1. RECOMMENDATIONS OF THE NDAC (ENDOCRINOLOGY AND METABOLISM) HELD ON 07.01.2012:-

The NDAC (Endocrinology and Metabolism) deliberated the proposals on 07.01.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Linagliptin**		Recommended for approval subject to laboratory testing for quality control before launching the product in the market.
2	**BI 10773**		Recommended for approval subject to submission of document and clarification of following: i) Carcinogenicity study report. ii) The study has been mentioned as treat-to-target study; however it is more of an exploratory study. This needs to be clarified. i) Special monitoring for adverse events should be done in subjects with history of recurrent urosepsis and diabetic cystopathy. ii) Ethics committee must be from the same area where the clinical trial site is situated.
3	**BI 10773**		Recommended for approval subject to submission of document and clarification of following: i) Rescue medication needs to be defined in the protocol. ii) Anti hypertensive drugs therapy allowed as per the protocol should be defined. iii) Information required, if there any drug Interaction between SGLT inhibitors and thiazides. iv) Ethics committee must be from the same area where the clinical trial site is situated.
4	**BI 10773 / Linagliptin**		Recommended for approval subject to submission of document and clarification of following: i) Carcinogenicity study report. ii) Rationale for combining the two drugs iii) Rational for selecting the proposed doses of the FDC iv) Data regarding drug-drug interaction if any between the study drug and

			linagliptin etc. to be used in the study. v) Ethics committee must be from the same area where the clinical trial site is situated.
5	**PF-04991532**		Further clarification is required on following issues:- i) Repeat dose toxicity data conducted in mice is required to be submitted. ii) Rationale for selecting the doses for the proposed phase II based on projected change in HBA1c (%) from 2 week phase 1 data should be submitted as 300 mg dose caused hyperglycemias. Further, 450 mg dose caused increase in triglyceride 750 and 900 units in two cases in Phase 1 study. Necessary clarification for the same should be submitted. iii) Data (imaging and histological) regarding glycogen hepatopathy should be submitted after the use of the drug. iv) Reasons for choosing the sitagliptin as comparator may be submitted. v) What is the effect on renal glycogen content and whether it also causes renomegaly and renal dysfunctions? vi) Cardiovascular safety profile of the drug is required to be ensured. Vi) Rosiglitazone mentioned as an alternative option in ICD should be deleted. Vii) Ethics committee must be from the same area where the clinical trial site is situated.
6	**PF-04991532**		Further clarification is required on following issues:- i) Repeat dose toxicity data conducted in mice is required to be submitted. ii) Rationale for selecting the doses i.e. 25, 75, 150 & 300 bid for the proposed phase II based on projected change in HBA1c (%) from 2 week phase 1 data should be submitted as 300 mg dose caused hyperglycemias. Further, 450 mg dose caused increase in triglyceride 750 and 900 units in two cases in Phase 1 study. Necessary clarification for the same should be submitted.

			iii) Data (imaging and histological) regarding glycogen hepatopathy should be submitted after the use of the drug. iv) Reasons for choosing the sitagliptin as comparator may be submitted. v) What is the effect on renal glycogen content and whether it also causes renomegaly and renal dysfunctions? vi) Cardiovascular safety profile of the drug is required to be ensured. Vi) Rosiglitazone mentioned as an alternative option in ICD should be deleted. vii) Ethics committee must be from the same area where the clinical trial site is situated.
7	**Saxagliptin**		Use of placebo in children with significant hyperglycemias say FBG more than 200 units) or high HbA1C say > 9 is not justified. Following observations were also made: i) If the child have very high blood glucose advising him on placebo and exercise as per protocol may be deleterious to his health. ii) DPP inhibitors have been reported to influence immune functions, there are 6 reported cases of TB in exposed patients. However, immunotoxicity data in juvenile animals as per EMA guidelines have not been submitted. As immunity is important concern in children in Indian context. iii) Although nearly 20% of subjects are proposed to be included in India, there are no representation in Data Monitoring Committee from India. iv) Details of the amendments as suggested by MHRA (UK) and USFDA are not provided to the office of DCGI. v) Detail about the development and maturation of DPP IV for enzyme activity in children and adolescent is not submitted. Similar details regarding the growth and maturation of entero-insular axis in this younger population are also

			not provided though this has relevance in this group of population. vi) Deleterious effect on pancreatic ductal epithelial cells are not required to be monitored as per the protocol though pancreatitis has been reported in infants of mothers receiving saxagliptin during pregnancy. vii) Growth in children is not required to be monitored as per the protocol which should be done as GLP-1 has also effect on GH-IGF-1 axis. In view of above the committee did not recommend for approval of the present proposal.
8.	**Atorvastatin / Glimepiride**		The following issues were raised during the deliberation: i) The firm proposes eight different formulation of atovastatin and glimepiride. The only intention is to improve patient compliance in patients requiring Atorvastatin (10 and 20 mg) and anti diabetic drugs. With this combination the physician is indirectly inclined to automatically prescribe Glimipride. ii) The dose titration of hypolipedimic agent and antidiabetic agent will be difficult in the field scenario. iii) Having eight different permutation combinations is likely to add confusion in the mind of clinicians, pharmacist and the patients. iv) The possibility of increasing incidence of overdose and under dose of hypoglycaemic agent leading to hypoglycaemia or uncontrolled diabetics is not ruled out particularly in the backdrop of Indian scenario. After raising all these issues, the company representative stated that they will market only 1mg and 2 mg Glimipiride plus Atorvastain 10 / 20 mg in two formulations only. The separate proposal for the same should be submitted which will be evaluated accordingly. In view of above the committee did not

			recommend for approval of the present proposal.
9.	**Exenatide**		Recommended for granting permission subject to the following conditions:- i) PK/PD data of once weekly 2000mcg dose should be submitted to the office of DCGI ii) Ethics committee must be from the same area where the clinical trial site is situated. iii) Clarification in respect of degradation / distribution of SC injection of 2000 mcg of exenatide weekly should be submitted in light of the fact that conventional formulation of exenatide is administered only at a dose of 10 mcg bid.
10.	**Dulaglutide**		Dulagultide is not approved in any country for primary indication of Type II diabetes and it is stated to be in Phase III study in other countries. Hence, long term safety and efficacy of the drug has not yet been established. Under such circumstance, proposed cardio vascular outcome study which is primarily a long term adverse events driven study in large population with visits of 3 – 6 months interval is not recommendable for approval. In view of above the committee did not recommend for approval of the present proposal.

2. RECOMMENDATIONS OF THE NDAC (ENDOCRINOLOGY AND METABOLISM) HELD ON 28.04.2012:-

The NDAC (Endocrinology and Metabolism) deliberated the proposals on 28.04.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Mozavaptan HCl 30mg tablet**		The drug is approved only in Japan. The data of safety and efficacy of the drug is very limited. Committee recommended that the drug could be tried in patients with euvolemic and hypervolemic hyponatremia. Clinical trial in statistically significant number of subjects with euvolemic and hypervolemic hyponatremia is required to be conducted in India. Accordingly protocol etc should be submitted which should be placed before the committee for further consideration. The complete safety data of the drug as available should also be submitted.
2	**Linagliptin**		Recommended for giving permission to conduct the study subject to the following conditions:- i) Age of patients to be included in the study should be 18 to 65 years. ii) 50% of the sites should be multispecialty hospitals. iii) The screening period should be maximum 3 days and placebo run in period should be maximum 7 days. iv) No symptomatic patients should be included in the study.
3	**Linagliptin**		Recommended for giving permission to conduct the study subject to the following conditions:- i) Age of patients to be included in the study should be 18 to 65 years. ii) 50% of the sites should be multispecialty hospitals.
4	**PF-04937319**		As per protocol patients with fasting blood glucose less than 270 will be included in the study and the subjects have to discontinue sulphonylurea at least 6 weeks prior to visit 3 and metformin will be initiated. Committee recommended for giving permission to conduct the study subject to the following conditions:- i) Patients with metformin therapy only should be included in the study. ii) All sites should be multispecialty hospitals.

