Strategy for Managing Risks associated with Cross Contamination of Products in Shared Manufacturing Facility

Annexure-04 – Summary of Toxicological Assessment and HBEL /PDE Value of API molecules handled at site

Manufacturing Site: **Revision No.: 00** **Effective Date:**

Section 1- Summary data of Toxicological Assessment and PDE Value of API

Serial No.	Active Ingredient	Pharmacological category	Pharmaceutical dosage form / Strength of API (mg)	Reference document number for toxicological assessment	Evaluation of toxicological assessment				
					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive / Developmental toxicity	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE value (µg/day)
1.	Paracetamol	Analgesic and Antipyretic	Tablet and caplet 500 mg and 325 mg	Module-02 Toxicological review and PDE for Paracetamol	**a. Genotoxicity :**Not mutagenic Acetaminophen was not mutagenic in the bacterial reverse mutation assay. But tested positive in the in-vitromouse lymphoma assay and invitro chromosomal aberration assay using human lymphocytes. Acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6 times the MHDD, based on a body surface area). Also no clastogenecity was noted at a dose of 750 mg/kg/day (1.8 times the MHDD based on body surface) **Based on above data considered as Negative** Classified as **Low Hazard** **b. Carcinogenicity: Non-Carcinogenic** Long term studies in rats has been conducted for 2 years up-to 6000 ppm. there was equivocal evidence of carcinogenic activity of acetaminophen in female F344/ N rats based on incr incidences of mononuclear cell leukemia. There was no evidence of carcinogenic activity of acetaminophen in male and female B6C3F1 mice that recived 600, 3000, or 6000 ppm. **Based on above data considered as Non-Carcinogenic** Classified as **Low Hazard**	Pregnant rats were treated with paracetamol (150, 500 or 1500 mg/kg, once a day) from the first day upto term pregnancy. In the group treated with the lowest dose no historical changes were noted in maternal and fetal livers or kidneys when examined under light or electron microscopy. **No maternal toxicity, Non fetotoxic & non teretogenic** Classified as **Low Hazard**	No data available for serious target organ toxicity Classified as **Low Hazard**	Sensitizing potential not reported Classified as **Low Hazard**	81.02 Classified as **Moderate Hazard**
2.	Dicyclomine Hydrochloride/ Dicycloverine Hydrochloride	Anticholinergic Antispasmodic	Tablet 10 mg 20 mg	Module-02 Toxicological review and PDE for Dicyclomine Hydrochloride	**a. Genotoxicity :** No Relevant data available **b. Carcinogenicity:** No Relevant data available Classified as **Low Hazard**	Not teratogenic, The high dose group also had fever live fetuses, more resorptions, and a lower average fetal weight than the other groups. These effects were attributed to maternal toxicity which was apparent at the 100 mg/ kg dose level Classified as **Low Hazard**	No data available for serious target organ toxicity Classified as **Low Hazard**	Sensitizing potential not reported Classified as **Low Hazard**	100 Classified as **Moderate Hazard**
3.	Phenylephrine Hydrochloride	Anti-cold	Tablets 10 mg	Module-02 Toxicological review and PDE for Phenylephrine	**a. Genotoxicity :** Non-Mutagenic in several studies. **b. Carcinogenicity:** None Carcinogenesis studies of USP grade Phenylephrine hydrochloride were conducted in Rat & Mice of each 2 years. Dosage of 0, 620 & 1250 ppm for rat and 0, 1250, 2500ppm for Mice. In the 2 year of study approx. amount consumed per day was 24mg/Kg for Low dose rats, 50mg/Kg for high dose rat, 133mg/Kg for low dose mice & 270mg/Kg for high dose Mice. There	Fetotoxicity Reported. Phenylephrine given to pregnant rabbit during the last third of gestation produced a decrease in fetal weight and the onset of early labor at a dose of 1mg 3x/day(3mg/3Kg or 1mg/Kg) Classified as **Low Hazard**	No data available Classified as **Low Hazard**	Non-sensitizing Classified as **Low Hazard**	183.33 Classified as **Low hazard**

