1. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS AND RHEUMATOLOGY) HELD ON 17.03.2012:-

The NDAC (Analgesics, Anesthetics and Rheumatology) deliberated the proposals on 17.03.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
New Drugs			
1	**Meclofenamate Sodium**		The firm has requested for 3 indications viz mild to moderate pain, dysmenorrhoea and rheumatoid arthritis and osteoarthritis. Committee recommended that the firm should conduct double blind comparative clinical study of Meclofenamate sodium with diclofenac (100mg/day) in 4 sites distributed geographically in the country. 50% of the sites should be in multispeciality hospitals which have their own Institutional Ethics Committee. Ethics Committee approval should be from the same area where the site is located. The firm should submit protocol etc. to the office of DCGI and DCGI may issue approval to the study. Based on the data generated, committee may consider their proposal for the three indications proposed.
2	**Flupirtine-D-Gluconate**		Committee considered the protocol for conduct of local clinical trial in Indian population. However protocol etc. should be forwarded to the members for evaluation and recommendation to DCG(I).
3	**Apixaban**		Committee recommended for approval of the drug in the country subject to submission of CDTL test report to DCG(I). Phase IV clinical trial should be conducted on 500 patients within 2 years. Protocol for the Phase IV trial should be submitted to DCG(I) within 3 months of approval of the drug which can be considered and approved by DCG(I).
4	**Dexmedetomidine**		In view of cardiovascular safety concern, committee recommended for giving permission to conduct the study subject to condition that the study should be conducted in subjects aged 8 years and above.
5	**Dexmedetomidine**		Committee recommended that the study should be designed as a comparative study of ropivacaine versus ropivacaine +

			dexmedetomidine. Accordingly revised protocol should be submitted to the office of DCGI and DCGI may issue approval.
6	**Paracetamol + Tapentadol**		The committee considered the proposal and also the written opinions of other members and opined that the proposed FDC is not required in majority of the patients. Further there is potential for misuse of this combination. Hence the committee did not recommend for approval of the FDC.
7	**Paracetamol +Diclofenac + Omeprazole**		Paracetamol is required to be given 3-4 times daily. Diclofenac is given 2-3 times daily whereas omeprazole is generally given once daily. Further, use of this FDC may lead to use of all the 3 drugs in many patients unnecessarily and may cause side effects without any benefit. Hence the committee did not recommend for approval for the FDC.
Global Clinical Trials			
1	**Oxycodone-Naloxone**		The Committee recommended for giving approval of the clinical trial subject to the following conditions:- 1) The study should be conducted only in patients with cancer pain. 2) Oxycodone should be provided to such patients throughout their life span. 3) Upper age limit should be specified as 65 years. 4) Sites should be multispeciality hospitals having own Institutional Ethics Committee. 5) Complete thyroid tests should be included prior to study. 6) HMSC clearance should be obtained before initiation of the study. 7) Clearance from CBN Gwalior is also required to be obtained for import of the study drug.
2	**Masitinib**		Committee raised following objections:- 1. Group 3 (trial patients) will receive Methotrexate + Placebo who are already nonresponsive. Therefore giving Methotrexate to nonresponsive patients again will not be ethically justified. 2. All 3 groups will be given an escape arm of 6mg/kg of Masitinib in case of failure of treatment. However group 2 is already on 6mg/kg of Masitinib. So what is the rescue

			treatment for his group of patients? Clarification given by the firm's representative on the above points were not considered satisfactory by the committee. Hence the proposal was not recommended by the committee for approval.
3	**Macitentan**		Recommended for approval subject to condition that patients aged ≥ 18yrs and ≤ 65 yrs should be included in the study.
4	**Salsalate**		Use of placebo in this study is not justified. Further the study is proposed to be conducted only in India. Therefore the committee did not recommend for approval of the study.

2. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS AND RHEUMATOLOGY) HELD ON 13.04.2012:-

The NDAC (Analgesics, Anesthetics and Rheumatology) deliberated the proposals on 13.04.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**UC-II®**		Committee in principle agreed for clinical trial. However the firm should give clarification/information on the following points :- i) Detailed characterization/standardization of the product should be submitted. ii) Source of comparator drug condroitin plus glucosamine should be mentioned and the source should be from a standard company marketing it as a drug and not as nutraceutical. Glucosamine in the product should be in the form of hydrochloride and not as sulphate. iii) The sample size of 32 subjects per arm needs to be justified statistically. The sample size should be statistically significant. iv) Only patients of Grade 1 and 2 osteoarthritis should be included in the study. v) The study should be conducted in at least 4 sites. 50% of the sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country. The above data/information should be placed before the committee for taking final decision in the matter.
2	**Diflunisal tablet 250mg/500mg**		The firm has proposed for marketing of the drug in 3 indications viz. mild to moderate

			pain, osteoarthritis and rheumatoid arthritis. Committee recommended that the clinical trial design should be double blind, double dummy and the number of subjects should be statistically significant as the drug is reported to have several contraindications and side effects. 50% of the trial sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country. There should be rheumatologist in at least two sites. Accordingly protocol etc. should be submitted to DCG(I) for approval. Data generated from the above study may be considered for two indications:- mild to moderate pain and osteoarthritis. However for rheumatoid arthritis, a separate clinical trial is required to be conducted.
3	**Flupirtine SR Tablets 400 mg**		Committee recommended for giving permission to market Flupirtine SR Tablets 400 mg. The conventional formulation of Flupirtine Tablets 400 mg is already approved in the country. The tablet is a scored tablet. The firm should submit comparative dissolution profile of each half of the scored tablet should be submitted to DCG(I) before formal approval.
4	**Diclofenac Potassium+Trypsin Chymotripsin**		The proposed FDC is required for short term period only. Trypsin and chymotrypsin is required for much shorter period as compared to diclofenac. The use of this combination may lead to misuse as many patients may take all the three drugs in the form of FDC even if they do not need all the drugs. Further clinical trial data generated is not adequate.

			In view of above, the committee did not recommend for giving permission to market the proposed FDC.
5	**EFC11072**		Recommended for giving permission to conduct the study for 52 weeks subject to the following conditions:- i) 50% of the trial sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country. ii) Patients who benefits in the trial and wish to receive study drug after completion of the study should be given access to drug until marketing or withdrawal of the drug in the country. The firm should come out with a policy in this regard and submit the same to DCG(I).
6	**Infliximab**		Recommended for giving permission to conduct the study with the following conditions: i) The firm should record how many patients were on other DMARDs drugs including hydroxychloroquine in the last six months and how many of those patients withdrew in the last four weeks with reasons for withdrawal. Data in this regard should be submitted to DCGI ii) 50% of the trial sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country.
7	**Teriparatide**		Recommended for giving permission to manufacture and market the drug with the condition to conduct a phase IV trial with 2 years duration of therapy in statistically significant number of subjects assessing the changes in BMD. Protocol should be submitted to DCG(I) within 1 month of product approval and study should be initiated within 3 months of protocol approval by DCG(I).

8	**Teriparatide**		Recommended for giving permission to manufacture and market the drug with the condition to conduct a phase IV trial with 2 years duration of therapy in statistically significant number of subjects assessing the changes in BMD. Protocol should be submitted to DCG(I) within 1 month of product approval and study should be initiated within 3 months of protocol approval by DCG(I).
9	**Moxifloxacin Hydrochloride**		The applicant has withdrawn their proposal.
10	**CF101**		Recommended for giving permission to conduct the study subject to the following conditions:- i) Only DMARD naïve patients should be included in the study. ii) The age limit of subjects to be included in the study should be 40 to 65 years. iii) The number of subjects to be enrolled from India in the study should not be more than 30 %. iv) 50% of the trial sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country.
11	**PF-04171327**		Recommended for giving permission to conduct the study subject to the following conditions:- i) Upper age limit of subjects to be included in the study should be 60 years. ii) All examinations, investigations etc. for the trial subjects should be done free of cost. iii) 50% of the trial sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country.
12	**PF-05208752**		Recommended for giving permission to conduct the study subject to the condition that 50% of the trial sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country.

