MINUTES OF THE 24th MEETING OF THE APEX COMMITTEE HELD ON 19-08-2015 UNDER THE CHAIRMANSHIP OF SECRETARY, HEALTH AND FAMILY WELFARE FOR SUPERVISING CLINICAL TRIALS ON NEW CHEMICAL ENTITIES IN THE LIGHT OF THE DIRECTIONS OF THE HON'BLE SUPREME COURT OF INDIA DATED 03.01.2013.

Present:

1. Shri B. P. Sharma,
   Secretary, Department of Health and Family Welfare
   and Chairman, Apex Committee

2. Dr Soumya Swaminathan,
   Secretary, Department of Health Research and
   DG , ICMR.

3. Dr. Jagdish Prasad,
   Director General of Health Services,
   New Delhi

4. Shri K. L. Sharma,
   Joint Secretary,
   Department of Health and Family Welfare, New Delhi

**Special Invitee:**

1 Shri K. B. Aggrawal
  Addl. Secretary (Food and Drugs)
  Department of Health and Family Welfare, New Delhi

2 Dr G N Singh ,
  Drugs Controller General(I)

3 Dr. V.G. Somani,
  Joint Drugs Controller (I), FDA Bhawan, New Delhi

Initiating the discussion, the Chairman, Apex Committee welcomed the members of the Committee and special invitees to the meeting. Thereafter, the Committee deliberated upon each of the agenda items and recommended as following-

**Item No. 1. Proposals of Clinical Trials related to New Chemical Entities (NCEs) recommended by Technical Committee.**

(1) An open-label, multi-center, extension study to evaluate the long-term safety of subcutaneous 240 mg QGE031 given every 4 weeks for 52 weeks in

allergic asthma patients who completed study CQGE031B2201. Protocol No: CQGE031B2201E1

The Apex Committee after detailed deliberations, concurred with the recommendations of Technical Committee detailed in agenda notes annexed herewith as **Annexure-I**. Further, the Committee directed that the proposals for extension protocols of the clinical trials of NCEs which are already approved are not required to be brought to the Apex Committee.

**(2) A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients. Protocol No: D5740C00001**

The Apex Committee after detailed deliberations, concurred with the recommendations of Technical Committee , asking firm to submit revised protocol, as detailed in agenda notes annexed herewith as **Annexure-I**.

**(3) A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis. Protocol No: D5740C00002**

The Apex Committee after detailed deliberations, concurred with the recommendations of Technical Committee, asking firm to submit revised protocol, as detailed in agenda notes annexed herewith as **Annexure-I**.

**Item No. 2. Waiver of Clinical Trial in Indian population for approval of New Devices falling under the category of Drugs, which have already been approved outside India.**

**(1) Bone Cement of M/s. Heraeus Technologies India Pvt. Ltd.**

The Apex Committee after detailed deliberations concurred with the recommendations of Technical Committee detailed in agenda notes annexed herewith as **Annexure-II**.

The Committee noted that only a category or class of medical device is mentioned in the agenda, from which the product identity does not become clear. Therefore, the Committee further desired that the details of the product which differentiate it from other products in the same medical device category may be indicated.

The details of the product are as below:

**Generic Name:** Bone Cement
**Brand Name:** COPAL G+C
**Composition:** 42.7 g of COPAL G+C powder contains:
1.0 g Gentamicin (as gentamicin sulphate)

1.0 g Clindamycin (as Clindamycin hydrochloride) other ingredients

**Regulatory Status Worldwide:** It is approved for marketing in Germany, Jordan, Thailand and Vietnam.

**(2) Bone Cement of M/s. Heraeus Technologies India Pvt. Ltd.**

The Apex Committee after detailed deliberations concurred with the recommendations of Technical Committee detailed in agenda notes annexed herewith as **Annexure-II**.

The details of the product are:

**Generic Name:** Bone Cement
**Brand Name:** COPAL G+V
**Composition:** 43.0 g of COPAL G+V powder contains:
0.5 g Gentamicin (as gentamicin sulphate)
2.0 g Vancomycin (as Vancomycin hydrochloride), other ingredients

**Regulatory Status Worldwide:** It is approved for marketing in Europe and USA.

**(3) Orthopaedic Implant of M/s. Johnson & Johnson Ltd.**

The Apex Committee noted the recommendations of Subject Expert Committee (SECs) and Technical Committee and after detailed deliberations, concurred with the recommendations of Technical Committee detailed in agenda notes annexed herewith as **Annexure-II**.

The details of the product:

**Generic Name:** Orthopaedic Implant
**Brand Name:** Reclaim Revision Hip System – Stem Proximal Body & Locking Bolt.
**Composition:** Titanium Alloy, Cobalt Chromium Molybdenum Alloy, Polyetheretherketone (PEEK).

**Regulatory Status Worldwide:** It is approved for marketing in USA, Austria, Belgium, France, Denmark, United Kingdom, Sweden, Italy, Ireland and many more.