5	**PF-04937319**		As per protocol patients with fasting blood glucose less than 270 will be included in the study and the subjects have to discontinue sulphonylurea at least 6 weeks prior to visit 3 and metformin will be initiated. Committee recommended for giving permission to conduct the study subject to the following conditions:- i) Patients with metformin therapy only should be included in the study. ii) All sites should be multispecialty hospitals. iii) Upper age limit of subjects to be included in the study should be 65 years.
6	**Sitagliptin**		Sitagliptin is reported to cause side effects like pancreatitis, renal failure etc. In the proposed clinical trial, sitagliptin will be given for upto 3 years in subjects with impaired glucose tolerance. There is no preclinical and dose finding data in support of use of the drug in such condition in current form and at present time. Hence committee did not recommend for giving permission to conduct the study.
7	**Glimepiride/ Metformin**		Recommended for giving permission to conduct the study subject to condition that upper age limit of subjects to be included in the study should be 65 years.
8	**Saxagliptin**		Recommended for giving permission to conduct the study subject to condition that herbal medicines should be discontinued in the study.
9	**Vildagliptin**		Recommended for giving permission to conduct the study.
10	**Niacin/ Laropiprant**		Recommended for giving permission to conduct the study subject to condition that upper age limit of subjects to be included in the study should be 65 years.
11	**Niacin/ Laropiprant**		Recommended for giving permission to conduct the study subject to condition that upper age limit of subjects to be included in the study should be 65 years.
12	**Sitagliptin**		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 65 years. ii) 50% of the sites should be multispecialty

			hospitals.
13	**Sitagliptin**		As per the protocol, placebo will be used in pediatric subjects with fasting blood glucose upto 250 for 16 weeks which is not justified. Therefore committee did not recommend for giving permission to conduct the study.
14	**Sitagliptin**		Recommended for giving permission to conduct the study.
15	**Alglucosidase alfa**		Pompe is a rare disease and currently there is no therapy to treat such disease. Committee recommended for giving permission to conduct the study subject to the following conditions:- i) The study should be termed as Phase 3 study. ii) Complete regulatory documents should be submitted to DCG(I) before initiation of the study . iii) The applicant should submit an undertaking stating that the patients who benefit from the study will be given the study drug under post trial access programme. iv) Safety data in humans on 4000 litre reactor should be submitted.
16	**Insulin lispro (BE study)**		Recommended for giving permission to conduct the study.
17	**Insulin lispro**		The firm could not present the complete data before the committee. Committee opined that complete data should be submitted to them and the proposal will be deliberated in the next meeting.
18	**Continued marketing of pioglitazone**	Misc.	The matter needs to be deliberated in the next NDAC (Metabolism and Endocrinology) meeting in a detailed manner.

3. RECOMMENDATIONS OF THE NDAC (ENDOCRINOLOGY AND METABOLISM) HELD ON 22.08.2012:-

The NDAC (Metabolism and Endocrinology) deliberated the proposals on 22.08.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Phentermine Hydrochloride**		Committee recommended for granting permission to conduct the clinical trial subject to the following conditions:- i) Study sites should be distributed geographically across the country and at least 50%of the patients should be enrolled in Govt. hospitals. ii) Sample size should be appropriate. iii) Upper limit of BMI should be reduced to 40 kg/m^2 in the protocol. iv) 12 weeks treatment duration should be followed up by another 12 weeks follow up. Accordingly committee opined that firm should submit revised protocol to DCGI which should be placed before the committee for further consideration.
2	**VSL#3 Capsules**		Committee recommended for granting permission to conduct the study subject to the following conditions:- i)The title of the study should mention the study as pilot study. ii) Glucose monitoring profile should be included in the study. iii)Change in insulin requirement, if any should be mentioned in the protocol. iv) Duration of diabetes should be less than 5 years in inclusion criteria. v) Patients with serious diseases should be excluded from the study.
3	**Voglibose Mouth Dissolving Tablet/Voglibose Tablet 0.2/0.3 mg**		Committee opined that there is no data on Indian patients and data of Japanese study cannot be extrapolated to Indian patients as such. Moreover there is little rationale of mouth dissolving tablet. Committee opined that without Phase III trial

			in India, permission may not be granted. Accordingly committee opined that firm should submit revised protocol to DCGI which should be placed before the committee for further consideration.
4	**Alpha LipoicAcid+ Methylcobalamin +Inositol+Biotin+ Vitamin B6+Folic Acid+Selenium+ Zinc+Chromium**		Committee opined that there is little rationale for the proposed FDC and many constituents are in very subtherapeutic doses and only few constituents have been shown to have beneficial effects in diabetic neuropathy. Therefore committee did not recommend for the proposed FDC.
5	**Metformin + Glimepiride + Pioglitazone**		Committee did not recommend the proposed FDC due to the following reasons:- i) Recently there are safety concerns on Pioglitazone. ii) Sufficient Pharmacokinetic and Pharmacodynamic data have not been submitted. iii) There can be medication error while prescribing many strengths.
6	**Metformin + Orlistat**		Committee opined that the proposed FDC is not rationale and the clinical data submitted is not adequate. The proposed FDC was not recommended by the committee due to the following reasons: i)Larger percentage of people which include patients with diabetes in India are carbohydrate eaters and not predominantly fat eaters, therefore long term use of orlistat has limited use. ii)Long term use of orlistat containing metformin may adversely affect the absorption of lipid soluble vitamins together with the fact that vit D deficiency is common in the country. iii)Even with the proposed FDC, the number of pills can be reduced, however frequency of administration remain same, therefore does not add to patients compliance. iv)The data presented by the firm was of only 28 days which has no relevance to any of the antiobesity drugs.

7	**Sitagliptin+ Simvastatin**		The committee opined that Phase III clinical trial study should be conducted in the country and accordingly firm should submit CT protocol for consideration by the committee.Before submitting the protocol, the firm should take the following points into consideration:- i)The cost of the FDC should not be expensive. ii)Risk of nocturnal hypoglycemia should be assessed during the clinical trial. iii) Study sites should be distributed geographically across the country and at least 50%of the patients should be enrolled in Govt. hospitals. iv)Sample size should be appropriate.
8	**Sitagliptin+ Atorvastatin**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i)Glycemic Rescue criteria should be amended ii)Upper age limit of subjects to be included in the study should be 65 years. iii)Study sites should be distributed geographically across the country and at least 50%of the patients should be enrolled in Govt. hospitals.
9	**Biphasic Insulin aspart (BIAsp) 30 plus sitagliptin**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i)Study sites should be distributed geographically across the country and at least 50%of the patients should be enrolled in Govt. hospitals. ii) During the trial, the test drug and the antidiabetic medications should be provided by the Sponsor to the patients free of cost.
10	**Liraglutide**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i)Study sites should be distributed geographically across the country and at least 50%of the patients should be enrolled in Govt. hospitals. ii) During the trial, the test drug and the

			antidiabetic medications should be provided by the Sponsor to the patients free of cost.
11	**Insulin degludec/ Liraglutide**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i)Study sites should be distributed geographically across the country and at least 50%of the patients should be enrolled in Govt. hospitals. ii) During the trial, the test drug and the antidiabetic medications should be provided by the Sponsor to the patients free of cost.
12	**Wosulin 70/30**		The firm did not turn up for presentation. Therefore the proposal was deferred.
13	**Insulin degludec injection (r-DNA origin)**		The proposal was not recommended and the committee was of the opinion that more data with respect to following should be submitted and presented for the next NDAC meetings:- i)Complete study report explaining the cause of deaths in two Indian patients during the trial. ii)DSMB report on the trial comparing the adverse events in Indian population and other patients enrolled globally should be submitted. iii)PMS protocol should be submitted to DCGI.
14	**R-TPR-007 Somatropin**		Committee recommended for approval of the proposed study. However for marketing authorization, committee recommended that a Phase III study would be required.
15	**Insulin degludec/Insulin aspart injection (r-DNA origin)**		The proposal was not recommended and the committee was of the opinion that more data with respect to following should be submitted and presented for the next NDAC meetings:- i)Complete study report explaining the cause of deaths in three Indian patients during the trial. ii)DSMB report on the trial comparing the adverse events in Indian population and other patients enrolled globally should be submitted. iii)PMS protocol should be submitted to DCGI.
16	**r-H**		Experts felt that treatment of Pompe

	alglucosidasealfa (Myozyme)		disease is an unmet need and the firm should be allowed for marketing the drug for two years with the condition to collect the safety and efficacy report on the patients receiving the drug to this office for review for continued marketing of the drug.
17	**r-Hu-Insulin injInsugen R (Regular) and Insugen N (Isophane)**		Committee recommended for giving permission to conduct the study subject to condition that children ≥ 12 years should be enrolled in the study.