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					is no evidence of carcinogenicity. Classified as **Low Hazard**				
4.	Chlorpheniramine Maleate	Anti-cold	Tablet 2 mg	Module-02 Toxicological review and PDE for Chlorpheniramine Maleate	**a. Genotoxicity :** It is found negative in vitro- Salmonella microsomal assay and mouse lymphoma test. Classified as **Relatively safe** **b. Carcinogenicity:** In two year mice Carcinogenity studies in rat, no evidence of carcinogenitywsa seen either in sex when the compound was administered 5 days a week in water at dosages 30/mg/kg body weight. Classified as **Low Hazard**	Female were treated 21 days before mating, until sacrifice at either 14 days of gestation or 21 days parturition. A NOEL of 5 mg/kg of Chlorpheniramine Maleate (3.5 mg/kg bw of Chlorpheniramine Maleate) was established based on postnatal survival of the pups. Classified as **Low Hazard**	No target organ toxicity reported Classified as **Low Hazard**	Non-sensitizing Classified as **Low Hazard**.	20.00 Classified as **Moderate Hazard**.
5.	Gliclazide	Anti-diabetic	40mg 80 mg	Vittarthaa project number VC041-S082	**a. Genotoxicity : Not Mutagenic** Gliclazide was used in the presence of 5 strain of Salmonella typhimurium with and without metabolic activator. No mutagenic effect was seen in the qualitative and quantitive test at dose of 0.005 to 8 mg/dish. In an in vivo chromosomal aberration test, Gliclazide was not found to have any clastogenic activity. In vivo chromosomal aberration test, three groupof 10 of 1 mice: 1 negative control , 1 high dose (2g/kg x 2), 1 Gliclazide low dose (1g/kg x 2) and 1 group of 5 positive control mice given cyclophosphamide (50mg/kg x 2) were used. No evidence was found of any significant variation in the number of erythrocyte micronuclei. Gliclazide was not associated with any mutagenic action detectable by the micronucleus test. Classified as **Relatively safe** **b. Carcinogenicity: Non carcinogenic** Long term toxicity study did not reveled any evidence of Carcinogenicity. Specific carcinogenicity studies have not been performed. Gliclazide belongs to the chemical class of Phenylsulfonyl urea which did not demonstrate any mutagenic or carcinogenic potential. 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 **Relatively safe**	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**	Not sensitizing reported. Classified as **Relatively safe**	400.00 Classified as **Low Hazard**

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					Any hazard related to Genotoxicity/ Carcinogenicity	Any hazard related to Reproductive / Developmental toxicity	Any hazard related to Target organ toxicity	Any hazard related to sensitizing potential	Details of PDE value (µg/day)
6.	Metformin Hydrochloride	Anti-Diabetic	Tablet 400 mg, 500 mg and 1000 mg	Module-02 Toxicological review and PDE for 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. Classified as **Relatively safe**	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. 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. These effects are based on dose Classified as **Low Hazard**	Reported Hypersensitivity to metformin hydrochloride or to any of the excipients. Classified as **Low Hazard**	20.00 Classified as **Moderate Hazard**
7.	Glimepiride Tablets	Anti- Diabetic	Tablet 1 mg 2 mg	Module-02 Toxicological review and PDE for Glimepiride	**a. Genotoxicity :** There were negative results in multiple In-vitro studies performed at various doses. Concluded as Non mutagenic **b. Carcinogenicity:** There was no Carcinogenecity demonstrated in multiple studies conducted for a period of 30 months with a maximum dose upto 5000. These studies were performed using Mouse and Rat Wistar Classified as **Relatively safe**	There was no effect on fertility during studies conducted in Mouse and Rat up-to dose of 2500 mg/ kg Terotology studies were conducted upto 2500 mg/ kg. No effect on pregnancy, 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. Hypoglycemeia during pregnancy and fetus with dose of 0.0067 and 0.0212 mg /kg Classified as **Low Hazard**	Glimepiride does not exhibit toxicity at doses in animal studies. Human TDLo reported with 0.028 mg/kg. Blood Hemorrhage and Thrombocytopenia Dermatitis has been reported and considered ad POD for PDE calculation. In case of severe renal or hepatic function disorders, a changeover to insulin is required. Reported based on dose **Classified as Low Hazard**	Not sensitizing reported. Classified as **Low Hazard**	3.33 Classified as **Highly hazard**
8.	Atenolol	Antihypertensive	Tablets 50 mg	Module-02 Toxicological review and PDE for Atenolol	**a. Genotoxicity :** Non –Mutagenic No evidence for induced mutagenicity was seen with an in vitro microbial test system (Ames test) with or without metabolic activation. Atenolol was not mutagenic in vivo cytogenicity test in Chinese hamsters or the dominant lethal assay in mice. b. **Carcinogenicity:** Non-Carcinogenic No evidence of carcinogenicity was observed following administration of atenolol at dosage	No toxicity Atenolol did not revealed evidence of impaired fertility in female and male rats. Developmental or reproductive toxicity produced a dose –related increase in embryo/ fetal resorptions in rats at doses equal to or greater than 50mg/kg/day although similar effects were not seen in rabbits. Fetal loss at highest doses by gavage studies on rats. But no increase in congenital defects found. Dose levels of 50 or more mg/kg/day associated with an increase	Not reported Classified as **Low Hazard**	Non sensitizing Classified as **Low Hazard**	20 µg/day Classified as **Moderate hazard**

