CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

OBJECTIVE	**DETAILS TO BE EVALUATED TO PREPARE THE MATRIX FOR CLEANING VALIDATION AS PER CLEANING VALIDATION MASTER PLAN** **1. To include the new product: _____. (Note: This matrix has been prepared for updating the CVMP)** **Encircle the applicable sections to evaluate the need for cleaning validation.**
SECTION A	**Toxicological evaluation new product**
1	Name of API:
2	Dosage form :
3	Evaluation of product /or API, if it falls within highly hazardous category based on following a. Genotoxic (Specifically mutagenic) : Yes/No b. Reproductive and/or developmental effects at low doses (Clinical dose < 10 mg/day or dosage in animal studies < 1 mg/day): Yes/No c. Serious target organ toxicity or other significant adverse effects at low doses (Clinical dose < 10 mg/day or dosage in animal studies < 1 mg/day) : Yes/No d. High pharmacological potency (Recommended daily dose of <1 mg)): Yes/No e. High sensitizing potential : Yes/No
4	Is new product highly hazardous? :Yes/No a. If No, then execute as per Path A mention in Annexure I and proceed as per Section B b. If Yes, then execute the following
4.1	New product introduced at site is a worst case product
4.2	Risk assessment based on evaluation of toxicological data collected and evaluation if product can be manufactured at site a. Can the product be manufactured at site? Yes/No , If No, then execute as per process flow mention in Annexure I b. Does highly hazardous require dedicated equipments? Yes/No I. If yes, then execute as per process flow mention in Annexure I II. If No, then Perform additional exercise of calculation of PDE 1.0 Identify difficult to clean product contact locations 2.0 Perform calculation of MACO based on PDE
5	Conclusion:

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

SECTION B	**Evaluation of need for cleaning validation due to introduction of new product : Applicable / Not applicable**	If applicable , execute the following
1	Group the new product in the matrix as per section H to determine the worst case.	
2	Whether new product is worst case for cleaning validation : Yes / No Please Justify :	
3	Whether cleaning procedure for the equipment need to be revised : Yes / No if Yes, identify the cleaning activity as per annexure I Please Justify :	
SECTION C	**Evaluation of need for cleaning validation due to change in formulation of existing product: Applicable / Not applicable**	If applicable , execute the following
1	Whether change in formulation makes the product difficult to clean : Yes / No Please Justify :	
2	Whether cleaning procedure for the equipment need to be revised : Yes / No Please Justify :	
SECTION D	**Evaluation of need for cleaning validation due to introduction of new equipment in the train : Applicable / Not applicable**	If applicable , execute the following
1	Group the new equipment to be used in the equipment list as per section H	
2	Whether the cleaning procedure of the new equipment is different from the existing cleaning procedure : Yes / No Please Justify :	
SECTION E	**Evaluation of need for cleaning validation due to shift of product to another equipment train : Applicable / Not applicable**	If applicable , execute the following
1	Group the equipment to be used in the equipment list as per section H	
2	Whether the product shifted is worst case product on the shifted equipment train : Yes / No Please Justify :	

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

SECTION F	**Evaluation of need for cleaning validation due to modification of existing equipment : Applicable / Not applicable**	If applicable , execute the following
1	Whether the modification of the equipment makes it difficult to clean : Yes / No Please Justify :	
SECTION G	**Evaluation of need for cleaning validation due to Revision of cleaning procedure : Applicable / Not applicable**	If applicable , execute the following
1	Incorporation of additional step in the procedure : Yes /No Please Justify :	
2	Deletion of step from the procedure :Yes/No Please Justify :	
3	Whether the cleaning procedure is still validated : Yes/ No Please Justify :	