4. RECOMMENDATIONS OF THE NDAC (METABOLISM AND ENDOCRINOLOGY) HELD ON 06.10.2012:-

The NDAC (Metabolism and Endocrinology) deliberated the proposals on 06.10.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Benfotiamine + Metformin**		The firm presented one animal study conducted by them in support of their claim for the FDC. The committee recommended that the firm should submit biochemical basis of synergism of benfotiamine and metformin, mechanism of reduction of AGE alongwith the detailed report of the animal study conducted by them and protocol etc. for conducting drug-drug interaction study in humans which should be presented before the committee in the next meeting for further consideration.
2	**Metformin SR + Glimepiride (500mg/3mg, 850mg/1mg, 850mg/2mg, 850mg/3mg,1000mg /3mg)**		Glimepiride 1mg/2mg + Metformin 500mg/500mg SR and Glimepiride 1mg/2mg + Metformin 1000mg/1000mg SR is already available in the country which meets the requirement of majority of the patients. Further permutation/combination of this FDC will add to confusion, prescription error, dispensing error and increased risk of hypoglycemia. Therefore committee did not recommend for approval of the proposed additional strengths of the FDC.
3	**Repaglinide + Metformin**		Committee recommended for giving permission to conduct the study subject to the following conditions: i) In inclusion criteria, fasting plasma glucose should be between 140mg/dl and 180mg/dl. ii) In inclusion criteria, glycosylated

			haemoglobin levels should be between 7% and 9%. iii) Post prandial glucose levels should be monitored in the study. iv) The sites should be multispecialty hospitals/medical colleges having emergency rescue management facilities including 50% Govt medical colleges/hospitals and the study should be conducted by investigators who are experienced in treating diabetes for at least 5 years or qualified endocrinologists. Accordingly the details of sites and investigators should be submitted to DCG(I) for his approval.
4	**Glimepiride + Metformin** **(2mg/1000mg, 4mg/1000mg)**		Glimepiride 1mg/2mg + Metformin 500mg/500mg SR and Glimepiride 1mg/2mg + Metformin 1000mg/1000mg SR is already approved in the country which meets the requirement of majority of the patients. Committee opined that very few patients may need Glimepiride 4mg + Metformin 1000mg. Use of this strength of the FDC is likely to produce more incidence of hypoglycaemia in Indian patients where regular monitoring of glucose level is poor. The committee also opined that immediate release formulation of metformin with glimepiride is not rationale in current scenario. Therefore committee opined that the proposed formulation is not rationale, hence not recommended.
5	**Odanacatib**		In India, out of 987 patients enrolled in the base study, 316 patients were discontinued. There were about 200 SAEs. Committee recommended that the firm should submit detailed report of analysis of the 316 patients who were

			discontinued from the study alongwith the analysis report of all the SAEs and the report of DSMB, which should be placed before the committee for examination.
6	**Ranolazine**		Committee recommended that the PMS/PSUR data received by CDSCO from the companies who are marketing ranolazine as anti-anginal drug in India should be reviewed by the office of DCGI. If satisfied, approval may be given to conduct the proposed global clinical trial subject to condition that age limit of subjects to be included in the study should be 18 to 65 years.
7	**Dulaglutide**		Committee recommended for giving permission to conduct the study subject to the following conditions: i) The sites should be multispecialty hospitals/medical colleges having emergency rescue management facilities including 50% Govt medical colleges/hospitals and the study should be conducted by investigators who are experienced in treating diabetes for at least 5 years or qualified endocrinologists. ii) Age limit of subjects to be included in the study should be 18 to 65 years.
8	**Dulaglutide**		Committee recommended for giving permission to conduct the study subject to the following conditions: i) The sites should be multispecialty hospitals/medical colleges having emergency rescue management facilities including 50% Govt medical colleges/hospitals and the study should be conducted by investigators who are

			experienced in treating diabetes for at least 5 years or qualified endocrinologists. ii) Age limit of subjects to be included in the study should be 18 to 65 years.
9	**Wosulin 70/30 & 100 units/ml**		Committee recommended for giving permission to conduct the proposed study.
10	**Insulin Lispro injection and Insulin Lispro mix (70/30, 75/25, 50/50 formulations)**		Committee opined that the clinical data generated by the firm is not adequate for approval of the product. The committee recommended that a comparative clinical trial with the innovator's product in a well designed protocol should be conducted. Protocol etc. should be submitted to the committee for examination.

5. RECOMMENDATIONS OF THE NDAC (METABOLISM & ENDOCRINOLOGY) HELD ON 23.03.2013:-

The NDAC (Metabolism & Endocrinology) deliberated the proposals on 23.03.2013 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
Special Agenda			
1 to 5	**1. Aldurazyme (Laronidase) 2.9 mg** **2. Cerezyme (Imiglucerase) Injection 200 Units & 400 Units vial (A macrophage targeted β-glucocerebrosidase enzyme)** **3. Febrezyme (Agalsidae beta) 5mg/ml agalsidase beta** **4. FDC of pregabalin, methylcobalamin, alpha lipoic acid, pyridoxine and folic acid*** **5. Cinacalet**		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:- • Aldurazyme (Laronidase) 2.9 mg • Cerezyme (Imiglucerase) Injection 200 Units & 400 Units vial (A macrophage targeted β-glucocerebrosidase enzyme) • Febrezyme (Agalsidae beta) 5mg/ml agalsidase beta • FDC of pregabalin, methylcobalamin, alpha lipoic acid, pyridoxine and folic acid* • Cinacalet

			The NDAC (Metabolism & Endocrinology) 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 5 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."
6	**Pasireotide Solution for Injection**		The committee opined that Cushing's disease is

			a very rare disease and life threatening disease for which there is no medical therapy. The committee recommended for approval of the drug without local clinical trial subject to condition that Phase IV clinical trial on atleast 50 patients with one year duration of treatment should be conducted. After getting protocol etc. approved from DCG(I). The marketing permission should be reviewed after one year.
7	**Lixisenatide**		The drug Lixisenatide is approved in Europe and the drug has been launched for marketing in UK and Germany. Based on the safety and efficacy data including clinical data on 177 Indian patients from 3 global clinical trials. The committee recommended for approval of the drug subject to the condition that the Phase 4 clinical trial should be conducted on 500 patients after getting protocol tec. Approved form DCG(I). the study should be completed within a period of 2 years.
8	**Extended Injection 2mg/Vial**		The Extended Injection 2mg/Vial once weekly is approved by EMA. Based on the safety and efficacy data including the clinical data on 180 Indian patients enrolled in global clinical trial and considering the patients convenience of once weekly dose in instead of b.i.d. dose the committee recommended for approval of the drug.
9	**Metformin Hydrochloride + Linagliptin**		This F.D.C is already approved by USFDA. Based on safety and efficacy data including clinical data on 329 Indian subjects on free combination of metformin and linagliptin, the committee recommended for approval of the F.D.C. for marketing in the country.
10	**Alpha Lipoic Acid + Mecobalamin**		The committee recommended for comparative clinical trial with the FDC vs Mecobalamin alone. The sites should be medical college, multi-specialty hospitals with emergency facilities and institutional ethics committee. 50% should be government hospitals. Accordingly the study protocol etc. should be submitted to DCG(I) before giving the approval for the study.
11	**Alpha Lipoic Acid + Mecobalamin**		
12	**Glimepride + Metformin HCl +**		Committee opined that some patients with

	Voglibose		advanced duration of disease may be benefitted with sub-maximal dose of Glimepride 1mg + Metformin 500 mg + Voglibose 0.20 mg instead of step-up higher dose of two drugs of Glimepride + Metformin in which there may be higher side effects. Committee recommended for a comparative clinical trial of the FDC of above strength vs. step-up higher dose of Glimepride + Metformin. Protocol etc. should be submitted for examination by the committee. The sites should be medical college, multi-specialty hospitals with emergency facilities and institutional ethics committee. 50% should be government hospitals. Accordingly the study protocol etc. should be submitted to DCG(I) before giving the approval for the study.
13	**LAF237**		Committee recommended for giving permission to conduct the clinical trial subject to condition that upper age limit of subject should be 65 years. However the sites should be medical college, multi-specialty hospitals with emergency facilities and institutional ethics committee. 50% should be government hospitals. Accordingly the details of sites, investigator undertakings along with revised ICD and undertakings as per new rules on compensation should be submitted to DCG(I) before giving the approval for the study.
14	**Lixisenatide**		Committee recommended for giving permission to conduct the proposed global clinical trial subject to condition that upper age limit of the subject should be 65 years.. However, the trial should be conducted in medical college, multi-specialty hospitals with emergency facilities and institutional ethics committee. 50% should be government hospitals. Accordingly the details of sites, investigator undertakings along with revised ICD and undertakings as per new rules on compensation should be submitted to DCG(I) before giving the approval for the study.
15	**BI10773**		Committee recommended for approval for protocol amendment for extension study subject to condition that the extension study should be