13	**Teriparatide**		Recommended for giving permission to conduct the study subject to the following conditions:- i) Age limit of patients to be included in the study should be 50 to 65 years and those patients should be physiologically fit. ii) The firm should specify the implants to be used in the study. iii) There should be 3 or more screws in fixation. iv) There should be equal number of patients in each group. v) Regulatory approvals of the study from developed countries should be submitted to DCG (I). vi) 50% of the trial sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country.
14	**Teriparatide**		Recommended for giving permission to conduct the study subject to the following conditions:- i) Age limit of patients to be included in the study should be 50 to 65 years and those patients should be physiologically fit. ii) The firm should specify the implants to be used in the study. iii) There should be 3 or more screws in fixation. iv) There should be equal number of patients in each group. v) Regulatory approvals of the study from developed countries should be submitted to DCG (I). vi) 50% of the trial sites should be multispecialty hospitals preferably medical colleges having more than 500 beds and the sites should be geographically distributed in the country.

3. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS AND RHEUMATOLOGY) HELD ON 07.09.2012:-

The NDAC (Analgesics, Anesthetics and Rheumatology) deliberated the proposals on 07.09.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Tranexamic Acid injection**		Committee recommended for giving permission to conduct the proposed clinical trial.
2	**Rivaroxaban 10mg tablet**		Committee recommended for granting permission for the proposed phase IV study subject to the following conditions:- In exclusion criteria, the name of the excipient should be mentioned for which hypersensitivity is claimed. The patient should be educated about the adverse reactions at the time of discharge from the study. The sites should be preferably geographically distributed across the country. The patients who are on any other anticoagulant are to be excluded from the study. Amended protocol incorporating the above changes should be submitted to the DCG(I) for approval.
3	**Sphaeranthusindicus extract tablets 700mg**		Committee recommended that Phase II dose escalating study is required to be conducted before considering the proposal of phase III clinical trial. Accordingly phase II protocol etc. should be submitted to the committee for examination.
4	**Diclofenac sodium rectal spray**		The committee recommended for giving permission to conduct the proposed Bioequivalence study with the Diclofenac sodium rectal spray. Committee also recommended that based on result of the bioequivalence study, a phase III non inferiority clinical trial is required to be conducted to assess the safety and efficacy of the spray after getting protocol etc examined by the committee.
5	**Etodolac injection 400mg/2ml**		Centre 3 enrolled 68 patients all of whom consistently weighed 52, 60, 70, 75 or 80 kg and had a height of 150, 160, 165, or

			170 cm. was this due to approximation or due to defective measurement. The committee opined that the data generated is not adequate for approval of the drug. Therefore the committee recommended that clinical trial data on at least 100 more cases should be generated by conducting the clinical trial as per the approved protocol in other parts of the country. The details of sites etc. should be submitted to the DCG(I)
6	**Tapentadol ER tablets 200mg**		The proposed ER formulation is intended to be used as twice daily instead of conventional formulation which is given as 4 times daily. Committee recommended for giving permission to conduct the proposed bioequivalence study. However this ER formulation should be indicated for the same indication viz moderate to severe acute pain in adults 18 years of age or older. The committee discussed in detail the requirement of local clinical trial for approval of such modified release formulation. Committee opined that if modified release formulation is found to be bioequivalent to the conventional formulation in respect of AUC (Area Under Curve) in bioequivalence study, there is no need of local clinical trials. Committee therefore unanimously agreed that local clinical trial data is not required for approval of such modified release formulations.
7	**Flupirtine Maleate SR Tablet 400mg**		The firm has already conducted bioequivalence study with the modified release formulation. Committee opined that if modified release formulation is found to be bioequivalent to the conventional formulation in respect of AUC (Area Under the Curve) in bioequivalence study, there is no need of local clinical trials. Committee therefore unanimously agreed that local clinical trial data is not required for approval of such modified release formulations. The committee recommended for giving permission to manufacture and market Flupirtine Maleate SR Tablet 400mg.

8	**Lornoxicam + Paracetamol + Serratiopeptidase** **(4mg/8mg+325mg/325mg+7.5mg/15mg)**		Committee opined that there is no rationality in combiningLornoxicam, Paracetamol and Serratiopeptidase as the combination will lead to use of all the three drugs in some patients who may not need all the three drugs. The FDC is not approved anywhere in the world. Hence committee did not recommend for approval of this FDC.
9	**Paracetamol + Diclofenac Sodium** **(75mg+25mg per ml)**		Committee opined that there is no rationality in combining Paracetamol and Diclofenac Sodium in injectable formulation. The FDC is not approved anywhere in the world. Hence committee did not recommend for approval of this FDC.
10	**Aceclofenac + Paracetamol + Rabeprazole sodium (100mg+325mg+10mg)**		Committee opined that there is no rationality in combiningAceclofenac, Paracetamol and Rabeprazole sodiumas the combination will lead to use of all the three drugs in some patients who may not need all the three drugs. The FDC is not approved anywhere in the world. Hence committee did not recommend for approval of this FDC.
11	**Paracetamol + Zaltoprofen** **(325mg+80mg)**		Committee opined that there is no rationality in combiningParacetamol and Zaltoprofen as the combination will lead to use of the two drugs in some patients who may not need the two drugs. The FDC is not approved anywhere in the world. Hence committee did not recommend for approval of this FDC.
12	**BA058**		In the proposed study there is a placebo arm in which the trial patients with BMD T-score ≤ -2.5 and > -5 will receive placebo with calcium and vitamin D. The committee recommended for giving permission to conduct the study subject to following conditions. 1.The patients with only BMD T-score ≤ -2.5 to ≥ -3.5 should only be included in the study as patients having BMD T- score ≤ -3.5 and > -5 without standard care of therapy is unethical. 2. The Patient Information Sheet should clearly mention in a language understandable to the patient that there is possibility that he/she may be in placebo

			group when he/she will not receive any current standard care of therapy. 3. The no. of patients from India should not be more than 200.
13	**AMG 785**		The committee recommended for giving permission to conduct the study subject to following condition. 1. The Patient Information Sheet should clearly mention in a language understandable to the patient that there is possibility that he/she may be in placebo group when he/she will not receive any current standard care of therapy.
14	**Belimumab**		The committee opined that systemic Lupus Erythematosus is a rare disease and currently there is not many satisfactory therapy available for this disease. Therefore considered the clinical trial data on 449 patients including 66 Indian patients and recommended for approval of the drug subject to condition that phase IV clinical trial on 50 patients should be conducted within 2 years after getting protocol etc. approved from DCGI().
15	**Etanercept for injection 25mg/vial**		Committee recommended for giving permission to import and market the drug in the similar indication approved for Enbrel.
16	**Rituximab (Zydus Test) Vs Rituximab (Reference)**		Committee recommended that the single dose pharmacokinetic and pharmacodynamic study in 24 patients should be conducted and the data generated along with protocol for phase III clinical trial should be submitted to the committee for examination. Revised protocol should be submitted to the DCG(I) for approval.

4. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS AND RHEUMATOLOGY) HELD ON 07.11.2012:-

The NDAC (Analgesics, Anesthetics and Rheumatology) deliberated the proposals on 07.11.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Dexketoprofen Effervescent Tablet 25mg**		Committee examined the bioequivalence data and recommended for giving manufacturing and marketing permission to the Dexketoprofen effervescent tablet 25mg.
2	**Diclofenac Injection IV Bolus 75mg/2ml**		Committee examined the non clinical & clinical data of safety and efficacy of the product and recommended for giving permission to manufacture & market Diclofenac i.v. bolus injection 75mg/2ml for acute painful conditions in post painful conditions in post operative pain, renal colic and acute exacerbation of gouty arthritis.
3	**Diclofenac Resinate Capsules 145.6mg**		Committee recommended for the grant of permission to market Diclofenac Resinate Capsules 145.6mg for the proposed indication subject to condition that Post marketing (phase IV) clinical trial should be conducted on 1000 subjects within a period of 1 year after getting protocol etc. approved by the DCG(I).
4	**Diclofenac Resinate Oral Drops Suspension 15mg/ml**		Applicant has informed that they are not pursuing the proposal at present and the proposal has deferred.
5	**Tapentadol Tablets 25/37.5 mg**		The company did not present any data in support of efficacy, contraindication etc. of the proposed lower strength of Tapentadol tablet 25/37.5mg. Hence committee did not recommend the proposed new strength of the drug.
6	**Lobitridol**		The proposed indication is approved in many countries like France, Switzerland, UK, Begium and Austria etc. The committee recommended for

