CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-175Orig1s000

PHARMACOLOGY REVIEW(S)

N22175 Pancrecarb (pancrelipase) Delayed-Release Capsules

From A. Jacobs, AD
Aug 25, 2009

I concur that there are no outstanding pharm/tox issues.

I concur that the pregnancy category should be C. I noted that the sponsor's proposed labeling does not list a pregnancy category.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22175	ORIG 1	DIGESTIVE CARE INC	PANCRECARB

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABIGAIL ABBY C C JACOBS
08/25/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-175**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**October 27, 2008**
PRODUCT:	**Pancrecarb™ (Pancrelipase)**
INTENDED CLINICAL POPULATION:	**Exocrine Pancreatic Insufficiency**
SPONSOR:	**Digestive Care, Inc.**
DOCUMENTS REVIEWED:	**NDA Application (Module 2 and 4)**
REVIEW DIVISION:	**Division of Gastroenterology Products (DGP)**
PHARM/TOX REVIEWER:	**Tamal K. Chakraborti, Ph.D.**
PHARM/TOX SUPERVISOR:	**Sushanta K. Chakder, Ph.D.**
DIVISION DIRECTOR:	**Donna Griebel, M.D.**
PROJECT MANAGER:	**Elizabeth A.S. Ford, RN**

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability: From a nonclinical standpoint, this NDA is recommended for approval for the proposed use.

B. Recommendation for Nonclinical studies: None

C. Recommendations on Labeling: The draft labeling of Pancrecarb generally conforms to the format specified under 21CFR 201.56 and 21CFR 201.57 Requirements for PLR (Physician's Labeling Rule) Prescription Drug Labeling. However, the following changes should be incorporated.

8.1 Pregnancy

Sponsor's Version:

8.1. Pregnancy

(b) (4)

Evaluation: The text is in accordance with 21CFR 201.57(c)(14). However, the labeling text should be modified as proposed below.

Recommended Version:

"8.1 Pregnancy

Teratogenic effects: Pregnancy Category C

Animal reproduction studies have not been conducted with Pancrecarb. It is also not known whether Pancrecarb can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pancrecarb should be given to a pregnant woman only if clearly needed."

8.3. Nursing Mothers

Sponsor's Version

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8.3. Nursing Mothers

(b) (4)

[redacted]

Evaluation: The text is in accordance with 21CFR 201.57(c)(9)(iii). No further changes are needed.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's Version

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

[redacted]

Evaluation: The text is in accordance with 21CFR 201.57(c)(14)(i). However, the labeling should be modified as proposed below.

Proposed Version:

"13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

[redacted]

II. Summary of nonclinical findings

A. Brief Overview of Nonclinical Findings: As per the 2006 guidance on exocrine pancreatic insufficiency (EPI) drug products, no new pharmacology studies are needed because of the extensive use of the currently marketed EPI products. Accordingly, the sponsor did not conduct any nonclinical studies with Pancrecarb. For excipients, as outlined in The FDA Guidance for EPI

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products, no toxicology studies are needed if excipients are classified as GRAS (Generally Recognized as Safe) for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable. All of the excipients used in Pancrecarb are USP/NF compendial items, and some are also GRAS and/or present at levels previously found to be acceptable.

In a FDA communication dated July 11, 2006, the Division recommended that a comprehensive summary with sufficient details of chronic toxicology studies for the excipients would be needed for the NDA. The sponsor provided a comprehensive summary of the toxicology data available for each excipient used in the formulation of Pancrecarb. Based on the available toxicology data for each excipient used in the Pancrecarb drug product, there appears to be no significant safety concern for humans. The exposure assessment indicated that the exposures to all excipients appear to be safe at the specified levels based on the toxicity profile of each excipient. Overall, from a nonclinical perspective, there appears to be no anticipated risks associated with the use of Pancrecarb at the proposed clinical doses in patients with EPI.

B. Pharmacologic Activity: The sponsor did not conduct any pharmacology studies with Pancrecarb. As per the 2006 guidance on EPI drug products, no new pharmacology studies are needed because of the extensive use of the currently marketed products. The pharmacological activity of pancreatic enzymes in patients with EPI is well known and has been comprehensively documented in the literature. Administration of exogenous pancreatic enzymes is considered part of the standard of care for patients with EPI. The early preparations of pancreatic enzymes were often inactivated in the stomach due to the acidic pH of the gastric environment. Currently, microencapsulated enzyme preparations are used which help to deliver the necessary enzymes to the duodenum to facilitate digestion and subsequent absorption of nutrients.