	(Protocol Amendement)		carried out only in those sites which are multi-specialty hospital/institutions having emergency facilities and institutional ethics committee.
16	**liraglutide in combination with Metformin**		Committee recommended for giving permission to conduct the clinical trial. However the sites should be medical college, multi-specialty hospitals with emergency facilities and institutional ethics committee. 50% should be government hospitals. Accordingly the details of sites, investigator undertakings along with revised ICD and undertakings as per new rules on compensation should be submitted to DCG(I) before giving approval of the study. Dr. Anil Bhansali did not take part in deliberation & decision making process for this proposal.
17	**Dulaglutide**		The proposal has been withdrawn by the firm.
18	**SBC-102**		Committee recommended for the permission to conduct the clinical trial. The company agreed to provide this therapy free of cost to the subjects lifelong. And undertaking to this effect should be submitted by the firm to DCG(I).
19	**Insulin degludec/insulin as part BID and insulin degludec OD plus insulin aspart**		The proposal has been withdrawn by the firm.
20	**Semaglutide**		Committee recommended for giving permission to conduct the clinical trial subject to condition that upper age limit of subject should be 65 years. However the sites should be medical college, multi-specialty hospitals with emergency facilities and institutional ethics committee. 50% should be government hospitals. Accordingly the details of sites, investigator undertakings along with revised ICD and undertakings as per new rules on compensation should be submitted to DCG(I) before giving approval of the study. Dr. P.V. Rao and Dr. Anil Bhansali did not take part in deliberation & decision making process for this proposal.
21	**Somatropin**		Committee recommended giving approval of the product.

22	**(Re-examination)**		Committee recommended that the detailed clinical trial data, including the cause of death of patients during clinical trial and the copy of letter issued by USFDA asking the firm to conduct cardiovascular outcome study, should be forwarded to all the members of the committee for their detailed review and recommendation.
23	**(Re-examination)**		Committee recommended that the detailed clinical trial data, including the cause of death of patients during clinical trial and the copy of letter issued by USFDA asking the firm to conduct cardiovascular outcome study, should be forwarded to all the members of the committee for their detailed review and recommendation.
24	**(Re-examination)**		Committee recommended for giving permission to conduct clinical trial subject to the condition that sites should be medical college, multi-specialty hospitals with emergency facilities and institutional ethics committee. 50% should be government hospitals. Accordingly the details of sites, investigator undertakings along with revised ICD and undertakings as per new rules on compensation should be submitted to DCG(I) before giving approval of the study.

6. RECOMMENDATIONS OF THE NDAC (METABOLISM & ENDOCRINOLOGY) HELD ON 17.07.2013:-

The NDAC (Metabolism and Endocrinology) deliberated the proposals on 17.07.2013 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Teneligliptin 20 mg film coated tablet**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) Serum calcitonin levels and pancreatitis should be monitored during the study. ii) HbA1c levels should be between 7 to 8.5%. iii) Qualification of investigator should be at least MD. iv) 50% of the trial sites should be Govt hospitals/medical colleges. v) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. vi) The trial sites should have Institutional Ethics Committees registered with the office of DCGI. Committee also recommended that the firm should conduct a Bioequivalence study with their product compared to the Innovator's product approved in Japan.
2	**Metformin SR Tablet 500/1000mg**		The firm did not turn up for presentation, therefore the committee deferred the proposal.
3	**Metformin Hcl+Vildaglptin**		The FDC is already approved in India. The firm also provided clinical trial data conducted in India as a part of global clinical trial for the proposed additional indication. Committee recommended that the FDC may be approved as initial therapy in patients with Type 2 Diabetes mellitus having HbA1c > 8% where diabetes is not adequately controlled by diet and exercise alone.
4	**Empagliflozin& Metformin**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) In inclusion criteria, HbA1c levels should be between 7% to 9%.

			ii) BMI should be defined for lower level i.e. 23 to 45 kg/m^2. iii) 50% of the trial sites should be Govt hospitals/medical colleges. iv) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. v) The trial sites should have Institutional Ethics Committees registered with the office of DCGI.
5	**Empagliflozin & Linagliptin**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) In inclusion criteria, HbA1c levels should be between 7% to 9%. ii) BMI should be defined for lower level i.e. 23 to 45 kg/m^2. iii) 50% of the trial sites should be Govt hospitals/medical colleges. iv) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. v) The trial sites should have Institutional Ethics Committees registered with the office of DCGI.
6	**Saxagliptin & Dapagliflozin + Metformin**		The proposal has been withdrawn by the firm.
7	**MK-3102**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) In inclusion criteria, HbA1c levels should be between 7.5% to 9%. ii) BMI should be defined for lower level i.e. 23 to 45 kg/m^2. iii) 50% of the trial sites should be Govt hospitals/medical colleges. iv) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. v) The trial sites should have Institutional Ethics Committees registered with the office of DCGI. vi) Serum calcitonin levels should be monitored during the study.

			However before grant of formal approval by DCGI, data with regards to serum calcitonin rise after treating with long acting DPP4 inhibition should be submitted.
8	**Empagliflozin & Linagliptin**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) In inclusion criteria, HbA1c levels should be between 7% to 9%. ii) BMI should be defined for lower level i.e. 23 to 45 kg/m^2. iii) 50% of the trial sites should be Govt hospitals/medical colleges. iv) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. v) The trial sites should have Institutional Ethics Committees registered with the office of DCGI.
9	**MK-3102**		The proposal has been withdrawn by the firm.
10	**MK-3102**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) In inclusion criteria, HbA1c levels should be between 7.5% to 9%. ii) BMI should be defined for lower level i.e. 23 to 45 kg/m^2. iii) 50% of the trial sites should be Govt hospitals/medical colleges. iv) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. v) The trial sites should have Institutional Ethics Committees registered with the office of DCGI. vi) Serum calcitonin levels should be monitored during the study. However before grant of formal approval by DCGI, data with regards to serum calcitonin rise after treating with long acting DPP4 inhibition should be submitted.
11	**MK-0431D**		The rationale of this fixed dose combination is weak, therefore the proposal is not recommended by the committee.
12	**Anacetrapib**		Committee 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 65 years. ii) 50% of the trial sites should be Govt hospitals/medical colleges. iii) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. iv) The trial sites should have Institutional Ethics Committees registered with the office of DCGI.
13	**Dapagliflozin added to Saxagliptin**		Committee 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 65 years. ii) BMI should be defined for lower level i.e. 23 to 45 kg/m^2. iii) 50% of the trial sites should be Govt hospitals/medical colleges. iv) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. v) The trial sites should have Institutional Ethics Committees registered with the office of DCGI.
14	**MK-3102**		Committee recommended for giving permission to conduct the study subject to the following conditions:- i) In inclusion criteria, HbA1c levels should be between 7.5% to 9%. ii) BMI should be defined for lower level i.e. 23 to 45 kg/m^2. iii) 50% of the trial sites should be Govt hospitals/medical colleges. iv) The trial sites should have 24 hour emergency rescue facilities along with cardiac care facilities. v) The trial sites should have Institutional Ethics Committees registered with the office of DCGI. vi) Serum calcitonin levels should be monitored during the study.

			However before grant of formal approval by DCGI, data with regards to serum calcitonin rise after treating with long acting DPP4 inhibition should be submitted.
15	**Somatropin**		Committee recommended that the firm should submit the following information :- i) Advantages of their lyophilized formulation over the currently used solution for injection. ii) The time of administration of Eutropin (IMP) in the clinical trial should be mentioned. iii) Clarification regarding baseline Hb values of the patients included the clinical trial as anemia cannot be reported as adverse event. iv) Current regulatory status with regards to EU. v) Justification of use of lecithin and sodium hyaluronate as excipients from biosafety point of view. vi) Since high dose (24mg) is used in weekly preparation, therefore long term safety data is required to be generated. The above data submitted should be placed before the committee for further consideration in the next meeting.
16	**Levemir**		The firm did not turn up for presentation, therefore the committee deferred the proposal.
17	**Insulin degludec / Insulin Aspart**		The firm did not turn up for presentation, therefore the committee deferred the proposal.
18	**Somatropin**		The committee recommended that the firm should submit PMS data generated with the product worldwide and to be placed before this NDAC in it's next meeting for further consideration.
19	**Insulin degludec**		The firm did not turn up for presentation, therefore the committee deferred the proposal.