			the grant of permission to market Iobitridol for the proposed indication subject to condition that post marketing surveillance data with minimum 2 to 3 years of followup on the safety of the product should be collected and submitted.
7	**Aceclofenac 5% gel**		Committee recommended for giving permission to conduct the proposed clinical trial subject to condition that the study should be conducted in patients with sprain and muscular pain and site should be geographically distributed in the country with 50% site in government medical colleges/institutions. The details of sites etc. should be submitted to DCG(I) before formal approval of the study.
8	**Dabigatran Etexilate Mesilate Capsules 75/110/150 mg**		Firm has applied for the approval of additional indication of Dabigatran i.e. for the prevention of venous thromboembolic events in patients who have undergone orthopaedic surgery which indication is approved in many countries like EU and Canada. The firm presented the various supported data including reports of global clinical trials conducted in this indication on 2013 patients globally including 179 Indian patients. The committee observed that while efficacy of Dabigatran is not inferior to the Enoxaparin the incidence of asymptomatic DVT and all cause mortality in Indian patients is higher in Dabigatran group as compared to Enoxaparin group. Although the data Indian patients was stated to be not statistically powered. In view of above committee asked the applicant to present the safety data on the drug in Indian patients in atrial fibrillation (AF) which is already approved in India. Accordingly the applicant presented the global clinical trial conducted on 18,000 patients with AF including 578 Indian patients. The committee examined the overall safety profile of the drug and recommended for the marketing of the drug for the proposed indication.
9	**Diclofenac Sodium IV Injection (75mg/ml)**		Diclofenac Sodium IV bolus Injection 75mg/ml is already approved in India. Committee examined

			the clinical data of safety and efficacy of the product and recommended for giving permission to manufacture & market Diclofenac i.v. bolus injection 75mg/ml for acute painful conditions in post painful conditions in post operative pain, renal colic and acute exacerbation of gouty arthritis.
10	**Tapentadol 100/150/200 mg ER tablets.**		The applicant failed to present the report of bioequivalence study conducted by them and other supportive information. Hence committee was unable to take the decision.
11	**Paracetamol Injection 250mg/ml (2ml)**		The committee recommended for giving permission to conduct the proposed bioavailability study and clinical trials subject to condition that before initiation of clinical trials, the result of bioavailability study should be submitted to the o/o DCG(I) for examination.
12	**Ibuprofen + Paracetamol Sachet Granules**		Committee recommended for giving permission to conduct the proposed bioequivalence study with the drug formulation. Office of DCGI shall examine the report of the bioequivalence study and if found satisfactory the product may be approved by DCG(I).
13	**Naproxen + Paracetamol Tablets**		Committee opined that in acute painful/inflammatory conditions the individual drugs can be used instead of the FDC in patients who requires both the drug. Further there is chance of misuse of this FDC in chronic cases. Hence committee did not recommend the approval of the FDC.
14	**Aceclophenac + Paracetamol + Thiocolchicoside Tablets**		The rationale for the FDC presented by the company was inadequate. Hence committee did not recommend approval of the FDC of Aceclophenac + Paracetamol + Thiocolchicoside Tablets.

15	**Diclofenac Sodium SR + Tolperisone Hydrochloride SR Tablets**		Committee noted that recently (22.06.2012) EMA has recommended restricting the use of tolperisone authorized to treat a variety of different conditions, including spasticity due to neurological disorders and muscle spasms associated with disease of the spine and large joints in several EU countries. In view of this committee recommended that safety profile of tolperisone should be reviewed before taking any decision on such FDC of tolperizone with other drugs.
16	**FDC of Diclofenac Diethylamine BP 4.64% w/v (Eq. to Diclofenac Sodium IP) 4.00% w/v + Absolute Alcohol IP 10.00% v/v non aqueous topical solution.**		Committee examined the non clinical & clinical data of safety and efficacy of the product and recommended for giving permission to manufacture and market the product for acute lower back pain.
17	**Fixed Dose Combination of Diclofenac Deithylamine BP 2.32% w/v + (Eq. to Diclofenac Sodium IP 2.00% w/v + Methyl Salicylate IP 10.00% w/v + Menthol 5.00% w/v + Absolute Alcohol IP 10.00% v/v topical solution**		Committee examined the non clinical & clinical data of safety and efficacy of the product and recommended for giving permission to manufacture and market the product for acute lower back pain.
18	**Secukinumab**		The study is recommended for approval subject to the submission of the regulatory approval of the protocol from USA/Germany.
19	**Teriparatide (rhPTH1-34)**		The expert committee recommended that the applicant to submit the protocol for the PK, PD studies as per the requirement in the guidelines for the similar biologics of CDSCO before the conduct of phase III clinical trial and the same will be examined by the committee.
20	**Adalimumab**		The firm presented justification for waiver of PK, PD study mentioning that correlation between PK and PD for this drug has not been established which was considered by the committee and for recommended for the proposed phase III study with the condition that single dose safety data on

			first 10 patients should be submitted to this Directorate for examination before continuation of the study in other patients. However in the mean time the study may continue in the initial 10 patients recruited. Also the firm should take at atleast 100 evaluable subjects. The sites should be geographically distributed in the country including 50% sites at government medical college/institutions. 2D ECHO test should be done before enrolling the patients in the trial.
21	**Oxycodone**		The committee did not agree the proposal of providing the drug upto 25 weeks instead of their lifespan of cancer patients.

5. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS & RHEUMATOLOGY) HELD ON 22.03.2013:-

The NDAC (Analgesics, Anesthetics & Rheumatology) deliberated the proposals on 22.03.2013 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
Special agenda			
1 to 9	• **Abatacept Inj.250mg/15 ml vial** • **FDC of aceclofenac with drotaverine** • **Etodolac with paracetamol** • **Nimesulide Injection** • **FDC of acecelofenac with thiocolchicoside** • **FDC of tolperisone and paracetamol** • **FDC of diclofenac with serratiopeptidase** • **FDC of glucosamine with ibuprofen** • **Rivaroxaban**		The Committee was apprised that the Parliamentary Standing Committee (PSC) for the Ministry of Health & Family Welfare had presented its 59th report to the Parliament on 08.05.2012 on the functioning of the CDSCO. The report has made various recommendations and observation on various aspects such as approval of New Drugs, Pharmacovigilance, approval of clinical trials etc. The Ministry of Health & Family Welfare has submitted final action taken report on the observation/recommendations contained in the 59th report of the Hon'ble Parliamentary Standing Committee. As per the action taken report, it has been decided by the Ministry that 73 drugs including Fixed Dose Combinations, on approval of which the Hon'ble PSC has made various observations, would be referred to the NDACs for examination and review related to continued marketing of these drugs and updating of their product monographs in light of recent knowledge and regulatory changes overseas. Out of these 73 drugs, 9 drugs are in the category of (Analgesics, Anesthetics & Rheumatology) which are given below:- • Abatacept Inj.250mg/15ml vial • FDC of aceclofenac with drotaverine • Etodolac with paracetamol • Nimesulide Injection • FDC of acecelofenac with thiocolchicoside • FDC of tolperisone and paracetamol • FDC of diclofenac with serratiopeptidase

			• FDC of glucosamine with ibuprofen • Rivaroxaban The NDAC (Analgesics, Anesthetics & Rheumatology) discussed the issue and noted that Ministry of Health & Family Welfare has already constituted a Committee to formulate policy guidelines and SOPs for a) approval of new drugs, clinical trials, and banning of drugs under the Chairmanship of Dr. Ranjit Roy Chaudhury and b) for approval of the Fixed Dose Combinations under the Chairmanship Dr. C.K. Kokate. Therefore, the Committee opined that these drugs related to continued marketing and updating of the product monograph in the light of recent knowledge and regulatory changes overseas could be examined as per policies, guidelines and SOPs being prepared by the Dr. Ranjit Roy Chaudhury Committee and Dr. C.K. Kokate Committee. However, in the meantime the data/information on safety, efficacy of these five drugs including published data, PMS/PSUR, PSUR data especially on Indian patient required to be prepared in the Form of Dossier. Such data should be prepared from three different sources viz. i) by CDSCO ii) by Pharmacovigilance Programme of India (PvPI) and iii) the firm concerned. The Dossier shall be circulated to all the experts of the NDAC Analgesics, Anesthetics& Rheumatology for their further review. If needed manufacturer may be requested to make their Presentation before the NDAC on safety and efficacy of the drugs. The NDAC further recommended the following :- CDSCO may collect the following information on all the 9 drugs i) The date of approval of each drug. ii) The date of manufacturing and marketing of each drug by the manufacturer. iii) The mandatory PSUR reports submitted by these companies.