C. Nonclinical Safety Issues Relevant to Clinical Use: None

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-175
Review number: 001
Sequence number/date/type of submission: 000/October 27, 2008/Initial
Information to sponsor: Yes ( ) No (X)
Sponsor: Digestive Care, Inc., Bethlehem, PA
Manufacturer for drug substance: (b) (4)

Reviewer name: Tamal K. Chakraborti, Ph.D.
Division name: Division of Gastroenterology Products (DGP)
Review completion date: June 19, 2009

Drug:

Trade name: Pancrecarb™ (Pancrelipase) (b) (4) 8000 and 16000 USP units of lipase
Generic name: Pancrelipase (lipase, amylase and protease)
Chemical name: Lipase, amylase and protease

Relevant INDs: IND 45,223 (Digestizyme/Pancrecarb, Digestive Care, Inc., DGP)

Drug Class: Enzyme replacement therapy (ERT)

Intended Clinical Population: Pancrecarb is indicated for the treatment of EPI in adults and children.

Clinical Formulation: Pancrecarb capsules are a solid oral dosage form comprised of clear, gelatin capsules containing small enteric-coated microspheres of buffered pancreatic enzymes (lipase, amylase and protease). The pancreatic enzymes are isolated and concentrated from porcine pancreatic glands. Pancrecarb capsules are manufactured (b) (4) as described below in the following Table (from sponsor's submission): (b) (4) MS-8 (8,000 USP units of lipase) and MS-16 (16,000 USP units of lipase).

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Table (3.2.P.1)1. Active Ingredients of PANCRECARB®

Name of ingredients		Unit Quantity (Units/ capsule)	
Components		MS-8	MS-16
Pancrelipase, USP	Lipase (USP Units)	8,000	16,000
	Amylase (USP Units)	(b) (4)	
	Protease (USP Units)		

The drug product composition is shown in the following Table (from sponsor's submission).

Table (3.2.P.1)3. Composition Of The Drug Product

INGREDIENTS	mg/Capsule			% w/w			Function
	(b) (4)	MS-8	MS-16	(b) (4)	MS-8	MS-16	
Pancrelipase, USP (b) (4) 1206 (b) (4) 1208			(b) (4)			(b) (4)	Active Ingredient
Sodium Carbonate (b) (4) NF							(b) (4)
Sodium Bicarbonate, USP							
Sodium Starch Glycolate, NF							
Ursodiol, USP							
Polyvinylpyrrolidone, USP							
Cellulose Acetate Phthalate, NF							
Diethyl Phthalate, NF							
Talc, USP (b) (4)							
TOTAL MASS					100.0	100.0	

* Removed during drying

Route of Administration: Oral (enteric coated capsules)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data Reliance: Any information or data necessary for approval of NDA 22-175 that Digestive Care, Inc. (DCI) does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that

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DCI does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-175.

Background: DCI introduced Pancrecarb capsules to the US market in 1995 as pancreatic enzyme replacement therapy (ERT). Pancrecarb is available in three dosage strengths: MS-4, MS-8, and MS-16. The designations relate to the labeled lipase content of each capsule, 4,000, 8,000, and 16,000 USP Units, respectively.

In the Federal Register (FR) of April 28, 2004 (69 FR 23410), FDA announced that all exocrine pancreatic insufficiency drug products are new drugs and announced the conditions for continued marketing of the drug products. The FR notice further stated that manufacturers who wish to continue to market these products must submit marketing applications as required by section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR §314. An October 26, 2007 FR Notice (72 FR 60860) announced that FDA intends to exercise its enforcement discretion with respect to unapproved pancreatic enzyme drug products until April 28, 2010, if the manufacturers have investigational new drug applications (INDs) on active status on or before April 28, 2008, and have submitted new drug applications (NDAs) on or before April 28, 2009. FDA granted this extension to ensure the availability of EPI drug products during the additional time needed by manufacturers to obtain marketing approval.

As noted in The FDA Guidance (Exocrine Pancreatic Insufficiency Drug Products-Submitting NDAs, April 2006), no new pharmacology studies are needed because of the extensive use of the currently marketed EPI products. Also as outlined in the above-mentioned FDA Guidance, for excipients, no toxicology studies are needed if the excipients used are classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable. The sponsor conducted a search in the FDA's Inactive Ingredient Database (IID) in order to identify levels of each of the excipients in currently approved oral products. All of the excipients used in Pancrecarb are USP/NF compendial items, and some are also GRAS and/or present at levels previously found to be acceptable. The sponsor relied upon information available in the published literature and available information in the public domain for each excipient used in the drug product.