**(4) Bone Void Filler of M/s. Surya Surgical Industries**

The Apex Committee noted the recommendations of Subject Expert Committee (SECs) and Technical Committee and after detailed deliberations, concurred with the recommendations of Technical Committee detailed in agenda notes annexed herewith as **Annexure-II**.

The details of the product are:

**Generic Name:** Bone Void Filler
**Brand Name: CERAMENT**
**Composition:** Calcium sulphate and Hydroxyapatite and liquid component contains iohexol, concentration 180mg iodine/ml, as a radio-opacity enhancer.

**Regulatory Status Worldwide:** Approved for marketing in USA, Canada and European Union.

**Brand Name: CERAMENT G**
**Product Description:**
CERAMENT G is an injectable and mouldable bone graft substitute, consisting of Calcium sulphate, Hydroxyapatite and Gentamicin Sulphate

**Regulatory Status Worldwide:** Approved for marketing in European Union.

**(5) DC Bead Drug Delivery Embolization System of M/s. Eisai Pharmaceuticals India Pvt. Ltd.**

The Apex Committee noted the recommendations of Subject Expert Committee (SECs) and Technical Committee and after detailed deliberations, concurred with the recommendations of Technical Committee detailed in agenda notes annexed herewith as **Annexure-II**. The Committee further desired that after the hospital settings and conditions under which product will be given is submitted by the firm, the Technical Committee may review it again prior to according approval.

The details of the product are:

**Product Name:** DC Bead Drug Delivery Embolization System

**Regulatory Status Worldwide:** The proposed device is approved for marketing in USA, Australia, European Union, New Zealand, Turkey, Israel,- Brazil and may more..

**Item No: 03 Re-deliberation of the proposals of Clinical Trial Waiver in Indian population for approval of new drugs, which have already been approved outside India.**

**(1) Pralatrexate Injection 20mg/mL & 40mg/2mL of M/s. Hetero Drugs Limited for the treatment of patients with relapsed or refractory peripheral T-cell Lymphoma (PTCL).**

The Apex Committee after detailed deliberations, concurred with the recommendations of Technical Committee as detailed in agenda notes annexed

herewith **(Annexure III)**, that local clinical trial waiver may be granted for the said indication with a condition that a Pk study on 12 subjects should be conducted before issuing permission for marketing the drug in the country and shall be placed before Apex Committee. However, Committee opined that instead of phase IV trial, as recommended by SEC and Technical Committee, post marketing surveillance studies may be considered and in cases where waiver as a condition of conduct of phase IV studies is imposed, it shall be justifiable and monitored and based on the results, continuation of permission shall be decided.

**(2) Ibutilide Fumarate Injection 0.1mg/ml of M/s Zuventus Healthcare Ltd for the rapid conversion of atrial fibrillation or atrial flutter of recent onset to sinus rhythm.**

The Apex Committee after detailed deliberations concurred with the recommendations of Technical Committee detailed in agenda notes annexed herewith as **Annexure-III.**

**(3) Bovine lung surfactant–a drug powder lyophilisate for intratracheal instillation 54 mg/0.7 mL of M/s Bharat Serum and Vaccine Ltd For the treatment of respiratory distress syndrome in the pre-term new born infants.**

The Apex Committee after detailed deliberations concurred with the recommendations of Technical Committee detailed in agenda notes annexed herewith as **Annexure-III.**

**Item No.4 Proposal for re-consideration of condition imposed by DCG (I) and Committee over the globally approved protocol of M/s INC Research, Gurgaon with drug DS-5565 in Fibromyalgia.**

The Committee noted the recommendation of the Technical Committee and that the proposed clinical trial is approved in USA, UK and 11 other countries. After detailed deliberations, the Committee concurred with the recommendations of Technical Committee as detailed in agenda notes annexed herewith **(Annexure IV)**.

The meeting ended with vote of thanks to & from the Chairman.

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# Agenda Notes

## 24th Meeting of Apex Committee

## Agenda

1. Proposals of Clinical Trials related to New Chemical Entities (NCEs) recommended by Technical Committee.
2. Waiver of Clinical Trial in Indian population for approval of New Devices falling under the category of Drugs, which have already been approved outside India.
3. Re-deliberation of the proposals of Clinical Trial Waiver in Indian population for approval of new drugs, which have already been approved outside India.
4. Proposal for re-consideration of condition imposed by DCG (I) and Committees over the globally approved protocol of M/s INC Research, Gurgaon with drug DS-5565 in Fibromyalgia.