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					up to 300 mg/kg daily for 18 months in mice or 18 or 24 month in rats.However an increased of benign adrenal medullary tumar in male and female, mammary fibro adenomas in female, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in male was observed at 24 months in rat receiving high dose 500-1500 mg/kg of atenolol daily. Classified as **Low Hazard**	incidence of resorptions in rats. Classified as **Low Hazard**			
9.	Doxylamine Succinate	Antihistamine	10 mg	Module-02 Toxicological review and PDE for 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. 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. Classified as **Low Hazard**	The histological changes were identified in the lever and parotid salivary gland at high dose. Classified as **Low Hazard**	Non-sensitizing **Low Hazard**	**13.33** µg/day Classified as **Moderate hazard**
10.	Allopurinol	Antigout	Tablet 100 mg and 300 mg	Vittartha Project No. VC041-S067	**a. Genotoxicity :** No evidence of clastogenisity was observed in an in-vivo micronucleus test in rat. **b. Carcinogenicity:** No evidence of tumorgenicity was observed in male or female mice or rat that receive oral allopurinol for majority of the life spans (greater than 88 weeks) at doses up to 20 mg/kg/day, this dose is equivalent to 0.3 and 0.6 times the maximum human recommended dose. Classified as **Relatively safe**	Reproduction studies in rat and rabbit using dosage up to 20 times of the human dosage have not revealed evidence of impaired fertility. There was no evidence of fetotoxicity or teratogenicity in rats or rabbits treated during the period of organogenesis with oral allopurinol at dosage up to 200 mg/kg/day and up to 100 mg/kg/day respectively. Classified as **Moderate Hazard**	No serious target organ toxicity has been identified Classified as **Low Hazard**	Reported Featal cases of toxic epidermal nacrolysis, hypersensitivity angitis and allergic vasculitis involving erythematous macualopapular rash with desquamation, severe exfoliative dermatitis , steven-johnson syndrome has been reported as adverse indication. Classified as **Low Hazard**	80.00 µg/day Classified as **Moderate hazard**
11.	Ketorolac Tromethamine	NSAID	10 mg	Vittartha Project No. VC041-S068	**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	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	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	1440 µg/day Classified as **Low hazard**

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					Any hazard related to Genotoxicity/ Carcinogenicity	**Any hazard related to Reproductive / Developmental toxicity**	**Any hazard related to Target organ toxicity**	**Any hazard related to sensitizing potential**	**Details of PDE value (µg/day)**
					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**	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**		**Low Hazard**	
12.	Mecobalamin	Vitamins Supplement	0.5	Module-02 Toxicological review and PDE for Mecobalamin	**a. Genotoxicity** There is no evidence that vitamin B12 is Carcinogenic or Genotoxic in Vitro and Vivo. There are some limited inconsistent evidence to suggest that high dose of Vitamin B12 may have tumour promoting activity. Classified as **Low Hazard** **b. Carcinogenicity** There is no evidence that vitamin B12 is Carcinogenic or Genotoxic in Vitro and Vivo. There are some limited inconsistent evidence to suggest that high dose of Vitamin B12 may have tumour promoting activity. Classified as **Low Hazard**	There is no vitamin B12 and teratogenicity or adverse effect on fertility or postnatal development. Parenteral methylcobalamine is classified as pregnancy category C. Adequate study in human have not been conducted , however no maternal or fetal complication have been associated with that are recommended during pregnancy. Classified as **Low Hazard**	Not reported Classified as **Low Hazard**	Sensitization to methylcobalamine is rare, but may present as an itching exanthema and axceptionally an anaphylatic shock. Classified as **Low Hazard**	59.50 µg/day Classified as **Moderate hazard**
13.	Pyridoxine Hydrochloride	Vitamins supplement	10mg	Module-02 Toxicological review & PDE for Pyridoxine Hydrochloride	**a. Genotoxicity: None** There were no Genotoxicity studies submitted for the combination doxylamine and pyridoxine or pyridoxine alone. Classified as **Low Hazard** **b. Carcinogenicity : None** 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. Classified as**Low Hazard**	Not reported Classified as **Low Hazard**	Non sensitizing Classified as **Low Hazard**	50.00 µg/day Classified as **Moderate hazard**
14.	Folic Acid	Vitamins supplement	5	Module-02 Toxicological review & PDE for Folic Acid	**a. Genotoxicity** There has been no carcinogenicity related studies identified during literature review. Classified as **Low Hazard** **b. Carcinogenicity** Folic acid has been associated with an increased incidence of Oropharynx, hypopharynx and all cancer, but as indicated	There is no known hazards to use of folic acid in pregnancy; supplements of folic acid are often beneficial. Classified as **Low Hazard**	Not reported Classified as **Low Hazard**	Hypersensitivity ma occur, but is most likely very rare. Classified as **Low Hazard**	20.00 µg/day Classified as **Moderate hazard**