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

SECTION H (SELECTION OF WORST CASE PRODUCT)
TOXICOLOGICAL ASSESSMENT DATA OF API

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Paracetamol	Antipyretic	500	a) API/ TOXASSESSMENT/ PARACETAMOL / b) Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No
	Dicyclomine Hydrochloride	Anti cholinergic	20	a) API/TOXASSESSMENT/DICYCLOVERINE/ DICYCLOMINE b) Module 2, Ver. 02 Dicyclomine	**a. Genotoxicity :** No relevant data available **b. Carcinogenicity:** No relevant data available **(Refer page 15 of 18 of module 2 , Ver. 02)**	Maternal toxicity Observed at 100 mg/kg **(Refer page 16 of 18 of module 2)** Reproductive study performed in rat and rabit at dose up to 100 times maximum recommended dose reveled no evidence of impaired facility or harm to the fetous. **(Refer page 13 of 18 of module 2 , Ver. 02)**	No data available for serious target organ toxicity but Certain contraindication are identified as per the precaution identified under section 8.2 **(Refer page 11 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	Non sensitizing potential Classified as **Low Hazard**	0.1000 mg/day	No	No
	Phenylephrine Hydrochloride	Anticold	10	a) API/TOXASSESSMENT/ PHENYLEPHRINE HYDROCHLORIDE b) Module 2, Ver. 01 Phenylephrine	**a. Genotoxicity** Phenylephrine hydrochloride tested negative in the in vitro bacterial reverse mutation assay (S.typhimurium strains TA98, TA100, TA1535 and TA1537), the in vitro chromosomal aberrations assay, the in vitro sister chromatid exchange assay, and the in vivo rat micronucleus assay. Positive results were reported in only one of two replicates of the in vitro mouse	Possible teratogenic effect observed when treatment was initiated during first trimester or latter and pre mature labor when treatment was initiated at the second trimester or later. The dose administered were 1.9 times the total daily human dose of 10 mg/day based on the body surface area comparison. Published studies in pregnant normotensive sheep	No data available Classified as **Low Hazard**	Non-sensitizing Classified as **Low Hazard**	0.18333 mg/day	Yes	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
					lymphoma assay. **b. Carcinogenicity** Several non-neoplastic lesions considered related to phenylephrine hydrochloride were observed in the liver (both species), prostate (rats), and lungs (rats). There was no evidence of carcinogenicity in mice administered approximately 270 mg/kg/day Classified as **Low Hazard**	demonstrate that iv phenylephrine administered during the third trimester of pregnancy decreased uterine blood flow by 42%. , The clinical significance of these finding is not clear. However the results suggest the potential for cardiovascular effects on the fetus when phenylephrine is used during pregnancy. Classified as **Low Hazard**					
	Paracetamol	Antipyretic	500	a. API/TOXASSESSMENT / PARACETAMOL b. Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No
	Chlorpheniramine Maleate	Anticold	2	a. API/TOXASSESSMENT/ CHLORPHENIRAMINE MALEATE b. Module 2 Chlorpheniramine Maleate	**a. Genotoxicity :** It is found negative in vitro-Salmonella microsomal assay and mouse lymphoma test. **(Refer page 12 of 15 of module 2)** **b. Carcinogenicity:** In two year mice carcinogenity studies in rat , no evidence of carcinogenity was seen in either sex when the compound was administered 5 days a week in water at dosages 30/mg/kg body weight. **(Refer page 10 of 15 of module 2)**	No Maternal but foetal toxicity **(Refer page 12 of 15 of module 2)** Classified as **Low Hazard**	No target organ toxicity reported Classified as **Low Hazard**	Non sensitizing but Chlorpheniramine Maleate tablets are contra-indicated in patients who are hypersensitive to antihistamines Classified as **Low Hazard**.	0.01200 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
					Classified as **Low Hazard**						
	Gliclazide	Anti diabetic	40	VC041-S082	**a. Genotoxicity** The mutagenic potential of gliclazide has been sought using five mutagenesis tests, No mutagenic effect was seen in the qualitative test. **(Refer page 9 section 6.5 of module VC041-S082 Ver. 1)** **b. Carcinogenicity** Long term toxicity studies did not reveal any evidence of carcinogenicity. **(Refer page 7 & 8 section 6.5 of module VC041-S082 Ver. 1)** Classified as **Low Hazard**	There was no evidence of any change in fertilization or abortion rate No teratogenic effect observed at the dose of 500 mg/kg/day. Classified as **Low Hazard (Refer page 8 section 6.5 of module VC041-S082 Ver. 1)**	Repeat dose Histological examination showed an increase in the weight of the liver and kidneys in male animals, not accompanied by any histological lesion. Classified as **Low Hazard**	Gliclazide should not be used in cases where diabetes is complicated by acidosis, ketosis or coma, or in patients with a history of repeated ketoacidosis or coma. Classified as **Low Hazard**	2.000 mg/day for adult **/** 0.400 mg/day for paediatric	No	No
	Metformin Hydrochloride	Anti diabetic	400	a. API/ TOXASSESSMENT/ METFORMIN b. Module 2 Ver. 02 Metformin	**a. Genotoxicity :** Not reported **b. Carcinogenicity:** None, Long term carcinogenicity study have been performed in rat (dosing duration 104 weeks) and Mice 91 weeks. The above dose are approximately 4 times the MRDD dose of 2000 mg. No evidence of carcinogenicity with metformin was found either male or female mouse. **(Refer page 16 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Reported at high dose. Reproduction studies in rat and rabbit given metformin Hydrochloride dosages of 600 mg/kg daily have not reveled teratogenicity. No evidence of impaired fertility was observed in the rats. **(Refer page 15 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Metformin is contraindicated in Hepatic insufficiency, acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure. **(Refer page 11 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Reported Hypersensitivity to metformin hydrochloride or to any of the excipients. **(Refer page 11 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	0.02000 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Gliclazide	Anti diabetic	80	VC041-S082	**c. Genotoxicity** The mutagenic potential of gliclazide has been sought using five mutagenesis tests, No mutagenic effect was seen in the qualitative test. **(Refer page 9 section 6.5 of module VC041-S082 Ver. 1)** **d. Carcinogenicity** Long term toxicity studies did not reveal any evidence of carcinogenicity. **(Refer page 7 & 8 section 6.5 of module VC041-S082 Ver. 1)** Classified as **Low Hazard**	There was no evidence of any change in fertilization or abortion rate No teratogenic effect observed at the dose of 500 mg/kg/day. Classified as **Low Hazard** **(Refer page 8 section 6.5 of module VC041-S082 Ver. 1)**	Repeat dose Histological examination showed an increase in the weight of the liver and kidneys in male animals, not accompanied by any histological lesion. Classified as **Low Hazard**	Gliclazide should not be used in cases where diabetes is complicated by acidosis, ketosis or coma, or in patients with a history of repeated ketoacidosis or coma. Classified as **Low Hazard**	2.000 mg/day for adult **/** 0.400 mg/day for paediatric	No	No
	Metformin Hydrochloride	Anti diabetic	500	a. API/ TOXASSESSMENT/ METFORMIN b. Module 2 Ver. 02 Metformin	**a. Genotoxicity :** Not reported **b. Carcinogenicity:** None , Long term carcinogenicity study have been performed in rat (dosing duration 104 weeks) and Mice 91 weeks. The above dose are approximately 4 times the MRDD dose of 2000 mg. No evidence of carcinogenicity with metformin was found either male or female mouse. **(Refer page 16 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Reported at high dose. Reproduction studies in rat and rabbit given metformin Hydrochloride dosages of 600 mg/kg daily have not reveled teratogenicity. No evidence of impaired fertility was observed in the rats. **(Refer page 15 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Metformin is contraindicated in Hepatic insufficiency, acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure. **(Refer page 11 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Reported Hypersensitivity to metformin hydrochloride or to any of the excipients. **(Refer page 11 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	0.02000 mg/day	No	No
	Glimepiride	Anti diabetic	2	a. API/TOXASSESSMENT/ GLIMEPIRIDE b. Module 2 Glimepiride	**a. Genotoxicity :** Non mutagenic **b. Carcinogenicity:** Non Carcinogenic. **(Refer page 19 of 22 of module 2)** Classified as **Low Hazard**	No effect on pregenancy, parturition or intrauterine development of fetuses, other than uni-or bilateral microphthalmia seen in 2 and 4 fetuses in 1 and 50 mg/kg group which was due to pharmacologically induced hypoglycemia. **(Refer page 20 of 22 of module 2)** Classified as **Low Hazard**	In case of severe renal or hepatic function disorders, a changeover to insulin is required. Classified as **Low Hazard**	Not sensitizing **(Refer page 21 of 22 of module 2)** Classified as **Low Hazard**	0.00196 mg/day	Yes	**Yes** This molecule has been identified for cleaning validation due to pharmacological potency closure to 1mg

