1. RECOMMENDATIONS OF THE NDAC (GASTROENTEROLOGY & HEPATOLOGY) HELD ON 02.04.2012:-

The NDAC (Gastroenterology & Hepatology) deliberated the proposals on 02.04.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Trimethobenzamide**		The firm has applied for marketing approval of the drug in two indications viz i) post operative nausea and vomiting ii) nausea associated with gastroenteritis. Committee recommended that a comparative clinical trial of trimethobenzamide vs. ondansetron on 200 subjects with post operative nausea and vomiting in atleast 4 centres is required to be conducted. 50% of the sites should be multispecialty hospitals and the sites should be geographically distributed in the country. Clinical trial protocol etc. should be submitted to DCGI for approval. Clinical data when generated as above should be placed before the committee for evaluation and consideration for approval of the drug in the above two indications.
3	**Mesalamine**		Committee noted that there is no reason for using placebo in the trial on a well-established drug in a well-established clinical setting. Also patients who are already on treatment for active ulcerative colitis will have to stop treatment 7 days prior to randomization. These are not ethically acceptable. In view of above, the committee did not recommend for giving permission to conduct the study.
4	**Acetylated High Amylose Maize Starch**		Recommended for giving permission to conduct the study subject to the following conditions: i) The study should be conducted in subjects aged 18 to 65 years. ii) The applicant shall submit an undertaking before initiation of the study that the Investigational Product to be used in the proposed study is manufactured under GMP conditions. iii) The Informed Consent Document should be revised to include the clause that in case

			of study related injury or death, the applicant will provide complete medical care alongwith compensation for the injury or death. Accordingly revised Informed Consent Document should be submitted to DCGI before initiation of the study.
5	**CP-690,550**		The proposed study is a placebo controlled study. However concomitant medications viz. oral 5-ASA, oral steroids, antibiotics etc. for the treatment of crohn's disease are allowed for all subjects in the study. Committee recommended for giving permission to conduct the study subject to condition that the study should be conducted in patients aged 18 to 65 years.
6	**Ceftazidime avibactam**		Committee recommended for giving permission to conduct the study subject to condition that the study should be conducted in patients aged 18 to 65 years.
7	**Levosulpiride + (S)Pantoprazole/ Pantoprazole**		M/s Emcure did not turn up for the presentation. However the committee examined the rationality of the FDC. Less than 20% of patients with GERD may need a prokinetic alongwith a PPI. Therefore there may be chance of misuse of the FDC in patients who may not need both the drugs. Therefore the committee did not consider the FDC as rationale and did not recommend for approval.

2. RECOMMENDATIONS OF THE NDAC (GASTROENTEROLOGY & HEPATOLOGY) HELD ON 14.09.2012:-

The NDAC (Gastroenterology & Hepatology) deliberated the proposals on 14.09.2012 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Taurourso-deoxycholic Acid**		Tauroursodeoxycholic Acid (TUDCA) has no role in chronic hepatitis and gallstone dissolution in current scenario. Hence Committee did not recommend for the proposed clinical trial.
2	**Ribavirin**		Currently there is no available specific therapy for HEV induced liver failure in patients with cirrhosis. Both groups will receive standard of care. Ribavirin capsule is an approved drug for the treatment of chronic hepatitis C in combination with interferon. Ethics Committee of AIIMS has already approved the protocol on 14.11.11 from ethical angle. Committee recommended for giving permission to conduct the proposed study.
3	**Probiotic Lactobacillus GG**		Committee recommended for conducting the proposed clinical trial subject to the following conditions: i)Patients requiring antibiotics should be excluded from the study. ii) Proper storage facilities should be ensured as the drug is required to be stored below 250C.
4	**Lafutidine Injection 5mg/10mg**		Committee recommended for conducting a well designed comparative study with Lafutidine Injection5mg/10mg based on objective parameters on homogenous population using standard accepted criteria of research methodology in multispecialty hospitals including Govt medical colleges/hospitals under the supervision of qualified investigators. Accordingly protocol etc should be submitted to the committee for evaluation.
5	**Troxipide ER Tablets 200/300mg & Suspension 50mg/5ml**		Committee members were not satisfied with the design, methodology and outcome measures of the study. Committee recommended for conducting a well designed comparative study with Troxipide ER Tablets 200/300mg based on

			objective parameters on homogenous population using standard accepted criteria of research methodology in multispecialty hospitals including Govt medical colleges/hospitals under the supervision of qualified investigators. Accordingly protocol etc should be submitted to the committee for evaluation. The proposal for injection and suspension of the drug will be considered based on the results of the study as mentioned above.
6	**Troxipide 25/50/100 mg**		Committee members were not satisfied with the design, methodology and outcome measures of the study. Committee recommended for conducting a well designed comparative study based on objective parameters on homogenous population using standard accepted criteria of research methodology in multispecialty hospitals including Govt medical colleges/hospitals under the supervision of qualified investigators. Accordingly protocol etc should be submitted to the committee for evaluation.
7	**Ademetionine Powder for Solution for Injection 500 mg/5ml**		Although cholestasis is a disease for which there is very limited therapy, the tabletofademetionine is already available for the indication. Committee recommended for conducting a statistically powered comparative clinical trial to prove superiorirty of Ademetionine Powder for Solution for Injection over ademetionine tablets by at least 10%. Accordingly protocol etc should be submitted to DCGI for approval.
8	**VSL#3 Sachet**		Committee examined the report of clinical trial conducted with VSL#3 in 147 Indian patients with mild to moderately active ulcerative colitis as an adjunctive therapy. The report of the study has been published in the journal “Clinical Gastroenterology and Hepatology 2009:1202-1209”. Committee recommended for giving permission to market the drug for mild to moderately active