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## Item No: 01

**Proposals of Clinical Trials related to NCEs recommended by Technical Committee.**

The Technical Committee evaluated the 03 cases related to clinical trial of NCEs considering all aspects of safety, efficacy especially in terms of the three parameters viz. risk versus benefit to the patients, innovation *vis-a-vis* existing therapeutic option and unmet medical need in the country. After detailed deliberations, the Technical Committee recommended for approval of all the 03 cases. The recommendations of the Technical Committee in respect of these 03 cases related to clinical trial of NCEs are enclosed as **Annexure-I.**

The details of these three proposals and recommendations of the Technical Committee and SEC are as given below for consideration of Apex Committee:

**1) Proposal No: 01**

Phase II study of the drug QGE031 is a Global Clinical trial which will be carried out in USA, UK, Germany and Canada besides India vide Protocol No: CQGE031B2201E1, details of which are as following:

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| **Protocol title of the Clinical trial:** | An open-label, multi-center, extension study to evaluate the long-term safety of subcutaneous 240 mg QGE031 given every 4 weeks for 52 weeks in allergic asthma patients who completed study CQGE031B2201 |
| **Name of the Drug:** | QGE031 |
| **Name of the Applicant** | M/s Novartis Healthcare Private Limited, Sandoz House , Dr. Annie Besant Road, Worli, Mumbai – 400 018 |
| **Name of the Sponsor:** | Novartis Healthcare Private Limited, Sandoz House , Dr. Annie Besant Road, Worli, Mumbai – 400 018 |
| **Name of the Manufacturer:** | Novartis Pharma AG, Lichtstrasse 35, CH-4056 Basel, Switzerland. |
| **Type of Clinical Trial:** | Global |
| **Phase of the study:** | Phase-II |

Consideration by Subject Expert Committee:

Recommendation of the SEC meeting on 31.03.2015:

The proposal was deliberated upon by the SEC in its meeting held on 31.03.2015. After detailed deliberation, the Committee did not recommend the conduct of the study protocol CQGE031B2201E1, since this study is not an extension of approved protocol CQGE031B2201. The committee also noted that the objectives of both these studies are different and therefore the protocol presented by the firm cannot be treated as extension to the previous study as claimed by the firm. Recommendations of the SEC are at **Annexure –I**.

**Recommendation of the SEC meeting on 30.06.2015:**

Based on firm's representation, the proposal was again deliberated upon by the SEC in its meeting held on 30.06.15 wherein the Committee recommended as following:

The said proposal was deliberated upon by the SEC on 31.03.15, after detailed deliberation, the committee did not recommend the conduct of the study protocol CQGE031B2201E1, since this study is not an extension of approved protocol CQGE031B2201. The committee also noted that the objectives of both these studies are different and therefore the protocol presented by the firm cannot be treated as extension to the previous study as claimed by the firm. The firm made presentation before the committee with proper justification in respect of above recommendations.

After detailed deliberation the committee recommended the conduct of the extension protocol no: CQGE031B2201E1 version 01 dated 22-04-2015 in its presented form. Recommendations of the SEC are at **Annexure –I**.

**Consideration by Technical Committee**

The proposal was deliberated upon by the Technical Committee on 23.07.2015. After detailed deliberation, the Technical Committee recommended to conduct the study as per the SEC recommendation. Recommendations of the Technical Committee are at **Annexure –I**

Proposal No: 02

Phase III study of the drug Roxadustat is a Global Clinical trial vide Protocol No: D5740C00001, details of which are as following:

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|---|---|
| **Protocol title of the Clinical trial:** | A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients |
| **Name of the Drug:** | Roxadustat |
| **Name of the Applicant** | AstraZeneca Pharma India Ltd. |
| **Name of the Sponsor:** | AstraZeneca Pharma India Ltd. |
| **Name of the Manufacturer:** | AstraZeneca Pharma India Ltd. |
| **Type of Clinical Trial:** | Global Clinical Trial |
| **Phase of the study:** | Phase-III |

**Consideration by Subject Expert Committee:**

The proposal was deliberated upon by the SEC in its meeting held on 28.01.2015. After detailed deliberation the committee observed that the detailed carcinogenicity study data is not available. The committee opined the firm should submit preclinical carcinogenicity data and initiates the study with primary objective i.e. to evaluate the cardiovascular safety of Roxadustat for the treatment of Anaemia in Chronic Kidney Disease Patients in dialysis, the firm may submit revised protocol accordingly. Recommendations of the SEC are at **Annexure –I.**

**Consideration by Technical Committee**

The proposal was deliberated upon by the Technical Committee on 23.07.2015. After detailed deliberation, the Technical Committee recommended to conduct the study as per the SEC recommendation. Recommendations of the Technical Committee are at **Annexure –I**

## Proposal No: 03

Phase: III study of the drug Roxadustat is a Global Clinical trial which will be carried out in vide Protocol No: D5740C00002, details of which are as following:

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|---|---|
| **Protocol title of the Clinical trial:** | A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis. |
| **Name of the Drug:** | Roxadustat |
| **Name of the Applicant** | AstraZeneca Pharma India Ltd. |
| **Name of the Sponsor:** | AstraZeneca Pharma India Ltd. |
| **Name of the Manufacturer:** | AstraZeneca Pharma India Ltd. |
| **Type of Clinical Trial:** | Global Clinical Trial |
| **Phase of the study:** | Phase-III |

**Consideration by Subject Expert Committee:**

The proposal was deliberated upon by the SEC in its meeting held on 28.01.2015. After detailed deliberation the committee observed that the detailed preclinical carcinogenicity study data is not available. The committee opined the firm should submit preclinical carcinogenicity data and initiates the study with primary objective i.e. to evaluate the cardiovascular safety of Roxadustat for the treatment of Anaemia in Chronic Kidney Disease Patients in non dialysis, the firm may submit revised protocol accordingly. Recommendations of the SEC are at **Annexure –I**.