7. RECOMMENDATIONS OF THE NDAC (METABOLISM & ENDOCRINOLOGY) HELD ON 25.09.2013:-

The NDAC (Metabolism & Endocrinology) deliberated the proposals on 25.09.2013 and recommended the following:-

AGENDA NO.	DRUG NAME		RECOMMENDATIONS
1	**Alogliptin tablets 6.25/12.5/25mg-**		The firm presented global clinical trial data including the clinical trial data generated on 921 Indian subjects in phase-III trial. The committee noted that efficacy & safety data of Indian population is comparable with global data and the drug has already been approved in key countries such as USA, Japan. After detailed deliberation the committee recommended for the approval of the drug Alogliptin tablets 6.25/12.5/25mg subject to the co ndition that Post Marketing (Phase-IV) trial be conducted. Accordingly, protocol etc. should be submitted to the office of DCGI within 1 month of approval of the drug for further review by the committee.
2	**Hydroxychloroquine Sulphate Tablet (Addl. Indication)**		The proposal was deferred.
3	**Metformin HCl 750mg ER Tablet (Addl. Dosage Form)**		Firm has withdrawn the proposal
4	**Glimepiride+Metformin HCl ER+Voglibose tablets 1mg/2mg/1mg/2mg+500mg/ 500mg/500mg/500mg+0.2m g/0.2mg/0.3mg/0.3mg**		The committee recommended for conducting a superiority trial.i.e., superiority of proposed FDC over Glimepiride+Metformin HCl ER with a study duration of 6 months.. Accordingly, revised protocol should be submitted for further examination by the Committee.
5	**Alpha Lipoic**		Earlier the proposal was deliberated by NDAC (Metabolism & Endocrinology) committee in its meeting held on

	Acid+Mecobalamin jard gelatine capsule 300mg+1500mcg		23.03.2013wherein the committee opined that comparative clinical trial with the FDC vs. Mecobalamin alone should be carried out. The sites should be medical college, multi-specialty hospitals with emergency facilities and institutional ethics committee, 50% should be government hospitals. the firm represented that the FDC is already approved in soft gelatin capsule form and they want to manufacture the same FDC in hard gelatin dosage form with same active ingredients and in same strength. Firm requested for waiver of CT. Firm deliberated the proposal in detail along with bioequivalence study protocol. The committee opined that clinical trial is not required as there is only change in pharmaceutical dosage form. The committee recommended for conducting the proposed Bio-equivalence study with higher strength on 28 subjects after getting the approval from DCG(I) before considering for Manufacturing and marketing in the country. Accordingly, the firm should submit the proposed BE study protocol to the DCG(I) office for further approval.
6	**Alpha Lipoic Acid+Mecobalamin jard gelatine capsule 100mg+500mcg**		Same as above
7	**HM10560A**		The committee opined that as the phase 1 single dose escalation data from 0.5-4 IU/kg showed unusual pharmacokinetic data which is difficult to explain the Cmax and AUC for 0.2 and 4 IU/kg which may have significant clinical implication particularly when multiple doses would be administered more ever phase I study with single dose administration, the phase I data not sufficient so not recommended.
8	**Inslin Lispro Mix25**		The committee recommended for conducting phase IV clinical trial

	InsulinMix50		
9	**Myozyme**		The committee recommended for conducting clinical trial.
10	**Semaglutide**		The committee recommended for conducting clinical trial. (Dr. P V Rao did not participate in the delibration.)
11	**FIASP (Faster Acting Insulin Aspart)**		The committee recommended for conducting clinical trial. (Dr. P V Rao did not participate in the delibration.)
12	**FIASP (Faster Acting Insulin Aspart)**		The committee recommended for conducting clinical trial. (Dr. P V Rao did not participate in the delibration.)
13	**Linagliptin**		Based on the safety data emerging from the 104 week study the committee recommended for continuation of the trial.
14	**Levemir (Insulin determir) (Application for approval of the updates to Levemir (Insulin determir) prescribing information)**		The committee recommended for the marketing authorisation for Levamir in children aged 2-5 years, levamir in pregnancy as add on to Victoza subject to the condition that the firm submits the PSURs which will be reviewed by the NDAC experts.
15	**Oral Recosulin (Manufacture and market)**		Firm didn't turn up for meeting. Deferred for next meeting
16	**Insulin degludec/Insulin Aspart (Import & Marketing Permission)**		The committee opined that the firm was granted Ma for insulin degludec with a condition that they should carry out a PMS study in addition to the PSUR's. Before considering marketing authorisation for the combination with Insulin degludec/Insulin As part the PMS protocol to capture cardiovascular outcomes needs to be submitted by the firm for further consideration.

17	**Biochaperone PDGF-BB (Application for permission to conduct Phase III to assess the effectiveness of Biochaperone PDGF-BB in treatment of Chronic Diabetic Foot Ulcer)**		The O/o DCG(I) sought certain Query regarding the Indian agent handled the proposed clinical trial however firm had not replied the raised query. Committee opined that firm should first reply the query raised by the office of DCGI.
18	**Insuman (Human insulin)**		The committee recommended for approval for manufacturing and marketing of Insuman (Human insulin) to the firm being the drug is old and already .approved drug.The source of bulk drug is the same. (only difference being change in facilities for processing bulk drugs for further processing.) however the manufacturing premises should be inspected for regulatory compliance. Post Marketing (Phase-IV) trial be conducted. Accordingly, protocol etc. should be submitted to the office of DCGI within 1 month of approval of the drug for further review by the committee. Marketing authorization shall be granted only after scrutiny of other data such as CMC/administrative information etc.
19	**Oral Insulin**		The firm has presented the drug-drug interaction however the committee opined that the firm the phase IIa data and placebo control data along with long term toxicity data shall be submitted to the committee for further evaluation and proposal is deferred to next meetting

8. RECOMMENDATIONS OF THE NDAC (METABOLISM & ENDOCRINOLOGY) HELD ON 21.11.2013:-

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

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

The NDAC (Metabolism & Endocrinology) deliberated the proposals on 21.11.2013 and recommended the following:-

AGENDA NO.	DRUG NAME		RECOMMENDATIONS
1.	**Canagliflozin 10mg/30mg tablet**		Canagliflozin belongs to a new class of orally-active inhibitor of sodium –glucose co-transporter2(SGLT2) The drug has been approved for marketing in USA on 29 March 2013. The firm presented various data of safety and efficacy including results of global clinical trials with India as participating country in which more than 1100 Indian patients were involved. After detailed deliberations the committee recommended that the firm should submit details of SAEs of Hypoglycemia, Urosepsis, bladder cancer, if any, reported in the clinical trial along with renal histology data and causality analysis with medical history of the Indian subjects who died during clinical trial for review. The firm should also submit the copy of COPP/FSC form countries from where the drug is proposed to be imported or from any other key country.
2.	**Phentermine Hydrochloride**		Earlier the proposal was examined by the committee in its meeting held on 22.08.2013 and the committee recommended that the protocol should be revised as under:- 1. Study sites should be distributed geographically across the country and at least 50% of the patients should be enrolled in the Government Hospitals. 2. Sample size should be appropriate. 3. Upper limit of BMI should be reduced to 40 kg/m^2 in the protocol. 4. 12 weeks treatment duration should be followed up by another 12 weeks follow up.