In a FDA communication dated July 11, 2006, the Division recommended that a comprehensive summary with sufficient details of chronic toxicology studies for the excipients is needed for the NDA. Information from published reports of toxicology studies should also be included in the NDA.

Studies Reviewed Within This Submission: Acute oral toxicology study with Pancrecarb in rats

Studies Not Reviewed Within this Submission: None

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2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The sponsor did not conduct any pharmacology studies with Pancrecarb.

2.6.2.2 Primary pharmacodynamics

None

2.6.2.3 Secondary pharmacodynamics

None

2.6.2.4 Safety pharmacology

None

2.6.2.5 Pharmacodynamic drug interactions

None

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The sponsor did not conduct any pharmacokinetic study with Pancrecarb.

2.6.4.2 Methods of Analysis

None

2.6.4.3 Absorption

None

2.6.4.4 Distribution

None

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2.6.4.5 Metabolism

None

2.6.4.6 Excretion

None

2.6.4.7 Pharmacokinetic drug interactions

None

2.6.4.8 Other Pharmacokinetic Studies

None

2.6.4.9 Discussion and Conclusions

None

2.6.4.10 Tables and figures to include comparative TK summary

None

2.6.5 PHARMACOKINETICS TABULATED SUMMAY

None

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: The sponsor did not conduct any toxicology study with Pancrecarb except an acute oral toxicology study in rats. In an acute oral toxicology study in rats, the maximum nonlethal dose of Pancrecarb was >5000 mg/kg. There were no treatment-related clinical signs. For excipients, as outlined in the FDA Guidance for the EPI products, no toxicology studies are needed if the excipients used are classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable. However, as requested by the FDA, the sponsor submitted a comprehensive literature review of the toxicology data for each excipient used in Pancrecarb. All of the excipients used in Pancrecarb are USP/NF compendial items, and some are also GRAS and/or present at levels previously found to be acceptable. The literature confirmed that the excipient levels used in Pancrecarb do not represent a safety concern for humans.

Genetic toxicology: None.

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Carcinogenicity: None.

Reproductive toxicology: None.

Overall, based on the available toxicology data for each excipient used in Pancrecarb drug product, there appears to be no significant safety concern for humans. In addition, the exposure assessment indicated that the exposures to all excipients appear to be safe at the specified level based on the toxicity profile of each excipient.

2.6.6.2 Single-dose toxicity

Acute Oral (Gavage) Toxicity Study with Pancrecarb in Rats

Report No.	Testing Laboratory	Species/ Route	Date Started	Date Completed	Batch No.
92-0745	(b) (4)	SD Rat	11/23/92	6/8/93	U230901, P230001, U228901, D206501

GLP Compliance: The statement of compliance and the QAU statement were included.

Methods: In this study, four groups each composed of 5 male and 5 female SD rats were administered by oral gavage either placebo (0.5% carboxymethyl cellulose), urosdeoxycholic acid (DCI Formula No. 081594-31), Ursocarb (DCI Formula No. 081594-28) and Pancrecarb (DCI Formula NO. 21-5) at a single dose of 5000 mg/kg at a dose volume of 20 mL/kg. The study design is shown below from the study report (page 6).

II. EXPERIMENTAL DESIGN

DCI Formula	Test or Control Material Name	No. of Animals Male	No. of Animals Female	Dose (mg/kg)	Concentration (mg/ml)	Dose Volume (ml/kg)
#081594-30	Placebo	5	5	5000	250	20
#081594-31	Ursodeoxycholic acid (UDCA)	5	5	5000	250	20
#081594-28	URSOCARB™ (Carbonate-buffered UDCA)	5	5	5000	250	20
#21-5	DIGESTIZYME™ (Carbonate/UDCA-buffered pancreatin)	5	5	5000	250	20

III. DATES OF STUDY

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Mortality, clinical signs and food consumption were observed on a daily basis. Body weights were recorded on Day -1, and on Days 7 and 14. In addition, at termination of the study, all surviving animals were sacrificed and examined macroscopically.

Results: The following Table (from page 12 of the sponsor's submission) shows the mortality data.