**Consideration by Technical Committee:**

The proposal was deliberated upon by the Technical Committee on 23.07.2015. After detailed deliberation, the Technical Committee recommended to conduct the study as per the SEC recommendation. Recommendations of the Technical Committee are at **Annexure –I**

The Committee may deliberated the proposals and give its recommendations.

## Item No: 02

**Waiver of Clinical Trial in Indian population for approval of New Devices falling under the category of Drugs, which have already been approved outside India.**

05 proposals of Medical Device recommended by the Technical Committee in its meeting on 23.07.2015 based on SECs recommendations for their approval for manufacture/ import for marketing in the country without local clinical trial are placed before the Committee for deliberation (**Annexure- II.**)

The Committee may deliberate the proposals.

## Item No: 03

**Re-deliberation of the proposals of Clinical Trial Waiver in Indian population for approval of new drugs, which have already been approved outside India.**

It may please be noted that the 03 proposals have been recommended by the SECs for their approval for manufacture/ import for marketing in the country without local clinical trial. The details of the same along with recommendations of SEC were placed before the Technical Committee in its meeting held on 11.02.2015 (**Annexure- III**). Thereafter, the proposals were deliberated in the Apex Committee in its meeting 27.02.2015 wherein the Committee did not recommend and deferred the proposals for re-deliberation with further details.
The Committee may deliberate the proposals.

## Item No: 04

**Proposal for re-consideration of condition imposed by DCG (I) and Committee over the globally approved protocol of M/s INC Research, Gurgaon with drug DS-5565 in Fibromyalgia.**

**Study title** "A Randomized, Double-Blind, Placebo- and Active-Controlled Study of DS-5565 in subjects with Pain Associated with Fibromyalgia"

Accordingly, the proposal was re-deliberated in Technical Committee and Apex Committee in its 23$^{rd}$ and 22$^{nd}$ meeting respectively. The details of the

deliberations by these Committees are annexed at **Annexure-IV** wherein due to patient showing SAE of myocardial infarction in Phase-I, the condition of clinical trial in ICU set up was imposed.

There after the applicant represented the matter to DCG (I) for waiver on the condition imposed under CT NOC mentioning that it was not related to the drug but was the underlying condition of the patients due to reasons as explained.

The proposal is placed for before the Committee for deliberation. The Committee may deliberate the proposals.

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Annexure-I

List of 03 case of clinical trial of NCEs along with their evaluations and recommendations of the Technical Committee in its 27th Meeting.

| Proposal No | Details of the proposal | Assessment of the Proposal *vis – a vis* specified Parameters | Recommendation<br>1. Technical Committee<br>2. Subject Expert Committee |
|---|---|---|---|
| 1. | **Name of the Drug:** QGE031<br><br>**Protocol No :** CQGE031B2201E1<br><br>**Phase of the study:** Phase II<br><br>**Name of the Applicant** : Novartis Healthcare Private Limited, Sandoz House , Dr. Annie Besant Road, Worli, Mumbai – 400 018<br><br>**Name of the Sponsor:** Same as above<br><br>**Name of the Manufacturer:** Novartis Pharma AG, Lichtstrasse 35, CH-4056 Basel, Switzerland.<br><br>**Title:** An open-label, multi-center, extension study to evaluate the long-term safety of subcutaneous 240 mg QGE031 given every 4 weeks for 52 weeks in allergic asthma patients who completed study CQGE031B2201 | **Risk versus benefit to the patients-** The safety profile of the test drug from various pre clinical studies including repeat dose, reproductive and development toxicity, juvenile toxicity, immunogenicity study and clinical phase I, II studies justify the conduct of the study.<br><br>**Innovation vis-a-vis existing therapeutic option** The purpose of study is to evaluate the long-term safety and tolerability of test drug given every 4 weeks for 52 weeks in allergic asthma patients who completed the core study CQGE031B2201<br><br>**Unmet need in the country-** The test drug may be an alternative treatment option in asthma patients. | **1. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.<br><br>**2. Recommendation of the SEC on 30-06-15:**<br><br>After detailed deliberation the committee recommended the conduct of the extension protocol no: CQGE031B2201E1 version 01 dated 22-04-2015 in its presented form. |
| 2. | **Name of the Drug:** Roxadustat<br><br>**Protocol no:** D5740C00001<br><br>**Phase of the study:** Phase-III<br><br>Name of the Applicant: | **Risk versus benefit to the patients** The safety profile of the test drug from various pre clinical studies including repeat dose toxicity study, embryo fetal development study, carcinogenicity and phase I, II clinical study justify the conduct of this study. | **1. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.<br><br>2. Recommendation of the SEC. |