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					by the author of this epidemiological study, these cancers are largely smoking – and /or alcohol related and this finding likely related to these confounding factor. In other studies an inverse relation was found between folate intake and / or status and colorectal cancer, and with cervical cancer. Treatment of smokers with 10mg folic acid plus 500 µg hydroxocobalamine for 4 months resulted in a reduction in atypical bronchial squamous metaplasia. Classified as**Low Hazard**				
15.	Calcium Citrate	Calcium Supplement	1000	Module-02 Toxicological review & PDE Calcium Citrate	**a. Genotoxicity : None** **b. Carcinogenicity: None** Classified as **Low hazard**	Some time kidney stone and renal impairement may occur . Classified as **Low hazard**	No target organ toxicity reported. Classified as **Low Hazard**	Not sensitizing Classified as L**ow hazard**	1250 µg/day Classified as **Low hazard**
16.	Cholecalciferol (Vitamin D3)	Source of Vitamin D	200 I.U /5 µcg	Module-02 Toxicological review & PDE for Vitamin D3	**a. Genotoxicity :** Vitamin D3 was tested in Salmonella typhimurium assay at doses 0.033 to 10 mg/plate in Salmonella typhimurium (strains TA1535, TA1537, TA97,TA98 and TA100) in the absence and presence of rat or hamster liver S9. VitaminD3 was negative in these tests. Dose above 1mg/plate exhibited slightly toxicity. **b. Carcinogenicity:** No data available Classified as **Low hazard**	There is a report on treatment during pregnancy of women suffering from hypoparathyroidism. In the latter case the mother had extremely high plasma and normocalcaemia. At parturition the cord serum concentration was strongly elevated and the child had mild hypercalcaemia the first two days of life. None of the children had other sign of toxicity. Classified as **Low hazard**	No target organ toxicity reported Classified as **Low Hazard**	Not sensitizing Classified as L**ow hazard**	2.5 Classified as **Highly hazard**
17.	Azithromycin	Antibiotic	100mg, 250 & 500mg	Vittartha Project No. VC041-S085	**a. Genotoxicity :** In the Ames Salmonella typhimurium tester strains TA1535, TA1537, TA98 and TA100, the presence of Azithromycin was not associated with an increase in the number of his - revertants In vivo assessment of this compound was completed in male and female mice with a single dose of 200 mg/kg followed by sacrifice at 6,26 or 48 hr later and metaphase analysis of bone marrow for chromosomal aberrations. No statistically significant elevation of chromosomally aberrant cells were found. **b. Carcinogenicity:** Long –term studies in animal have not been performed to evaluate carcinogenic potential.	Azithromycin was not teratogenic at any dose level. Similar study in albino mice at the same dose level did not produce embryo toxic, Fetotoxic, or teratogenic effects, and foetal tissue concentration were higher than the maternal plasma or amniotic fluid. Classified as **Low hazard**	No target organ toxicity reported Classified as **Low Hazard**	Not sensitizing Classified as L**ow hazard**	667 µg/day Classified as **Low hazard**