			ulcerative colitis as an adjunctive therapy subject to condition that it should not be used in patients who are on steroids or immunocompromised.
9	**Hyoscine Butylbromide+ Mefenamic Acid Tablets**		The study conducted by the firm was examined and the committee opined that the data generated is not adequate. Hence committee did not recommend for the proposed FDC.
10	**Silymarin+ Ursodeoxycholic Acid Tablets**		The FDC of Ursodeoxycholic Acid +Silymarin has a very mild effect or improvement in liver diseases. Further Primary Biliary Cirrhosis is extremely rare in our country. Moreover combination of these two drugs in medical practice is not recommended. Hence committee did not recommend for the proposed FDC.
11	**CP-690,550**		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) Many of the patients are sick and may not continue in placebo arm and require rescue therapy. They should be included as failure in the final analysis.
12	**CP-690,550**		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) Many of the patients are sick and may not continue in placebo arm and require rescue therapy. They should be included as failure in the final analysis.
13	**CP-690,550**		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) Many of the patients are sick and may not continue in placebo arm and require rescue therapy. They should be included as failure in

			the final analysis.
14	**CP-690,550**		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) Many of the patients are sick and may not continue in placebo arm and require rescue therapy. They should be included as failure in the final analysis.
15	**CP-690,550**		Committee recommended for giving permission to conduct the study subject to the following conditions:- 1. Upper age limit of subjects to be included in the study should be 65 years. 2. Many of the patients are sick and may not continue in placebo arm and require rescue therapy. They should be included as failure in the final analysis.
16	**DEB025**		The study is an observational study and there is no therapeutic intervention. Committee recommended for giving permission to conduct the study.
17	**DEB025**		The study is an observational study and there is no therapeutic intervention. Committee recommended for giving permission to conduct the study.
18	**Ranitidine oral suspension**		Committee recommended that the firm should conduct a bioequivalence study withRanitidine oral suspension vis-à-vis ranitidine oral tablets. Acordingly protocol etc. should be submitted to DCGI for approval.
19	**Tenofovir Disoproxil Fumarate in combination with PEG interferon alfa 2a**		Committee recommended for giving permission to conduct the study.

3. RECOMMENDATIONS OF THE NDAC (GASTROENTEROLOGY AND HEPATOLOGY) HELD ON 15.03.2013:-

The NDAC (Gastroenterology and Hepatology) deliberated the proposals on 15.03.2013 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
Special agenda 1 to 8			
1 to 8	**1. FDC of Ofloxacin with Ormidazole** **2. Irsogladine** **3. Rifaximin** **4. Lafutidine** **5. Buclizine** **6. Camostate** **7. Cinitapride** **8. Ramosetron**		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, 8 drugs are in the category of Gastroenterology and Hepatology which are given below:- FDC of Ofloxacin with Ormidazole Irsogladine Rifaximin Lafutidine Buclizine Camostate Cinitapride Ramosetron The NDAC (Gastroenterology and Hepatology) 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 the above five 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 (Gastroenterology and Hepatology) for their further review. If needed manufacturer may be requested to make their Presentation before the NDAC on safety and efficacy of the drugs.
9	**Thalidomide**		The committee approved for the proposed Phase II study.
10	**Dexlansprazole delayed release 30/60mg capsule**		Committee recommended for giving permission to conduct the study subject to the following conditions:- Age limit of subjects to be included in the study should be 18 to 65 years. The ratio of enrollment of erosive and non erosive patients should be 1:2. Sites with Independent Ethics Committee are not recommended.
11	**S. indicus extract Tablet 700 mg**		The committee opined that the study centers and the sample size have to be specified before considering the grant of CT NOC. Further, it opined to review the non-clinical data before considering the CT