			iv) Pharmacovigilance data if any from PVPI on these drugs. v) Marketing status of these drugs. vi) Global Marketing status of these drugs. vii) Clause, condition and opinion under which permission was granted for these drugs. As soon as the above information is available, a meeting may be called. In the meeting, the recommendations of the other 2 committees may be placed which would be discussed.
10	**Simvastatin**		Committee recommended for giving permission to conduct the study subject to condition that only patients with mild to moderate osteoarthritis should be included in the study who are taking monotherapy of paracetamol and no claim cartilage modifying drug. Revised protocol incorporating the above should be submitted to the office of DCG(I).
11	**UC-II®**		The committee deferred the proposal.
12	**8Platelet Rich Plasma (PRP)**		The protocol should be revised incorporating the following:- **i)** To standardize the autologous PRP specifically the dose. **ii)** Only mild to moderate arthritis patients should be included in the study. **iii)** MRI should be done for better assessment of cartilage status.
13	**Oral Transmucosal Fentanyl Citrate Tablet 200mcg**		The firm has presented two clinical trial protocols for two different indications:- **i)** In the management of pain during dressing changes in adult burn patients. **ii)** In the management of breakthrough post operative pain. For the first indication committee recommended fro approval of clinical trial subject to condition that the firm is required to submit Bioequivalence data of Oral Transmucosal Fentanyl Citrate (OTFC) Tablet 200mcgfor which application has already been

			submitted by the firm to DCG (I) before initiationof the clinical trial of OralTransmucosal Fentanyl Citrate Tablet 200mcg in the management of pain during dressing changes in adult burn patients. For clinical trial of OTFC tablet In the management of breakthrough post operative pain, committee opined that OTFC tablet is contraindicated that due to risk of respiratory depression, OTFC tablet is contraindicated in opoied non-tolerant patient and in management of acute or post operative pain.In view of above committee opined that firm should submit detail justification for conducting of clinical trial of OTFC tab in post operative pain with supportive document in light of the above contraindication.
14	**Diclofenac Potassium Sachet 50mg**		Diclofenac potassium sachet 50mg is already approved in USA. The committee recommended for grant of permission for BE study of Diclofenac potassium sachet 50mg.
15	**Tapentadol ER Tablets 100mg/150mg/200mg**		Tapentadol has high potential for respiratory depression and addiction. This ER formulation is of Tapentadol is already approved in US, UK. The committee recommended for approval of the ER formulation for use in in-patients under hospital settings for sever acute pain for a period not exceeding 5 days. Committee also recommended that all preparation of Tramadol and Tapentadol should be used for the above indications only.
16	**Tapentadol ER Tablets 100mg/150mg/200mg**		Tapentadol has high potential for respiratory depression and addiction. This ER formulation is of Tapentadol is already approved in US, UK. The committee recommended for approval of the ER formulation for use in in-patients under hospital settings for sever acute pain for a period not exceeding 5 days. Committee also recommended that all preparation of Tramadol and Tapentadol should be used for the above indications only.

17	**Diclofenac Rapid Release Tablet 50mg**		Committee recommended for the approval of the product.
18	**Tramadol 200mg Continus Release**		Committee examined the proposal. Tramadol has high potential for respiratory depression and addiction. The committee recommended for approval of the CR formulation for use in in-patients under hospital settings for sever acute pain for a period not exceeding 5 days. Committee also recommended that all preparation of Tramadol and Tapentadol should be used for the above indications only.
19	**Tapentadol Nasal Spray 250mg/ml and 385mg/ml**		Tapentadol has high potential for respiratory depression and addiction. The committee recommended that this formulation of Tapentadol should be intended to be used in in-patients under hospital settings for sever acute pain for a period not exceeding 5 days. Based on preclinical data presented by the firm committee recommended for approval of the Phase I clinical trial. However ICD and Undertaking by the sponsor to provide compensation should be submitted to the DCG (I).
20	**Dexketoprofen + Thiocochicoside**		Committee noted that FDC of Dexketoprofen+Thiocochicoside was launched by M/s Sanofi in the country and subsequently it was withdrawn by the firm. The reason of withdrawal is not known to the committee. The rationality of this formulation with thiocochicoside 2% needs to justification on pharmacokinetic basis. Hence committed did not recommend for approval of the product.
21	**FDC of Glucosamine Sulphate Potassium Chloride + Omega 3 Fatty Acids (Flexijoints capsules)**		The committee noted that the data generated is not adequate to demonstrate the efficacy of this product. Hence a placebo controlled trial in patients with mild to moderate OA on add-on monotherapy of Paracetamol should be conducted on statistically significant number of subjects in multispecialty hospitals/institute including Government hospitals having own Institutional Ethics Committee is required to be conducted. Accordingly protocol etc. should be submitted to the DCG (I) for approval.
22	**FDC of Lomoxicam**		The committee opined that the proposed FDC is

	8mg + Paracetamol 325mg + Chlorzoxazone 500mg tablets		not rational as there will be misuse of this FDC in patients who may not need all the three drugs. Hence committee did not recommend for approval of the FDC.
23	**FDC of Thiocolchicoside SR 16mg/8mg + Lornoxicam SR 16mg/8mg tablets**		The committee noted that as FDC of Thiocolchicoside + Lornoxicamin IR form is already approved by the DCG (I) for marketing in the country and the proposal of the firm is to manufacture and market the same approved FDC but in SR formulation. Therefore based on the data generated by the applicant on the FDC the committee recommended for grant of approval of the FDC for manufacturing and marketing in the country.
24	**FDC of DiclofenacDiethylamine BP 2.32% w/v Eq. to Diclofenac Sodium IP 2.0% w/v + Thiocolchicoside IP 0.25% w/v + Absolute Alcohol IP 10.0% v/v non aqueous topical solution**		Committeeobserved that the clinical data generated is inadequate for approval of the drug. Hence committee recommended that a comparative phase III clinical trial of the product comparing with diclofenac gel on statistically significant number of subjects with minimum 500 subjects in multispecialty hospitals/institute including Government hospitals having own Institutional Ethics Committee is required to be conducted. The protocol etc. should be submitted to the DCG(I) for approval.
25	**MK8457**		The committee recommended for the approval of the clinical trial subject to condition that cardiac site monitoring should be done carefully. In the event of heart block proposer medical management must be provided.
26	**Etanercept**		The committee recommended that pharmacokinetic study should be conducted in a subset of patients under phase III. Accordingly revised protocol etc. should be submitted to DCG (I) for approval. Phase III clinical trial should be conduct for each indication. The study site should be multispecialty hospitals/institute including Government hospitals having own Institutional Ethics Committee.
27	**Rituximab**		The committee recommended that pharmacokinetic study should be conducted in a subset of patients under phase III. Accordingly revised protocol etc. should be submitted to DCG (I) for approval. Phase III clinical trial should be

			conduct for each indication. The study site should be multispecialty hospitals/institute including Government hospitals having own Institutional Ethics Committee.
28	**ABATACEPT**		Abatacept is included in list of 9 drugs as mentioned in the agenda no 1-9 above. The committee opined that decision on this proposal will be considered after examination of the Abatacept drug as per agenda 1-9.
29	**FDC of Lornoxicam 4mg/8mg + Paracetamol 325mg/325mg + Serratiopeptidase 7.5mg/15mg tablets**		The committee opined that the proposed FDC is not rational as there will be misuse of this FDC in patients who may not need all the three drugs. Hence committee did not recommend for approval of the FDC.
30	**FDC of Aceclofenac 100mg + Paracetamol 325mg + Rabeprazole Sodium 10mg tablet**		The committee opined that the proposed FDC is not rational as there will be misuse of this FDC in patients who may not need all the three drugs. Hence committee did not recommend for approval of the FDC.
31	**FDC of TolperisoneHCl SR 450mg/300mg/150mg + Diclofenac Sodium SR 100mg tablets**		The committee noted that Toleprisone as well as FDC of TolperisoneHCl + Diclofenac Sodium in IR form is approved by DCG (I) for marketing in the country. Also no restriction has been imposed on the marketing of the Tolperisone in the country. The proposal of the firm is to manufacture and market the same approved FDC but in SR formulation. Hence based on the data generated by the applicant on the FDC, the committee recommended for grant of approval of the FDC for manufacturing and marketing in the country.
32	**Dexmedetomidine**		Committee recommended for giving permission to conduct the study.

6. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS & RHEUMATOLOGY) HELD ON 10.05.2013:-

The NDAC (Analgesics, Anesthetics & Rheumatology) deliberated the proposals on 10.05.2013 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Analgin**	**Special Agenda**	The firm presented the data on safety and efficacy of the drug. The committee deliberated the issues at length and noted that there is no adequate data on Indian population in support of either ban of the drug or to allow the continued marketing of the drug in the country. However considering the issues related to safety aspect of the drug and regulatory actions in many other countries and the fact that alternate analgesics are available, committee recommended that the marketing of the drug in the country should be put under suspension and the firm should be asked to generate adequate data in Indian scenario to consider the matter further.
2	**Ropivacaine**		The firm did not turn up for presentation, therefore the committee deferred the proposal.
3	**Platelet rich plasma**		The committee recommended for approval of the study subject to condition that the protocol should be revised incorporating the following and submitted to the DCG(I) before initiation of the study- i) To standardize the autologous PRP specifically the dose. ii) MRI should be done for better assessment of cartilage status. Dr. P. P. Kotwal did not participate in the decision making process.
4	**Lornoxican Orally disintegrating Strips 4/8mg**		Committee recommended for conducting a bioequivalence study of proposed drug. However a clinical trial is also required to be carried out due to the change in route of administration.
5	**Baricitinib**		Committee deliberated the protocol and after discussion expressed the concern that out of 500 subjects enrolled globally, 100 subjects are from India. Hence, the committee recommended that not more than 10% of total subjects should be included

			from India. Further, the firm proposed the comparison of baricitinib monotherapy vs. methotextrate monotherapy. The committee debated the issue and considered that if permission is given for this trial, then the firm should give an undertaking that they will not ask for a marketing permission of barcitinib as first line therapy for rheumatoid arthritis.
6	**Baricitinib**		Committee deliberated the protocol and after discussion expressed the concern that out of 500 subjects enrolled globally, 100 subjects are from India. Hence, the committee recommended that not more than 10% of total subjects should be included from India. Further, the committee recommended for giving permission to the trial. However the sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country.
7	**Baricitinib**		Committee deliberated the protocol and after discussion expressed the concern that out of 500 subjects enrolled globally, 100 subjects are from India. Hence, the committee recommended that not more than 10% of total subjects should be included from India. Further, the committee recommended for giving permission to the trial. However the sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country.
8	**Diclofenac gel**		Committee opined that the firm should submit an affidavit for marketing the product in India. The committee recommended for giving permission to the trial. However the sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country.
9	**Blisibimob**		The committee recommended for giving permission to the trial. However the sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country. Further, the patients who response to the therapy in

			this trial should be provided with the study drug free of cost till the time the drug is commercially available in India.
10	**Teriparatide**		The committee recommended for giving permission to the trial. However the sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country.
11	**UC-II** **Re-examinartion**		The firm presented the study as a nutritional supplement. Insufficient data was presented regarding characterization of the molecule. The committee considered that since the product is a nutritional supplement, it falls outside the purview of the committee and DCGI. Hence the applicant may approach some other appropriate authority.
12	**Platelet rich plasma** **Re-examination**		The applicant submitted clarification in respect of concerns raised by the committee in earlier meeting held on 22.03.13. After deliberation, the committee recommended for the proposed study. Dr. R. K. Arya did not participate in the decision making process.
13	**Flupirtine-D-Gluconate injection** **Re-examination**		The firm deferred the proposal.

7. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS & RHEUMATOLOGY) HELD ON 27.07.2013:-

The NDAC (Analgesics, Anesthetics & Rheumatology) deliberated the proposals on 27.07.2013 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Tofacitinib 5mg Tablet**		The firm presented the global clinical trial data including the clinical trial data generated on 120 Indian subjects. The committee noted that the no. of patients enrolled in the Indian study is not statistically significant for recommending Marketing Authorisation. Hence the committee recommended for conducting a trial on statistically significant no. of Indian subjects. However the sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country. Accordingly CT protocol etc., may submitted to DCG(I) for further review of the committee.
2	**Sugammadex solution for injection**		The committee recommended that the Clinical Trial is required to be conducted in the country for the evaluation of efficacy and safety of the drug in Indian population. Further, the clinical sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country. Accordingly CT protocol etc., may submitted for further review by the committee.
3	**Hydroxychloroqui neSulphate 300mg tablets**		The committee opined that the 200 mg and 400mg are approved already and the safety and efficacy is already established. The committee opined that some group of patient may require 300mg dose depending on the body weigth. the committee has recommended for the approval 300mg strength.
4	**Paracetamol 665 mg Sustained Release tablets**		The committee opined that the O/o DCG(I) has already approved 650mg SR tablets and there is no therapeutics benefit and rationale between the proposed Paracetamol 665mg and the already approved Paracetamol 650mg. Hence the committee did not recommend for the proposed

			formulation.
5	**Buprenorphine transdermal patches 5mg/10mg/20mg**		The committee opined to rectify the inclusion and exclusion criteria to include terminally ill cancer patients who are non-responsive to other agents, and to include oncologists as investigators. The sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country.
6	**Tapentadol ER tablets 250mg**		The tapentadol ER tablet has been already approved for use in in-patients under hospital settings for severe acute pain for a period not exceeding 5 days. The committee recommended for conduct of the proposed BE study. However the clinical trial should either be conducted in already approved indications or in chronic pain in terminally ill cancer patients in case the firm intend to market the product for chronic pain. Accordingly CT protocol etc., may submitted for further review by the committee.
7	**Diclofenac Rapid Release Tablet 50mg (Re-Examination)**		The committee opined that Bioequvalencestudy have shown higher Cmax of approximately 3 times with the test product as compared to conventional dispersible tablet. Therefore the committee recommended that clinical trial comparing the proposed drug with conventional formulation is required to be conducted. Accordingly CT protocol etc., may submitted for further review by the committee. The sites should be Multispecialty hospitals/institutes having own Institutional Ethics Committee including 50% of sites being government hospitals across the country.
8	**Diclofenac Sodium 150 mg SR tablets (two layered tablet)**		The firm has submitted the clinical trial report of the study conducted on the product in Germany and the firm has conducted BE study with the formulation manufactured in India. The committee recommended for the approval of the proposed formulation for the indication Symptomatic treatment of pain and inflammation in irritations in association with degenerative joint disease / osteoarthritis.
9	**Sarilumab**		Committee recommends for grant clinical trials permission in multi-specialty hospitals/ medical colleges having own Institutional Ethics Committee including 50% of sites being

			government hospitals across the country.
10	**SAR153191**		Committee recommends for grant clinical trials permission in multi-specialty hospitals/ medical colleges having own Institutional Ethics committee.
11	**Teriparatide**		The committee has recommended for conducting the PK/PD study
12	**Rituximab**		The committee has recommended for conducting the Phase IV (PMS) study (ML28550 Ver 3.0 dated 20/05/2013). Since the disease is a very rare disease the study may be conducted with the proposed no of patients of 30. The firm shall submit the report to this committee for review.

8. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS & RHEUMATOLOGY) HELD ON 20.09.2013:-

The NDAC (Analgesics, Anesthetics & Rheumatology) deliberated the proposals on 20.09.2013 and recommended the following:-

AGENDA NO.	DRUG NAME		RECOMMENDATIONS
1	**Palonosetron**		The committee recommended the grant of clinical trial protocol subject to the following changes in CT protocol. 1. Each individual side effects of Palonosetron should be mentioned in the protocol and should have follow-up program. 2. Delayed complication of the administration of Palonosetron should also be a part of CT protocol.
2	**Tizanidine**		The committee recommended the grant of clinical trial protocol subject to the following changes in CT protocol. 1. Provide the published safety data of Tizanidine on paediatric age group patients on 2 years age. 2. The trial should be active control comparative trial. Revised protocol should be submitted to office of DCG (I) and opinion on approval of revised protocol should be taken from experts before consideration of CT NOC.
3	**Zaltoprofen SR Tablets 240mg**		Firm has requested for withdrawal of the proposal.
4	**Diclofenac Diethylamine**		The committee has recommended that firm should conduct a phase III trial in statistically

	Topical Patch 1.16%		significant geographically distributed population. The study should be conducted in two different arms i.e., one arm for trauma and one arm for Osteoarthritis. Accordingly revised protocol incorporating the above should be submitted to DCG(I) office for further review and approval of this Committee.
5	**Tapentadol HCl ER Tablets 50 mg (Re-examination proposals)**		Tapentadol ER Tablet 50/100/150/200 mg is approved By US FDA. Further this Directorate has already approved Tapentadol ER tablet 100/150/200 mg. Hence, the committee recommended for the approval of Tapentadol ER 50 mg tablets being used for dose titration.
6	**Dexketoprofen / Tramadol HCl**		The proposed FDC is for the treatment of chronic pain. On chronic use Tramadol HCL has addiction liability & hence there is no justification for its FDC with Dexketoprofen. In acute pain these drugs can be used as separate pills rather than as FDC. Further the rescue medication i.e., metanizole whose import and use in the country is suspended hence this trial cannot be approved.
7	**Dexketoprofen / Tramadol HCl**		The proposed FDC is for the treatment of chronic pain. On chronic use Tramadol HCL has addiction liability & hence there is no justification for its FDC with Dexketoprofen. In acute pain these drugs can be used as separate pills rather than as FDC. Further the rescue medication i.e., metanizole whose import and use in the country is suspended hence this trial cannot be approved.
8	**Belimumab**		Committee recommended for giving permission to conduct the study subject to condition that the number of subjects to be enrolled from India should not be more than 480. List of sites along with PI undertakings should be submitted by the firm to the office of DCG(I). Dr. S.K. Das did not take part in the decision making process of the proposal.

9	**SB2**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) The number of subjects to be enrolled from India should not be more than 60. ii) The firm should also include sites from north and north-east India.
10	**SB4**		Committee recommended for giving permission to conduct the study subject to the condition that the number of subjects to be enrolled from India should not be more than 50.
11	**BCD-020**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) Sites should be geographically distributed across the country. ii) 50% of the sites should be Govt. Hospitals and the sites should be multispecialty hospitals with emergency facilities. iii) The number of subjects to be enrolled from India should not be more than 20.
12	**Rituximab**		The proposed additional indication of the drug for the treatment of Rheumatoid arthritis has been already approved by this Directorate. The committee recommend for the grant of additional indication of Rituximab for the treatment of Rheumatoid arthritis.
13	**Golimumab**		The committee recommended that the drug should be used for the cases in RA patients whose disease is insufficiently controlled by DMARD(s). The Drug should be sold against the prescription of rheumatologist only. Also the firm shall submit phase IV PMS protocol to this

			Directorate in the course of time. The drug should be marketed only for the indication stated below: Rheumatoid arthritis (RA): Golimumab by subcutaneous administration, in combination with methotrexate (MTX),is indicated for : • Reducing signs and symptoms • Inducing major clinical response • Inhibiting the progression of structural damage • Improving physical function
14	**Adalimumab**		The committee recommended for granting phase III clinical trial as per the protocol submitted to this Directorate provided the sites are Geographically distributed, multispeciality with emergency facilities and having Institutional ethics committee approvals

9. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS & RHEUMATOLOGY) HELD ON 24.10.2013:-

The NDAC (Analgesics, Anaesthetics & Rheumatology) deliberated the proposals on 24.10.2013 and recommended the following:-

AGENDA NO.	DRUG NAME		RECOMMENDATIONS
1	**Minodronic Acid**		The firm has claimed that Minodronic acid has following advantages **1)** Higher potency and greater efficacy **2)** Less incidence of GER (Gastroesophageal Reflux Disease) The committee noted that advantages of GER is not significant and is not a major problem as patients are adequately educated for treatment. The proposed duration of clinical trial is 12 weeks. However the changes in BMD (Bone mineral density) generally appears in 1 year. Hence clinical trial duration should be for a period of 1 year with proper evaluation of bone marker and BMD.
2	**Iguratimod tablets 25 mg**		Firm presented that the Iguratimod tablets 25 mg would be useful in patients where Methotrexate has inadequate/partial response. The Committee noted that the protocol mentions that those patients will be included which do not shows adequate response to 2-6 mg of MTX weekly. The Committee is of view that this is inadequate dose of MTX to be considered to show adequate response and labeled as patients as MTX failure. Therefore the proposed trial design is not effective; the trial design dose not defined the basic queries. The other concerns raised by the committee are the possibility of additive adverse effect on hepatic enzyme since MTX as well as Iguratimod both are known to be hepatotoxicity. The firm has been asked to submit the

			PSUR data as the drug has already been used for two years in support to their claim for safety.
3	**Institutional**		The committee noted that the proposed study is a investigator initiated academic study. The study compares two regimes of well-known and approved drugs for indication Axial spondyloarthropathy. This is not a new intervention. The committee recommended for the proposed study. (Dr. S.K.Das did not participate in the deliberation and decision making process.)
4	**Institutional**		The committee raised the following concerns **1)** Whether the investigational product (PRP) is prepared under GMP conditions. **2)** Objectivity for evaluation of results needs to be MRI **3)** Dose of platelets to be standardize The applicant furnished clarification and adequately replied i.r.o. all the concerns raised by the Committee. The committee after deliberation recommended for the study. (Dr. S.K.Das did not participate in the deliberation and decision making process).
5	**Institutional**		The applicant made the presentation in respect of queries raised by the Committee in its earlier meeting held on 20.09.13. After deliberation the Committee recommended for the proposed study.
6	**Flurbiprofen 8.75mg Lozenge**		The firm has proposed for import and marketing of Flurbiprofen 8.75mg Lozenge and requested for clinical trial waiver. The committee noted the following: 1) The Maximum intake of proposed product is 8.75 mg X 5 lozenges per day which is lower to the approved 50 mg Flurbiprofen orally tablet. 2) Onset of action with Flurbiprofen 8.75mg Lozenge for pain relief 0.6 hrs vs 1.5 hrs by orally Flubiprofen tablets which is an advantage proposed

			drug. 3) The drug has been exposed to 60 million patients in 48 countries. 4) In these countries proposed drug is marketed as OTC drug. However in India it will be sold as prescription drug. Considering above facts the committee recommended for import and marketing permission of Flurbiprofen 8.75mg Lozenge, With following condition. 1) There should be 5 lozenges blister pack only. 2) Package insert should include dosing schedule not more than 3 days. 3) Phase IV study required to be carried out.
7	**Disintegrating Tablets 7.5mg & 15mg**		The Committee recommended for grant of BE study as proposed by the firm for the proposed drug Meloxicam Orally Disintegrating Tablet.

8	**S-Bupivacaine Solution for Injection 7.5 mg/ml (with preservative) and 5 mg/ml (Hyperbaric)**		The firm has proposed seeking for the following:
			a) S-bupivaccaine solution for injection 5mg/ml (Hyperbaric)
			b) S-Bupivaccaine solution for injection 7.5mg/ml (with preservative) with multidose vials.
			For (a):-The Committee opined that phase III clinical trial is required to be conducted in statistically significant and geographically distributed population.
			For(b):-The Committee does not recommend for multidose vials

9	**Etancercept**		The firm presented the Study protocol. The NDAC recommended for issuing permission to the firm to carryout phase I PK / PD study.