Mortality for each of the DCI Formulas occurred as follows:

DCI Formula	Dose Level (mg/kg)	Mortality			Time Found Dead
		Male	Female	Total	
081594-30	5000	0/5	0/5	0/10	-
081594-31	5000	0/5	2/5*	2/10	Day 1
081594-28	5000	1/5	1/5*	2/10	Day 2
21-5	5000	0/5	0/5	0/10	-

*The deaths of the two females treated with UDCA (DCI Formula No. 081594-31) and the one female treated with Ursocarb (DCI Formula No. 081594-28) were attributed to dosing accidents, based on macroscopic postmortem observations of perforation of the esophagus and/or apparent test material in the lungs and/or thoracic cavity. The only death which may be attributed to administration of one of the test materials occurred in one male treated with Ursocarb.

Clinical signs seen acutely only in the group treated with Ursocarb (DCI Formula No. 081594-28), which included excessive salivation, lethargy, labored breathing and absence of stool. In addition, slight ano-genital stains, chromodacryorrhea, excessive salivation, red nasal discharge, lethargy, labored breathing and absence of stool were seen in one moribund animal. Other signs were limited to emaciation, decreased food consumption and/or decreased fecal volume in one or two treated animals. Macroscopic examinations of three of the four animals which were found dead revealed perforation of the esophagus and/or changes in the lungs and thoracic cavity (discoloration, edema, irregular surface, apparent test material) which were considered indicative of dosing accidents. Overall, the maximum nonlethal dose for Pancrecarb was >5000 mg/kg.

2.6.6.3 Repeat-dose toxicity

None

2.6.6.4 Genetic toxicology

None

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2.6.6.5 Carcinogenicity

None

2.6.6.6 Reproductive and developmental toxicology

None

2.6.6.7 Local tolerance

None

2.6.6.8 Special toxicology studies

None

Safety of Excipients:

Sodium Carbonate: Sodium carbonate is present in Pancrecarb as (b) (4) Sodium carbonate is considered as GRAS and is an approved inactive ingredient in oral dosage forms up to 25 mg/unit dose. As per the OECD (Organization for Economic Co-Operation and Development) SIDS (Screening Information Dataset) (SIDS Initial Assessment Report for SIAM 15, October, 2002) assessment report for sodium carbonate, repeated dose inhalation study revealed local effects on the lungs. However, the long term hazard of sodium for humans is well known. Recommendations on daily dietary sodium intake were reported to be 2.0-3.0 g for a moderately restricted intake and 3.1-6.0 g was considered to be a normal intake. Carbonate is expected to be neutralized in the stomach. Furthermore, sodium carbonate is not expected to be systemically available in the body due to neutralization by gastric acid following oral administration. Based on these, additional testing for repeated dose toxicity was considered unnecessary for sodium carbonate.

Sodium Bicarbonate: Sodium bicarbonate is present in Pancrecarb as (b) (4) Sodium bicarbonate is considered as GRAS and is an approved inactive ingredient in oral dosage forms up to 267 mg/unit dose. As per the OECD SIDS (Screening Information Dataset) (SIDS Initial Assessment Report for SIAM 15, October, 2002), oral LD-50 values were >4,000 mg/kg, and an inhalation study in rats using a concentration of 4.74 mg/L inhalable dust produced no deaths. There are no directly relevant studies on repeated dose exposure, however, knowledge of prior use and available literature does not indicate any adverse effects of long-term exposure *via* any route. *In vitro* bacterial and mammalian cell tests showed no evidence of genotoxic activity. Based on the available information there are no indications that sodium bicarbonate has carcinogenic effects. Sodium bicarbonate has a long history of use in foodstuff, feed and industrial processes. The bicarbonate ion is a normal constituent in vertebrates, as the principal extracellular

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buffer in the blood and interstitial fluid is the bicarbonate buffer system. Excess sodium and bicarbonate ions are readily excreted in the urine. Sodium bicarbonate is also used as an antacid, with a recommended initial dose (for adults) of 4 g, supplemented by 1-2 g every 4 hours. Overall, considering the history of human use of sodium bicarbonate, it is considered safe to ingest up to 4 g/dose.