			application for Phase II trials. Accordingly, the firm may be asked to furnish the proposed centres alongwith sample size for consideration by the NDAC.
12	**Essliver Injection 250mg/5ml**		The company has requested for the grant of manufacturing and marketing permission for Essliver inj. No study was conducted for this dosage form and indication in Indian patients. The committee opined that a protocol for conducting CT specifically for Severe alcoholic hepatitis in reputed hospitals across the country and suitable sample size and submit the proposal to this committee for consideration.
13	**Rabeprazole (EC)+Zinc Carnosine**		The committee opined that there is no rationality in combining rabeprazole (EC) with zinc carnosine. The safety profile of the combination is also not known. The proposed combination is not approved anywhere in the world. The committee opined that the proposal cannot be considered.
14	**Lafutidine + Domperidone**		The proposed FDC is likely to be misused as most of the patients require only one drug and adding Domperidone in the FDC will lead to increase in side effects. There is no published clinical study with respect to the proposed FDC and is not approved anywhere in the world. Hence the committee did not recommend
15	**Metformin Hydrochloride SR+Ursodeoxycholic Acid**		The firm did not present any published study for the proposed combination. Further recent guidelines do not recommend either of these two drugs individually in the treatment of NAFLD. Metformin is used in patients who have Diabetes. Hence, the committee did not recommend for this FDC.
16	**Esomeprazole DR + Levosulpride ER**		The committee opined that there are chances of misuse of the proposed FDC. As most of the patient would require only one drug. Further both the firm i.e., M/s. Torrent pharmaceuticals & M/s Sun Pharma did not present any data with respect to the Adverse Reactions occurred during the trial. There is no published study as well as the proposed FDC is not marketed anywhere in the world. Hence the Committee did not recommend.

17	**Racemethionine+Taurine**		There is no published literature on the efficacy of liver disease for the proposed FDC. There is no data for the use of Taurine in alcoholic liver disease further the inclusion criteria as presented by the firm in the protocol consist five different indications and the proposed FDC for the treatment of the specific indication was not clear. The proposed FDC is not approved anywhere in the world. Further, Taurine has been used for preventing relapse and for alcohol withdrawal but not for treatment of liver disease. Hence the committee did not recommend for the proposed FDC.
18	**Methylcobalamin+ Rabeprazole Sodium**		The company opined that the vitamin B12deficiency due to long term PPI use is rarely reported. The requirement of VitaminB12 is 1 mcg/day and the same can be separately given once a month. The combination is of no use. Hence the committee did not recommend.
19	**Cilostazol+Telmisartan**		The committee recommended for the phase II trial and the results of the trial should be placed before the Committee.
20	**Rabeprazole Sodium (ER) + Cinitapride (ER)**		The committee opined that there are chances of misuse of the proposed FDC. As most of the patient would require only one drug. There is no published study as well as the proposed FDC is not marketed anywhere in the world. Hence the Committee did not recommend.
21			Committee recommended to conduct the Phase IV trial and accordingly the firm has been advised to resubmit the revised title of the protocol proposed for approval.
22			Committee recommended to allow the market Authorization subject to the condition that the firm has to submit the Phase IV protocol with specific emphasis on immunogeneticity data in the patients population for which the marketing authorization is requested.
23	**VSL#3 capsules**		The company agreed that they will design the CT so that the secondary outcome is statistically significant. Accordingly they will submit revised protocol with justification.

4. RECOMMENDATIONS OF THE NDAC (GASTROENTEROLOGY AND HEPATOLOGY) HELD ON 11.04.2013:-

The NDAC (Gastroenterology and Hepatology) deliberated the proposals on 11.04.2013 and recommended the following:-

AGENDA NO.	NAME OF DRUG		RECOMMENDATIONS
1	**Atorvastatin**		Committee recommended for giving permission to conduct the study. However following suggestions may be incorporated:- Patients with underlying liver and renal disease should be excluded. Relapse should be clearly defined. The study should focus on patients of ulcerative colitis in remission at least 1 month with MAYO score less than 2. It should focus on relapse rate within a period of 1 year. Randomization should be stratified.
2	**Pancrelipase DR Capsule**		Pancrelipase delayed release capsule is already approved in India. The product is as per USP standards. Ithas been tested in CDTL, Mumbai. Committee recommended for approval of the product.
3	**Ilaprazole Immediate Release Tablets 5/ 10 mg**		Ilaprazole gives its peak effect in 24 hours. Committee opined that there is no rationality of having immediate release formulation of ilaprazole. Hence committee did not recommend for the proposed new dosage form.
4	**Omeprazole Dual Delayed Release Capsules 60 mg**		Omeprazole 60 mg is a high dose. Committee recommended that the study should be a 7days, multiple dose 3-arm study of omeprazole 40mg test formulation of the firm vis-a vis omeprazole 20mg bid vis -a- vis omeprazole 40mg od. Protocol should be revised incorporating the above points which should be submitted to DCGI for evaluation. Results of the study should be submitted to the committee for evaluation.
5	**Lubiprostone soft gelatin Capsule 24 mcg**		The proposed study is for export purpose. The study drug is already approved in the country. Committee recommended for giving permission to conduct the study in sites which are multispeciality or superspeciality hospitals having Institutional Ethics Committee and adequate emergency facilities.
6	**Everolimus 0.25/0.5/0.75/1.**		Since the drug is in use in India since Year 2005, committee recommended that safety profile of the