10	**Etanercept & DMARD**		Proposal Withdrawn by the firm.
11	**Secukimumab**		Though it appears to be an extension study the company's presentation revealed it will be a roll over study to administer the drug to the existing patients who have derived benefit from the on-going trial. Hence the committee recommended for approval of the proposed extension study subject to the condition that an undertaking is submitted by the applicant that it is a roll-over study on the exiting subjects.
12	**Sarilumab**		Since the drug Adalimumab is not yet approved in India, therefore giving it to patients to create the adalimumab -failure subjects for evaluation of safety & efficacy of the applicant's IND namely, Sarilumab cannot be permitted. Therefore the proposed phase III study with sarilumab on adalimumab failure subjects cannot be accepted.
13	**Abatacept**		The committee recommended for approval of the trial, subject to inclusion of 50 % trial centers from Govt. Hospitals. (Dr. S.K.Das of KGMC (Lucknow) did not take part in the deliberations and decision making process as he is one of the PIs in the proposed study.)
14	**Masitinib**		The committee recommended the proposed trial subject to the condition that 50% trial sites are from Govt. Hospitals and not more than 45 patients from India. The trial sites should be geographically distributed throughout the country.

10. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS & RHEUMATOLOGY) HELD ON 10.12.2013:-

The committee while evaluating the following proposals, the committee kept in view the three following aspects:

1. Risk versus benefit to the patient
2. Innovation viz a viz existing therapies
3. Unmet need in Indian population

The NDAC (Analgesics, Anaesthetics & Rheumatology) deliberated the proposals on 10.12.2013 and recommended the following:-

AGENDA NO.	DRUG NAME		RECOMMENDATIONS
1	**Tizanidine**		The applicant presented the clarification sought by the committee in its earlier meeting. The committee deliberated on the revised clinical trial protocol and recommended for the grant to permission to conduct the proposed study as per the protocol submitted.
2	**Hydroxychloroquine sulphate tablet 100mg**		This office had granted clinical trial permission for Hydroxychloroquine and Methotrexate combination in treatment of Juvenile Rheumatoid arthritis. Now the firm has proposed amendment in the CT protocol for the dosing in children with certain body weight (Approx. Between 17kg to 28kg) 100mg of Hydroxychloroquine sulphate tablet will be very less and 200mg of Hydroxychloroquine sulphate tablet will be very high. The committee after examination recommended for the amendment in the Clinical trial protocol.
3	**Thiocolchicoside oral Spray 4%**		The firm presented the Clinical data carried out in 214 patient firm also requested waiver of BE study. After deliberation the committee opined that study carried out was in small private clinics and the committee recommended to conduct the trial in 3 additional Govt. Hospitals/medical colleges centres in at least 100 patients in each arm. Further, other medicines or therapy used concomitantly in patients in the both arms should be reported in CT report. The committee opined that the firm should conduct BE study with the reference product.

4	**Apitox**		The firm presented their proposal for conducting phase III trial of **Apitox** in Subjects with **Osteoarthritis of the Knee**. Apitox® is purified honeybee (Apis mellifera) venom. Apitox, 1.0 mg of lyophilized honeybee venom is reconstituted in 1 mL of 0.5% preservative-free lidocaine. The proposed study drug is marketed in Korea since 2003**.** The proposed study is conducted in two countries i.e. USA and India. The study drug will be imported from a cGMP certified facility in USA. The most common adverse experiences in phase I and III study (Korean subjects), phase II study (Korean and USA subject) and six years post marketing surveillance study in Korean subject were injection site itching, generalized body aches and eruption blister. The product acts on the arachidonic acid pathway like other NSAID's. It produces catecholamine and cortisol in human body but in minimal amount as presented by the Korean presenter. The proposed indicated dosage will be monthly once for lifelong in OA patients. The committee after due deliberation opined that data from phase –I and phase II studies in Indian subjects is required before conduct of the proposed phase –III . Further the committee also opined that the drug Apitox per-se has had no substantial benefit over and above the existing therapies for OA, but is meant for palliative care only.
5	**Prolia (Denosumab 60 mg/ml)**		Firm presented their proposal for Marketing Authorization. The following observations were noticed by the committee members: • Screening of patients for adverse events had not been done properly and some of the events happened selectively in placebo group, however this could be due to small number of patients. • 3 years global data was submitted. However, in India study was done only for BMD for 6 months which is not adequate and would require atleast 2 years.

			Based on the above observations, the committee concluded that marketing authorization may be granted only for the indication for which study was conducted subject to condition that firm should submit a proposal for Phase IV study which is to be approved by NDAC / Authority before marketing the drug, to evaluate the efficacy and safety in atleast 1000 patients for a minimum of 2 years. The sites for the study should be effective and competent facilities. The drug shall be prescribed only by registered Endocrinologists /Orthopaedicians /Obstetricians /Rheumatologists and Internal Medicine Specialist.
6	**Reditux**		Firm presented their clinical study proposal. The committee recommended for conducting the clinical trial subject to following conditions: • The inclusion criteria should be changed with respect to treatment of Methotrexate for 6 months with atleast 15-25 mg/wk on stable dose for atleast 3 months stable. • The firm has been advised to review the selection of sites shown during NDAC meeting and should include 50% Govt. Institutions and 50% should be multi-speciality hospitals having 24 hrs emergency and multi-speciality facility. Accordingly, revised protocol etc. should be submitted to this Directorate for further review.

11. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS & RHEUMATOLOGY) HELD ON 19.02.2014:-

The NDAC (Analgesics, Anesthetics and Rheumatology) deliberated the proposals on 19.02.2014 and recommended the following:-

AGENDA NO.	FILE NO		RECOMMENDATIONS
1.	**Abatacept**		The Committee evaluated the Pharmacovigilance data generated from India as well as globally by the firm and noted that Indian Pharmacovigilance data is in line with global Pharmacovigilance data. No major safety signals have been seen . However, for ample precaution, the committee recommended that Phase IV Clinical trial in Indian subjects should be carried out while marketing of the drug should be continued. Accordingly, the firm is required to submit Phase IV clinical trial protocol along with details of clinical sites, etc. for the further review by the committee.
2.	**Prednisone modified release tablets**		Predinsone old approved drugs predinosne MR tablets is approved and marketed in USA, Europe and other countries. Firm has been proposed clinical trial protocol & BE protocol for the proposed formulation. After deliberation the committee opined the following. 1. The design of CT protocol should be revised and it should be double blind , double dummy randomized comparative multicentre study 2. The Rheumatologist shall be included in the clinical trial and sites should be geographically distributed 3. In the efficacy measurement should include HDAI parameter. 4. In the exclusion criteria other than Methotraxate and Hydroxy chloroquine as a concomitant medicine should not be allowed in

			the trial. 5. In inclusion criteria pain intensity criteria should be included. 6. The dosage schedule shall properly defined and shall include tapering of the dose. Accordingly CT protocol shall be revised and submitted to the committee for further review.
3.	**Hydroxychloroquine sulphate tablet 300 mg**		The committee opined that the proposed strength of 300 mg be given for the patients with lower body weight i.e., 45 to 60 kg. The committee opined that the phase IV trial protocol shall be submitted within 6 months.
4.	**Diclofenac Sodium Rectal Spray 25% w/v**		The committee evaluated the proposal on diclofenac sodium rectal spray and the firm had applied for marketing approval on the basis of bioavailability study compared to diclofenac rectal suppository. A phase III trial has not been done so far, the committee felt that since the route of administration/dosage form is different than as ever been used anywhere in the world. The firm may be asked to perform phase III Clincal Trial. It should also be considered as a diclofenac rectal solution with applicator rather than rectal spray.
5.	**Tacrolimus Tablet 1 mg**		The committee opined that firm shall conduct a Phase II trial initially to find out the dose and accordingly the protocol shall be submitted before the committee.
6.	**Acetominophen(Paracetamol)500mg + caffeine (anhydrous)25mg**		The committee opined that FDC is rational for mild to moderate pain. Committee recommended to conduct a phase III clinical trial and according a phase III trial protocol shall be submitted.
7.	**Glucosamine 500 mg +Ibuprofen 200 mg**		The firm did not turn up for presentation, hence the proposal was deferred
8.	**Tolperisone HCl 150 mg**		The firm did not turn up for presentation,