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Glimepiride	Anti diabetic	1	c. API/TOXASSESSMENT/ GLIMEPIRIDE d. Module 2 Glimepiride	**c. Genotoxicity :** Non mutagenic **d. Carcinogenicity:** Non Carcinogenic. **(Refer page 19 of 22 of module 2)** Classified as **Low Hazard**	No effect on pregenancy, parturition or intrauterine development of fetuses, other than uni-or bilateral microphthalmia seen in 2 and 4 fetuses in 1 and 50 mg/kg group which was due to pharmacologically induced hypoglycemia. **(Refer page 20 of 22 of module 2)** Classified as **Low Hazard**	In case of severe renal or hepatic function disorders, a changeover to insulin is required. Classified as **Low Hazard**	Not sensitizing **(Refer page 21 of 22 of module 2)** Classified as **Low Hazard**	0.00196 mg/day	Yes	**Yes** This molecule has been identified for cleaning validation due to pharmacological potency closure to 1mg
	Amlodipine Basilate	Hypertensive	5	API/TOXASSESSMENT/AMLODIPINE	**a. Genotoxicity** Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level. **b. Carcinogenicity** Rats and mice treated to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic Classified as **Low Hazard**	Amlodipine has been shown to prolong the duration of labor in rats. No evidence of teratogenicity or other embryo/fetal toxicity was observed in rats or rabbits. Classified as **Low Hazard**	Liver injury from Amlodipine is rare and described only in isolated case Classified as **Low Hazard**	Not sensitizing Classified as **Low Hazard**	PDE calculation not done#	No	No
	Atenolol	Hypertensive	50	**a.** API/ TOXASSESSMENT/ATENOLOL **b.** Module 2 Ver. 02 Atenolol	**a. Genotoxicity** No evidence of atenolol induced mutagenicity was seen with an in in-vitro microbial test system with or without metabolic activation. **b. Carcinogenicity** No evidence of carcinogenicity was observed following administration of dose up to 300 mg /kg/day for 18 months in mice or 18 or 24 months in rat. **Low Hazard –module 2 Ver. 02**	Atenolol associated malformations were not observed when atenolol was administered at oral dose of up to 200 mg/kg/day, days 6-15 of gestation in rat or dose of up to 25 mg/kg/day, days 6-18 of gestation in rabbit. **(Refer page No. 17 of 19 Module 2 Ver. 02)** Classified as **Low Hazard**	Repeat dose: Atenolol (Starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose) and increased incidence of artial degeneration of hearts of male rats at 300mg/kg/day Classified as **(Refer page No. 8 of 15 Ver. 02)** Classified as **Low Hazard**	Not sensitizing Classified as **Low Hazard**	0.01500 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Paracetamol	Antipyretic	500	a) API/ TOXASSESSMENT/ PARACETAMOL b) Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No
	Paracetamol	Antipyretic	500	a) API/ TOXASSESSMENT/ PARACETAMOL b) Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Doxylamine Succinate	Anti Histamine	10	a. API/TOXASSESSMENT / DOXYLAMINE SUCCINATE b. Module 2 Ver. 02 Doxylamine Succinate	**a. Genotoxicity :** Non-Mutagenic **b. Carcinogenicity:** Possibly Carcinogenic. Two year carcinogenic study in Rats were conducted at 2000 PPM. There were no increase in neoplastic lesions in female rats. Lever neoplasms in male rats were found only in high dose group. These lesions was within the range, historically observed in this strains of rats and the results are not considered to have clinical relevance in human. **(Refer page 16 of 22 of module 2 Ver. 02)** Classified as **Low Hazard**	Maternal Toxicity No teratogenic effects were found even at the maternally toxic dose of 800 mg/kg/day. Teratology studies for Doxylamine in combination in rabbits and rats revealed no increase in congenital malformations or other adverse effect during pregnancy. **(Refer page 18 of 22 of module 2 Ver. 02)** **Low Hazard**	The histological changes were identified in the lever and parotid salivary gland at high dose. **(Refer page 15 of 22 of module 2 Ver. 02) Low Hazard**	Non-sensitizing **Low Hazard**	0.01333 mg/day	No	No
	Pyridoxine Hydrochloride	Vitamins suppleme-nt	10	API/TOXASSESSMENT/PYRIDOXINE HYDROCHLORIDE	**a. Genotoxicity** There were no Genotoxicity studies submitted for the combination doxylamine and pyridoxine or pyridoxine alone. **b. Carcinogenicity** The carcinogenic potential of pyridoxine hydrochloride has not been evaluated. Classified as **Low Hazard**	No adverse effect has been reported with the use of physiologic doses during pregnancy. However the use of high dose during pregnancy has been implicated in some cases of vitamin B6 dependent syndrome in infant. Classified as **Low Hazard**	No data available	No data available	0.050 mg/day	No	No
	Allopurinol	Anti gout	300	API /TOXASSESSMENT/ALLOPURINOL	**a. Genotoxicity** No evidence of clastogenicity was observed in an in vivo micronucleus test in rats, or in lymphocytes taken from patients treated with allopurinol (mean duration of treatment 40 months), or in an in vitro assay with human lymphocytes.	Reproductive studies in rats and rabbits indicated that allopurinol did not affect litter size, the mean weight of the progeny at birth or at three weeks postpartum, nor did it cause an increase in animals born dead or with malformations.	At 90 mg/kg/day for one year, there was some accumulation of xanthine in the kidneys with resultant chronic irritation and slight tubular changes.	Not sensitizing Classified as **Low Hazard**	0.080 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Allopurinol	Anti gout	100		**b. Carcinogenicity** No evidence of carcinogenicity was seen in either mice or rats (at doses about 1/6 or 1/3 the recommended human dose on a mg/m2 basis. Classified as **Low Hazard**	Classified as **Low Hazard**	**(Please refer page 6 of 13)** Classified as **Low Hazard**				