	0 mg tablets &Everolimus 0.1/0.25 mg dispersible tablets		drug in Indian patients should be submitted for examination of the committee. In case of absence of safety profile of the drug in Indian setting, the same should be generated in India. However the issue of continued marketing of everolimus is under examination of NDAC in light of action taken report of MOHFW on 59th Parliamentary Standing Committee report. Therefore final decision on the proposal will be made after action is taken on above.
7	**Troxipide ER 200/300 mg tablets For Re-examination**		Committee examined the proposal for re-examination and opined that a detailed scientific presentation by a technical person should be presented along with details of the study sites, number of subjects in each site, details of Investigators, Ethics Committees and outcome measures.
8	**TenofovirDisoproxilFumarate**		Committee recommended for giving permission to conduct the study subject to condition that the study should include four additional sites which should be multispeciality or superspeciality hospitals having Institutional Ethics Committee and adequate emergency facilities and the sites geographically distributed across the country.
9	**CP-690550**		Committee recommended for giving permission to conduct the study in sites which are multispeciality or superspeciality hospitals having Institutional Ethics Committee and adequate emergency facilities.
10	**Pegylated Interferon**		Committee recommended for giving permission to conduct the study.
11	**MK-3415, MK-6072 & MK-3415A**		Committee recommended for giving permission to conduct the study in sites which are multispeciality or superspeciality hospitals having Institutional Ethics Committee and adequate emergency facilities.
12	**Peginterferon Lambda-1a**		The firm has withdrawn their proposal.
13	**BMS-945429**		Committee recommended for giving permission to conduct the study in sites which are multispeciality or superspeciality hospitals having Institutional Ethics Committee and adequate emergency

			facilities.
14	**Suppl.changes -V**		Committee recommended for giving permission to conduct the Phase IV study subject to condition that the study should be conducted on atleast 100 patients. However Committee also recommended that the firm should also conduct Phase IV study on at least 100 patients with Hepatitis B for which protocol etc. should be submitted to the committee for evaluation.
15	**ST10-021**		The firm has withdrawn their proposal.
16	**ST10-021**		The firm has withdrawn their proposal.

5. RECOMMENDATIONS OF THE NDAC (GASTROENTEROLOGY & HEPATOLOGY) HELD ON 22.08.2013:-

The NDAC (Gastroenterology & Hepatology) deliberated the proposals on 22.08.2013 and recommended the following:-

Agenda no.	Drug Name		Recommendations
New Drug			
1	**Buclizine Hydrochloride Tablet 25 mg and Buclizine Syrup 6 mg/5ml**		M/s. UCB India Pvt. Ltd. has informed office of DCG (I) that they had sold the manufacturing and marketing rights for Buclizine formulation to M/s. Mankind Pharma Ltd. and is no more marketing or manufacturing the product since last 3.5 years. M/s Mankind Pharma Ltd. approached the committee and informed that due to short notice they were not able to prepare for the presentation and requested for more time. The committee opined that there is no convincing current literature in support of use of drug in appetite stimulant, However M/s. Mankind Pharma Ltd. should be given an opportunity to make a presentation on the drug in next NDAC meeting along with supportive data.
2	**12-79/12-DC Folic Acid Tablets (Mouth Dissolving Tablets)**		The committee recommended that the firm should submit the published report on BA study of Mouth Dissolving Folic Acid Tablet 5 mg. In the mean time Prof. Ranjit Roy Chaudhary Committee report may also be considered for grant of BE waiver of proposed product as and when available.
3	**12-15/2013-DC Micronized Purified Flavonoid Fraction (contains 90% diosmin and 10% hespiridine) 1000mg tablet**		MPFF 500 is an old drug approved in year 1987. The proposed formulation is scale up formulation of MPFF 500 to MPFF 1000. The ratio of active ingredient and excipients are same in proposed formulation MPFF 1000 & MPFF 500. The recommended dosing of MPFF 500 in acute hemorrhoids is as follows: ▪ MPFF 500:Dosing 6 tablets in divided doses(2 tablets tid) x 4 days followed by 4 tablets in divided doses (2 tablets bid) x 3

			days. The firm has proposed MPFF 1000 mg tablet which will be recommended as 3 tablets in divided doses (1 tablets tid) x 4 days followed by 2 tablets in divided doses (1 tablet bid) X 3 days. Thus the MPFF 1000 mg tablet will be reduce the tablet burden on patients. The committee recommended for the approval of Flavonoid Fraction (contains 90% diosmin and 10% hespiridine) 1000mg tablet for acute haemorrhoid piles
4	**12-53/08-DC (Pt-Alkem) Lansoprazole DR/OD 30mg Tablets**		The firm didn't turned up. Therefore the proposal was deferred.
5	**12/149-2008 Troxipride ER tablets 300 mg , 200 mg And Suspension 50 mg/5ml**		Troxipride conventional tablet of 100 mg is already approved with dosage schedule tid. The firm has proposed Troxipride 300 mg ER once a day tablet to improve the patient compliance. The firm has conducted Clinical trial for proposed formulation, which was presented before the committee and committee recommended for approval of Troxipride ER tablet 300 mg. For Troxipride Suspension 50 mg/5ml, the committee opined a BE study is required to carried out according to BE protocol should be submitted to office of DCG (I) for evaluation & approval.
Fixed dose Combination			
6	**4-21/2010-DC(Pt.SUN) Levosulpiride SR+Pantoprazole Sodium 75mg+40mg capsules**		The firm has conducted comparative phase III trials of Pentoprazole + Levosulpride vs pantoprazole alone. The CT data was presented before committee. The Committee recommended for approval of the FDC indicated for short term therapy in patients who do not respond to PPI alone. Committee also recommended that a phase IV study should be conducted on 500 Patients.
Global Clinical Trial			
7	**CT/18/2013 DCG(I) Sofosbuvir**		The firm presented the protocol and other relevant data before committee. The