Sodium Starch Glycolate: In Pancrecarb, sodium starch glycolate is used as (b) (4) It has not been designated as GRAS; however, it is approved for use as an inactive ingredient in oral dosage forms up to 876 mg/unit dose. Sodium starch glycolate was considered well-tolerated at a level of 5% which would correspond to a daily intake of about 5 g/kg (EPA, 40 CFR180, OPP-301210; FRL-6818-2, RIN 2070-AC18). In its 1993 correspondence, TNO (Central Institute for Nutrition and Food Research) estimated the maximum amount of sodium starch glycolate that would be consumed by humans as a result of these FDA-approved uses as 13 mg/kg/day for adults and 80 mg/kg/day for children. Based on the information, EPA (Environmental Protection Agency) concluded that there is a reasonable certainty of no harm from aggregate exposure to sodium starch glycolate. Based on this, the projected clinical exposure to sodium starch glycolate from Pancrecarb does not appear to pose safety concerns for the EPI patients.

Ursodiol: Ursodiol serves as (b) (4) It is approved by the FDA for use in humans to manage cholestatic liver disease. The safety of ursodiol has been comprehensively studied. Urosodiol was not acutely toxic in rats with oral LD-50 values ranged from 2 to 10 g/kg. Repeated oral dosing in rats revealed minimal toxicity even at high doses; the liver was a target organ. There was no evidence of mutagenicity or carcinogenicity. Reproduction and fertility in rats were unaffected by treatment with ursodiol. Ursodiol was not a teratogen in rats and rabbits and did not adversely affect post-natal development in rats. Based on these data, the no-observed-effect-level (NOEL) for urosodiol in rats was 50 mg/kg/day. The established NOEL of 50 mg/kg/day in rats offers sufficient (about 11-fold) margin of safety over the estimated maximum exposure of 4.5 mg/kg/day from Pancrecarb.

Povidone: Povidone (K-90, approximate molecular weight of 360,000), also known as polyvinylpyrrolidone (PVP), serves as (b) (4) It is an approved inactive ingredient in oral dosage forms up to 78 mg/unit dose. The only reported biological effect attributed to oral administration of povidone is stool softening or diarrhoea. In long-term feeding studies in rats, there was no evidence of carcinogenicity. Povidone was not acutely toxic; the intravenous LD-50 was >10 g/kg. There was no evidence of mutagenicity or developmental toxicity. The NOEL in rats was reported to be 2500 mg/kg/day. The established NOEL of 2500 mg/kg/day in rats offers sufficient (about 625-fold) margin of safety over the estimated maximum exposure of 4 mg/kg/day from Pancrecarb capsules.

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Cellulose Acetate Phthalate: Cellulose acetate phthalate (also known as Cellacefate) is used as (b) (4) . It has not been designated as GRAS, but is approved for use as an inactive ingredient in oral dosage forms up to 70 mg/unit dose. In a 1-year toxicology study in rats, animals survived administration in the diet of up to 30% (approximately equivalent to 15000 mg/kg/day). Administration of 16 g/day to dogs (approximately equivalent to 2000 mg/kg/day) for one year did not produce significant treatment-related adverse effects. No information on the genetic toxicity, carcinogenicity or reproductive or developmental toxicity of cellulose acetate phthalate was available. Based on the 1-year study in dogs, the NOEL was considered to be 2000 mg/kg/day. The established NOEL of 2000 mg/kg/day in dogs offers sufficient (about 25-fold) margin of safety over the estimated maximum exposure of 79 mg/kg/day from Pancrecarb capsules.

Diethyl Phthalate (DEP): Diethyl phthalate is used as (b) (4) It is approved as an inactive ingredient in oral dosage forms up to 16.8 mg/unit dose. Comprehensive reviews of the toxicology data for DEP have been conducted by the World Health Organization (Concise International Chemical Assessment Document 52, Diethyl Phthalate, WHO 2003).

The acute oral LD-50 values in mice and rats were 8600 and 9200 mg/kg, respectively. Intraperitoneal LD-50 values were 2800 mg/kg in mice and 5675 mg/kg in rats. The lowest lethal dose in rabbits and guinea pigs were 4000 and 5000 mg/kg, respectively. Minimal ocular irritation and slight to moderate dermal irritation were noted in rabbits.

In a one-week dietary study, ten male Wistar rats were dosed with 2% (approximately equivalent to 2000 mg/kg/day) DEP. Body weight was unaffected, but an increase in the liver weight was observed. Similarly, in a three-week dietary study in four male Fischer 344 rats, animals were exposed to 2% (approximately equivalent to 2000 mg/kg/day) DEP. Significant treatment-related findings included a reduction in serum triglyceride levels, an increase in the liver weight and increases in peroxisomal enzyme activities.