	Amlodipine Besilate	Hypertensive	5	API/TOXASSESSMENT/AMLODIPINE	**a. Genotoxicity** Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level. **b. Carcinogenicity** Rats and mice treated to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic. Classified as **Low Hazard**	Amlodipine has been shown to prolong the duration of labor in rats No evidence of teratogenicity or other embryo/fetal toxicity was observed in rats or rabbits. Classified as **Low Hazard**	Liver injury from Amlodipine is rare and described only in isolated case Classified as **Low Hazard**	Not sensitizing Classified as **Low Hazard**	PDE calculation not done[#]	No	No
	Paracetamol	Antipyretic	650	a. API/TOXASSESSMENT / PARACETAMOL b. Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Metformin Hydrochloride	Anti diabetic	1000	a. API/ TOXASSESSMENT/ METFORMIN b. Module 2 Ver. 02 Metformin	**c. Genotoxicity :** Not reported **d. Carcinogenicity:** None , Long term carcinogenicity study have been performed in rat (dosing duration 104 weeks) and Mice 91 weeks. The above dose are approximately 4 times the MRDD dose of 2000 mg. No evidence of carcinogenicity with metformin was found either male or female mouse. **(Refer page 16 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Reported at high dose. Reproduction studies in rat and rabbit given metformin Hydrochloride dosages of 600 mg/kg daily have not reveled teratogenicity. No evidence of impaired fertility was observed in the rats. **(Refer page 15 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Metformin is contraindicated in Hepatic insufficiency, acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure. **(Refer page 11 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	Reported Hypersensitivity to metformin hydrochloride or to any of the excipients. **(Refer page 11 of 20 of module 2 Ver. 02)** Classified as **Low Hazard**	0.02000 mg/day	No	No
	Dicyclomine Hydrochloride	Anti cholinergic	20	a) API/TOXASSESSMENT/DICYCLOVERINE/ DICYCLOMINE b) Module 2, Ver. **02**Dicyclomine	**a. Genotoxicity :** No relevant data available **b. Carcinogenicity:** No relevant data available **(Refer page 15 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	Maternal toxicity Observed at 100 mg/kg **(Refer page 16 of 18 of module 2)** Reproductive study performed in rat and rabit at dose up to 100 times maximum recommended dose reveled no evidence of impaired facility or harm to the fetous. **(Refer page 13 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	No data available for serious target organ toxicity but Certain contraindication are identified as per the precaution identified under section 8.2 **(Refer page 11 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	Non sensitizing potential Classified as **Low Hazard**	0.1000 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Mefenamic Acid	NSAID	250	API/TOXASSESSMENT/ MEFENAMIC ACID	No data is available related to Genotoxicity and carcinogenicity from the scientific literature.	Rats given up to 10 times the human dose showed decreased fertility, delay in parturition and a decreased rate of survival to weaning. No drug-related gross abnormalities were seen either in the mother or offspring. There were no fetal anomalies observed neither in these studies nor in dogs at up to 10 times the human dose. **(Refer page 7 of 11)** Classified as **Low Hazard**	Three monkeys showed periodic transaminases value elevation. After sacrifice, microscopic lesions were detected in the kidney, heart, liver, psoas muscle, colon and stomach in animals receiving the highest dose (600 mg/kg). In the mid-dose animals (400 mg/kg), similar lesions were seen in the kidney, heart, stomach and pylorus. **(Refer page 7 of 11)** Classified as **Low Hazard**	Non sensitizing potential Classified as **Low Hazard**	PDE calculation not done#	No	No
	Mefenamic Acid	NSAID	250	API/TOXASSESSMENT/ MEFENAMIC ACID	No data is available related to carcinogenicity from the scientific literature	Rats given up to 10 times the human dose showed decreased fertility, delay in parturition and a decreased rate of survival to weaning. No drug-related gross abnormalities were seen either in the mother or offspring. There were no fetal anomalies observed neither in these studies nor in dogs at up to 10 times the human dose. Classified as **Low Hazard**	Three monkeys showed periodic transaminases value elevation. After sacrifice, microscopic lesions were detected in the kidney, heart, liver, psoas muscle, colon and stomach in animals receiving the highest dose (600 mg/kg). In the mid-dose animals (400 mg/kg), similar lesions were seen in the kidney, heart, stomach and pylorus. Classified as **Low Hazard**	Non sensitizing potential Classified as **Low Hazard**	PDE calculation not done#	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Dicyclomine Hydrochloride	Anti cholinergic	20	a) API/TOXASSESSMENT/DICYCLOVERINE/ DICYCLOMINE b) Module 2 , Ver. 02 Dicyclomine	**a. Genotoxicity :** No relevant data available **b. Carcinogenicity:** No relevant data available **(Refer page 15 of 18 of module 2 , Ver. 02)**	Maternal toxicity Observed at 100 mg/kg **(Refer page 16 of 18 of module 2)** Reproductive study performed in rat and rabit at dose up to 100 times maximum recommended dose reveled no evidence of impaired facility or harm to the fetous. **(Refer page 13 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	No data available for serious target organ toxicity but Certain contraindication are identified as per the precaution identified under section 8.2 **(Refer page 11 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	Non sensitizing potential Classified as **Low Hazard**	0.1000 mg/day	No	No