			Accordingly the firm submitted the revised CT protocol before the committee. After detailed deliberation the committee recommended for the conduct of the proposed study as per revised protocol and to monitor the quality of life during the study period.
3.	**Linagliptin Tablets 5 mg**		This Directorate has approved Linagliptin 5mg Tablets **Indication:** As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Important limitations of Use: 1. Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis 2. Has not been studied in combination with insulin The firm applied for deletion of limitation of use “has not been studied in combination with insulin.” The firm has presented Clinical supporting trial data of Linagliptin Tablet in combination of Insulin as per protocol no 1218.36 and 1218.43 conducted globally and committee opined grant permission for removal of limitation “has not been studied in combination with insulin.”
4.	**Oral Recosulin**		The firm presented their Phase III clinical trial report with Oral Recosulin (Metered Dose Buccal Spray Insulin). The committee opined that clarifications on following points is sought for review in the next NDAC: • Data on blood glucose levels of the experimental dogs. • Data on Salivary changes of Insulin. • Proof of concept studies details conducted on healthy Human volunteers with justification. • Copy of approval from NRA, Israel for conduct of proof of concept studies. • Difficult to comprehend C-peptide studies graph. Therefore, raw data for the same is to be submitted. • Clinical study data generated by M/s Generex, Canada, internationally with

			greater details or any other internationally published studies. • PMS data generated after seeking marketing authorization in Ecuador. The above data is required to be submitted to the committee for further review
5.	**Oral Insulin (IN-105)**		Earlier, the subject proposal of the firm was discussed in the NDAC meeting held on 25/09/2013 wherein the committee opined that Phase IIa data and placebo control data along with long term toxicity data has to be submitted for further evaluation. Firm has now provided and presented desired data. The committee opined that the safety and efficacy of IN-105 has not been conclusively proved through the data submitted by the firm from the study to use Oral Insulin to enhance the absorption of Metformin is not justified and not practicable. In view of above, the committee rejected the proposal.
6.	**Somatropin**		The subject proposal of the firm was deliberated. The committee opined that as the product is already marketed internationally for many years. However, the firm should first submit the Phase IV clinical trial protocol before granting MA to the firm.
7.	**Biochaperone PDGF-BB**		The firm deliberated their Phase III clinical trial proposal. The committee recommended for conducting Phase III study. However, 50% of the investigator sites should be government hospital and all sites should have emergency facilities.
8.	**Eutropin plus 4IU**		Earlier, the subject proposal of the firm was discussed in the NDAC meeting held on 17/07/2013 wherein certain queries were raised by the committee. Firm has submitted the clarifications on the queries raised. Firm informed that Recombinant Somatropin is approved by Korea. The committee reviewed and discussed the response submitted by the firm. and opined that the firm be granted permission to import and market Eutropin Plus

			24 mg injection with the following conditions: • Phase IV clinical trial should be conducted with the subject product. • Patients should be followed-up for life-long for occurrence of tumor (if any) during the treatment and database for the same is to be maintained by the firm.
9.	**Glucagon (synthetic origin) injection 1 mg (1 mg/vial)**		The firm proposed to conduct a BE study of synthetic origin glucagon for US registration. The committee has gone through the protocol. The committee opined that the approval for BA BE study may be considered. However, the opinion of pharmacologists may be obtained through e-mail before granting the approval of proposed BE study.
10.	**Glimepride + Metformin HCL 0.5mg+500 mg tablets**		FDC of Glimepride + Metformin HCL tablets is already approved in various strengths and also approved in international market. Firm has proposed with the lower strength of Glimepride. The committee opined that there is no safety issues with respect to the proposed strength and this lower dose will provide flexibility in dose titration. The committee recommended for the approval of the proposed strength of the FDC.
11.	**PF04634817**		The proposed trial is in **Diabetic nephropathy** patients having **albuminurea of >8.5 g /Day** with the dose of **200 mg OID for 12 weeks**. The applicant submitted the Pre-clinical and phase-I clinical data in support of the proposed phase II study. The committee reviewed and deliberated the matter and recommended that the trial permission can be accorded, subject to the condition that 50% centres will be at Govt. Medical colleges/ Hospitals and institutions like AIIMs. SGPGI, PGI (Chandigarh). All the trial sites should have multi-specialty and emergency facilities. However the Renal histological data in animal studies has to be submitted for further review, prior to the grant of clinical trial permission.
12.	**LIK066**		The proposed phase II trial with the drug LIK066 is to evaluate the change in HbA1c after 12 wks monotherapy with various doses in TypeII diabetes.

			In support of the proposed trial the applicant has submitted the preclinical and clinical data. Out of a total of 750 subjects to be recruited globally 120 subjects are proposed from India. The committee after detailed review of the data and presentation made opined that the proposed clinical trial permission can be granted subject to the following conditions: That 50% centres will be at Govt. Medical colleges/ Hospitals and institutions like AIIMs. SGPGI, PGI (Chandigarh). All thetrial sites should have multi-specialty facilities with emergency services. The proposed PI Dr. Rakesh Sahay is associated with Osmania medical college , therefore his trial site at Mediciti (Hyd.)will not be accepted. Dr. mohan's association with Madras Diab. Res. Foundation is also not acceptable as it has no emergency / critical care facilities. Dr. Anil Bhansali did not participate in the decision making process.
13.	**Dapagliflozin Tablet 5mg/ 10mg**		Dapagliflozin belongs to a new class of orally-active inhibitor of sodium –glucose co-transporter 2 (SGLT2). The drug is recently approved for marketing by EMA. However, the application to market the drug in USA was rejected by the US-FDA in January 2012 due to safety issues associated with the use of the drug as reported in clinical trials. Earlier in Dec. 2011 due to increased risk of bladder, breast cancer and Urosepsis, associated with the use of Dapagliflozin the proposal of the firm for a Phase-III clinical trial for registration of the drug in the country was not considered for approval. The firm presented various safety and efficacy data including pharmacological and toxicological data and results of global clinical trials, in which India was a participating country and more than 400 Indian patients were involved. The committee observed from the data presented that there is lack of cause of and effect relationship between the Dapagliflozine and bladder cancer. After detailed deliberation the committee

			recommended that a clinical trial with Dapagliflozin with one year duration of treatment in adequate number of subjects is required to be conducted in the country to address the issue of Urosepsis, bladder cancer etc. Accordingly CT protocol etc. is required to be submitted before the committee for further review.

9. RECOMMENDATIONS OF THE NDAC (METABOLISM & ENDOCRINOLOGY) HELD ON 17.12.2013:-

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

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

The NDAC (Metabolism & Endocrinology) deliberated the proposals on 17.12.2013 and recommended the following:-

AGENDA NO.	DRUG NAME		RECOMMENDATIONS
1.	**MK-0431**		This is a phase IV study with Sitagliptin (MK0431) (100mg) once daily Vs. Vildagliptin (50mg) b.i.d. proposed by M/s MSD Pharmaceuticals. It was reported that 2 Phase-I studies, 7 Phase-2 studies, 28 Phase-3 studies have been completed with MK0431. More than 9900 patients have been exposed Sitagliptin in clinical research studies conducted worldwide. 636 subjects planned to enroll from India. The study is planned to be conducted only in India. The firm has proposed 4-weeks duration study However, the NDAC has opined that 4-weeks study with FPG as end point will not give any meaningful results. A 12-16 weeks study with HbA1c as an end-pont may be a better option.
2.	**Liraglutide**		The firm has applied for the grant of permission to conduct a **phase IV** clinical trial with Liraglutide which is approved for marketing in India. Globally 396 subjects and 90 subjects from India are planned to be enrolled. About 52 clinical trials have been completed, and the safety database includes more than 11,000 subjects, of whom more than 7500 were treated with liraglutide have been completed have been completed. The drug is approved in more than 60 countries. Switching from Sitagliptin to Liraglutide showed better glycemic control. This is a Liraglutide switch trial with the background therapy of 3-months Sitagliptin (100mg) + Metformine (may go upto upper limit of 1500 mg). Trial duration will be 26

			weeks. The NDAC has recommended for the proposed trial subject to inclusion of DSMB and the condition that those who have less than 18.5 kg /m^2 BMI will be excluded. Dr. P.V. Rao of NIIMS (Hyderabad) is one of the trial PIs in this trial and therefore he did not participate in the deliberation and decision making process.
3.	**Semagluitde**		This is Phase III-a trial with Semaglutide a potent, long acting GLP-1 analogue (Recombinant technology derived prepared as injection for subcutaneous use for the treatment of type 2 diabetes. As of 6 April 2013, 5 clinical pharmacology trials and 1 phase 2 trial have been performed with semaglutide. 2 trials are ongoing; one with phase 1 bioequivalence and a phase 3 confirmatory clinical trial to assess cardiovascular risk and long term safety. Globally 1200 subjects from 18 countries and India 250 subjects are planned to be enrolled in the study. The NDAC has recommended for the proposed trial subject to inclusion of DSMB. This is also subject to condition that those who have less than 18.5 kg /m^2 BMI will be excluded.
4.	**Dapagliflozin**		The firm has proposed for approval of a phase IIIb clinical trial with Dapagliflozin (10mg once daily) to evaluate its cardiovascular safety amongst Diabetes Mellitus patients (NIDDM). As of 15 July 2011 treatment with Dapagliflozin has been investigated worldwide in subjects with T2DM in 19 phase 2b and 3 studies (5 phase 2b and 14 phase 3 studies). Dapagliflozin is approved to market in EU, Australia, Mexico, New Zealand and Brazil. In India 200 patients will be enrolled in 15 centers. The NDAC has recommended for approval of a phase IIIb clinical trial with Dapagliflozin with the condition that that all PIs should be Specialist of Internal medicine, Diabetologist or endocrinologists instead of Cardiologist and upper age limit should be 65 years. The firm will give the details of the status of their DSMB .