			committee recommended the approval for conduct of proposed clinical trial.
8	**CT/20/13 Tenifovir Alafenamide Fumarate**		The firm presented the protocol and other relevant data before committee. The committee recommended the approval for conduct of proposed clinical trial.
9	**CT/21/13 Tenifovir Alafenamide Fumarate**		The firm presented the protocol and other relevant data before committee. The committee recommended the approval for conduct of proposed clinical trial.
10	**CT/22/13 RAD001**		The firm presented the protocol and other relevant data before committee. The committee recommended the approval for conduct of proposed clinical trial.

6. RECOMMENDATIONS OF THE NDAC (GASTROENTEROLOGY & HEPATOLOGY) HELD ON 15.11.2013:-

The NDAC (Gastroenterology & Hepatology) deliberated the proposals on 15.11.2013 and recommended the following:-

Agenda no.	Drug Name		Recommendations
1	**Alvimopan 12 mg Capsules**		Alvimopan is a peripherally- acting μ-opioid receptor (PAM-OR) antagonist which belongs to the class of opioids reversal agents. Alvimopan has been indicated for accelerating the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. Firm presented the published clinical trial reports, safety data of Alvimopan. The drug was approved by US FDA in 2008. Firm proposed an open label, randomized, multi-centric, placebo controlled, parallel group, comparative Phase III study to evaluate the Efficacy and Safety of Alvimopan in patients undergoing major abdominal surgery versus placebo added to the standard treatment protocol. The committee recommended for the issue of clinical trial approval with the following changes in clinical trial protocol 1. Design of clinical trial should be double blind placebo controlled with standard care of treatment. 2. The proposed drug is approved for bowel surgery hence the clinical trial should be carried out in patients undergoing bowel surgery only. 3. In the exclusion criteria, the patient with peritoneal involvement or multiple strictures should be excluded. 4. The Committee opined that clinical trial should be conducted in statistically significant and geographically distributed population.
2	**Ulinastatin Injection**		Ulinastatin 50000/100000 IU has already been approved for the treatment of severe sepsis in the country..

			The firm proposed to manufacture and market Ulinastatin Injection for the treatment of mild or severe acute Pancreatitis. The drug is reported to be approved and marketed in Japan, China and Korea for acute and chronic pancreatitis. The firm presented the clinical trial data of "A prospective, muticentre, double blind, randomized, Phase III Clinical study to compare the efficacy and safety of intravenous Ulinastatin versus placebo along with standard supportive care in subjects with mild or severe acute Pancreatitis" conducted on Indian population. A total of 129 patients (62 subjects in the Mild Pancreatitis study group and 67 subjects in the severe Pancreatitis study group) at 15 clinical sites were enrolled in the study, the committee noted that there were 3 SAEs in the study. The Committee examined the safety and efficacy data of Ulinastatin for proposed indication and recommended for grant of permission to manufacture and market Ulinastatin Injection (50000/100000 IU) indicated for the treatment of mild to severe acute Pancreatitis.
3	**Domperidone Orally Disintegrating tablets 10 mg**		The firm applied for grant for manufacturing and marketing of Domperidone Orally Disintegrating tablets 10 mg Domperidone 10 mg ODT tablet is reported to be approved in UK. However the committee opined that the formulation is neither desirable nor has any clinical relevance in the country. Therefore, the committee doesn't recommend considering the application for grant of manufacturing and marketing of Domperidone Orally Disintegrating tablets 10 mg.
4	**Lubiprostone Soft Gelatin Capsules 24 mcg**		Firm has requested for waiver of bioequivalence study of Lubiprostone soft gelatin capsules and stated that Lubiprostone has low systemic availability following oral administration and concentration of Lubiprostone in plasma are below the level of quantification 10 pgm/ml. However, the mean Cmax, AUC value for M3 (Metabolite of Lubiprostone) is detectable in plasma. The committee opined that the request of the firm for BE waiver is not reasonable and

			justifiable. Hence the Committee doesn't recommended for grant of BE waiver for Lubiprostone Soft Gelatin Capsules 8/24 mcg.
5	**Interferon alfa 2a**		Firm made detailed presentation of their proposal but the committee did not consider the PK/PD study protocol as proposed by the firm. The committee recommended that the firm should conduct Phase I study in Indian population at least on 50 subjects with 45 days safety response before conducting the Phase II/III study. Accordingly, the firm should submit revised protocol for phase-I study to the committee for further consideration.
6	**Sodium Alginate + Sodium Bicarbonate + Calcium Carbonate Chewable tablets**		Firm Did not turn up for the presentation hence the proposal is deferred
7	**Esomeprazole DR + Levosulpiride ER capsules**		M/S Torrent Pharma and M/S Sun Pharma presented the clinical trial data along with adverse events data in details before the committee. The Committee recommended for the approval of the FDC indicated for short term therapy in patients who do not respond PPI alone. Committee also recommended that a Phase-IV study should be conducted on 500 patients. The study shall also include monitoring of Prolactin level in women as well as liver functions.