	Dicyclomine Hydrochloride	Anti cholinergic	20	a) API/TOXASSESSMENT/DICYCLOVERINE/ DICYCLOMINE b) Module 2 , Ver. 02 Dicyclomine	**a. Genotoxicity :** No relevant data available **b. Carcinogenicity:** No relevant data available **(Refer page 15 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	Maternal toxicity Observed at 100 mg/kg **(Refer page 16 of 18 of module 2)** Reproductive study performed in rat and rabit at dose up to 100 times maximum recommended dose reveled no evidence of impaired facility or harm to the fetous. **(Refer page 13 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	No data available for serious target organ toxicity but Certain contraindication are identified as per the precaution identified under section 8.2 **(Refer page 11 of 18 of module 2 , Ver. 02)** Classified as **Low Hazard**	Non sensitizing potential Classified as **Low Hazard**	0.1000 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Paracetamol	Antipyretic	500	a) API/ TOXASSESSMENT/ PARACETAMOL b) Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No
	Mefenamic Acid	NSAID	250	API/ TOXASSESSMENT/ MEFENAMIC ACID	No data is available related to Genotoxicity and carcinogenicity from the scientific literature.	Rats given up to 10 times the human dose showed decreased fertility, delay in parturition and a decreased rate of survival to weaning. No drug-related gross abnormalities were seen either in the mother or offspring. There were no fetal anomalies observed neither in these studies nor in dogs at up to 10 times the human dose. **(Refer page 7 of 11)** Classified as **Low Hazard**	Three monkeys showed periodic transaminases value elevation. After sacrifice, microscopic lesions were detected in the kidney, heart, liver, psoas muscle, colon and stomach in animals receiving the highest dose (600 mg/kg). In the mid-dose animals (400 mg/kg), similar lesions were seen in the kidney, heart, stomach and pylorus. **(Refer page 7 of 11)** Classified as **Low Hazard**	Non sensitizing potential Classified as **Low Hazard**	PDE calculation not done[#]	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Mecobalamin/ Methylcobalamin	Vitamins Supplement	0.5	API/ TOXASSESSMENT/ METHYLCOBALAMIN	**a. Genotoxicity** Studies indicates there is no evidence suggesting that vitamin B12 is Genotoxic **b. Carcinogenicity** Expert Group on Vitamins and Minerals (EVM) stated that there is no evidence suggesting that vitamin B12 is carcinogenic. Classified as **Low Hazard**	There is no evidence relating to toxicity on reproductive organs and teratogenicity or adverse effects on fertility or postnatal development. **(Refer page 9 of 13)** Classified as **Low Hazard**	There has been no target organ adverse effect observed during any studies conducted. Classified as **Low Hazard**	No data available	0.0595 mg/day	No	No
	Pyridoxine Hydrochloride	Vitamins supplement	10	API/TOXASSESSMENT/PYRIDOXINE HYDROCHLORIDE	**a. Genotoxicity** There were no Genotoxicity studies submitted for the combination doxylamine and pyridoxine or pyridoxine alone. **b. Carcinogenicity** The carcinogenic potential of pyridoxine hydrochloride has not been evaluated. Classified as **Low Hazard**	No adverse effect has been reported with the use of physiologic doses during pregnancy. However the use of high dose during pregnancy has been implicated in some cases of vitamin B6 dependent syndrome in infant. Classified as **Low Hazard**	No data available	No data available	0.050 mg/day	No	No
	Folic Acid	Vitamins supplement	5	API /TOXASSESSMENT/ FOLIC ACID	**a. Genotoxicity** There was no evidence of Mutagenecity during studies conducted **b. Carcinogenicity** There has been no carcinogenicity related studies identified during literature review. Classified as **Low Hazard**	Very high dose of folic acid have been shown to cause foetal abnormalities in rats; however harmful effects in the human foetus, mother or pregnancy have not been reported. **(Refer page 14 of 19)** Classified as **Low Hazard**	Histopathological studies in some strains of mice showed that toxic doses may also cause renal tubular necrosis. Classified as **Low Hazard**	Not identified in assessment	0.020 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Calcium Citrate	Calcium Supplement	1000	API/TOXASSESSMENT/ CALCIUM CITRATE	**a. Genotoxicity** There was no data available regarding the studies conducted for any evidence of carcinogenicity of Calcium Citrate during usage. **b. Carcinogenicity** There was no data available regarding the studies conducted for any evidence of carcinogenicity of Calcium Citrate during usage. Classified as **Low Hazard**	There was no data available regarding the studies conducted for any evidence of carcinogenicity of Calcium Citrate during usage. Classified as **Low Hazard**	Patients taking more than 4 g of Calcium a day are at the hypercalcemia and metabolic alkalosis. Chronic intake of calcium supplements is associated with adverse gastrointestinal symptoms such as constipation and flatulence. **(Refer page 5 of 9)** Classified as **Low Hazard**	No data available	1.25 mg/day	No	No
	Vitamin D3	Vitamins supplement	2	API/TOXASSESSMENT/ VITAMIN D b. Module 2 Vitamin D 3	**a. Genotoxicity** Vitamin D3 was tested in Salmonella typhimurium assay at doses 0.0332 10mg/plate. Test was negative in this test. Dosage above 1 mg /plate exhibited slight toxicity. **(Refer Page 12 of 20 module 2)** **b. Carcinoginecity** Analysis indicated that higher vitamin D intakes at baseline were associated with a lower risk of pancreatic cancer Classified as **Low Hazard**	Vitamin D (25µg/day) during the last trimester reduced the fraction f infants displaying growth retardation. Classified as **Low Hazard**	No data available	No data available	0.0025 mg/day	Yes	Yes
	Mecobalamin/ Methylcobalamin	Vitamins Supplement	0.5	API/ TOXASSESSMENT/ METHYLCOBALAMIN	**a. Genotoxicity** Studies indicates there is no evidence suggesting that vitamin B12 is Genotoxic **b. Carcinogenicity** Expert Group on Vitamins and Minerals (EVM) stated that there is no evidence suggesting that vitamin B12 is carcinogenic. Classified as **Low Hazard**	There is no evidence relating to toxicity on reproductive organs and teratogenicity or adverse effects on fertility or postnatal development. **(Refer page 9 of 13)** Classified as **Low Hazard**	There has been no target organ adverse effect observed during any studies conducted. Classified as **Low Hazard**	No data available	0.0595 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