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					Classified as **Low hazard**				
18.	Cetirizine	Anti-Histamine	Tablets/ 10 mg	Module-02 Toxicological review and PDE for Cetirizine	**a. Genotoxicity :** Non –Mutagenic Non mutagenic in the Ames test and not clastogenic in the human lymphocytes assay, the mouse lymphoma assay, and in vivo micronucleus test in rats. b. **Carcinogenicity:** Non-Carcinogenic In a 2 year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg. Classified as **Low Hazard**	**Non Teratogenic** Reproductive and fertility mouse oral 64mg/kg/day NOAEL No effect at maximum dose embryo/Fetal Development mouse oral 96 mg/kg/day NOAEL Not Teratogenic. Embryo/Fetal development rat oral 225 mg/kg/day NOAEL not teratogenic. Embryo/Fetal development rabbit oral 135mg/kg/day NOAEL not teratogenic. **Maternal Toxicity**-Reported at high doses Reproductive toxicology studies in segment I (mouse) only notable toxicity was increase liver weights in the HD. Segment II study, 8 dams died (5 due to drug toxicity), maternal toxicity was seen at 75 and 225 mg/kg/day. Classified as **Low Hazard**	No target organ toxicity reported Classified as **Low Hazard**	Clinical studies shown that minor undesirable effect on the CNS including somnolence, fatigue, dizziness and headache. In some cases, paradoxical CNS stimulation has been reported**.** Classified as **Low Hazard**	**33.33** µg/day Classified as **Moderate hazard**
19.	Magnesium Hydroxide	Antacid	400 mg	Study title PDE determination for Magnesium Hydroxide **VC041-S074**	**a. Genotoxicity :** Not Genotoxicity Magnesium hydroxide was tested in the Salmonella typhimurium reverse mutation assay with four histidine-requiring strains of Salmonella typhimurium (TA1535, TA1537, TA98 and TA100) and in the Escherichia coli reverse mutation assay with a tryptophan-requiring strain of Escherichia coli (WP2uvrA). Based on the results of this study, it is concluded that Magnesium hydroxide is not mutagenic in Salmonella typhimurium reverse mutation assay and in the Escherichia coli reverse mutation assay. **b. Carcinogenicity:** Non carcinogenic Preventive effect of magnesium hydroxide on carcinogen-induced, large bowel carcinogenesis was examined in three experiments using F344 rats. The results of the three experiments suggest that magnesium, one of the essential metals, is a promising chemopreventive agent in	The reproductive effects of magnesium hydroxide (pH = 10) were studied in rats that received the test material via gavage. Groups of 10 male and 10 female Wistar rats received 0, 110, 330 or 1000mg/kg bw/day magnesium hydroxide in water daily. Males were exposed for 29 days (i.e. 2 weeks prior to mating, during mating, and up until treatment end) and females were exposed for 41-45 days (i.e.2 weeks prior to mating, during mating, during post-coitum, and during at least 4days of lactation). No treatment-related effects were observed on clinical signs, body weight or weight gain, feed consumption or hematology Classified as **Low Hazard**	Not Reported Classified as **Low Hazard**	Sensitization reported Three groups of 5 female CBA/J mice were treated with one test substance concentration per group. The Stimulation Index (SI) values calculated for the substance concentrations 10, 25 and 50% were 2.0, 3.6 and 5.9 respectively. These results indicate that the test substance could elicit an SI >= 3. According to the recommendations made in the test guidelines, Magnesium hydroxide would be regarded as a skin sensitizer.	40000 µg/day Classified as **Low hazard**