7. RECOMMENDATIONS OF THE NDAC (GASTROENTEROLOGY & HEPATOLOGY) HELD ON 26.02.2013:-

The NDAC (Gastroenterology & Hepatology) deliberated the proposals on 26.02.2014 and recommended the following:-

Agenda no.	Drug Name		NDAC Recommendations
			For the proposals of drugs at Sr. No. 1-6 , the Parliamentary Standing Committee (PSC) of the Ministry of Health & Family Welfare had presented its 59th report to the Parliament on the functioning of CDSCO. The report has made various recommendations and observations on approval of these new drugs. As per action taken report (ATR) the matter was referred to NDAC for further review of the current data and for clarification whether the same should be allowed for continued marketing and whether there is any requirement of updating the product monographs in light of recent knowledge & regulatory changes overseas if any. Accordingly, the recommendations of NDAC for these drugs are as under.
1	**Camostat Mesylate**		Camostat mesylate is one of such drug. This Directorate had approved the Camostat mesylate 100mg (Tablets) on 29th Jan. 2008, treatment for remission of acute symptoms of chronic pancreatitis and post-operative reflux esophagitis. Firm informed the Committee that they have discontinued marketing the drug in the country. The Committee noted that the applicant had discontinued marketing of the drug in India due it's commercial reasons. However, the firm is required to furnish information in respect of no. of patients exposed, safety issues reported, PSUR data collected during the period of marketing and reasons for not marketing the drug.
2	**Lafutidine**		This Directorate had approved the Lafutidine (Tablets) for the treatment of gastric **ulcers, duodenal ulcers and stromal ulcers, gastric**

			mucosal lesions (erosion, hemorrhage, redness or edema) associated with acute gastritis and acute exacerbation of chronic gastritis. The firm presented published clinical trial reports along with clinical trial data generated in Indian subjects. The Committee noted that the data generated is not adequate to reflect the actual prevalence of adverse events in the volume of patients exposed. The Committee recommended for continued conduct of PMS of around 500 patents each of 4 zones of India (2000 patents)
3	**Irsogladine**		This Directorate had approved the Irsogladine (Tablets) for gastric ulcers, improvement of gastric mucosal lesion (erosion, hemorrhage, redness and edema) caused by acute gastritis and acute exacerbation stage of chronic gastritis. The Committee noted that the applicant had not launched the drug in India due to its commercial reasons.
4	**Rifaximin**		This Directorate had approved the Rifaximin 200mg (Tablets) on 28th Aug. 2006, for the treatment of adult patients with infectious diarrhoea. The firm has presented published clinical trial reports pertaining to safety & efficacy of the drug along with the data generated in Indian subjects. The Committee noted that so far approx. 971500778 subjects in India have been exposed to the drug after marketing Authorization. The firm reported that there is no change in the characteristics of the listed reactions e.g Severity, outcome, target population have been reported. After deliberation, the Committee recommended that the drug should be indicated for treatment of non-invasive bacterial diarrhea

			instead of infectious diarrhea in adults only and accordingly the package insert required to be changed.
5	**Cinitapride Hydrogen Tartrate**		This Directorate had approved the Cinitapride 1mg (Tablets) on 04th Jan. 2008, for treatment of gastroesophageal reflux disease and functional inconveniences of the gastrointestinal motility. The firm presented published clinical trial reports pertaining to safety & efficacy of the drug alongwith clinical trial data generated in Indian subjects. Approx. 36,807 patients were exposed to the drug during the four years from Jan. 2008 to Dec. 2011, while reporting PSUR. The Committee noted that the data generated is not adequate to reflect the actual prevalence of adverse events in the volume of patients exposed. The committee recommended for continued conduct of PMS of around 500 patents each of 4 zones of India (2000 patents)
6	**Ramosetron**		This Directorate had approved the Ramosetron hydrochloride 0.1mg (Tablets) and 0.3mg/2ml (Injection) for the prevention and treatment of gastrointestinal symptoms (nausea and vomiting) associate with emetogenic cancer chemotherapy. The firm presented published clinical trial reports pertaining to safety & efficacy of the drug alongwith clinical trial data generated in Indian subjects. Approx. 10,408 patients were exposed to the drug during the four years from Dec. 2009 to Nov. 2013, while reporting PSUR. The Committee noted that the drug is indicated for the prevention and treatment of gastrointestinal symptoms (nausea and vomiting) associate with emetogenic cancer chemotherapy. After detailed deliberation the Committee recommended for continued marketing of the drug.
7	**Prucalopride**		The firm presented the preclinical and clinical data, mechanism of action international regulatory approval etc. of drug. It was informed that Prucalopride1 mg and 2mg