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					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Pyridoxine Hydrochloride	Vitamins supplement	10	API/TOXASSESSMENT/PYRIDOXINE HYDROCHLORIDE	**a. Genotoxicity** There were no Genotoxicity studies submitted for the combination doxylamine and pyridoxine or pyridoxine alone. **b. Carcinogenicity** The carcinogenic potential of pyridoxine hydrochloride has not been evaluated. Classified as **Low Hazard**	No adverse effect has been reported with the use of physiologic doses during pregnancy. However the use of high dose during pregnancy has been implicated in some cases of vitamin B6 dependent syndrome in infant. Classified as **Low Hazard**	No data available	No data available	0.050 mg/day	No	No
	Folic Acid	Vitamins supplement	5	API /TOXASSESSMENT/ FOLIC ACID	**a. Genotoxicity** There was no evidence of Mutagenecity during studies conducted **b. Carcinogenicity** There has been no carcinogenicity related studies identified during literature review. Classified as **Low Hazard**	Very high dose of folic acid have been shown to cause foetal abnormalities in rats; however harmful effects in the human foetus, mother or pregnancy have not been reported. **(Refer page 14 of 19)** Classified as **Low Hazard**	Histopathological studies in some strains of mice showed that toxic doses may also cause renal tubular necrosis. Classified as **Low Hazard**	Not identified in assessment	0.020 mg/day	No	No
	Azithromycin	Antibiotic	100	a) API/TOXASSESSMENT/AZITHROMYCIN b) VC041-S085	a. **Genotoxicity** Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. **b. Carcinogenicity** Long-term studies in animals have not been performed to evaluate carcinogenic potential. Classified as **Low Hazard**	Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These daily doses in rats and mice, based on body surface area, are estimated to be 4 and 2 times, respectively, an adult daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. Classified as **Low Hazard**	Phospholipidos has been observed at very high dose. Classified as **Low Hazard**	No data available Classified as **Low Hazard**	0.667 mg/day	No	No
	Azithromycin	Antibiotic	250								
	Azithromycin	Antibiotic	500								

