, New Zealand, Japan and China. Since launch over 20,853,065 doses have been distributed. From the review of the entire clinical data and post-marketing surveillance data, it has been concluded that the benefit/risk profile of Shingrix is favorable and the safety profile of the vaccine is adequately reflected in the proposed Indian label.
2. No regional or ethnic differences have been observed in the clinical and epidemiological studies conducted in approximately 32,059 subjects enrolled in Europe, North America, Latin America, Asia and Australia which impact the efficacy or safety of the product. Clinical Studies included a broad population with limited exclusion criteria, to allow inclusion of subjects with a wide range of pre-existing medical conditions.
3. Shingrix fulfills 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
4. Commitment to run a robust Phase IV clinical trial in India

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and recommended that the firm should conduct local clinical trial as per requirements.

Agenda No. 10

Proposal of M/s. Mascot Health Series Pvt Ltd., has applied for grant of permission to manufacture and market FDC of Rifaximin 200mg + Metronidazole Benzoate IP eq. to Metronidazole 400mg for the treatment of travellers diarrhoea

Applicant: M/s. Mascot Health Series Pvt Ltd.

Drug name: Fixed dose combination of Rifaximin 200mg + Metronidazole Benzoate IP eq. to Metronidazole 400mg

Type of Application: Manufacturing and Marketing

Proposed Indication: For the treatment of travellers diarrhoea.

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

Recommendations of 92nd SEC (Antimicrobial & Antiviral) held on 14.07.2020;

The committee opined that,

1. Firm could not present any scientific literature published in peer reviewed journal supporting this FDC.

2. Management of diarrheal infection guidelines do not recommend usage of these two drugs concomitantly.

3. The FDC is not approved in any other country.

Hence, the committee did not recommend for the proposed FDC.

On subsequent response of the applicant, the proposal was again deliberated in 31st SEC (Gatroenterology & Hepatology) held on 14.10.2020

In light of the earlier recommendation of the committee (Antimicrobial) dated 14.07.2020, the committee opined that

1. Metronidazole will counter the beneficial effect of Rifaximin.

2. Firm did not present any additional scientific literature or justification in support of various points raised by earlier committee.

Hence, the committee did not recommend for approval.

In view of the above, now the firm has requested for deliberation in the Technical Committee meeting.

Recommendation of the Committee: The committee after detailed deliberation agreed with the recommendations of SEC and did not recommend for approval of the proposed FDC.

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