			tablets are approved in EU (since 2009), Switzerland (since 2010), Australia (since 2011), Macau, Peru and Canada. The firm presented the proposed clinical trial and bioequivalence protocol before the Committee. After deliberation, the Committee recommended for the conduct of the study clinical trial and bioequivalence study as per protocol subject to the condition that under inclusion criteria in the clinical trial protocol gender specific QTc interval has to be specified.
8	**Eltrombopag Olamine Tablet**		The applicant Pharma company requested for permission to Import & market **Eltrombopag Olamine 25/50 mg tablets** for the treatment of thrombocytopenia (To enable the initiation of interferon based therapy & to optimize interferon based therapy) in patients with chronic hepatitis C virus infection. The USFDA has already approved Eltrombopag Olamine for the treatment of thrombocytopenia in patients with HCV This Directorate has approved Eltrombopag Olamine tablet 25 mg/ 50 mg for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP) who have had an insufficient response to corticosteroids immunoglobulins, or splenectomy where the drug should be used only in patients with ITP whose degree of thrombocytopenia and clinical conditions increase the risk for bleeding. It should not be used in an attempt to normalize platelet counts. **The firm presented that 41 Indian patients were included in the trial as a part of global trial for the proposed additional indication. The NDAC recommends the proposed additional indication for import and marketing.**
9	**Zinc Sulphate 20mg**		The firm requested for approval of the acceptability study of Zinc sulphate 20mg dispersible tablets In pediatric patients for diarrhea which was already

	dispersible tablet		approved by this Dte. For the treatment of acute diarrhea. The NDAC has noted that all 8 proposed sites are from Maharashtra states and therefore recommends that the trial should be conducted in geographically distributed four regions of the country. The details shall be submitted to the DCGI for further action.
10	**VSL#3 Sachets**		The applicant firm requests for permission to market the Sachet formulation of VSL#3 in **Irritable Bowel Syndromme.** The firm presented data of the trial from only one center as a part of the global trial which was conducted on 59 patients only . The trial was conducted in 2007. The data was not very convincing and adequate . The committee did not recommend for the proposed additional indication.
11	**Folic acid tablet**		The applicant firm requested for permission to manufacture Mouth dissolving Tablets of Folic Acid. The NDAC recommends that a bioequivalence studies of the proposed formulation in male and female healthy subjects.
12	**Sodium Alginate 250mg+ Sod. Bicarbonate 133.55 mg+ Calcium Carbonate 80mg chewable tablets**		The firm requested for permission to import and market the proposed product in india. The product is marketed as OTC in international market . Firm claimed that the product is already approved in the country in liquid dosage form. The committee, in view of Sodium and calcium content recommended that label/ Package insert cautioning its use in patients with hypertension, renal and cardiac failure, Edema states and in hypercalcemiic states. Committee recommended for import and marketing with the condition as above. Further a well designed PMS study should be conducted in an appropriate number of patients for collecting further data.
13	**Peg Interferon alfa 2b**		The NDAC committee approved the study and pointed out that the upper age of the participants should be 45 years. Accordingly the revised protocol shall be submit to the DCG(I) office

14	**Cepeginterferon-alfa 2b**		The firm requests for permission to conduct a phase III clinical trial entitled “An open-label (as the end point is to assess the virus), randomized multicenter Phase III clinical study comparing safety and efficacy of Algeron (**cepeginterferon alfa-2b Solution for subcutaneous injection, 200µg/ml**. mfgd. By CJSC Biocad, Russia) and **ribavirin** with Pegasys **(peginterfetries are Indai and Brazilron alfa2a,** of M/s F. Hoffmann-La Roche Ltd, Switzerland) with **ribavirin** for treatment of patients with **chronic hepatitis C**”. The Russian representative of the Indian importer presented data of Pre-clinical studies Single and repeated doe toxicity studies, Phase-II & III study data. The comparative trial (Phase-II & III) data of Algeron and Pegintron in Patients of HCV genotypes 1,2,3,4 are also submitted. So far the health authorities Russia, Thailand and Belarus had approved the proposed protocol, the other two participating countries are Brazil and India. **The NDAC recommends for the proposed trial subject to the condition that at least one centers should be included from the north Eastern part of the country.**
15	**Ifetroban Injection**		The firm requests for permission to conduct a phase IIa clinical trial entitled “A Multi-Center, Double Blind, Randomized, Controlled Study to Determine the Safety and Pharmacokinetics of Ifetroban IV Injection in patients with Hepatorenal Syndrome”. With the new drug namely **Ifetroban diluted with** 5% dextrose in water for intravenous (IV) solution, The is pharmacological antagonist of the thromboxane (Tx) A2 / prostaglandin endoperoxide receptor (TPr). Ifetroban inhibits TPr-dependent contraction of vascular smooth muscles in all species tested (Rat, guinea pig, dog, pig and cow) Single dose toxicity study data generated in mice and rats and Repeated dose toxicity study data generated in rats and dogs reported not to have clinical signs or gross findings at doses up to 400 mg/kg in rat and 100 mg/kg in dogs.