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

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					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Ketorolac Tromethamine	NSAID	10	API /TOXASSESSMENT/ KETOROLAC TROMETHAMINE	**a. Genotoxicity** Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. It did not cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590 µg/Ml and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells. Classified as **Low Hazard** **b. Carcinogenicity** An 18-month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg, showed no evidence of tumorigenicity. Classified as **Low Hazard**	Impairment of fertility did not occur in male or female rat at oral dosage of 9mg/kg and 16 mg/kg of Ketorolac Tromethamine respectively. Reproduction studies have been performed during organogenesis using daily oral doses of ketorolac tromethamine at 3.6 mg/kg (0.37 times the human AUC) in rabbits and at 10 mg/kg (1.0 times the human AUC) in rats. Results of these studies did not reveal evidence of teratogenicity to the fetus. However, animal reproduction studies are not always predictive of human response Classified as **Low Hazard**	None Classified as **Low Hazard**	Ketorolac tromethamine is contraindicated in patients who are hypersensitivity to the active substance or to any of the excipients Classified as **Low Hazard**	1.440 mg/day	No	No
	Ibuprofen IP	Anti-inflammatory	400	a) Module 2 Ibuprofen	**a. Genotoxicity:** No genotoxicity observed. **b. Carcinogenicity:** No carcinogenicity observed. Classified as **Low Hazard**	Not teratogenic. Classified as **Low Hazard**	**26 – weeks Oral toxicity study in rats-** Hematological study showed that both male and female at 180 mg/kg/day were anemic with low erythrocyte count s, hemoglobin concentrations and hematocrits. Male exhibit a slight increase in thyroid glands weight. However, the leukocytes counts were not affected significantly.	Hypersensitive reported to certain patient during consumption of Ibuprofen. **(Refer page 8 of 14 of module 2** Classified as **Low Hazard**	0.0375 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

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					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Paracetamol	Antipyretic	325	a) API/ TOXASSESSMENT/ PARACETAMOL b) Module 2 Paracetamol	**c. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **d. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No
	Ibuprofen IP	Anti-inflammatory	400	a) Module 2 Ibuprofen	**e. Genotoxicity:** No genotoxicity observed. **f. Carcinogenicity:** No carcinogenicity observed. Classified as **Low Hazard**	Not teratogenic. Classified as **Low Hazard**	**26 – weeks Oral toxicity study in rats-** Hematological study showed that both male and female at 180 mg/kg/day were anemic with low erythrocyte count s, hemoglobin concentrations and hematocrits. Male exhibit a slight increase in thyroid glands weight. However, the leukocytes counts were not affected significantly.	Hypersensitive reported to certain patient during consumption of Ibuprofen. **(Refer page 8 of 14 of module 2** Classified as **Low Hazard**	0.0375 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Paracetamol	Antipyretic	325	b) API/ TOXASSESSMENT/ PARACETAMOL b) Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No
	Etamsylate BP	Anti-fibrinolytic	250	VC041-S075	**a. Genotoxicity :** Two in vitro studies for gene mutation using Salmonella Typhimurium TA98, TA100, TA1535 and TA1538, both with and without activation were performed. In the first assay , concentrations of ethamsylate of 0.001 to 10% produced no mutagenicity. In second assay, concentrations of ethamsylate of 0.312 to 10.0 mg/plate produced no mutagenicity. **(Refer page 6 of 18 of Version 3)** **b. Carcinogenicity:** No reports available on Carcinogenicity of Ethamsylate. Classified as **Low Hazard**	Group of pregnant female wistar rats and swiss albino mice were given dose of 0, 100, 200 and 300 mg/kg bw/day and rabbit were given oral dose of 0, 150, 200 or 300mg/kg bw/day during gestation. No evidence of maternal toxicity or teratogenicity observed. **(Refer page 6 of 18 of Version 3)** Classified as **Low Hazard**	None Classified as **Low Hazard**	No data available Classified as **Low Hazard**	12.500 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

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					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Etamsylate BP	Anti-fibrinolytic	500	VC041-S075	**a. Genotoxicity :** Two in vitro studies for gene mutation using Salmonella Typhimurium TA98, TA100, TA1535 and TA1538, both with and without activation were performed. In the first assay, concentrations of ethamsylate of 0.001 to 10% produced no mutagenicity. In second assay, concentrations of ethamsylate of 0.312 to 10.0 mg/plate produced no mutagenicity. **(Refer page 6 of 18 of Version 3)** **b. Carcinogenicity:** No reports available on Carcinogenicity of Ethamsylate. Classified as **Low Hazard**	Group of pregnant female wistar rats and swiss albino mice were given dose of 0, 100, 200 and 300 mg/kg bw/day and rabbit were given oral dose of 0, 150, 200 or 300mg/kg bw/day during gestation. No evidence of maternal toxicity or teratogenicity observed. **(Refer page 6 of 18 of Version 3)** Classified as **Low Hazard**	None Classified as **Low Hazard**	No data available Classified as **Low Hazard**	12.500 mg/day	No	No
	Aluminium Hydroxide USP	Antacid	306	VC041-S073	**a. Genotoxicity :** No data available **b. Carcinogenicity:** Aluminium Hydroxide was not carcinogenic after daily administration to mice for 4 months at doses up to about 200 mg Aluminium Hydroxide /kg/day. **(Refer page 11 of 30 of Version 2)** Classified as **Low Hazard**	No significant maternal toxicity was observed at any dose level of Aluminium Hydroxide . **(Refer page 9 of 30 of Version 2)** Classified as **Low Hazard**	No significant target organ toxicity observed Classified as **Low Hazard**	No data available Classified as **Low Hazard**	30.72 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