In a 16-week dietary study in rats, Sprague-Dawley rats (n = 15/sex/group) were treated with 0, 0.2, 1, and 5% (approximately 0, 150, 770, and 3160 mg/kg/day in the males and 0, 150, 750, and 3710 mg/kg/day in the females, respectively). There were no significant treatment-related effects on hematology, serum chemistry, or urinary parameters. Significant decreases in body weight gain were observed at the high dose (5.0%) in both sexes (about 23–32% for males, 15–20% for females) and in the 1.0% group in females at (about 8%). A concurrent paired-feeding experiment indicated that the decrease in body weight gain was primarily attributable to lower food consumption and/or poorer food utilization, rather than to a direct toxic action of DEP. At the high dose, there were over 30% increases in relative liver weight in both sexes. The increases in relative liver weight of females at all doses were significant and dose-related. Similar effects were also observed in relative weights of the stomach and small intestine. Relative weights of kidney were also significantly increased at the highest dose (18% for males and 11% for

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females). However, there were no abnormal histopathological findings in the liver, kidney, digestive organs, or any other organs. Although there was a decrease in body weight at the 1% dose; however, the magnitude of the body weight change at the 1.0% dose was much smaller when compared to that at the 5.0% dose, and the change was primarily considered due to a decrease in food consumption, as described above. Therefore, the dose of 1.0% (750 mg/kg/day) was considered to be the NOAEL (no-observed-adverse-effect-level).

In a 17-week drinking water study in Sprague-Dawley rats, animals were exposed to 0 or 50 mg/L. There were no adverse effects on body weight, but serum liver enzymes were elevated. Liver weight was comparable to controls; however, liver glycogen and cholesterol levels were increased and pathological changes were noted.

The National Toxicology Program (NTP) has conducted a battery of *in vitro* genetic toxicity tests on DEP. DEP was negative in the Ames test and chromosome aberration test in Chinese hamster ovary (CHO) cells. However, a concentration-related increase in sister chromatid exchanges (SCE) occurred at 0.05 to 5 μg/L in the presence of metabolic activation only. Overall, *in vitro* genotoxicity results were considered equivocal.

Two-year dermal carcinogenicity studies were conducted in mice and rats by the NTP. B6C3F1 mice (n = 60/sex/group) were dosed dermally with 0, 7.5, 15, and 30 μL/day for 103 weeks (approximately equivalent to 0, 280, 520, and 1020 mg/kg/day in the males and 0, 280, 550, and 1140 mg/kg/day in the females, respectively). Survival, clinical signs, body weight, hematology and clinical chemistry were unaffected by treatment with DEP. No skin lesions or skin tumors were observed, but an increase in combined hepatocelluar ademonas/carcinomas was reported. There was a dose-related increase in hepatocellular carcinoma in the males, which was within the historical control range, but no dose-response was seen in the females. Overall, the findings were considered equivocal. Fischer 344 rats (n = 60/sex/group) were dosed dermally with 0, 100, and 300 μL/day for 103 weeks. These doses were equivalent to 0, 320, and 1010 mg/kg/day in the males and 0, 510, and 1560 mg/kg/day in the females, respectively. Survival, clinical signs, body weight, hematology and clinical chemistry were unaffected. No dermal lesions or skin tumors were noted, and no increase in tumors was reported.

NTP reported the findings of a continuous breeding fertility study in CD-1 mice at dietary concentrations of 0, 0.25, 1.25 and 2.5% (which corresponded to doses of 0, 340, 1770, and 3640 mg/kg/day, respectively). Animals were treated for 14 weeks beginning 1 week prior to mating. No significant treatment-related adverse effects were observed on reproductive parameters including number of litters per pair, number of pups per litter, viability of pups, and pup weight in the parental generation. The offspring (F1) from the control and high-dose group were then mated. There was no effect on reproductive parameters, but fewer pups were delivered. At necropsy, body weight was decreased in F1 animals, liver weight was increased, and epididymal sperm concentration was reduced.