5.	**Insulin Glargine (rDNA origin) 100IU /ml. for Protocol amendment Vesrsion 7**		The firm has applied for the grant of permission of Protocol Version 7.0 dated 13 Feb 2013 in phase III clinical trial for Insulin analogue Glargine (Glaritus®). The Test drug Insulin Glargine, an Insulin Analogue is manufactured by M/s Wockhardt Ltd by recombinant technology. This Insulin analogue has prolonged duration of action that permits once daily dosing. Globally 520 patients and from India 260 subjects (11 sites) are planned to be enrolled. Reference Product is already approved and marketed in India. This study is proposed to be conducted to generate data on the indigenously manufactured Insulin glargin Inj. for regulatory registration in USA. The Committee has recommended for the said study with the current version (7) of Protocol amendment.
6.	**Pasireotide LAR**		This is for phase III clinical trial with pasireotide LAR. Pasireotidedi asparate (SOM 230), which has been extensively investigated in the clinical trial development program for healthy volunteers (15 studies) and various patient population (14 studies). The proposed trial will include patients of Cushng's disease and planned to be conducted in 18 countries by enrolling 148 patients (Globally) and 24 patients at 4 sites from India. The committee has recommended for this study. (Dr. A.C. Ammini has not participated in deliberation and decision making process).
7.	**MOD-4023**		**Firm has withdrawn protocol**
8.	**Somatropin Subcutaneous Inj.**		The Drug Somatropin manufactured by M/s USV Ltd is a biosimilar to Eutropin. The Committee recommended that SOMATROPIN SC. Inj. should be strictly on the prescription of Specialists in Pediatrics, Endocrinology and internal Medicines only
9.	**Insulin degludec Inj.**		The committee recommended for giving

			permission for conducting the PMS study vide Protocol No. NN1250-4129 version 1.0 dated 29/07/2013 (as per the condition stated on Marketing authorization for Insulin Degludec). However, the firm shall make a separate application for their proposal of conducting cardiovascular outcomes study in connection with their earlier discussed proposal of Insulin Aspart & Insulin Degludec combination.

10. RECOMMENDATIONS OF THE NDAC (METABOLISM & ENDOCRINOLOGY) HELD ON 31.01.2014:-

The 10th meeting NDAC (Metabolism & Endocrinology) deliberated the following proposals on 31.01.2014 and recommended the following:-

AGENDA NO.	DRUG NAME		RECOMMENDATIONS
1.	**Gemigliptin Tablets 50mg**		The firm presented detailed phase –III clinical trial data in respect of safety and efficacy data generated in 237 Indian subjects as part of two global clinical trials i.e study LG-DPCL005 and LGDPCL006. The drug is approved only in Korea in June, 2012 and is marketed since December-2012. The committee noted that the there is no need for conduct of another clinical trial in Indian subjects. The efficacy data in Indian subjects is encouraging. However, there is no long term safety data and the available safety data is not adequate for approval of the drug. The Committee recommended that the firm should present *REMS (Risk Evaluation and Mitigation Strategy)* plan and pharma-economics analysis for further review by the committee.
2.	**Vitamin K2**		The proposal was for permission to import bulk API of Vitamin-K2, an analogue of Vitamin-K and the same is not approved in India. This matter is out of the purview of this NDAC. Hence no comments
3.	**Cinacalcet**		Firm did not turned up
4.	**Pragabalin + Methylcobalamin + Alpha lipoic Acid + Pyrodoxine HCl + Folic Acid (PSC)**		The committee noted that FDC is approved by DCG(I). However as recommended by PSC in its 59th report, the FDC was examined by the committee. The firm presented pharmacological aspects of each ingredient in the proposed FDC. Alpha lipoic acid has potential anti-oxidant effect as shown in animal studies but not so encouraging in human studies. All the

			ingredients present in the FDC are put in sub-optimal doses and are lacking in scientific rationality. Pregabalin and Methylcobalamin are mostly used for Diabetic Neuropathy. In view of these the NDAC opined that this combination would not be rational in treatment of Diabetic neuropathy in present scenario.
5.	**Combipack of Sitagliptin Phosphate + Metformin HCl**		The firm presented the data before the committee. The committee noted that FDC of metformin 500 mg/ 850mg/1000mg + Sitagliptin 50mg/50mg/50mg tablet is already approved in the country. The proposed formulation is a combipack of Sitagliptin 100 mg and metformin 1000mg sustained release which is approved in US, Canada and Australia in FDC form. The committee recommended the proposed combi-pack.
6.	**Glimepiride 1mg/2mg/1mg/2 mg/1mg + Voglibose 0.2mg/0.2mg/0.3 mg/0.3mg + Metformin hydrochloride ER 500mg /500mg / 500mg /500mg tablet**		The firm presented the detailed protocol before the committee. The committee recommended for conducting Phase III trial subject to the verification of sample size by an independent Bio- statistician (AIIMS/ICMR) and certificate in this regard shall be submitted to DCG(I)..
7.	**Teneligliptin + Metformin HCl**		The firm presented data and reports on the new DPP-4, Teneligliptin. It is metabolized by Kidney and liver. The firm proposes to conduct 16-weeks duration double blind, comparative study on 238 Type-II DM subjects to evaluate the superiority of combination over Metformine. The proposed combination is not approved anywhere in the world. The drug Teneligliptin is approved and marketed only in Japan by M/s Tanabi pharma in the year 2012. Firm stated that clinical trial is ongoing with the drug

			Teneligliptin in the country. The NDAC recommended to submit published safety & efficacy data on Teneligliptin clinical trial. The duration of trial should be of at least 24 –weeks. Committee opined that the sample size of 238 is too small. The sample should be sufficiently calculated on the basis of comparative data on two drugs and HbA1c level of 0.5%.
8.	**MK-0431AXR**		The firm has applied for the grant of permission to conduct a phase III clinical trial with MK-0431A XR (a fixed dose combination of Sitagliptin (50 mg) and Extended release Metformin-500mg /1000mg) in Pediatric subjects with Type 2 Diabetes Mellitus. Globally 240 subjects and 20 subjects from India are planned to be enrolled. The study is planned to be conducted in 15 countries which include Colombia, Russia, Canada, USA and India. The phase III A will consist of 20 weeks out of the total 54 weeks study duration. The firm has presented their proposal before the NDAC expert and the committee has recommends for conduct of the trial with inclusion of 50 % Govt. sites. The children's Obesity criteria should be included with ranges of BMI. Glutamic Acid de-carboxylase (GAD) antibody should be negative. C-Peptide should be more that 0.6 ng /ml and Type-I Diabetes Mellitus should be excluded. **Note :** - Dr. PV. Rao being one of the investigators in this study, being the PI in this trial, did not participate in the decision making.
9.	**Pasireotide**		The firm has applied to this Directorate for the grant of permission to conduct a phase II clinical trial with Pasireotide s.c alone or in combination with cabergoline in patients with **Cushing's disease.** Globally 128 subjects and 20 subjects from India are planned to be enrolled. **Pasireotide** is approved in US

			FDA, EMEA and Swiss Medic but not in India. The study is planned to be conducted in 17 countries which include Colombia, Germany, France, UK, United States and India. Insufficient therapeutic effects and hyperglycemia in 70% of the patients found in 6 and 12 months treatment. The firm has presented their proposal before the NDAC expert and the committee has recommended for the proposed clinical trial.
10.	**Liraglutide**		The firm has applied for the grant of permission to conduct a phase IV clinical trial with liraglutide versus sulphonylurea both in combination with metformin during Ramadan in subjects with type 2 diabetes. Globally 320 subjects and 80 subjects from India. The proposed study is planned to be conducted in Algeria, India, Israel, Lebanon, Malaysia, South Africa & UAE. (7countries). Liraglutide is approved in India. The firm has presented their proposal before the NDAC expert and the committee has recommended for proposed clinical trial.
11.	**Degludec Inj.**		The firm has applied to this Directorate for the grant of permission to conduct a phase IIIb clinical trial with insulin Degludec versus insulin Glargine in subjects with type 2 diabetes at high risk of cardiovascular events. The **primary objective** is to confirm the **cardiovascular safety** of insulin degludec compared to that of insulin glargine. Globally 7500 subjects and 500 subjects from India to be enrolled. The proposed study is planned to be conducted in 21 countries including Canada, India, Italy, Japan, Malaysia, Russia, United Kingdom & USA. In India, Insulin Degludec Inj. was approved in India on 05-07-2013.