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| | AstraZeneca Pharma India Ltd.<br><br>**Name of the Sponsor:** AstraZeneca Pharma India Ltd.<br><br>**Name of the manufacturer:** AstraZeneca Pharma India Ltd.<br><br>**Title:** A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients. | **Innovation vis-a-vis existing therapeutic option** The purpose of study is to assess Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients<br><br>**Unmet medical need in the country:** The study drug may provide additional treatment option in patients with anemia. | After detailed deliberation the committee observed that the detailed carcinogenicity study data is not available. The committee opined the firm should submit preclinical carcinogenicity data and initiates the study with primary objective i.e. to evaluate the cardiovascular safety of Roxadustat for the treatment of Anaemia in Chronic Kidney Disease Patients in dialysis, the firm may submit revised protocol accordingly. |
| 3. | **Name of the Drug:** Roxadustat<br><br>**Protocol no:** D5740C00002<br><br>**Phase of the study:** Phase-III<br><br>**Name of the Applicant:** AstraZeneca Pharma India Ltd.<br><br>**Name of the Sponsor:** AstraZeneca Pharma India Ltd.<br><br>**Name of the manufacturer:** AstraZeneca Pharma India Ltd.<br><br>**Title:** A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis | **Risk versus benefit to the patients** The safety profile of the test drug from various pre clinical studies including repeat dose toxicity study, embryo fetal development study, carcinogenicity and phase I, II clinical study justify the conduct of this study.<br><br>**Innovation vis-a-vis existing therapeutic option** The purpose of study is to assess the Safety and Efficacy of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis<br><br>**Unmet medical need in the country:** The study drug may provide additional treatment option in patients with anemia. | **1. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.<br><br>**2. Recommendation of the SEC :**<br><br>After detailed deliberation the committee observed that the detailed preclinical carcinogenicity study data is not available. The committee opined the firm should submit preclinical carcinogenicity data and initiates the study with primary objective i.e. to evaluate the cardiovascular safety of Roxadustat for the treatment of Anaemia in Chronic Kidney Disease Patients in non dialysis, the firm may submit revised protocol accordingly. |

Annexure-II

Recommendation of the SEC and Technical Committee of the 05 proposals of Clinical trial waiver in Indian population:

| Sr. no. | Drug Name | Name of the Firm | Indication | 1. Recommendation of the Technical Committee<br>2. Recommendation of the SEC |
|---|---|---|---|---|
| 1. | Bone Cement<br><br>Brand Name: COPAL G+C<br><br>**Composition:** (Gentamycin + Clindamycin) | M/s. Heraeus Technologies India Pvt. Ltd., | Indicated for stable anchoring of all suitable joint prosthesis in primary arthroplasty operations, with added protection against infection. It is also used in revision operations resulting from the aseptic loosening of the prosthesis and infection of the prosthesis by organisms sensitive to Gentamicin and/or-Clindamycin. | **1. Recommendation of the Technical Committee**<br>After detailed deliberation, the Committee noted that the product is globally marketed since many years and as such there is no requirement of clinical trial for such product. Therefore, the Committee agreed with SEC recommendations.<br><br>**2. Recommendations of the SEC:**<br>The committee **Orthopaedics** after detailed examination came to the conclusion that the firm may be granted permission for import & marketing of the product under Rule-122A of D & C Act & Rules as new Medical device with a condition to submit PMS data in Indian Population to the O/o DCC(I) every 6 months for the next 3 years. |
| 2. | Bone Cement<br><br>**Brand Name:**<br><br>**COPAL G+V**<br><br>**Compositions:** (Gentamycin + Vancomycin) | M/s. Heraeus Technologies India Pvt. Ltd., | It is indicated for filling, stabilizing or permanently fixing revision joint endoprostheses in surgically cleaned bone cavities which were previously infected by pathogens sensitive to Vancomycin and when solely Gentamicin containing cement is considered inadequate or undesirable during single-stage and two-stage | **1. Recommendation of the Technical Committee**<br>After detailed deliberation, the Committee noted that the product is globally marketed since many years and as such there is no requirement of clinical trial for such product. Therefore, the Committee agreed with SEC recommendations.<br><br>**2. Recommendations of the SEC:**<br>The case has been reviewed by SEC – **Orthopaedics** in its meeting held on 28.01.2015. The Committee after detailed examination came to the conclusion that the firm may be granted permission for import & marketing of the product under Rule-122A of D & C |