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In a Segment II teratology study in rats, animals (n = 27-32/group) were exposed orally (diet) at concentrations of 0, 0.25, 2.5, and 5% (0, 198, 1909, and 3214 mg/kg/day, respectively) on Gestation Days (GD) 6 to 15. Animals were sacrificed on GD20. Body weight gain and food consumption were decreased at 2.5 and 5%. There were no treatment-related adverse effects on the numbers of corpora lutea, implantations, resorptions, live fetuses, and fetal body weight. An increased incidence of extra ribs (skeletal variation) was seen at the high-dose. This was considered secondary to maternal toxicity. DEP was not teratogenic in rats. The NOAEL was identified as 1900 mg/kg/day for both the mother and the offspring.

In a Segment II teratology study in mice, ICR mice (n = 18-20/group) were treated dermally with DEP at 0, 500, 1600, and 5600 mg/kg/day on GD0 to GD17. There were no test article-related adverse effects on body weight, pregnancy index, numbers of corpora lutea, implantations, and live fetuses. In the dams, adrenal and kidney weights were increased at 5600 mg/kg/day. Fetal body weight was reduced at 5600 mg/kg/day. DEP was not teratogenic in mice. The NOAEL was identified as 1600 mg/kg/day for both the mother and the offspring.

In a Segment III pre- and postnatal development study in rats, Sprague-Dawley rats (n = 3-16/group) were dosed orally (gavage) at 0 and 750 mg/kg/day on GD14 through postnatal day 3 (PND3). Parameters evaluated included body weight, organ weights, pup development, and pup reproductive organs. No treatment-related adverse effects on any of the parameters in the dams or the offspring were noted. The NOAEL was identified as 750 mg/kg/day.

Overall, DEP had an oral LD-50 values greater than 8000 mg/kg. Repeated dosing studies indicated that the liver could be the potential target organ. There was no evidence of any significant reproductive adverse effects, or developmental toxicity in animals. DEP gave equivocal results in *in vitro* genotoxicity studies. Equivocal evidence of carcinogenicity was obtained following dermal treatment in mice only. In the rat, the NOAEL was determined to be 750 mg/kg/day. The NOAEL for reproductive toxicity was determined to be 1600 and 1900 mg/kg/day in mice and rats, respectively. The established NOAEL of 750 mg/kg/day from the 16-week study in rats offers sufficient (about 36-fold) margin of safety over the estimated maximum exposure of 21 mg/kg/day from Pancrecarb capsules. In addition, the established NOAELs of 1600 and 1900 mg/kg/day in mice and rats, respectively, derived from teratology studies, also offer adequate (about 76- and 90-fold, respectively) margin of safety over the estimated maximum exposure of 21 mg/kg/day from Pancrecarb capsules.

Talc: Talc is used as (b) (4) Talc is considered as GRAS and is approved in oral dosage forms up to 220.4 mg/unit dose. Talc was not shown to produce significant organ toxicity following repeated oral dosing in animals. There was no evidence of mutagenicity, carcinogenicity (oral exposure), or teratogenicity. The NOEL in rats following oral exposure was 50 mg/kg/day. The established NOEL of 50 mg/kg/day in rats offers sufficient (about 83-

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fold) margin of safety over the estimated maximum exposure of 0.6 mg/kg/day from Pancrecarb capsules.

Exposure Assessment for Excipients:

The 2006 FDA guidance document on EPI drug products recommends a starting dose of 500 to 1,000 lipase units/kg/meal and titrating to less than 2,500 lipase units/kg/meal. Assuming four meals per day, this results in 10,000 lipase units/kg/day. The corresponding doses for adults and young adults or adolescents are 600,000 and 350,000 lipase units/day, respectively. Each Pancrecrab MS-8 capsule contains 8,000 lipase units. Thus, the maximum anticipated number of MS-8 capsules ingested per day for an adult would be 75 and for an adolescent would be 44 (these estimates represent the high-end of the potential exposure range, since they are based on 2,500 lipase units/kg/meal). The following Table (from page 23 of the sponsor's submission) summarizes the excipient exposures under these maximum conditions and compares these values to the NOEL/NOAEL values identified in the toxicology literature.

Table 3. Maximum Anticipated Daily Exposure to PANCRECARB® MS-8 Excipients

Excipient	Adult Amount per Day (mg)	Adult Dose (mg/kg/day)	Young Adult Amount per Day (mg)	Young Adult Dose (mg/kg/day)	NOEL/ NOAEL (mg/kg/day)	MOS** (Adult)	MOS (Young Adult)
Sodium Carbonate	(b) (4)						
Sodium Bicarbonate							
Sodium Starch Glycolate							
Ursodiol							
Povidone							
Cellulose Acetate Phthalate							
Diethyl Phthalate							
Talc							

NL = no limitations. * Extrapolated doses based on the approved level of 876 mg for sodium starch glycolate in FDA's Inactive Ingredient Database divided by body weights from the DC1 studies for adults (60 kg) and young adults or adolescents (35 kg). ** Margins of safety are calculated by dividing the NOEL or NOAEL from the toxicology data by the daily projected human dose.