			an. In human plasma, ifetroban is 96% protein bound and is primarily bound to albumin. However, patients with cirrhosis generally have low plasma albumin concentrations, so exposure to free ifetroban may be higher in cirrhotics than in subjects with normal albumin levels. The range of ifetroban doses in the current study is 5 mg to 150 mg administered once daily as a 60-minute IV infusion. The 5-mg daily dose was chosen as a safe starting dose that will be sufficient to produce measurable plasma exposure to ifetroban for evaluation of ifetroban pharmacokinetics, including evels of ifetroban acylglucuronide. The proposed 28 day study will consist of a 48 hour Screening/Baseline period, a 72-hour treatment period, and a 25 day post treatment period at 4 **centers** in India on a Total number of 25 Indian subjects out of Globally 64. The proposed study is planned to be conducted in 2 countries which includes USA and India **The NDAC recommends the proposed trial protocol subject to exclusion of the female subjects.**

8. RECOMMENDATIONS OF THE NDAC (GASTROENTEROLOGY & HEPATOLOGY) HELD ON 12.06.2014:-

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 (**Gastroenterology & Hepatology**) deliberated the proposals on 12.06.2014 and recommended the following:-

Agenda no.	Drug Name		Recommendations
1.	**Acotiamide tablet**		Committee deliberated the proposal. The committee recommended for approval of the proposed clinical trial subject to following conditions. Firm should submit revised list of multispeciality hospitals with emergency facilities and are distributed geographically. Cholinergic side effects should be assessed by ECG/Spirometry pre and post treatment. Follow-up should be done for 4 weeks after discontinuing the therapy. Bioequivalence study should be conducted with the Innovator product.
2.	**Ademetionine**		The committee was informed that the Parliamentary standing committee had presented its 59th report to the Parliament on functioning of CDSCO. The Committee had made various recommendations and observations on approval of certain new drugs. Ademetionine is one such drug. DCGI office had approved Ademetionine 200/400mg tablet for the management of intrahepatic cholestatsis and liver diseases. As per action taken report, it was decided that the drug would be referred to NDAC for examination and review the issue related to continue marketing of the drug and updating of the product monograph in light of recent knowledge and regulatory changes overseas. The firm presented clinical data of the observational studies conducted on Indian subjects in alcoholic and non-alcoholic liver disease along with bio-chemical information on drug and international regulatory status of the drug at present. The firm also presented brief information of published reports of Clinical trials conducted with Ademetionine in different indications. The committee noted that the firm

			has not been able to provide data in respect of patients exposed to the drug so far. After detailed deliberation and in view of above facts, the committee recommended for submission of following for further review by the committee. a. Comparative analysis of published data on the Adverse events/SAEs reported from global literature vis-à-vis that which have been recorded from PSURs specific indication wise. b. Details of subjects exposed to the drug in India.
3.	**VSL#3 sachets**		Firm opted for deliberation in next NDAC.
4.	**Vitamin D3 orally disintegrating strips 2000IU**		Committee recommended that the firm shall conduct a Bioequivalence study using a comparator. Accordingly BE Study protocol shall be submitted to the office of DCG(I). Results should be presented to the Committee for further consideration.
5.	**Mesalamine sachets 500mg,1000mg,1500mg, 2000mg**		Committee opined that firm may be permitted to conduct proposed BE Study with 2.0 g PR. Committee also opined that Mesalamine 500mg PR as well as 1.5g PR did not seem justified The results of the BE Study shall be placed before the committee for further consideration.
6.	**Omeprazole Dual Delayed Release Capsules 60mg**		Committee found that revised protocol is satisfactory and committee recommended for conducting the BE and Pharmacodynamic study. Proposal of Phase-III will be considered based on the results of above studies.
7.	**VSL#3 sachets**		Committee did not recommended for deleting the caution mentioned in indication “should not be used in patients who are on steroids, or immunocompromised,” as there is no adequate scientific evidence to support its use or safety in immnocompromised patients.
			The study design raised ethical concerns as the trial molecule was not being compared with the

8.	**sucralfate suspension 1gm/10 ml**		standard of care recommended for the particular medical condition. Sucralfate is also not a standard care of treatment of peptic ulcer disease. The committee also opined that DCG(I) office shall also review as to whether such trial can be permitted as Reference product will be manufactured and imported from M/s Bio-Pharm, USA who will manufacture for M/s Cadila under contract agreement, and comparator will be of M/s Aptalis, USA. Only the patients will be used in India for generating the data.
9.	**Tenofovi Disoproxil Fumerate**		The NDAC members examined the proposal from various angles, and the proposed amendments were approved
10.	**DFA-02**		The firm did not turn up for presentation.
11.	**Peg-interferon alpha-2a**		The NDAC expert committee examined the proposal of M/s Virchow. The committee recommended for the conduct of the study with geographically distributed study centres across India. The two sub groups (HBeAg positive and negative) of study should have adequate numbers for stratified randomization to ensure adequate numbers for comparison of defined end points with published standard.