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| | | | replacement procedures. | Act & Rules as new Medical device with a condition to submit PMS data in Indian Population to the O/o DCG(I) every 6 months for the next 3 years. |
| 3. | Orthopaedic Implant<br><br>**Brand Name:** Reclaim Revision Hip System– Stem Proximal Body & Locking Bolt<br><br>Compositions: Titanium Alloy, Cobalt Chromium Molybdenum Alloy, Polyetheretherketone (PEEK). | M/s. Johnson & Johnson Ltd | Total Hip Arthroplasty is intended to provide increased patient mobility and reduce pain by replacing the damaged hip joint articulation in patients where there is evidence of sufficient sound bone to seat and support the components. | **1. Recommendation of the Technical Committee:** After detailed deliberation, the Committee noted that the product is globally marketed since many years and as such there is no requirement of clinical trial for such product. Therefore, the Committee agreed with SEC recommendations.<br><br>**2. Recommendations of the SEC:** The case has been reviewed by SEC – **Orthopaedics** in its meeting held on 28.01.2015. The committee after deliberation recommended the firm may be granted permission for import and marketing of the product under Rule – 122A of Drugs & Cosmetics Act & Rules as new Medical Device with a condition to submit PMS data in Indian population to the O/o DCG (I) every 6-months for the next 3 years. |
| 4. | Bone Void Filler<br><br>**Brand Name:** Cerament<br>**Compositions:** Calcium sulphate and Hydroxyapatite and liquid component contains iohexol, concentration 180mg iodine/ml, as a radio-opacity enhancer<br><br>**Compositions:** Cerament G Calcium sulphate and Hydroxyapatite and liquid component contains iohexol, concentration 180mg | M/s. Surya Surgical Industries | Intended Use:<br>1) It is a Ceramic Bone void filler intended only for orthopaedic applications as filler for gaps and voids that are not intrinsic to the stability of the bony structure. CERAMENT Bone Void Filler is indicated to be injected into bony voids or gaps in the skeletal system. These defects may be surgically created osseous defects or osseous defects from | **1. Recommendation of the Technical Committee:** After detailed deliberation, the Committee noted that the product is globally marketed since many years and as such there is no requirement of clinical trial for such product. Therefore, the Committee agreed with SEC recommendations.<br><br>**2. Recommendations of the SEC:** The case has been reviewed by SEC – **orthopaedics** in its meeting held on 28.01.2015. The Committee after deliberation recommended the firm may be granted permission for import and marketing of the product under Rule–122A of Drugs & |

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|---|---|---|---|---|
| | Iodine/ml, as a radio-opacity enhancer Gentamycin sulphate | | traumatic injury to the bone. It provides bone void filler that resorbs and is replaced by bone during the healing process.<br>2. It is resorbable ceramic bone graft substitute intended to fill gaps and voids in the skeleton system to promote bone healing. It provides void/gap filler that during the surgical procedure can augment hardware and bone alignments. Gentamicin is included in CERAMENT G to prevent colonization of Gentamicin sensible micro-organisms in order to protect bone healing. | Cosmetics Act & Rules as new Medical Device with a condition to submit PMS data in Indian population to the O/o DCG (I) every 6-months for the next 3 years. |
| 5. | DC Bead Drug Delivery Embolization System<br><br>(Macromer derived from Polyvinyl alcohol) | M/s. Eisai Pharmaceuticals India Pvt. Ltd., Mumbai | DC Bead is intended to be loaded with doxorubicin for the purpose of :<br>• Embolization of vessels supplying malignant hyper vascular tumor (s).<br>• Delivery of a local controlled sustained dose of doxorubicin to the tumor(s). | **1. Recommendation of the Technical Committee:**<br>After detailed deliberation, the Committee opined that there is no alternative therapy available and agreed with the SEC recommendations subject to the condition that the firm shall submit the detail of the conditions and hospital setting under which the device to be given.<br>**2. Recommendations of the SEC:**<br>The case has been reviewed by SEC – **Oncology** in its meeting held on 17.03.2015. The Committee after deliberation recommended the grant of approval for import and marketing of the proposed product to be loaded with Doxorubicin for the purpose of embolization of blood vessels supplying hepatocellular carcinoma. |

## Annexure-III

Recommendations of the Technical Committee and SEC of the 3 proposals of clinical trial waiver in India.