Although as per the above Table, the margins of safety for sodium carbonate and sodium bicarbonate are about 2- and 3-fold, respectively; however, there is extensive human experience with these ingredients as discussed above. For sodium starch glycolate, a higher intake may occur in adults than is established in the FDA's Inactive Ingredient Database (876 mg). Sodium starch glycolate was considered well-tolerated at a level of

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5% which would correspond to a daily intake of about 5 g/kg (EPA, 40 CFR180, OPP-301210; FRL-6818-2, RIN 2070-AC18). In its 1993 correspondence, TNO (Central Institute for Nutrition and Food Research) estimated the maximum amount of sodium starch glycolate that would be consumed by humans as a result of these FDA-approved uses as 13 mg/kg/day for adults and 80 mg/kg/day for children. Based on the information, EPA concluded that there is a reasonable certainty of no harm from aggregate exposure to sodium starch glycolate. Based on this, the projected clinical exposure to sodium starch glycolate from Pancrecarb does not appear to pose safety concerns for the EPI patients. The estimated human exposure to cellulose acetate phthalate would be 79 mg/kg/day from Pancrecarb capsules. The established NOEL of 2000 mg/kg/day for cellulose acetate phthalate in dogs offers about 25-fold margins of safety. For DEP, the established NOAEL of 750 mg/kg/day from the 16-week study in rats offers sufficient (about 36-fold) margin of safety over the estimated maximum exposure of 21 mg/kg/day from Pancrecarb capsules. In addition, the established NOAELs of 1600 and 1900 mg/kg/day in mice and rats, respectively, derived from teratology studies, also offer sufficient (about 76- and 90-fold, respectively) margin of safety over the estimated maximum exposure of 21 mg/kg/day from Pancrecarb capsules. Overall, from a nonclinical perspective, the estimated maximum daily exposure of cellulose acetate phthalate (79 mg/kg/day) and diethyl phthalate (21 mg/kg/day) from Pancrecarb capsules appears to be safe and the levels of cellulose acetate phthalate and diethyl phthalate in Pancrecarb capsules are acceptable.

2.6.6.9 Discussion and Conclusions

As per the 2006 guidance on exocrine pancreatic insufficiency (EPI) drug products, no new pharmacology studies are needed because of the extensive use of the currently marketed EPI products. As outlined in The FDA Guidance for exocrine pancreatic insufficiency products, no toxicology studies are needed if excipients are classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable. The sponsor did not conduct any nonclinical studies with Pancrecarb. All of the excipients used in Pancrecarb are USP/NF compendial items, and some are also GRAS and/or present at levels previously found to be acceptable. The sponsor provided a comprehensive summary of the toxicology data available for each excipient used in the formulation of Pancrecarb as per the Agency's recommendation. Overall, the exposure assessment indicated that the exposures to all excipients are safe at the specified level based on the toxicity profile of each excipient. There appeared to be no anticipated risks associated with the use of Pancrecarb at the projected clinical doses in patients with EPI.

2.6.6.10 Tables and Figures

None

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2.6.7 TOXICOLOGY TABULATED SUMMARY

None

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on the extensive clinical experience with EPI products and the literature evidence for each excipient used in the Pancrecarb drug product, there appears to be no indication of a safety concern for the clinical population from Pancrecarb capsules. The exposure assessment indicated that the exposures to all excipients are safe at the specified level based on the toxicity profile of each excipient reported in the literature. Overall, there appears to be no anticipated risks associated with the use of Pancrecarb at the projected clinical doses in patients with EPI.

Unresolved toxicology issues: None

Recommendations: From a nonclinical perspective, this NDA is recommended for approval.

Suggested labeling: The sponsor should be asked to modify the proposed label of Pancrecarb as suggested in the "Executive Summary: Recommendations on Labeling".

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

None

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tamal Chakraborti
6/19/2009 11:53:44 AM
PHARMACOLOGIST

Sushanta Chakder
6/19/2009 12:25:36 PM
PHARMACOLOGIST