			The firm has presented their proposal before the NDAC expert and the committee has recommended for conduct of the proposed trial. **Note :** Dr. Shubhanker Choudhury of IPGMER Kolkata, being the PI in this trial , did not participate in the decision making.
12.	**Somatropin Inj.**		This is recombinant technology derived growth hormone Somatropin. This is developed in Pichia pestoris (Yeast). In the NDAC meeting held on 20th December 2012 the firm proposed to conduct PK /PD studies and now they have come out with a plan for phase –III studies. The firm has presented analytical results in comparison to Nordotropin of M/s Novo nordisk. What test are required to be done GH deficiency should be defined and uniform for all trial sites. The **GH level** and **IGF (Insulin like Growth Factor)** should be measured at a central lab with validated method. Only isolated GH hormone deficiency of non-tumoral origin patients should be included. The NDAC recommends to conduct this study on at least 12+12 subjects and also to include Govt. hospitals associated with PG medical colleges.
13.	**Glucagon (synthetic origin) Injection 01 mg (1 mg/vial)**		Committee recommended for conducting the study. However committee opined that GTT should be done prior to enrolling the subjects further. C-peptide should be measured along with glucose and glucagon. Subject's receiving ACE inhibitors and ARBs should be excluded. Committee also opined that the firm shall also apply for obtaining Marketing authorization in the country.

11. RECOMMENDATIONS OF THE NDAC (METABOLISM & ENDOCRINOLOGY) HELD ON 30.06.2014:-

The 11th NDAC (Metabolism & Endocrinology) deliberated the proposals on 30.06.2014 and recommended the following:-

Agenda no.	Drug Name		Recommendations
1.	**Cincalet**		The firm did not turn-up for presentation.
2.	**Canagliflozin Tab**		The Committee was informed that proposal of the firm for the import and marketing of Canagliflozin 100 mg/300mg tablet was earlier deliberated by NDAC (Metabolism & Endocrinology) in its meeting held on 21.11.2013 and the Committee had recommended that the firm should submit details of SAEs of Hypoglycaemia, Urosepsis, bladder cancer, if any, reported in the clinical trial along with renal histology data and causality analysis with medical history of the Indian subjects who died during clinical trial, for review. The firm was also asked to submit the copy of COPP/FSC form countries from where the drug is proposed to be imported or from any other key country. The firm presented the above data/information before the Committee and the committee was satisfied. After detailed deliberation the Committee recommended for Import & Marketing of Canagliflozin 100 mg/30mg tablet in the country subject to the condition that the interim results of ongoing cardiovascular outcome study (284 31754 DIA 3008 CANVAS study) should be submitted.
3.	**Lanreotide**		The firm did not turn -up for presentation.

4.	**Dapagliflozin tab**		The Committee was informed that proposal of import and marketing Dapagliflozin 5mg/10mg tablet was earlier deliberated in the NDAC (Metabolism & Endocrinology) meeting held on 21.11.2013. After detailed deliberation the Committee had recommended that a clinical trial with Dapagliflozin with one year duration of treatment in adequate number of subjects is required to be conducted in the country to address the issues of Urosepsis, bladder cancer etc. Accordingly clinical trial protocol etc. was required to be submitted before the Committee for further review. The firm did not make the presentation of the protocol for phase III trail but made request for grant of permission for marketing authorization. After deliberation the Committee recommended that firm be asked to give specific request to DCGI to this effect along with appropriate evidence, justification as well as supportive data for further consideration.
5.	**Teneligliptin**		The Committee noted that the firm has already been granted permission to conduct "A Randomized, Double blind, Comparative, Prospective, Placebo-controlled, Parallel-group Study to evaluate the Safety and Efficacy of Teneligliptin in patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise Alone" The study is likely to be completed by this year end. The Firm proposes to conduct another non inferiority study to compare , randomized, double-blind, non-inferiority, parallel-group, study to evaluate efficacy and safety of Teneligliptin tablets compared to Vildagliptin tablets and Sitagliptin tablets as Add on to Metformin. After deliberation the committee recommended that this study can only be considered after safety and efficacy data of ongoing Tenegliptin trial are available.
6.	**Hydroxy chloroquine sulphate tab 400mg (additional Indication)**		Firm presented the report of clinical trial conducted in 15 sites across India in 267 patients before the Committee. The Committee recommended for marketing and manufacturing permission of Hydroxy

			chloroquine sulphate tablets 400 mg as an adjunct to diet and exercise to improve glycemic control of patients on metformin, sulfonylurea combination in patients with Type II Diabetes with the condition that the proposed drug shall not be used in patients with Retinopathy. The Committee also recommended for conducting a Phase IV trial in 600 patients.
7.	**LY2605541**		The risk versus benefit of the test drug from various preclinical toxicity studies including repeat dose toxicokinetics, reproductive toxicology studies, phase I, Phase II clinical studies etc justify the conduct of this clinical trial. The test drug has a longer half-life compared to the existing long acting insulins and its PK profile is expected not to be influenced by chronic kidney disease and has low variability in glucose control. The test drug may potentially provide an alternate choice for long acting insulins. After detailed deliberation the NDAC committee recommended for the conduct of the proposed trial protocol.
8.	**Genz-112638 (Protocol amendment 04 and 05)**		After detailed deliberation the NDAC committee opined that the firm should submit the interim efficacy and safety data for this global trial along with DSMB report. The same will be further evaluated by NDAC experts before recommending the protocol amendment for trial duration extension in India from 42 weeks to 60 weeks.
9.	**Insulin Degludec Aspartate**		**The firm has withdrawn the proposal**
10.	**Semaglutide**		The risk versus benefit of the test drug from various preclinical toxicity studies including single- and repeat-dose toxicity, phase I, II clinical studies etc justify the conduct of this Clinical Trial. The purpose of the study is to compare efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulphonyl urea in insulin-naïve subjects with type 2 diabetes.Semaglutide with once

			weekly dosing may potentially provide an add on therapy for type 2 DM patients. After detailed deliberation the NDAC recommended for the conduct of the trial.
11.	**MK-3102**		The risk versus benefit of the test drug from various preclinical toxicities including oral repeated dose toxicity, phase I, II clinical studies etc justify the conduct of this clinical study. The test drug is a selective DPP-4 Inhibitor with a pk profile amenable for once weekly human doses. The Purpose of the study is to assess cardiovascular outcomes following treatment with the test drug i.e. MK-3102 in Subjects with Type 2 DM. The test drug may be more potent than other class of drugs in Type-2 DM patients with CV complications. After detailed deliberation the NDAC opined that the conditions regarding HbA1c, BMI and monitoring of serum calcitonin levels, in view of the rationale now presented by the applicant is justified. As such the committee recommended the conduct of the study with the other conditions, previously recommended regarding 50% govt sites ,undertaking to market the drug in India once successfully launched in other countries etc The firm also presented protocol amendment versions 5 and 6.The same were reviewed by the members and found them to be acceptable except that the SAE reporting should meet the requirements of the provisions of the Drugs and cosmetics Rules.
12.	**Somatropin**		After reviewing the revised protocol # RLS/TP/2012/02, Version 2.0 dated 7th March 2014, committee recommended for conduct of the study with test drug with a condition that study centers should be Multispecialty facility/ Government hospitals having Emergency services. The bed strength of the sites should be more than 50.
13.	**Insulin Degludec/Insulin**		Committee recommended for Marketing authorization of Insulin Degludec/Insulin

	Aspart		Aspart subject to condition that the firm shall carry out India specific phase IV study with the subject drug in addition to regular PSURs for which the protocol should be submitted.
14.	**Liraglutide**		The risk versus benefit of the test drug from various preclinical toxicity studies including single- and repeat-dose toxicity,phase I, II,III clinical studies etc justify the conduct of this clinical trial. Liraglutide is approved for marketing in India. The purpose of the study is to investigate the efficacy and safety of switching from sitagliptin 100 mg/day + metformin to liraglutide 1.8 mg/day + metformin in subjects with T2DM who have not achieved adequate glycaemic control on sitagliptin100 mg/day + metformin. The proposed combination metformin + Liraglutide may potentially provide an alternate therapy in type II DM treatment. The applicant has requested for waiver from constituting DSMB to oversee the proposed trial. This clinical trial has been approved with a condition that a DSMB has to be constituted. After detailed deliberation, the NDAC agreed for waiver from constituting a DSMB for this study with a condition that an internal safety committee should be constituted