| Sr. no. | Details of the proposals | Name of the Firm holding permission outside the country | Indication | 1.Recommendation of the Technical Committee<br>2. Recommendation of the SEC |
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| 1. | **Name of the Drug:** Pralatrexate Injection 20mg/mL & 40mg/2mL<br><br>**Name of the Applicant:** M/s. Hetero Drugs Limited | M/s Alloys therapeutics/ M/s spectrum pharma. | For the treatment of patients with relapsed or refractory peripheral T-cell Lymphoma (PTCL). | **1. Recommendation of the Technical Committee:** After detailed deliberation, the Technical Committee recommended the waiver of local clinical trial as per the recommendation of the SEC.<br>**2. SEC Recommendation:** After detailed deliberation, the Committee observed that incidence of PTCL in the Country is very rare and is an Orphan disease. The Committee recommended that local clinical trial waiver may be granted for the said Indication with a condition that a PK study on 12 subjects should be conducted before issuing permission for marketing the drug in the country and a Phase IV post marketing trial should be conducted on 100 patients in the country. The PK study data should be submitted before the Committee for review. |
| 2. | **Name of the Drug:**<br><br>Ibutilide Fumarate Injection 0.1mg/ml<br><br>**Name of the Applicant:** M/s Zuventus Healthcare Ltd | 1. M/s Pharmacia and Upjohn<br><br>2. M/s Paddock Lab<br><br>3.M/s Genera Medix<br><br>4. M/s Mylan | For the rapid conversion of atrial fibrillation or atrial flutter of recent onset to sinus rhythm | **1. Recommendation of the Technical Committee:** After detailed deliberation, the Technical Committee recommended the waiver of local clinical trial as per the recommendation of the SEC.<br><br>**2. SEC Recommendation:** In response to the SEC recommendation of 30/09/2014 the firm has requested for waiver of local clinical trial. Earlier the firm was granted NOC for conduct of clinical trial and it was further mentioned that after one year no patients could be recruited. The Committee deliberated on this issue and decided that the company should provide specific reason with evidence from all the approved centers, and comments for non-recruitment of the trial patients and as per SEC recommendation of 16.12.2014, the firm presented its proposal in detail, it was noted that the firm has not yet submitted the specific reason(s) for non-recruitment of subject in clinical trial from the five investigating sites with information to respective Ethics Committee by investigator(s) as communicated earlier. The SEC recommended that the firm may be asked to submit the above documents from all sites as per the recommendation of the SEC meeting held on 30.09.2014. In response the firm has submitted comments of 4 out of 5 investigators out of which 3 have categorically |

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| | | | | stated that they have not recruited any subject in the said study. One of the Investigator site has clearly sited difficulty in obtaining consent in emergent situations as the reason for non recruitment. The firm has submitted this in reply dated 15.01.2015. The Committee further deliberated on the matter in details. It was noted that 1. Atrial fibrillation / flutter is a condition needing urgent treatment 2. There is no satisfactory drug for pharmacological cardio version in this situation (Atrial fibrillation / flutter). 3. The said drug is approved by USFDA for the new onset atrial fibrillation since 1995. 4. In certain specific situation like atrial fibrillation in post surgery patients and congenital heart disease, this is established as drug of choice. 5. Hence it may be categorized as a drug to be used in condition of extreme urgency category. Considering all the above conditions, the Committee recommended for a waiver of local clinical trial. The Committee however recommended that a Phase- IV clinical trial in minimum 120 patients be conducted. Accordingly the firm shall submit the protocol. |
| 3. | **Name of the Drug:**<br><br>Bovine lung surfactant–a drug powder lyophilisate for intratracheal instillation 54 mg/0.7 mL<br><br>**Name of the Applicant:**<br><br>M/s Bharat Serum and Vaccine Ltd (Authorized agent of M/s Lyomark Pharma for Import in India ) | M/s Lyomark Pharma GmbH, Germany<br><br>Product is approved in 30 countries across the world | For the treatment of respiratory distress syndrome in the pre-term new born infants. | **1. Recommendation of the Technical Committee:** After detailed deliberation, the Technical Committee recommended the waiver of local clinical trial as per the recommendation of the SEC.<br><br>**2. SEC Recommendation:** The proposal was deliberated in the NDAC (Now renamed as SEC) in its meeting held on **28.01.2012**<br>Recommendation of SEC (Pulmonary): After detailed deliberation the Committee recommended that phase III clinical trial with the drug should be conducted. Accordingly protocol etc. should be submitted for consideration of the Committee. The protocol etc. would be deliberated in the next meeting. Two neonatologists should also be invited in the deliberation in the next meeting.<br><br>The proposal of the firm was then referred to SEC vaccine where neonatologist was present<br>Recommendation of SEC (Vaccine) **12.01.2015**: The committee deliberated the proposal in detail. The firm has stated that the drug qualifies to be considered as Orphan Drug based on the published data and the firm has presented the proposed drug in a lyophilised formulation with better shelf life than the existing liquid formulation available in India and can be stored at 25°C. Further, the drug is reported to have been approved in Germany and many other countries. The committee recommended for the grant of Permission for Marketing Bovine Lung Surfactant in the Country with the condition that PMS data on at least 100 patients to be submitted within a year to get more safety data. |

Annexure-IV

Details of the recommendation by the Committees

1. **Deliberation of proposal by SEC:-**

The proposal was deliberated in the meeting of SEC (Neurology and Psychiatry) held on 28.08.2014. The Committee after deliberation recommended as under:-

After detailed deliberation the Committee recommended to conduct the trial subject to the condition that-

1. The investigator should be orthopaedics or rheumatologist. The team include clinical psychiatric/psychologist for the assessment of inclusion and exclusion criteria.
2. The number of proposed subjects from India is 105. Considering drop out 50% as per protocol statistical analysis, therefore this cannot be applicable for marketing permission in India.
3. The pk rationale for trying the drug OD or BD should be provided.