	+Paracetamol 500 mg		hence the proposal was deferred
9.	**Aceclofenac 100 mg+Drotaverine 80 mg**		The firm did not turn up for presentation, hence the proposal was deferred
10.	**Etodolac 300 mg+Paracetamol 500 mg**		The committee noted the recommendations of the PSC. The committee evaluated the safety and efficacy reports presented by the firm. The committee observed that the product shall not be prescribed more than 10 days as claimed by the firm. The committee opined that FDC is not required for short term use as paracetamol can be prescribed separately when required and can be tapered off early if need arises. The committee recommended that the FDC is not rationale at present scenario.
11.	**Infliximab**		Firm presented their study report for Phase III clinical trial. The committee reviewed the efficacy and safety data submitted by the firm for their product Infliximab (R-TPR-015) and found that the same is non-inferior to the innovator product, Remicade. The committee recommended for Marketing authorization of Infliximab. The product is to be prescribed by registered Internal Medicine, Orthopedics Surgeons and Rheumatologists only.
12.	**Rituximab**		The committee considered the application of the firm for Market Authorization of Rituximab (indigenously developed) with a waiver of Phase III clinical trial. For this purpose, M/s Cadila Healthcare have submitted PK-PD data and immunogenicity data of their product which is no different from the innovator product – Rituximab by M/s Roche. The firm has claimed that they had pursued the development of the product according to the Guidelines on

			Similar Biologics published by DBT & CDSCO. And as per these guidelines the firm is entitled to Phase III waiver if it is ready to carry out Phase IV Post Marketing trial. If the Guidelines on Similar Biologics of 2012 is being implemented the firm may be given marketing authorization with the rider of performing Phase IV trial which will gather additional safety data with a specific emphasis on gathering immunogenicity data or if the guideline is not being applicable then the firm may be required to conduct a Phase III clinical trial for both the indications – RA & NHL.

12. RECOMMENDATIONS OF THE NDAC (ANALGESICS, ANESTHETICS & RHEUMATOLOGY) HELD ON 26.05.2014:-

The committee while evaluating the following proposals, the committee kept in view the three following aspects:

1. Risk versus benefit to the patient
2. Innovation viz a viz existing therapies
3. Unmet need in Indian population

The NDAC (Analgesics, Anaesthetics & Rheumatology) deliberated the proposals on 26.05.2014 and recommended the following:-

AGENDA NO.	DRUG NAME	RECOMMENDATIONS
1.	**Apixaban tablet**	The applicant has applied for permission to conduct phase IV clinical trial entitled "A Phase IV, Open – label, Multicenter Study to Evaluate the Safety of Apixaban in Indian Subjects Undergoing Elective Total Knee Replacement or Total Hip Replacement Surgery ". Apixaban 2.5mg tablet was approved by this Directorate on 03-08-12 for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery on 03.08.2012, subject to condition Phase IV clinical trial with the drug on at least 500 patients is required to be condition within two years. The firm presented the phase-IV protocol before the Committee. After detailed deliberation the Committee recommended for giving permission subject to following conditions: 1. Single Clopidogrel use should be excluded 2. In case of death either autopsy or verbal autopsy has to be performed. 3. In case of SAE, Causality assessment should be done 4. Clinical trial sites should be restricted to 05 and cardiologist and Hematologist should be

		included as Co-investigators Accordingly, Protocol etc. should be submitted to DCGI.
2.	**Pulse steroid**	Clinical Trial NOC was already issued to the applicant. Now the applicant has requested for certain amendment in the design of the study The proposed amendments are deliberated in details by the committee. The Committee has recommended for approving the proposed amendment.
3.	**Glucosamine + Ibuprofen**	Firm didn't turn up for presentation. Deferred for next meeting.
4.	**Tolperisone HCl + Paracetamol**	Firm didn't turn up for presentation. Deferred for next meeting.
5.	**Aceclofenac + Drotaverine**	Firm didn't turn up for presentation. Deferred for next meeting.
6.	**Combikit of 4 tablet of FDC of Paracetamol + Phenylephrine HCL + caffiene tablet. & 2 tablet of FDC of chlorophenrimine maleate tablet + Paracetamol + phenylephrine HCL**	Firm didn't turn up for presentation. Deferred for next meeting.

7.	**Diclofenac Diethylamine BP + Thicolchicoside + Absolute Alcohol**	The applicant firm has applied for permission to manufacture and market FDC of Diclofenac Diethylamine BP 2.32% w/v Eq. to Diclofenac Sodium IP 2.0% w/v + Thiocolchicoside IP 0.25% w/v + Absolute Alcohol IP 10.0% v/v non aqueous topical solution. The product was earlier deliberated committee in the meeting of the NDAC (Analgesics, Anesthetics & Rheumatology) held on 22.03.2013, wherein the committee recommended that the clinical data generated is inadequate for approval of the drug. Hence committee recommended that a comparative phase III clinical trial of the product comparing with Diclofenac gel on statistically significant number of subjects with minimum 500 subjects in multispecialty hospitals/institute including Government hospitals having own institutional Ethics Committee is required to be conducted. The firm has submitted Prospective, randomized, open label, two arm, parallel, active controlled, comparative, multicentre clinical study protocol to conduct the study at 7 centers on 212 patients . In view of above, NDAC has re-examined the proposal in all aspects. Recently it has been shown that Thiocolchicoside is not safe when administered orally amd intramuscularly, as it can lead to aneuploidy and subsequently to malignancies. The committee felt that the product, if permitted in market has the potential for long term misuse, and hence the safety concern will be questionable. The committee hence does not recommend the Clinical trial due to the safety concerns.
8.	**Aceclofenac SR + Pregabalin SR**	Firm didn't turn up for presentation. Deferred for next meeting.
9.	**Baricitinib**	The applicant firm requested for permission to conduct a phase III, multicentre study to evaluate

		the long term safety and efficacy of Baricitinib in patients with Rheumatoid Arthritis (RA) who have completed a Phase 2 or Phase 3 [I4V-MC-JADY (JADY)] extension (up to 2 years). Safety and tolerability assessment will include: • Treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) • Temporary investigational product interruptions and permanenet investigational product discontinuations • Vital signs and laboratory evaluations (including schemistry anf hematology) Out of Globally 2400-3000 subjects,120 will be enrolled in 21 centers in India. Dr. S.K. Das did not participate in the discussion as he is one of the PIs in the trial. The other members of the NDAC examined the proposal and recommended the conduct of this study i.e. the extended therapy with the drug in patients who had responded in the previous trials may be allowed subject to the condition that the extended Lipid profile monitoring shall be done every three months till the study ends. The committee also opined that there is an unmet need in management of RA in the country.
10.	**GP 2013 (a Biosimilar to Rituximab)**	The applicant firm was granted permission for phase II, randomized, double-blind, controlled study to evaluate PK & PD, safety and efficacy of GP2013 (a Biosimilar Rituximab, Concentration of 10mg/mL in 500mg/50mL, IV single-use vials) and Rituximab in patients with rheumatoid arthritis refractory or intolerant to standard DMARDs and one or up to three anti-TNF therapies, dated 06 Apr 2011. This Protocol amendment intends to introduce a 3rd arm of patients to be treated with Rituxan® (biosimilar reference product as licensed in the US). This patient population treated with Rituxan® will be compared to patients treated in the 1st arm with GP2013 and those treated in the 2nd arm with MabThera® (biosimilar reference

		product as licensed in the EU) to provide a bridge between Rituxan® and MabThera®. The committee opined that the drug Rituxan is not yet approved in India and inclusion of an arm to compare the safety/efficacy of the proposed product with this product cannot be considered.
11.	**MK-0822**	The applicant firm applied for permission to conduct phase III, randomized, placebo controlled observational clinical trial to assess the safety and efficacy of **Odanacatib (MK-0822)** to reduce the risk of fracture in osteoporotic postmenopausal women treated with Vitamin D and calcium (Protocol No. 018)". The study is planned to be conducted in 39 countries which includes Australia, China, France, Germany, USA and in India at 19 centers 935 subjects are planned to be enrolled for the proposed study. The committee opined that there is a gap of 2 years since the trial was concluded and during this period the subjects would have been taking other drugs such as steroids, antiepileptics bisphosphonates etc which can modify the disease and confound the adjudication of the observational study being proposed. Also the data that may be collected may not be dependable or meaningful. Hence the committee did not recommend the conduct of this study.
12.	**Rituximab**	Committee after reviewing the Phase I PK/PD protocol with their indigenously developed Rituximab, recommended for the conduct of the study vide Protocol No. LRP/RTX/2013/002 Version No. 1.0 dated 18th Dec 2013.