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					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Magnesium Hydroxide USP	Antacid	400	VC041-S074	**a. Genotoxicity :** Magnesium Hydroxide is not mutagenic in Salmonella typhimurium reverse mutation assay and in the E. coli reverse mutation assay. **(Refer page 8 of 22 of Version 2)** **b. Carcinogenicity:** Preventive effect of magnesium hydroxide on carcinogen induced, large bowl carcinogenesis was examined in three experiments using F344 rats. The results of the experiments suggest that magnesium, one of the essential metals, is a promising chemo-preventive agent in human. No carcinogenicity observed. **(Refer page 8 of 22 of Version 2)** Classified as **Low Hazard**	No reproductive toxicity observed when groups of 10 male and 10 female wistar rats received 0, 110, 330 or 1000mg/kg/day magnesium hydroxide in water daily. **(Refer page 8 of 22 of Version 2)** Classified as **Low Hazard**	No significant target organ toxicity observed Classified as **Low Hazard**	Very slight erythema observed for all animals treated at 50% was considered not toxicologically significant. Magnesium hydroxide regarded as a skin sensitizer. **(Refer page 9 of 22 of Version 2)** Classified as **Low Hazard**	40.00 mg/day	No	No
	Albendazole IP	Broad spectrum Anthelmintic	400	a) Module-02 Albendazole	**a. Genotoxicity :** Albendazole produced **negative results in bacterial mutation** tests using strains of Salmonella typhimurium . **b. Carcinogenicity:** No carcinogenicity observed. **(Refer page 16 of 22 of module 2)** Classified as **Low Hazard**	Reproductive toxicity of 15 to 44 Dorset Horn Cross and Clun mated ewes were given single dose of 0, 7.5, 10, 15 or 20mg/kgbw albendazole by oral drench. Treatment was on gestation day 17 and ewes wre allow to deliver naturally. There was no overt maternal toxicity. **Refer page 18 of 22 of module 2)** Classified as **Low Hazard**	Albendazole was tested in several repeat oral dose studies in mice, rats and dogs. An NOEL of 7 mg/kg bw/day has been identified for hepatotoxicity and testicular toxicity. **Refer page 16 of 22 of module 2)** Classified as **Low Hazard**	Hypersensitive rarely reported to certain patient **(Refer page 11 of 22 of module 2)** Classified as **Low Hazard**	0.020 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Cetirizine Hydrochloride IP	Anti Histamine	10	a) Module-02 Cetirizine Hydrochloride	**a. Genotoxicity :** No genotoxicity observed. **b. Carcinogenicity:** No carcinogenicity observed. **(Refer page 19 & 20 of 22 of module 2)** Classified as **Low Hazard**	Not teratogenic. **(Refer page 20 & 21 of 22 of module 2)** Classified as **Low Hazard**	The Target Organ of toxicity was the Liver. In mice up to 4 week study enlarge liver, increased liver weights, hepatocellular hypertrophy and vacuolation were observed. **(Refer page 14 of 22 of module 2)** Classified as **Low Hazard**	Hypersensitive reported very rarely. **(Refer page 12 of 22 of module 2)** Classified as **Low Hazard**	0.05556 mg/day	No	No
	Paracetamol	Antipyretic	500	a) API/ TOXASSESSMENT/ PARACETAMOL / b) Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

Name of Product	Active Ingredient	Pharmacological Category	Strength (mg)	Reference Document number for assessment	Details of toxicological assessment					Weather any technical/ organizational measures required	Whether identified for cleaning validation
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE (mg/day)		
	Paracetamol	Antipyretic	500	c) API/ TOXASSESSMENT/ PARACETAMOL / b) Module 2 Paracetamol	**a. Genotoxicity :** It is found not mutagenic in vivo but positive in vitro mouse lymphoma assay. In the published literature , acetaminophen has been reported to be clastogenic at 1500 mg/kg/day (3.6 times MHDD) **b. Carcinogenicity:** Female rat demonstrated equivocal incidence of carcinogenic activity at 0.8 times MHDD of 4 g/day. In contrast, there was no evidence of carcinogenic activity in male rat or mice **(Refer page 9 of 12 of module 2)** Classified as **Low Hazard**	Not teratogenic, Pregnant rat received oral acetaminophen during organogenesis at dose up to 0.85 times maximum human daily dose (4g/day) showed evidence of Fetotoxicity (reduced fetal weight and length) and a dose related bone variation. **(Refer page 10 of 12 of module 2)** Classified as **Low Hazard**	Contraindicated in the patient with severe hepatic impairment or severe active liver disease. **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	Hypersensitive reported to certain patient during consumption of Acetaminophen **(Refer page 8 of 12 of module 2** Classified as **Low Hazard**	0.0667 mg/day	No	No

Note: The molecules identified with '#' mark where PDE is not calculated shall not be taken for manufacturing.

Evaluation by:_____ _____ **(Quality Assurance)** **Verified by :** _____ **(Quality Assurance)**

SECTION I	**SUMMARY OF EVALUATION:** Based on the toxicological assessment of the active ingredients in the product manufactured at the site following is the summary: a. The least PDE value among all product mix is for Glimepiride (0.00196 mg/kg). Hence this molecule is identified for additional control measure during routine manufacturing along with the cleaning validation. These controls shall be implemented during routine manufacturing. Glimepiride is considered as a worst case molecule for which cleaning validation has been successfully completed with 3 run. All the molecules handled at the site has been evaluated with respect to toxicological aspect, however the PDE determination has been not completed for the following molecules: a. Amlodipine Basilate b. Mefenamic acid c. Rabeprazole d. Domeperidone The above mentioned molecules where the PDE values determination is not done are not released for routine manufacturing.
SECTION J	**CONCLUSION : Cleaning validation activity required : Yes / No**

CLEANING VALIDATION MASTER PLAN FOR PRODUCTION EQUIPMENTS (APPENDIX- I)

Effective Date:

SECTION K	COMMENTS AFTER COMPLETION OF CLEANING VALIDATION :
CHECKED BY :_____	
REVIEWED BY :_____	