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					humans. Classified as **Low Hazard**			Classified as **Low Hazard**	
20.	Aluminium Hydroxide	Antacid	306 mg	Study title PDE determination for Aluminium Hydroxide **VC041-S073**	**a. Genotoxicity :** **Unknown** **b. Carcinogenicity:** **Non carcinogenic** Aluminium hydroxide was not carcinogenic after daily i.p. administration to mice for 4 months at dosages up to about 200mg aluminium/kg/day. Classified as **Low Hazard**	Al(OH)3 was given by oral gavage at dose levels of 192, 384 and 768 mg/kg/day to groups of pregnant rats from day 6 through day 15 of gestation. No significant maternal or developmental toxicity was observed at any dose level of Al(OH)3. Classified as **Low Hazard**	Not Reported Classified as **Low Hazard**	Non sensitizing Classified as **Low Hazard**	30720 µg/day Classified as **Low hazard**
21.	Etamsylate	Anti-fibrinolytc	250 mg & 500 mg	Study title PDE determination for Etamsylate **VC041-S075**	**a. Genotoxicity :** Not reported **b. Carcinogenicity:** None, Classified as **Relatively safe**	Groups of pregnant female wistar rats and Swiss albino mice were given doses of 0, 100, 200 or 300 mg mg/kg/day and rabbits were given oral doses of 0, 150, 200 or 300 mg/kg/day during gestation, there was no evidence of maternal toxicity or teratogenicity at any dose level. Classified as **Low Hazard**	Not Reported Classified as **Low Hazard**	Non sensitizing Classified as **Low Hazard**	12500 µg/day Classified as **Low hazard**
22.	Ibuprofen	Anti-inflammatory	Tablet 400 mg	Module-02 Toxicological review and PDE for Ibuprofen	**c. Genotoxicity:** Not reported **d. Carcinogenicity:** None, Classified as **Relatively safe**	Reported at high dose. Fertility and embryonic development Rat rectal 200mg/kg/day Fetoxicity. Fertility and embryonic development Rat rectal 100mg/kg/day Fertility. Classified as **Low Hazard**	Cardiac, renal and hepatic impairment may precipitate renal failure. Pediatric population – risk of renal impairment in dehydrated children and adolescent. Gastrointestinal bleeding ulceration and perforation. Classified as **Moderate Hazard**	Reported Serious skin reaction some of the fetal ,including exfoliate dermatitis Steven-Johnson syndrome and toxic epidermal narcosis has been observed reported very rarely in association with the use of NSAIDs. Ibuprofen should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity. Classified as **Moderate Hazard**	37.50 µg/day Classified as **Moderate hazard**

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23.	Albendazole	Broad spectrum Anthelmintic	Tablet/ suspension 400 mg	Module-02 Toxicological review and PDE for Albendazole	**a. Genotoxicity :** **Non genotoxic** Albendazole produced negative results in bacteril mutation tests. There was no clstogenecity in an in-vitro metaphase analysis of Cjinese hamster ovary cells and was negative in an in-vitro cell transformation assay in BALB /3T3 mouse cells. **b. Carcinogenicity:** **Non Carcinogenic** Chronic exposure or Carcinogenecity was performed on groups of 100 male and 100 female Charles River CD-1 mice were fed diet containing albendazole for 25 months at doses of 0, 25, 100 or 400 mg/kgbw/day. Additional groups of 25 males and 25 females were given control and high dose treatments and used for hematology measurements. There was no toxic signs or effect on food intake and body weight. Classified as **Relatively safe**	A comprehensive series of development studies in mice, rats, rabbits and sheep showed Albendazole to be teratogenic. The malformation included visceral craniofacial and bone defects. The lowest NOEL for any of the studies was 5 mg/kg bw/day for Albendazole administered orally to rat and rabbits. Contraindicated during Pregnancy and for one month prior to conception. In animal studies Albendazole Classified as **moderate hazard**)	May cause damage to organs through prolonged or repeated exposure Classified as **Low Hazard**	Rarely reported. May cause skin irritation and respiratory irritation Classified as **Low Hazard**	17.50 µg/day Classified as **Moderate hazard**

Section 2: Segregation of API molecules based on PDE value < 10 µg/ day and Hazard (Moderate or Highly hazard)

Serial No.	Active Ingredient (API)	Details of area used for manufacturing	Details of PDE value (µg/day)	Details of hazard that require control measure	Details of specific Technical / Organizational controls identified
1.	Glimepiride	Tablet	3.33	• Molecule with PDE value < 10 µg/ day • Molecule is having pharmacological potency 1.0 mg which needs controls	a. Manufacturing shall be carried in campaign b. Cleaning validation shall be performed for all equipment's used in manufacturing process c. Cleaning verification shall be performed post every product changeover cleaning
2.	Albendazole	Tablet	20.00	Teratogenicity identified in animal study	a. Manufacturing shall be carried in campaign b. Cleaning validation shall be performed for all equipment's used in manufacturing process c. Cleaning verification shall be performed post every product changeover cleaning
3.	Cholecalciferol	Tablet	2.5	• Molecule with PDE value < 10 µg/ day	a. Manufacturing shall be carried in campaign b. Cleaning validation shall be performed for all equipment's used in manufacturing process c. Cleaning verification shall be performed post every product changeover cleaning

Section 3: Revision History

Revision No.	Effective date	Changes incorporated
		Revised certain statement in section of strategy documents and its annexure.

Prepared By (Sign/Date): _____ **Checked By (Sign/Date):** _____