2. **Deliberation of proposal in 21st Technical Committee (TC):-**

The proposal was placed before the Technical Committee along with the recommendations of the SEC in the 21st Technical Committee meeting held on 21-01-2015. The Committee after deliberation recommended as under:-

***"The Committee recommended for the conduct of trial as per the SEC recommendation subject to the condition that all the 105 subjects should be treated in hospitalized setting only with complete cardiac monitoring for duration of one month. If AEs are not reported after the period of one month, trial can be conducted on OPD setup."***

3. **Deliberation of proposal by 20th Apex Committee:-**

The proposal was deliberated in 20th Apex Committee meeting held on 30.01.2015, wherein Committee agreed with the recommendations of Technical Committee.

4. **Appeal by M/s INC Research for waiver on the condition imposed under CT NOC:-**

There after the applicant represented the matter to DCG (I) for waiver on the condition imposed under CT NOC. The appeal by firm was placed before the Technical Committee along with the justification furnished by firm.

The Committee after deliberation recommended as under:-

***"All the 105 subjects should be treated in hospitalized settings only, with complete cardic monitoring for duration of one week as various adverse events including acute transmuralinferon-lateral myocardial infarction was***

*reported in the phase-I study. If AEs are not reported after the period of one week, trial can be conducted on OPD setup"* which were accepted by the Apex Committee on 23.04.2015

**5. Deliberation of proposal by 22nd Apex Committee:-**

The proposal was then deliberated in 22nd Apex Committee meeting held on 23.04.2015, wherein Committee agreed with the recommendations of Technical Committee.

There after the applicant represented the matter to DCG (I) for waiver on the condition imposed under CT NOC based upon following justifications mentioning that it was not related to the drug but was the underlying condition of the patients due to reasons as explained ;

- Clarification on the cardiac event "acute transmural-infero-lateral myocardial infarction" listed in the Investigator Brochure (referenced in the minutes of meeting of Technical Committee held on 19 March 2015): the fatal MI in the Phase I renal study DS5565-A-E106 involved a 68 years old male with past medical history relevant for severe chronic renal insufficiency and hypertension who experienced a fatal MI 11 days after a single 5mg dose of study medication. Autopsy showed presence of the above mentioned transmural infarction, severe atherosclerosis of the coronary arteries with a complete obstruction of the right coronary artery, findings whose pathophysiology is more chronic in nature and is not temporally plausible within just 11 days. The mentioned cardiac event was not related to the study drug DS-5565 as assessed by the Medical Monitor and the "Investigator causality assessment" was also not related to the study medication.
- In the current Fibromyalgia Phase 3 Clinical trial program globally, across the three ongoing double-blind studies, 622 subjects have been randomized as of 25 May 2015, of which 80 patients have completed the 13 week double-blind treatment period. All these subjects have been treated as per protocol specified visits in an outpatient setting.
- The Clinical study protocol has adequate measures for the purpose for cardiac monitoring. Please refer section 6 and section 9.8 of the enclosed protocol. The exclusion criteria mentioned in the current protocol (section 4.1.2.) also takes proper care to monitor the cardiac condition of the subject during screening and excludes patients with cardiac abnormalities.
- The protocol for the study also refers to a thorough QT study done in the past to look at the effects of DS-5565 on the cardiac function (section 1.1.1.5. of the protocol). In this study, there were no clinically significant changes in 12-lead electrocardiogram (ECG) parameters; neither the therapeutic dose (15mg of DS-5565) nor the supratherapeutic dose (50mg of DS-5565) effected cardiac repolarisation.

- The current conditionality will affect the data collected in first week post randomization from Indian subjects as compared to that of the rest of the world subject's data. Frequent testing of subset of patients may introduce bias into the primary endpoint as there is a possibility of altered perception by the subject in severity of pain due to daily visits and due to treatment in hospitalized distress.
- The conditionality is not practical to be implemented by the site investigators as Fibromyalgia is an indication treated in routine clinical practice in an out-patients setup would inconvenience the patients and cause more psychological distress.
- No cardiac events/no SAEs were observed in the twenty one (21) subjects phase 1 study (DS5565-A-E114) conducted in India.

However, M/s INC did not agree for the basis of imposing additional condition for conduct of clinical trial and re-appealed the matter with the details of the actual patient in Phase-I who encountered myocardial infarction. The re-appeal was discussed in the Technical Committee meeting dated 23.07.2015 where the condition was modified by the Technical Committee as diabetic patients should be excluded and accordingly inclusion and exclusion criteria shall be suitably amended and submitted to DCGI.

The matter is placed before Apex Committee for consideration.